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Investigating investment strategies for tackling antibiotic resistance.
A quantitative and qualitative assessment.

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A thesis submitted to Imperial College London for the degree of Doctor of Philosophy

Declaration

I declare that this thesis submitted for the degree of Doctor of Philosophy has not been submitted for any other degree of professional qualification. The thesis is my own work, and that, unless otherwise referenced, the material presented in the thesis is my own original work. The thesis was completed under the supervision of Dr Julie V Robotham, Professor James Barlow, Professor Alison Holmes, and Professor Rifat Atun at the Department of Medicine in Imperial College London between September 2015 and June 2019.

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Abstract

Antibiotic resistance (AbR) is a growing, multifaceted public-health concern. Bacteria harbouring AbR are found in diverse hosts, human and animal, and in the environment. To further our current understanding of AbR, four key evidence frameworks are needed.

Firstly, there has been no systematic retrieval or assessment of the evidence on the multi-setting risk factors across all drug-bug combinations of AbR in humans. Secondly few frameworks examine how well the currently implemented interventions are targeting key risks driving AbR. Thirdly, future investment needs in light of the Points 1-2 above are lacking. Lastly, an assessment of the process-level-barriers to tackling AbR is needed for successful implementation of interventions. This thesis aims to inform these four evidence frameworks and provide policymakers tools to investigate investment strategies to tackle AbR in humans.

METHOD

Four key methods were utilised to meet the objectives of this thesis. Firstly, a systematic review was conducted to identify key risk factors of AbR. Secondly, a network-mapping technique was applied to explore clinical-effectiveness of currently implemented interventions. Thirdly, a dynamic transmission model was used to investigate areas of better resource-allocation. Lastly, a qualitative study was conducted using a systems-thinking approach to develop causal-loop models that identified process-level barriers to tackling AbR.

FINDINGS

Easier to quantify risks of AbR are being targeted by policy and ground-level interventions using a top-down implementation approach. Current interventions have limited evidence on their long-term efficacy of tackling AbR. For cost-efficiency, the model recommends policymakers to focus investment in the community. The interconnectivity of system-level factors (e.g. infrastructure,

competing-priorities) impact system-wide engagement which fuel the process-level barriers to tackling AbR.

CONCLUSION

To help identify targets for sustainable interventions, research investment is needed to further investigate underlying factors driving AbR. Awareness of the drivers of AbR leading to greater engagement could enable successful implementation of long-term measures to effectively tackle AbR.

Dedication

To my grandmother.

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LIST OF ABBREVIATIONS

AbR	Antibiotic Resistant Bacteria
Abx	Antibiotic Treatment
AMR	Antimicrobial Resistance
AMS	Antimicrobial Stewardship
ASP	Antibiotic Stewardship
CCG	Clinical Commissioning Group
CDC	Centers for Disease Control and Prevention
CLD	Causal Loop Diagram
CPE	Carbapenemase-Producing *Enterobacteriaceae*
CQC	Care Quality Commission
CQUIN	Commissioning For Quality And Innovation
CRE	Carbapenem Resistant *Enterobacteriaceae*
DNA	Deoxyribonucleic Acid
ECDC	European Centre For Disease And Control
EFSA	European Food And Safety Authority
EMP	The Earth Microbiome Project
ERIC	Estates Returns Information Collection
ESBL-ENT	Extended Spectrum Beta-Lactamase-Producing- *Enterobacteriaceae*
EU	European Union
GAP	The World Health Organization Global Action Plan
GDP	Gross Domestic Product
GLASS	The Global Antimicrobial Surveillance System
GP	General Practitioner
HCAI	Healthcare Associated Infections
HICs	High Income Countries
HPV	Hydrogen Peroxide Vapour (decontamination fogging machine)
HR	Hazard ratio
IACG	International Coordination Group For Antimicrobial Resistance
ICHCNT	Imperial College Healthcare NHS Trust
IPC	Infection Prevention And Control
LMIC	Low-Middle Income Countries
LUMICs	Low-Upper-Middle Income Countries
MDR	Multi-Drug Resistant
MRSA	Meticillin Resistant *Staphylococcus Aureus*
NHS	National Health Service
NICE	National Institute Of Health Care And Excellence
OECD	Organisation For Economic Co-Operation And Development
OIE	World Organization For Animal Health
OR	Odds Ratio
PCT	Procalcitonin Testing
PICOS	Population, Intervention, Comparator, Outcome, And Study Design
PRISMA	Preferred Reporting Items For Systematic Reviews And Meta-Analyses
RCT	Randomised Controlled Trial
SDGs	Sustainable Development Goals

SLR	Systematic Literature Review
SSI	Surgical Site Infection
UN	United Nations
US	United States
WHO	The World Health Organization
WSE	Whole System Engagement

CHAPTER 1.

1 ANTIBIOTIC RESISTANCE

1.1 Introduction

1.1.1 The Biological Background

Antimicrobial resistance (AMR) is a global threat to humans caused by life-threatening infection-causing microscopic-organisms, known as microbes. Some infection causing microbes are evolving at a much faster pace and developing novel resistant mechanisms compared to the human discovery rate of novel antimicrobials (1).

Human understanding of different types of microbes

Identifying all the species of microbes that currently live on Earth is still a work in progress. The *Earth microbiome project* (EMP) which formed in 2010 currently suggest that over 1 trillion microbial species exist on Earth (2). Out of these only 1% of species have been identified and genetically sequenced in laboratories (3). Therefore, humans only know about a fraction of the microbes they are currently living alongside on Earth (2,3).

'Microbes' is an umbrella term for several species comprising fungi, virus, parasites, and bacteria. Bacteria are a type of microbe that co-habit in a mutually beneficial manner with humans. They are single celled organisms that can be found in a variety of shapes and include a single strand of Deoxyribonucleic acid (DNA) (4).

Differentiating between different types of bacteria

Based on a violet colour dye staining test, called the Gram-stain test, bacteria are classified as either Gram-positive or Gram-negative (5). Gram-positive bacteria stain violet due to its cellular wall retaining the stain. However, the Gram-negative bacteria does not retain the stain due to a different cellular structure to Gram-positive bacteria (5). Both types of bacteria include an inner cell membrane, however, Gram-negative bacteria also include an outer membrane. This outer

membrane limits penetration of certain antibiotic classes, therefore, making Gram-negative bacteria structurally more resistant to antibiotics compared to Gram-positive bacteria (5,6).

Bacteria and types of resistant mechanisms

Both aforementioned types of bacteria have the capability to develop mechanisms to inherently become resistant to antibiotics, due to these varying cellular structures (5). The DNA within the bacteria also possesses the ability to mutate and make the bacteria resistant to certain classes of antibiotics. Additionally, bacteria can also acquire genetic material conferring antibiotic resistance from other resistant bacteria, which further facilitate the emergence of resistance. Thus, so far the commonly known mechanisms via which bacteria become resistant to antibiotics depend on inherent development of resistance as well as acquisition of resistant material due to transmission from other bacteria (7). Therefore, the mechanisms via which bacteria develop resistance and transmit the resistant material (i.e., genetic material) to other bacteria can vary depending on the individualised structure of the bacteria (5,7). Humans have a limited but growing body of knowledge identifying these various bacteria-led mechanisms of resistance, this knowledge is also often being used to develop newer classes of antimicrobials (5).

Reservoirs of different types of bacteria

Bacteria are known to live and thrive under various conditions such as in animals, soil, water, and the human gut. In the environment, bacteria play an essential role for example, in terms of mixing nutrients in the soil, which contribute towards crop production. Humans are not born with bacteria, however, soon after birth, become colonised by bacteria. In humans, a colony of bacteria inhabit the human gut, in the digestive system; the bacteria release enzymes which facilitates digestion. Thus, these types of bacteria are considered beneficial to humans (7,8).

Pathogenic bacteria and their transmission mechanisms

Aside from these mutually beneficial bacteria, there are harmful bacteria that have the capability to replicate rapidly and cause infections. Such infections commonly occur within a healthcare setting which are known as healthcare associated infections (HCAI). Ventilator associated pneumonia or catheter associated urinary tract infections are examples of HCAI. There are certain types of mutually beneficial gram-negative bacteria that may also become harmful infection-causing bacteria. *Enterobacteriaceae* are one such type of bacteria which inhabit in the human gut, however they can also cause certain types of non-healthcare associated infections (e.g. community acquired urinary tract infections) as well as HCAI (5,7).

Bacteria beneficial to humans, such as the ones found in the gut, becoming resistant to antibiotics and causing difficult to treat infections may give rise to substantial health and economic burden from a public-sector perspective. Specifically, the inability to successfully perform regular surgical procedures such as hip and knee replacements or caesarean sections have been highlighted as some of the common procedures where antibiotic resistant bacteria (AbR) could be growing cause for concern for humans (8–12).

Human-attributable factors driving AbR

Up to this point some of the development and transmission mechanisms adopted by AbR (i.e., bacteria-led factors) have been discussed. However, at the time the research plan for this thesis was being finalised, there was a growing body of evidence strongly supporting two key human-attributable factors that were driving the emergence and transmission of antibiotic resistant bacteria in humans (8). The first human-attributable factor being inappropriate use of antibiotics andthe second being ineffective infection control measures to prevent the onward spread of these AbR infections.

Antibiotic use as a driver of AbR was identified with the invention of the first ever antibiotic, penicillin. Soon after the discovery of penicillin in 1928, Sir Alexander Fleming cautioned both the

prescribers and the users of antibiotics about the unique survival mechanisms of bacteria (13,14). Since the invention of penicillin a large number of antibiotic classes were subsequently invented and introduced for use in humans as well as in animals and in the agricultural-farming industry (15). With each new antibiotic being discovered, bacteria have developed unique mechanisms to conferring resistance to them. Therefore, not only do humans have to constantly keep up with the emerging novel resistance mechanisms of bacteria, but also broaden their understanding about the largely unknown causal factors driving AbR to better tackle these pathogens.

1.1.2 The Growing Problem Of AbR

Rising levels of Gram-negative bacteria

Over the past decade, the resistance levels of bacteria against frequently used antibiotics have been escalating. As discussed previously, of particular concern is AbR associated with Gram-negative bacteria such as *Enterobacteriaceae* (e.g. *Escherichia coli*), with resistance steadily increasing across high income countries such as in Europe (16) and the United States (US) (Figure 1). In comparison, these rates are at critical levels, often twice as high (reaching 70-80% of all tested isolates) in low-upper-middle income countries (LUMICs) such as India and China (Figure 1) (17,18). Thus, highlighting the escalating global landscape of these organisms. These high and lower to middle income countries are increasingly becoming interconnected with time, as a result of trade, travel, migration, and medical tourism. These critical levels of AbR in certain areas of the world cannot therefore be treated as a mutually exclusive isolated problem. As a result, the global community has now acknowledged AbR as a global health threat for humans, having long term repercussions comparable to climate change (7).

Last line of antibiotics

Within the past five years, the problem of AbR has escalated to the point where clinicians are progressively reliant on last line antibiotics to treat certain HCAI. ‘Last line antibiotic’ gets its name from the fact that certain bacteria have become resistant to all antibiotic classes available apart from

this last line of antibiotics. Carbapenems are an example of one such last line antibiotic which are used in healthcare settings such as in the intensive care unit. These antibiotics are used to treat infections caused by AbR bacteria that cannot be cured by any other antibiotic. In particular, carbapenems are increasingly being used against AbR *Enterobacteriaceae* (e.g. Extended Spectrum Beta-Lactamase-producing- *Enterobacteriaceae* (ESBL-ENT)) species (8,19,20).

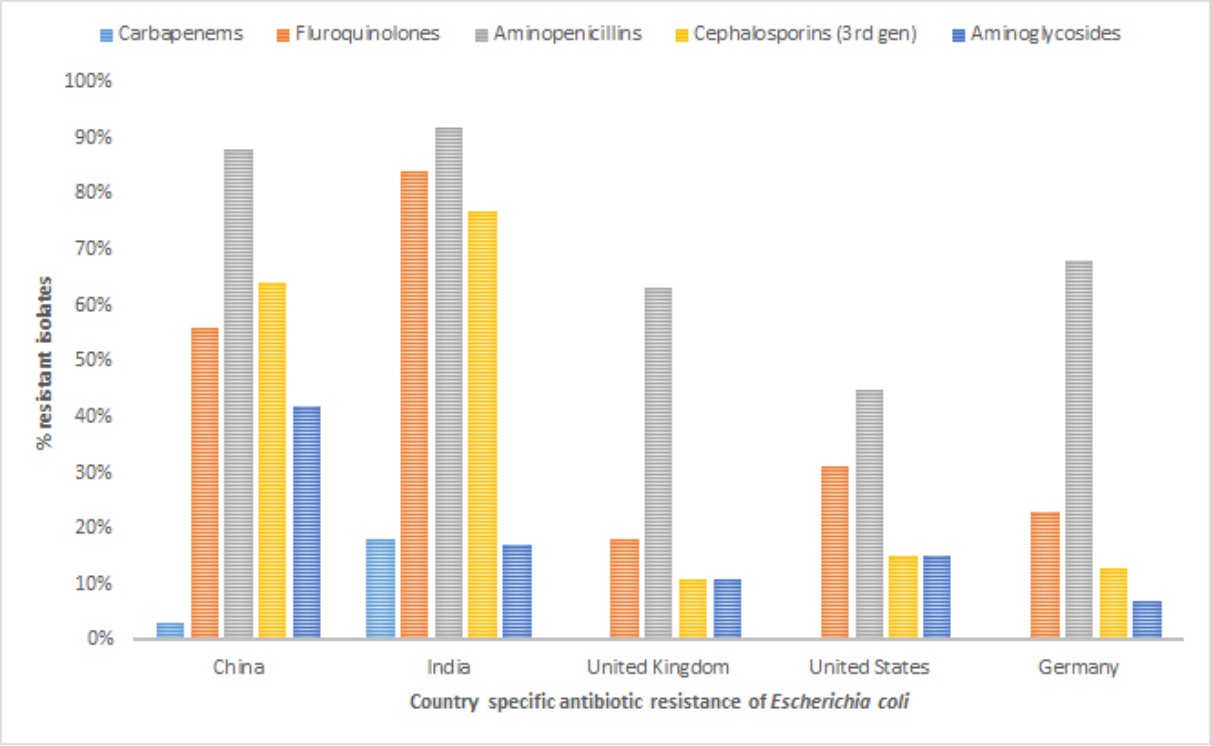


Figure 1: Cross country comparison of resistance levels of *E. coli* to key antibiotics

Source: The Center for Disease Dynamics Economics & Policy. ResistanceMap: [Antibiotic Resistance]. 2018 (21).

As seen from Figure 1, carbapenem resistant bacteria are slowly being observed across the globe, in particular high levels can be seen in LUMICs. Outbreaks of carbapenemase-producing *Enterobacteriaceae* (CPEs) are also being reported in high income countries (HICs) including in England (22).

Apart from carbapenems, clinicians also consider colistin a last line antibiotic. However, colistin has been a less popular antibiotic and has not been commonly used in clinical practice in the last 50 years. Colistin has previously been an unpopular antibiotic due to its high probability of causing nephrotoxicity. However, due to the increasing incidence of carbapenem resistant bacteria, colistin has now been brought back into clinical practice, despite the adverse events associated with its use. Colistin is the only antibiotic remaining that can treat CPE and other multi-drug resistant (MDR) gram-negative bacteria.

Worryingly, due to colistin's increased use in the agricultural-farming industry, colistin-resistant genes (MCR-1) have recently been reported, leaving limited options for treating pathogenic bacteria in the future (17,23). The problem of colistin resistant bacteria further highlights the need for a greater understanding and quantification of the causal factors driving AbR that are not only driven by human-only use of antibiotics.

1.1.3 The Health And Economic Burden Of AbR

The AMR review team projections

From a patient and a healthcare payer perspective, these increasing AbR prevalence levels have also been linked with a high health and economic burden. Recently in the United Kingdom (UK), the ex-UK Prime Minister – David Cameron had commissioned an AMR review team led by Lord Jim O'Neill – a prominent economist, to capture the current burden of AMR and forecast what the repercussions of AMR would be in terms of the health and economic burden to society. The AMR review team have quantified mortality rates, healthcare expenditure burden, and societal costs of tackling AbR (8,19,24–26). These projections show that the global death rate associated with drug resistant infections is currently estimated to be 500,000 in Europe and the US alone, which could rise to an additional 10 million a year within the next 50 years (19). Given that the future trajectory of AMR is uncertain, as highlighted in the AMR review reports, the authors explored alternative future scenarios. In the most extreme of these, resistant infection rates were doubled, which projects that

by 2050, the deaths associated with drug resistant infections could reach 700 million with an associated cost of US$100 trillion (24). Furthermore, the total loss of the working age population was estimated to be ranging from 11 to 444 million by 2050 (25).

OECD and World Bank projections

Alongside the AMR review and after publication of these aforementioned first ever large scale estimates of the impact of drug-resistant infections, a number of global organisations such as the Organisation for Economic Co-operation and Development (OECD) and the World Bank also commissioned similar AMR related cost projection projects. The OECD have estimated that by 2050 OECD countries could face losing up to 0.16% of their Gross Domestic Product (GDP), equivalent to US $2.9 trillion. The World Bank estimated that within a high-impact scenario, the global annual GDP loss by 2030 could be around $3.4 trillion (26). A US wide estimate of the direct cost of drug resistant infections was around US $20 billion in 2013 and productivity losses in terms of days lost at work or the caregiver burden cost was reported to be around $35 billion (27). More recently a systematic review on the economic burden of AMR identified over 200 studies reporting on variable levels of cost burden associated with AMR, ranging between US $21,000 (2013 costs) per patient to country level GDP losses of over $3 trillion (28).

Other country level projections

Besides these large-scale country level long term projections, a number of smaller scale setting-specific burden estimates of AbR have also published in peer reviewed journals. Amongst these, a US based study reported the cost of treating meticillin resistant *Staphylococcus aureus* (MRSA) to be twice as high in comparison to meticillin-susceptible *Staphylococcus aureus* (29). Another European Union (EU) country level hospital setting specific study estimated (based on 2007 prevalence levels) the excess hospital length of stay burden of MRSA to be US $63.1 million, whereas for some gram-negative infections (e.g. 3rd generation cephalosporin resistant *Enterobacteriaceae*) the estimated

cost was US $29.7 million (30). These setting specific studies have highlight the increasing burden of AbR seen within the secondary care hospital settings, where AbR adds to the existing increasing burden of HCAIs, in terms of prolonging the length of a patient's stay.

AbR and the Sustainable Development Goals

Recent cost estimates at a global and country level therefore highlight that the rising AbR levels are an increasing health and economic burden to the patient, their caregivers, the healthcare payer, and the overall society. AbR is a society-level failure of protecting a scarce commodity, the commodity being antibiotics. Inability to control AbR reduces the likelihood of meeting the 2030 sustainable development goals (SDGs) set by the United Nations (UN); goals which have been set to improve equality and growth around the globe. Increasing levels of AbR subsequently fails to meet seven out of the 17 core SDGs (31). The goals that rising level of AbR violate comprise of ensuring healthy lives for all ages, ending poverty and hunger in all its forms by improving food safety and sustainable agriculture, improving water quality and sanitation, promoting sustainable economic growth, consumption and production levels, reaching full ethical employment levels, and improving global partnership.

The rising levels of AbR is a threat to humans. To tackle the novel ways resistant bacteria are evolving across the various reservoirs within which bacteria can survive, humans need innovative interventions. A number of measures are already in place with further scope for more interventions to be effectively implemented.

1.1.4 Interventions And AbR

Infection control and antibiotic stewardship

Having worked closely with life-threatening infections caused by AbR, compared to other stakeholders, clinicians and healthcare workers have often been more informed and aware of the dangers and immediate repercussions of AbR (32). Secondary care settings have had strict infection

prevention and control (IPC) policies in place to restrict transmission of such infections. Rising awareness of AbR has also shifted focus towards antibiotic use and how it might be further driving AbR in humans. Clinicians and their antibiotic prescribing practices have come under scrutiny as a result of the increasing awareness of AbR. Therefore, alongside IPC measures, measures to control the use of antibiotics, also known as antibiotic stewardship (ASP) measures, are starting to be put into place across a number of countries.

Current recommendations to tackle AbR

WHO Global action plan

The World Health Organization (WHO) have spearheaded the development and deployment of strategies to tackle AbR worldwide. Nearly 18 years ago, in 2001, WHO had published a Global strategy to tackle AbR. The 2001 framework recommended: 1) Curbing the spread of infectious disease 2) Improving access to antibiotics 3) Improving use of antibiotics 4) Improving surveillance measures 5) Strengthening regulation and legislation and lastly 6) improving investment in new antibiotics and vaccines. Parallel to and following on from the UN political declaration surrounding AbR in 2015, a number of solutions to tackling AbR have been recommended. Amongst these, in 2013, in a renewed effort to engage stakeholders to tackle AbR, WHO published their first Global Action Plan (GAP) to tackle AbR (33). The WHO's GAP has become the most internationally recognised action plan that lays the foundation to individual national-country level action plans around the globe. At the heart of WHO's GAP are five key objectives. These five objectives closely resonate with the aforementioned 2001 recommendations of tackling AbR. Improving antibiotic use and surveillance measures, reducing incidence of infections, and promoting the development of antibiotic use and vaccines were previously touched upon in the 2001 recommendations. The importance of raising awareness surrounding AbR and building an economic case for new antibiotics and better diagnostics were additional action measures highlighted in the new action plans. Furthermore, the importance of the interconnections between both the human and animal health

when it comes to tacking AbR have been greatly emphasised within the action plan. The key difference between the 2001 efforts and the 2013 efforts is the way WHO are monitoring their action plan.

The AMR review team

Based on the large estimates and greater understanding of how AbR is able to weave into human health, the previously mentioned UK AMR review team also propose a number of recommendations (8) to tackling AbR that align with WHO's GAP. The AMR review recommends that to address the barriers of tackling AbR the following avenues for intervention should be explored 1) Preserving the current antibiotics and 2) Increasing the current range of antibiotics available. Out of these recommendations, there is an increasing focus on the one health aspect of AbR. In particular related to the use of antibiotics in the agricultural industry and the pollution of antibiotics in the environment. Within the context of AbR, 'One health' refers to the inter-relationship between the different reservoirs where AbR may emerge or transmit from; currently known reservoirs of AbR include humans, animals, and the environment.

1.1.5 Identification, Adoption, And Implementation Of Measures To Tackle AbR

Thus far, the commonly known mechanisms of AbR bacteria, the increasing burden of AbR, and the intervention options to tackle AbR have been discussed. Within the following section the importance of stakeholder engagement and importance of an understanding of barriers to intervention adoption and implementation will be discussed.

When assessing the progress of implementing the recommendations from the WHO Global Strategy document published in 2001 (34) into everyday practice, it can be concluded that the progress has been limited. Within an editorial, some researchers highlighted the rise of terrorism and bioterrorism (e.g. the World Trade Centre attacks and the anthrax attacks) overshadowing the risks of AbR to humans (32).

Next, based on recent events, it can be speculated that only following the aforementioned large scale estimates of the potential long term costs related to AbR, the members of the UN general assembly showed their political will to tackle AbR collectively (31). A political declaration to tackle drug-resistant infections globally was signed by all the heads of states of the UN (4). Moreover, despite the previously highlighted repercussion of AbR on the SDGs, tackling AbR had not been highlighted as an essential goal. Following the political declaration, AbR was also included as part of a SDG (31). This chain of evidence driving action towards political engagement highlights the importance of quantifying the burden and consequently also the drivers of AbR. By showcasing the quantified evidence on the potential repercussions of AbR, global political leaders were informed and brought together to understand how AbR weaves into all parts of society and prevents economic growth.

Political leaders possess the means to change the current healthcare infrastructure and delivery of a country, without which AbR could not be permanently addressed. Therefore, a whole system understanding of the key drivers of AbR is needed to develop policy targets.

Concurrently, engaging the appropriate stakeholders is needed so policy targets can be adopted and disseminated as ground level interventions to tackle AbR. Currently, the evidence base to show if the currently implemented interventions are targeting key drivers of AbR is lacking. Without this mapping process, avenues of new policy targets and areas of investment to tackle AbR would not be effectively identified.

Additionally, using the 2001 WHO strategy as an example, an understanding of the process-level barriers to tackling AbR is needed. Barriers that may be preventing an intervention from being adopted or implemented effectively. These barriers of intervention identification and effective implementation will be discussed in further detail within Section 1.2.2.

Therefore, the overarching rationale of this thesis are as follows:

- Identification of the causes of AbR, would lead to better engagement for adoption of interventions to tackle AbR.

- Monitoring the process-levels barriers to tackling AbR would enable quicker adoption and effective implementation of interventions.
    - In summary so the intended targets (i.e., the risk of AbR) of the interventions can be tackled effectively.

These rationales will be further discussed in detail in the subsequent sections below, starting with an analysis of AbR from a health policy perspective followed by the description of the current barriers that policymakers are facing when it comes to tackling AbR. The overall aim of this thesis is to help address some of these key barriers to enable policymakers make more efficient investment decisions when it comes to tackling AbR.

1.2 Thesis Rationale

1.2.1 Health Policy And AbR

Health policy has previously been framed as being driven by two key factors. Firstly, 'how' health policy is made and what the common tools are that stakeholders rely on. Secondly, the 'who' of health policy, i.e., the stakeholders in charge of making policy (35).

Tools to devise and implement health policy

Amongst the 'how' of health policy, evidence-based decision making tools are embedded. Evidence-based policy aims to uncover where the problems are, how big the problems are, and where external intervention are needed to prevent or contain the problem (35). Clinicians primarily rely on evidence-based information to make crucial life-saving decisions for their patients. Guidelines such as the ones developed by the National Institute of Health Care and Excellence (NICE) typically use methods that limit researcher bias, such as systematic reviews to select and quality assess the plethora of evidence. These systematic reviews of evidence along with expert consultations help support the National Health Service (NHS) in England in implementing evidence-based policies for their patients (36).

A top-down and a bottom-up approach

In terms of the implementation tools of 'how' policy is commonly implemented there are two key ways to implement policy to help reduce the gap between policy making and policy implementation. The aforementioned gap occurs when a policy has not been implemented as was originally intended by the policymaker (35). The first of the approaches is a top-down approach to policy implementation. A top down approach proposes that a central organisation develops and leads the policies to be implemented. Amongst other factors, there is a need for clearly identified objectives and a good grasp of the causal factors driving the policy problem for a top down approach to be successful. A common criticism of this method is the lack of importance given to the role of the people implementing these policies at the ground level. The implementers may identify underlying factors that could be driving the overarching problem at hand, which the central organisation may not think are significant enough to target.

When a top-down approach is not suitable for a complex policy problem, a bottom-up approach is applied. A bottom-up approach emphasises the role of the people who are implementing policy and gives them flexibility over how policy should be implemented. The interaction between policymakers and policy implementers lends itself to an iterative and less linear method of policy making.

The stakeholders devising and implementing health policy

In terms of the 'who' of the policy making decisions when it comes to AbR numerous stakeholders are involved. *ReACT,* within the remit of an independent international non-profit organisation carried out a study that compiled a list of the key stakeholders who are involved and responsible for tackling AbR from a global all the way to a regional level (37). These stakeholders are associated with clinical, pharmaceutical, political, health economic, and the agricultural sectors to name a few. Therefore, these stakeholders come from a variety of backgrounds with different levels of knowledge and priorities when it comes to tackling AbR. For example, the health economists may be more concerned with the most cost-effective strategy to tackle AbR, whereas the clinicians would be more

concerned with the safest option for their patients and not necessarily a cost-effective option for the policymakers. Therefore, there are numerous stakeholders ('whos') driving AbR policy-making with different objectives, often coming from conflicting interest groups with limited knowledge of the causal factors driving AbR.

As can be seen from the UN political declaration, influencing the correct 'whos' of AbR policy making is essential to promoting collaborative efforts to tackling AbR long term. To be able to engage the 'whos' in AbR policymaking, researchers would need to ensure that they have the relevant evidence-based knowledge about where the priorities of AbR should be. In addition, it is also necessary for researchers to understand the complexity surrounding decision making to tackle AbR, i.e., the process behind 'how' the decisions are being made to tackling AbR.

Moreover, combining the various 'whos' with 'how' to effectively implement health policy within the scope of AbR can be a barrier in itself to tackling AbR for a number of reasons. Firstly, using the top down approach as an example, a global multi-stakeholder issue like AbR without a central system governing the policymaking process at a global level would be challenging to monitor and implement. Additionally, given the various mechanisms of emergence and transmission of AbR at a country and global level, an understanding of the importance of the setting specific causal factors driving AbR are needed to govern change when it comes to policymaking in AbR. Lastly, in recent times, barriers to tackling AbR have also been compared with the classic economic issue of societal benefit and collective bargaining (38). The entity willing to invest time and/or resources in the implementation, audit, or regulation of these interventions may not directly benefit from this investment, whereas the wider society, which is not directly bearing the costs, is beneficiary (38). Therefore, given the need for a setting specific understanding of AbR, a bottom-up approach of understanding the challenges faced by individual policy implementers is a potentially better suited approach to identifying and implementing policy to tackle AbR.

Taking into account these barriers to AbR policy making and implementation, an evidence-based quantitative aspect of health policy making supplemented by an understanding of the process-level barriers to tackling AbR is needed to holistically inform investment decisions to tackle AbR. Such an aggregated framework would therefore enable policymakers to devise and implement AbR health policy using a bottom-up approach.

In conclusion, in light of the complex nature of AbR health policy, the overarching aim of this thesis is to help address some the barriers to AbR and enable policymakers make more efficient investment decisions when it comes to tackling AbR..

The sections below discuss the commonly known barriers to tackling AbR followed by the objectives of this thesis and the methods adopted to meet the objectives.

1.2.2 The Barriers Of Tackling AbR

Alongside the AMR review and the WHO, within a special edition in the Lancet on AMR, Laxminarayan et al. (39,40) discuss the problem of *access* and *excess* as the driving force of the barriers to tackling AbR. The concept of excess antibiotics relates to a preservation barrier in terms of existing antibiotics. On the other hand, the concept of access to antibiotics relates to a current supply barrier of the variety of antibiotics available to humans. While LUMICs are struggling to get access to the more expensive second and third generation antibiotic classes, in the HICs, the *excess* use of existing second and third generation antibiotics is increasing the risk of AbR and the future need for newer antibiotic classes.

Combining recent literature on AbR with the health policy challenges discussed, three key barriers can be identified. The first barrier refers to the economic barrier of the invention of newer antibiotics. The second barrier refers to the identification of the key risks of AbR which policymakers can target with the help of effective interventions.

The last barrier refers to the process level issues which limits a coherent understanding of the setting specific factors that could prevent effective adoption and implementation of interventions tackling AbR.

Barriers related to understanding where to target policy and bottle-necks related to initial adoption, diffusion, or implementation of existing policy driven interventions to tackle a problem are common barriers seen within health policy in general (40,41). Therefore, apart from the economic barrier of antibiotic inventions which is specific to AbR, the latter two barriers are issues also commonly seen within health policy research. All three barriers are discussed in a more detail below.

1.2.2.1 Economic barrier of the antibiotics pipeline

The concerns surrounding AbR have been fuelled in part by the lack of research and development in new antibiotics. Following the discovery of penicillin, many classes of antibiotics followed, which many describe as the 'golden era' of antibiotic discovery. Despite this initial expansion, there has been a considerable drop in the discovery of novel antimicrobials, in particular for Gram-negative bacteria, where a novel antimicrobial has not been discovered in over 30 years (42,43). Investment in new antibiotics contradicts the classic pharmaceutical industry's business models of profitability (44).

Profit driven businesses such as pharmaceutical companies model their businesses according to the net present value of a product. Based on a report by the Office of Health Economics, for a drug to be accepted for human use, the total cost to a pharmaceutical company from the research and development phase to Phase III trial, and approval, can be between US $802 million to US $1.7 billion. Most business models use net present value as a measuring tool to assess whether the product is worth investment. The net present value takes account of the current investment required and the amount of money that will be required from the market/consumers in the future in cash flows to make the product profitable, i.e., to receive a positive net present value. Based on current estimates, the net present value of an antibiotic is $100 million compared to for example, $1,150 million for investment in musculoskeletal drugs (44,45).

Investment in new antibiotics and classes generate a low and in some cases negative net present value and limited return on investment for the pharmaceutical company, since the use of any new antibiotic class would be restricted rather than encouraged in order to be preserved for a

'worst case' scenario (44). Therefore, the cash flows received would be staggered and limited. To encourage pharmaceutical companies to invest in research and development of antibiotics, society and the government will need to incentivise the antibiotic pipeline.

However, when weighing up the cost of incentivising new antibiotics with preventing the rise of AbR, it can be hypothesized that invention of new antibiotics will not help control AbR as a long term solution(46). New antibiotics are not a long term solution because it is simply targeting the symptom of the problem of AbR and a reactive approach to the problem of AbR. Overtime, as previously seen with the current antibiotics, bacteria will find new ways of survival against the new antibiotics. Instead prevention and control strategies are needed in tandem with new antibiotic development (19). Therefore, keeping this argument in mind, this thesis will not be focusing on investment in new drug development.

1.2.2.2 Barriers to identifying and quantifying the risks driving AbR

Prior to the UN political declaration, in recent public health history, a number of large global initiatives were developed and signed notably the Millennium Development Goals (11) followed by the SDGs (47), and the Universal Health Coverage (48) campaigns. These global initiatives are designed to promote equality and growth worldwide. At the time these agendas were developed, AbR had not yet been prioritised on the global political agenda or been seen as a significant threat to achieving these goals (31,49). In general, over the past decade, despite the recommendations by WHO in the 2001 strategy document and the increasing prevalence of resistant micro-organisms, as seen from the example of *E.coli* in Figure 1, concerns surrounding AbR, have been limited to the healthcare professional community and the civil society as opposed to large scale government and political agendas in the same way that poverty and climate change have.

In hindsight, AbR and safeguarding antibiotics should have been one of the key political agendas since the development of the first antibiotic. The impact of antibiotics and the ability of bacteria to evolve and develop resistant mechanisms was not a new concept. The opportunity cost of introducing new antibiotics was known to mankind. However, what was not known or predicted was how extensively antibiotics would be used in humans and particularly in animals and the agricultural industry, thus, making AbR a global one health issue.

Recent efforts to quantify the scale and scope of AbR by the AMR review group highlights the intricacy with which AbR weaves itself into all aspects of healthcare delivery and poses a threat to the overall health and wealth of low to high income countries. These quantification efforts made it possible for AbR to be recognised as a key health issue.

Following the initial indication of the emergence of AbR by Sir Alexander Fleming in 1945 (13) a breadth of literature surrounding the increased risk of AbR due to antibiotic use have been published. Amongst these risk factors, the inappropriate frequency, timing, and the strength of antibiotics that are prescribed by clinicians and consumed by patients are commonly cited as the biggest causes for concern (50–54). These risk factors vary depending on where the antibiotics are being prescribed(e.g. whether the antibiotics have been prescribed in the hospital setting or the community setting). Recent literature sources mention pre-emptive, precautionary, or unnecessary prescribing in the community settings by general practitioners and dentists that may be increasing the risk of AbR. Globalisation, trade, travel (50), migration (55), and increased antibiotic use in farming are also some of the potential factors cited at a community level facilitating the rapid transmission of these organisms at a global scale.

There is also similar literature surrounding increasing prophylactic use of antibiotics in the secondary care hospital settings, where clinicians also have to battle with the increased risk of sepsis, or the increased risk of transmitting a potential pathogenic bacterium. Some types of HCAI (including AbR HCAIs, for example MRSA) have been known to spread in these settings via patient to patient,

healthcare worker to patient, or the hospital environment (e.g. work tops or medical instruments) to patient (7). Therefore, this setting is a hotspot for AbR acquisition and transmission and a setting that cannot be overlooked when it comes to keeping a track on AbR. Combined with the higher cost burden borne by the hospitals due to the increased length of stay of patients with resistant infections, the potential impact of AbR in secondary care settings makes this an increasing area of concern when it comes to successful healthcare delivery.

Within their recommendations, the AMR review team (see Section 1.1.4) discuss the rising importance of the one health issue of AbR. In other words, the one health impact of the animal and environment and the cross reservoir drivers arising from these reservoirs also play a role in the risk of AbR in humans. Therefore, only focusing on drivers from within the human reservoir and not from cross reservoir drivers would partially help tackle the problem of AbR.

In order to bring together these different potential emergence and transmission related risks of AbR in the community and hospital settings and understand the problem from a whole health system perspective, the AbR research community have developed a conceptual framework of the mechanisms and the intricacies of AbR impacting human health. Figure 2 shows three interrelated circles, each circle representing a reservoir within which bacteria can survive and reproduce, subsequently reservoirs within which AbR can also emerge and transmit within and between (56).

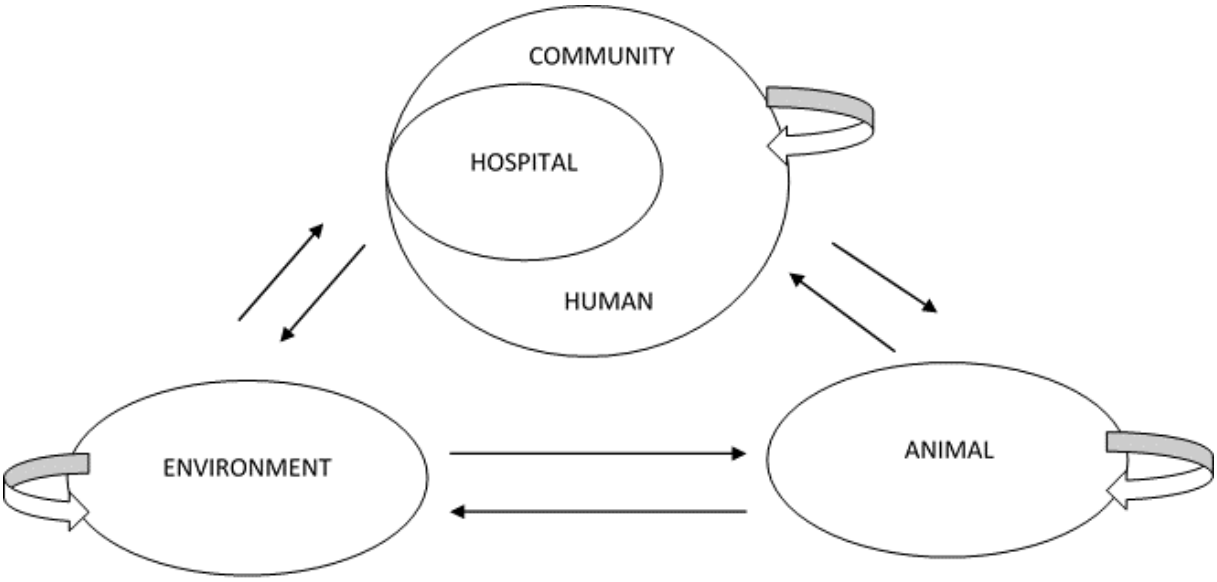


Figure 2: Framework of the potential risks of antibiotic resistance in humans

Source: Antimicrobial resistance Systems Maps (56)

However, the quantification of links within this conceptual framework is only partially complete. An overview of the quantity and quality of data supporting all these risks is needed. Furthermore, a framework is also needed to assess whether the key quantified risks are being targeted by global policy goals and country level interventions.

Antibiotic use has previously been identified as the key risk for AbR (51,52), resulting in interventions such as ASP efforts. However, underlying this key risk of antibiotic use there are also a number of more 'granular' risks, for example various setting-specific socioeconomic or regulatory risks, which may differ from one country to another. For example, buying over the counter antibiotics is not a regulatory issue in countries such as India and Pakistan (40,41), whereas purchasing antibiotics over the counter antibiotics without a valid prescription is not possible in countries like the UK and United States. There may also be knowledge barriers whereby consumers of antibiotics may not understand that antibiotics only work against bacteria and not viral infections (57). Similarly, regulatory issues often surround the use of antibiotics in animals within the agricultural and farming industry, where profit driven industries want to limit the spread of an infection in animals and so are willing to

provide cheap precautionary antibiotics in the animal feed. Scoping reports, such as those conducted by the Center for Disease Dynamics, Economics & Policy in India, are a first step towards breaking down the identification of underlying risks (41). However, there are only limited peer reviewed studies aiming to holistically understand the evidence surrounding underlying risks driving AbR. Quantified evidence of such risks could help health policymakers convince political leaders about potential long term repercussions of these risks on human health.

Many underlying risks remain unquantified or even unidentified. Without a broader understanding of what risks have already been quantified and what remains largely unquantified, researchers have a limited understanding of the risks of AbR.

Given the problem of AbR is not limited within the human reservoir and potentially spans three different reservoirs (see reservoirs in Figure 2), identification of the causal factors driving the currently established risk areas is needed. Identification of these underlying causal factors would potentially enable researchers and subsequently health policymakers understand the evidence-based hierarchy of risks and implement policy to target the root causes of these established risk areas.

Potential ways to address the barrier

A systematic approach is therefore needed to understand where current quantified evidence is on the risks of AbR and where evidence is currently lacking, to complete our understanding of the causal factors driving the established risks to help inform an evidence-based bottom-up policy making approach to tackle AbR in humans.

Thesis objective 1:

The first objective of the thesis is to quantify the evidence on the risks of AbR.

Rationale for objective 1: Quantifying the risks of AbR would highlight areas with little evidence, identify previously unconsidered risks, as well as identify more granular risks underlying those that

are more established. Furthermore, the quantified evidence would help inform how new policies should be devised, as well as what areas they should target

Thesis objective 2:

The second objective of this thesis is to assess whether current policy measures and interventions tackling AbR are targeting the key drivers of AbR identified from objective 1.

Rationale for objective 2: Simply understanding the evidence on the risks of AbR would not help inform policymakers where to target their policies. Research on risks of AbR would also need to be aligned with what policy is implemented. Currently there is a lack of studies focusing on such a 'bottom up' approach (See Section 1.2.1 for bottom up approach to policy making) of looking at where the risks lay and determining whether interventions and strategies are targeting these root causes. A number of exercises have been conducted to map the AbR policies and the activities that are being carried out to impact either the animal, human, or environment (37,46,58). However, there is currently a gap in overlaying the policies that are being proposed, the efficacy of the interventions being implemented, with the risks driving AbR.

1.2.2.3 Barriers to prioritising interventions according to risks of AbR

Without a holistic understanding of how important tackling one key risk of AbR might be over another, stakeholders may struggle to prioritise resources to tackle AbR.

Furthermore, some stakeholders may not want to invest in a large amount of resource to tackle AbR. A recent school of thought has framed this issue in terms of a microeconomic and an industrial economic concept namely the problem of a 'positive externality' which requires 'collective bargaining' (59). A positive externality occurs when the action of one person or organisation benefits other people and organisations, while only the person executing the action will bear the cost. Therefore, spill over benefits will be enjoyed by society as a whole without society having to pay for

it. The downside of this societal benefit is that the person or organisation may not want to bear the full cost of the action or in the case of AbR, intervention. The authors propose that it is possible to navigate around these deep rooted externality and collective bargaining issues by creating an overarching global regulatory body to form a *collective action* to align the various strategies that are being proposed and monitor their progress (60).Having an overarching global organisation may result in creation of more top-down approaches to policy implementation which might not be ideal when it comes to tackling AbR. (See Section 1.2.1 for more details)

In another effort to help prioritise risks of AbR, the WHO have also launched the Global Antimicrobial Resistance Surveillance System as a tool to quantify where the hotspots for resistant organisms are at a national, regional and global level, thus helping policymakers prioritise their policy efforts.

Both the Global Antimicrobial Resistance Surveillance System data dissemination approach and the overarching global regulatory body offer potential solutions to help prioritise and align targets to tackle AbR. Thus, these are an important step towards aligning the numerous stakeholders' goals of tackling AbR.

However, given the fluid nature of AbR, it makes it difficult to grasp the impact of the various moving (risk) targets of AbR and how they are counteracted by the current implemented interventions. A framework to pin down some of these targets is needed so policymakers could visualise how well their currently implemented policies are working against these prioritised risks of AbR (61).

To reiterate, having numerous stakeholders solve the problem of AbR amplifies the need for a framework to bring together the current quantified evidence on the risks and the efficacy of the interventions. Unlike other global diseases of concern, monitoring AbR not only requires data on the incidence and prevalence of the infections but also data on the susceptibility profiles of the causative organisms (i.e., data which requires special tests called antibiograms, enabling determination of which types of antibiotics the bacteria are resistant to). The WHO's Global Antimicrobial Resistance Surveillance System initiative is a step towards giving policymakers access to such data. However,

data also depends on the consistency and completeness of the methods used to collect it. Over the years, within the field of AbR, this need for data has given rise to multiple decision modelling approaches to help predict the burden and epidemiology of these organisms.

Potential ways to address the barrier

To help policymakers benefit from the available quantified information, mathematical and decision modellers have developed platforms to mimic real-life scenarios which cannot be ethically or logistically replicated in real life (62). Such models help extrapolate and analyse the mechanisms in which the interventions have an impact on risks of AbR in various settings (e.g. the community and the hospital settings). Such models show policymakers the potential long term benefit of targeting interventions or a bundle of interventions towards a risk factor. To get an idea of these long term outcomes, policymakers would have to wait a number of years to get access to long term follow up data from either randomised controlled trials or a longitudinal surveillance. Given the fluid and emerging nature of the risks of AbR, policymakers often do not have the time to wait for results from these real world evidence studies and need some evidence to back their interventions. Thus, mathematical modelling is often a good tool to help policymakers with this. Previous MRSA policymaking in England for example has relied on such decision modelling techniques to estimate the cost effectiveness of screening, patient isolation and decolonization strategies (63,64).

Previous reviews (60,64) have identified models which aimed to quantify the cost effectiveness of individual interventions (e.g. hand hygiene, isolation) targeted towards AbR in hospital settings. There is currently a need for a model which can link the various settings within the human reservoir (i.e., the community and the hospital setting). By linking these settings within which AbR develop and transmit in the human reservoir, it will be possible to explore the impact of interventions in terms of number of resistant infections and the cost impact across these settings.

Thesis objective 3:

The third objective of this thesis is to help policymakers prioritise where they should be investing resources to tackle AbR.

Rationale for objective 3: By bringing together the quantified evidence from objectives 1 and 2, the third objective of this thesis is to incorporate the best available evidence regarding the key risks of AbR and conduct a quantitative assessment of how well these interventions may be tackling these risks of AbR. The policymaker will therefore be able to see the impact of the interventions from one setting to another of the whole health economy within which AbR operates.

1.2.2.4 Process-level barriers to tackling AbR

The issue of adoption and implementation of an intervention is an inherent health policy level barrier seen within and also outside of AbR related policy making. These are general health policy barriers which are a result of a gap between what was originally planned to be implemented and what was eventually implemented.

Recent studies including Cochrane systematic reviews on interventions for AbR (65–68) suggest that targeting behaviour change is central to effective antimicrobial stewardship (AMS) programmes. Both the behaviour of the prescriber (i.e., the clinician) and the user (i.e., the patient) need to be taken into consideration. Furthermore, setting specific factors such as the number of stakeholders that need to be compliant with a specific intervention implementation, any resource constraints which may stop the stakeholders from executing a particular intervention appropriately may play a role in influencing this behaviour.

When comparing the setting specific factors within the human reservoir within which stakeholders implement policy, two key settings are most often discussed in AbR policy making. The first is the hospital setting and the second is the community setting, which is the setting outside of the hospitals. The community setting is large, encompassing a variety of stakeholders from different

countries, cultures, with variable levels of education and awareness of antibiotics and AbR. The stakeholders in the community are not limited to clinicians who prescribe antibiotics but also patients who consume antibiotics, along with third party stakeholders who use antibiotics for farming and agriculture and diffuse antibiotic waste within the community setting. The hospital setting is much smaller in comparison to the community, where the key stakeholders are the prescribers of antibiotics and the stakeholders in charge of controlling the spread of AbR. Despite being a smaller setting however, as highlighted in Section 1.1.3, the hospital setting substantially contributes to the economic burden of AbR.

The need for an understanding of the whole system issue of AbR to effectively devise and implement policy to tackle AbR has been recently discussed within a research article by Tomson and Vlad (69). The article discussed the need to analyse the problem of AbR from a household, community, government, as well as a hospital and healthcare setting perspective. In particular the paper concluded that an understanding of the 'interdependencies' between the different system level factors needs to be acknowledged before implementing policy to tackle AbR. The whole system factors discussed by Tomson and Vlad also resonate with a previously published paper on the factors which potentially impact increasing rates of MRSA (70). Where the impact of the broader socioeconomic (e.g. access to antibiotics, public awareness of AbR impacting health seeking behaviour) and health system factors (e.g. prescribing behaviour of clinicians) were some key factors discussed (70).

Within another paper, which analysed the intervention implementation process overall in healthcare, a conceptual framework was developed (Figure 3). The framework visualises how setting specific factors might impact the adoption and implementation of complex interventions (71). This is also appropriate for understanding the factors influencing the implementation of interventions to tackle AbR, given the whole system factors driving AbR overall as discussed in Tomson and Vlad (69) and Clements et al. (70).

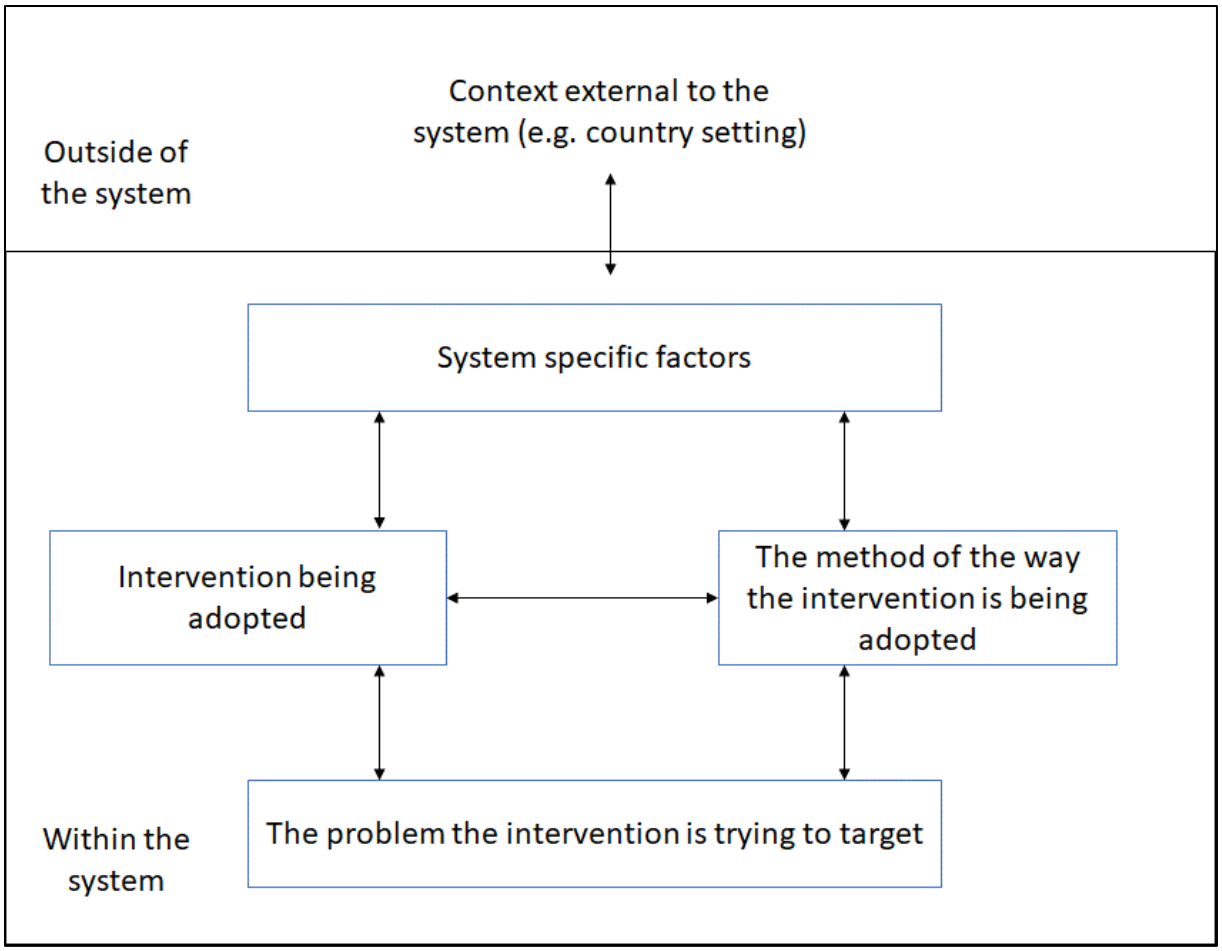


Figure 3: Intervention Adoption, Diffusion framework

Source: Adapted from Atun et al. (71)

Potential ways to address the barrier

The framework in Figure 3 is based on a *systems thinking approach* showing the inter-relationships between key system factors that influence the adoption and diffusion of an intervention within a healthcare context (72). Systems thinking shares its roots with a large number of disciplines, including biology, economics, computer engineering, and more recently healthcare.

At its most basic level, the idea behind this approach, which makes it a useful research method, is the notion of *ignorance* when critiquing a particular problem. This notion of ignorance means that

systems thinkers are told to approach a problem to understand it without a preconceived idea of what the underlying drivers of the problem might be so as not to assign blame too quickly to a particular stakeholder or issue occurring in the system. This notion empowers systems thinkers to really look at all the various mechanisms occurring in the system before coming to an immediate conclusion about the *where* and *whys* of the problem (in this case the process-level barriers of tackling AbR). This approach therefore proposes to constantly revise the researcher's understanding of a system and how it influences the problem or phenomenon (73).

The field of systems thinking often adopts a tool called the causal loop diagram (CLD), which is able to give qualitative factors, such as the impact of behaviour change on antibiotic use, a platform and incorporate them within a visual architype of, for example, a wider health system problem (74,75).

The CLD may therefore be an appropriate tool to identify the process-level barriers which prevent an intervention from either reaching its intended target or achieving optimal efficacy. Such barriers could come in the form of institutional hierarchy influencing strategic level decision making or factors related to the organisational size and structure. In the case of AbR use of CLD is a potentially useful tool by which to audit or assess the implementation barriers of ASPs. To help with the long term planning of a complex problem such as AbR, the visualisation process such of the CLD could help policymakers identify "fixes" or targets for future interventions, enabling the identification of causal factors driving AbR.

Given the scope of various causal factors driving the adoption and implementation process of an intervention shown in Figure 3, it is not surprising that even after the quantification of the long term repercussions of AbR and the global political will to tackle AbR, global action has been slow (31).

A recent WHO survey followed by analysis carried out by the OECD has estimated that 25% of countries worldwide have implemented a plan of action (76,77). Furthermore, fewer than 40% of countries have an IPC programme targeting AbR (10,78). Another recent study on global antibiotic use, reported a sharp increase in use especially in LUMICs between 2000 and 2015. Further, the

study also showed a 15% increase in broad-spectrum penicillin consumption in HICs (79). Within Europe, UK ranks the third highest in terms of secondary care antibiotic prescribing. Recent estimates show a 35% increase in AbR related infection levels, with resistant *E. coli* bloodstream infections driving this increase in the UK. Therefore, despite recent efforts in terms of the AMR review and the UK AMR five year strategy formed in 2015, and recently renewed again in 2019, the UK is struggling to control AbR levels (80). There is uncertainty surrounding the efficacy of currently implemented interventions and doubt surrounding if enough is being done to keep up with the fast pace of the survival mechanisms of pathogenic resistant bacteria. Knowing where to target interventions to tackle AbR partially addresses the threat of AbR. Evaluating the process behind how interventions are being adopted and implemented and acknowledging the process-level barriers of tackling AbR, is also a step towards better addressing the threat.

Thesis objective 4:

The fourth and final objective of this thesis is to understand the process-levels challenges of tackling AbR.

Rationale for objective 4: Given the need to understand the process-level factors which could make adopting and implementing interventions challenging the final objective of this thesis is to critically understand these process-level factors by speaking with the setting specific stakeholders implementing interventions and policy.

1.3 Thesis Overview

1.3.1 Scope

Given the vast field of AMR that includes micro-organisms such as fungi, parasites and mycobacteria such as Tuberculosis, this PhD focuses on AbR, primarily gram-positive and gram-negative resistant bacteria.

The overarching aim of this thesis is to investigate how best to tackle AbR in humans by addressing the aforementioned key barriers and enable policymakers make more efficient investment decisions. Cross-reservoir drivers from the animal and the environment are accounted for within the scope of this study considering AbR has been established as a one health issue. However, this thesis will not be focusing on animal health or the environment in particular.

It should be noted that within Chapters 3 and 5, the scope has been expanded to include AMR because global policy documents and publicly available documents from NHS hospitals in England discuss AMR as a whole and do not restrict their documents to AbR only organisms.

At the time of the research, I (or 'the author') was based at the Health Protection Research Unit at the Department of Medicine in Imperial College London. Because the Unit won an Economic and Social Research Council grant to explore community specific implementation barriers to tackle AbR in England, the latter part of the thesis focuses on the secondary care hospital setting only in order to reduce research overlap.

1.3.2 Methods

Within the scope of the thesis mentioned previously, the key research gaps and challenges surrounding AbR suggested in this introduction have shaped the thesis aim, objectives, and subsequently the research questions of this PhD.

Firstly, as discussed, there is a need to quantify the key risks that underpin AbR. For the first Study, a systematic review was carried out to determine which risk factors have been quantified and where there is still need for greater research efforts (Chapter 2).

Secondly, given the various stakeholders and organisations tackling AbR in humans, globally, transnationally and locally (UK), there is a need to align the risks of AbR with the policies and interventions that are being implemented to identify mismatches between identified risks of AbR and areas of policy focus. To enable this identification of policy mismatches (if any), a systematic mapping

method was adopted. As part of this systematic mapping process, AbR objectives were identified from the strategic plans of various organisations currently tackling AbR and mapping conducted to identify the alignment of the risk factors from the systematic review (Chapter 2) with policies and strategies (Chapter 3).

Thirdly, to bring together the evidence identified from Chapter 2 and Chapter 3, a framework was deemed necessary to enable policymakers to understand where the risks of AbR are being targeted by the current implemented interventions. Therefore, within this one framework the current quantified data on the risks of AbR and the evidence on the efficacy of interventions tackling these risks have been analysed collectively. It was hoped that this framework would help policymakers make evidence-based policy choices. To facilitate this framework a decision modelling exercise was conducted from an English country level perspective. Resistant *E.coli* was selected as the pathogen to model within this exercise due to increasing resistance (as previously presented and discussed) and current national policy initiatives in England are also focusing their targets to the reduce Gram-negative bloodstream infection. Consequently, given recent efforts to expand surveillance measures in England the input data was comparatively reliable to model this pathogen. The primary aim of this modelling exercise was to evaluate the costing impact of scaling up and scaling down interventions (Chapter 3). The model therefore brings together the key risks driving AbR and the best quality evidence of intervention effectiveness from Chapter 2 and 3 to inform policy about where investments may provide a better 'bang for their buck' (Chapter 4).

Finally, understanding where investment should be focused only attempts to solve part of the problem of AbR for health policymakers. Evaluating the process-level barriers surrounding how AbR is being tackled is also needed for effective adoption and implementation of policy measures. Based on the results of Chapters 3 and 4, research links[1] available to me at the time, and to reduce research

[1] I was based at the health protection research unit within the Department of Medicine in Imperial College London (ICL) research which provided me with good links to the ICHCNT

overlap across another research project[2] currently being executed at the unit I was based in, the hospital setting in England was chosen to understand the process-level factors which could be acting as facilitators or barriers to tackling AbR. Sixteen acute trusts (NHS and Foundation Trusts) were selected, based on high and low MRSA rates to conduct document analysis on their publicly available AbR specific documents. The focus of the content analyses was to determine what ground level interventions were being adopted, where the key risks of AbR are being reported, and what implementation barriers are being faced. Using the results from the document analysis, an in-depth qualitative analysis was conducted, using a systems thinking approach to create a framework characterising the process-level factors influencing how AbR is tackled at a single NHS Trust (Chapter 5).

1.3.3 Research Questions

To help meet the four objectives of this thesis, Box 1 summarises the research questions this thesis aims to answer. Figure 4 provides an overview of how these research questions are answered within the subsequent chapters of this thesis.

BOX 1: Research questions:

1. What are the factors driving AbR in humans?
2. How are the key quantified factors driving AbR in humans being targeted?
3. Based on the quantified evidence on the drivers of AbR and the effectiveness of current interventions tackling AbR, where should policymakers focus investment decisions to tackle AbR?
4. What are the process-level barriers of tackling AbR?

[2] A recent grant was won where the researchers would be exploring the primary care community setting in detail using qualitative research techniques (in particular interview studies)

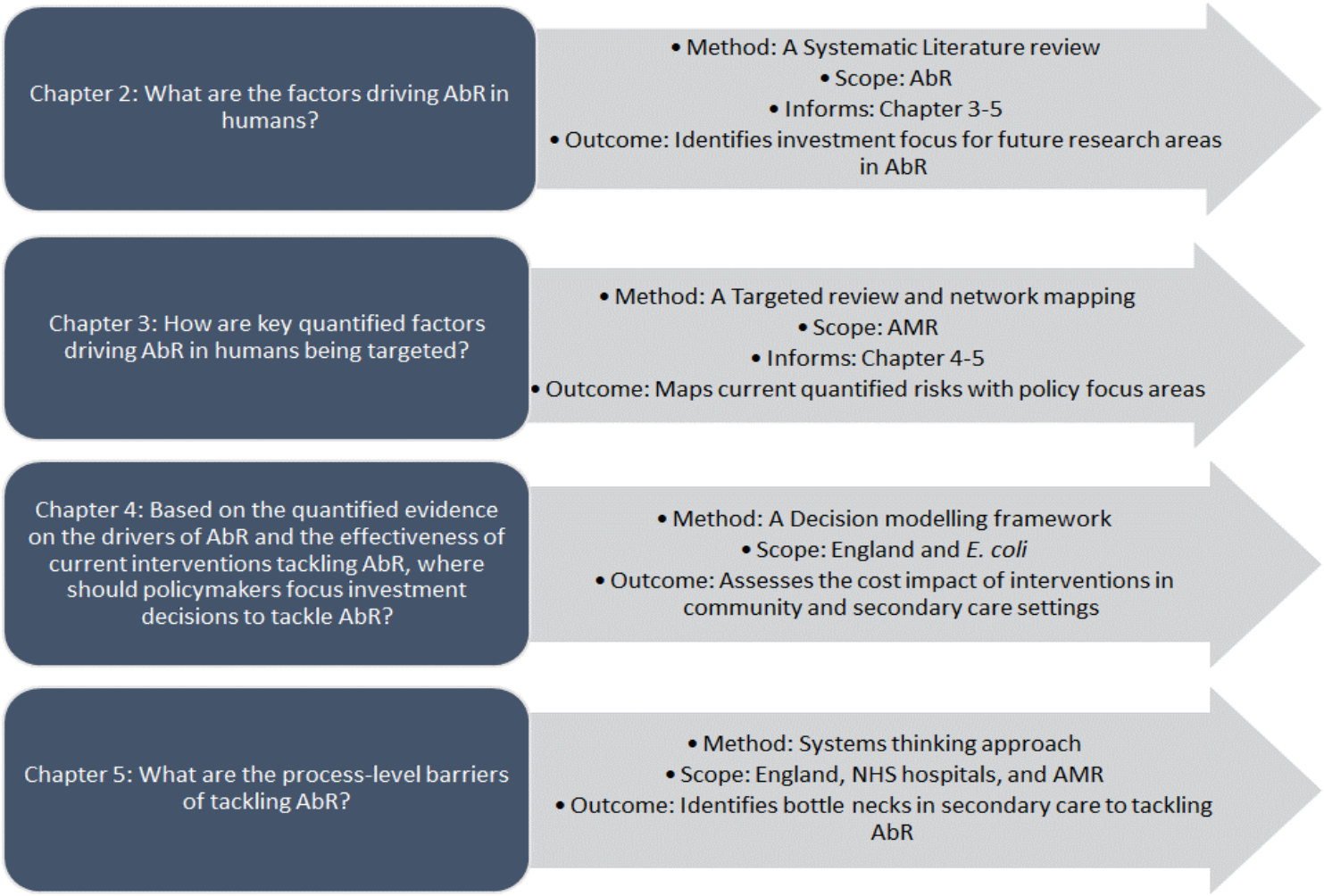


Figure 4: Thesis overview

1.4 Conclusion

Antibiotics were a turning point in healthcare that made curing simple ailments and performing operations possible and becoming part of more complex healthcare packages such as cancer-chemotherapy treatments (9,10). Antibiotics increased the likelihood of gaining equality and promoting global growth, by increasing the life expectancy and productivity of an economy (1,81) The development of AbR presents a turning point for healthcare which threatens the progress being made in treating communicable diseases and also adds to the increasing healthcare burden alongside non-communicable diseases (24).

By meeting the four objectives of this thesis, some of the challenges of tackling AbR will be investigated to inform policymakers about the intricacy of the public health problem of AbR. Each objective individually addresses a barrier of tackling AbR. Objectives 1,2, and 3 bring together the current best quality quantified evidence to provide a decision modelling framework to help policymakers understand the various setting-specific (i.e., community and hospital specific) pressures and levers of investing in the control and prevention of AbR. Objective 4 will identify the process-level factors which may be impacting how AbR is currently being tackled.

In summary, the four objectives of the thesis should be able to inform policymakers where more focus is needed when it comes to tackling AbR and offer options for future investment strategies to tackle AbR.

PART A: QUANTIFIED EVIDENCE-BASED APPROACH FOR INFORMING POLICY

CHAPTER 2.

2 DRIVERS OF ANTIBIOTIC RESISTANCE IN HUMANS

2.1 Introduction

In support of the United Kingdom's (UK) 5 year antimicrobial resistance (AMR) Strategy (82) the Department of Health and Social Care in England formed an Analytical Working Group[3] to assess the evidence base underpinning the work of the AMR Strategy. This working group developed a series of systems maps intended to provide a visual representation of the factors that lead to the development of antimicrobial resistance and the interaction between them (56).

These maps illustrated the human (including community and hospital settings), animal (including food animals and companion animals) and environmental (including water supply, manure and sewage) reservoirs and the interrelationships between them. Each of these reservoirs plays a role in the control and prevention of AbR (56). This underpins the global 'one health' perspective and approach stressed by clinicians, researchers and the World Health Organization (WHO) to tackle AbR. (9,56,83)[4]

Figure 5 provides an overview of the cross reservoir links that have been visualised in these systems maps.

[3] The analytical group also included the Department of Food, Environment, and Rural Affairs, Public Health England, and the Veterinary Medical Directorate.

[4] https://www.chathamhouse.org/sites/files/chathamhouse/field/field_document/AMR%20%20One%20Health%20Colloquium%20Meeting%20Summary%20jm-er%20ao%20-%2028%20April%2015.pdf (December 2014) ; (accessed 06/04/2016)

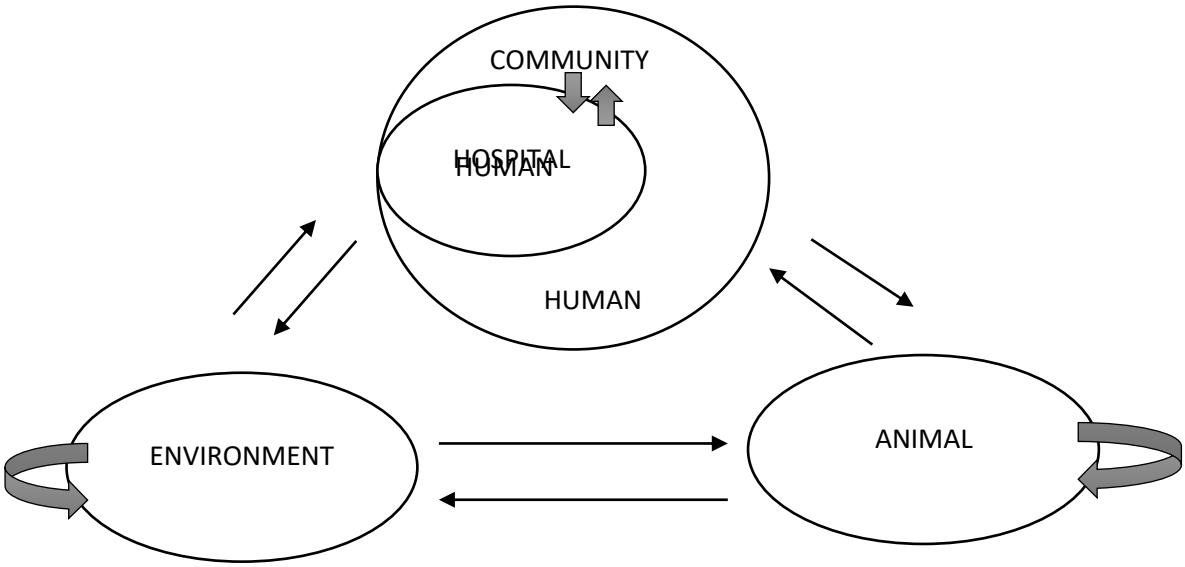


Figure 5: Overview of antimicrobial resistance systems maps

Source: Antimicrobial resistance Systems Maps (56)The systems maps identified a large number of potential risk factors[5] which may be driving AbR. However, these maps were largely based on what experts *viewed* as potential sources of AbR, rather than what the present evidence supported by real-word data were reporting as the drivers of AbR.

As such the risk factors driving AbR in humans are discussed in terms of factors which give rise to the development of AbR, with antibiotic use commonly reported as the cause of AbR. However, risk factors in terms of transmitters of AbR are also often reported to be related to infection control within the hospital setting. As also previously highlighted in Chapter 1, the mechanisms via which AbR arise in humans can be varied and are often discussed in terms of emergence and transmission of AbR (50).

When looking further into the current evidence on drivers of AbR, a recent systematic review concluded that across the studies within the review, a majority of the clinicians interviewed and included in the study sample, believed antibiotic use in humans and livestock contributed to

[5] Drivers and risk factors are terms which are used interchangeably in this Chapter, since most of the evidence on the drivers of AbR are reported as 'risk factors' of AbR in published literature

emergence of AbR (84). Another review and expert opinion article concluded that the increased prevalence of AbR was attributed to antimicrobial use in humans, animals, and the environment and the abundance of easily accessible antibiotics with variable quality; whereas transmission was attributed to lack of effective infection control, clean water, effective diagnostic tools, access to antibiotics, travel/migration from areas of poorly controlled antibiotic usage (7). The impact of the food chain on the emergence and spread of AbR was also separately highlighted in a recent review article (85). A number of systematic reviews have quantified the impact of individual factors driving AbR such as the impact of antibiotic use on emergence of resistant bacteria in the community and hospital settings (51,86).

Aside from reviews, a large body of literature also quantifies individual risk factors (e.g. antibiotic use or prior hospitalisation) and their impact on the occurrence and spread of antibiotic resistant bacteria (AbR) or associated infections in epidemiological and observational studies (54,87–90).

Despite these studies providing evidence on individual drivers arising from the human reservoir, there is a need for one study to pull together the current quantified evidence on these individual drivers to firstly assess whether one individual driver is more important over others and secondly to highlight where the gaps in the current evidence base remain with regards to these quantified drivers. Such an overview study could help support the holistic understanding of the present quantified evidence on the drivers of AbR in humans. To determine if a recent systematic review has indeed attempted to develop an evidence base of the holistic drivers of AbR in humans, a PubMed search using the following search string was conducted:

(((antibiotic resistan*) AND systematic review) AND risk factor and applying filters for publication date from 2005/01/01 to 2016/03/01).

This search did not retrieve any systematic reviews that summarised the most recent quantified evidence related to risk factors of AbR in humans arising not only from the human reservoir but also from the animal and environmental reservoirs. Previous reviews have summarised risks across these

individual reservoirs for a specific antibiotic resistant organism, but not on the risk factors in humans arising from all three reservoirs without restrictions to specific antibiotic (drug) and bacteria (bug) combinations.

An in-depth understanding of the current evidence on the risk factors contributing to AbR in humans would allow the key drivers of AbR in humans to be identified, and thus assist development and implementation of policy targets and subsequently interventions to tackle AbR in humans. Concurrently, an understanding of the evidence base on the risk factors of AbR could also highlight *where* evidence gaps exist, thus helping to focus future research investment within these understudied areas.

2.1.1 Overall Aim

Therefore, the aim of this Study is to answer research question 1 of this thesis, *which proposes to identify the factors driving AbR in humans*. To be able to answer this, an evidence base for the currently quantified risk factors of AbR in humans arising from the human, animal, and environment reservoirs will be created.

In order to meet this aim, a systematic horizon scan of published studies which have statistically quantified the risk factors for AbR in the community and hospital settings, including those that assess impact from other reservoirs (i.e., animal and environment reservoir) will be conducted.

Please note that this systematic review has been published and can be accessed via the following citation below:

Chatterjee A, Modarai M, Naylor NR, Boyd SE, Atun R, Barlow J, Holmes AH, Johnson A, Robotham JV. Quantifying drivers of antibiotic resistance in humans: a systematic review. The Lancet Infectious Diseases. 2018 Aug 29.

To enable successful publication of the review, a number of researchers including my PhD supervisors and peer researchers also contributed to this study.

CONTRIBUTOR DETAILS

Anuja Chatterjee designed the original protocol for the systematic review. Anuja Chatterjee, Julie Robotham, Rifat Atun, Sara Boyd and Nichola Naylor were involved in the finalisation of the study protocol.

Anuja Chatterjee developed the search strategy. This strategy was then checked with a medical librarian based at Charing Cross Library: Rebecca S Jones.

Anuja Chatterjee carried out the literature search, independent review of all title abstracts and full texts, completed quality assessment, data analysis, result dissemination and manuscript write up.

Maryam Modarai, Sara Boyd and Nichola Naylor were the three independent reviewers who checked the title/abstracts and full texts independent to Anuja Chatterjee. Maryam Modarai also checked at random the quality assessments conducted by Anuja Chatterjee. Julie Robotham and James Barlow were involved in the manuscript development and first draft. James Barlow, Julie Robotham, Nichola Naylor, Alison Holmes and Alan Johnson contributed to the final structure and content of the manuscript. The corresponding author and all co-authors contributed to the final version of the manuscript.

I would also like to acknowledge Dr Ceire Costelloe for her review and suggestions made at the study protocol development stage, followed by her advice during peer-research meetings with regards to the presentation of the odds ratio results.

Following the identification, quantification, and quality assessment of the literature, this Study should provide quantified evidence to supplement the previously developed systems maps (56).

2.1.2 Scope Of The Review

The European Centre for Disease and Control (ECDC), representing the European Union (EU), and the Food Safety Authority in UK, have summarised the AbR risks arising from the animal reservoir in a recent report (91) and also within a systematic review published as a white paper(92)(93). Therefore, drivers within-animal or within-environment reservoirs, or environment to animal (and vice versa) were beyond the scope of this thesis.

This review concentrates on any epidemiological, cohort, or case-control studies quantifying the risk factors for emergence and transmission of antibiotic resistance impacting the human reservoir. Evidence related to primary influence factors due to the impact of human actions on the human reservoir is the main concern of the review. For example, in-vivo, in-vitro, individual laboratory based studies reporting on molecular mechanisms, host cell defence mechanisms, alteration of genetic architecture, pharmacodynamics or pharmacokinetic are beyond the scope of this review.

With regards to the cross-reservoir drivers outside the human reservoir, only the quantified effect of the animal and/or environment on the human reservoir is within the scope of this review.

Given the scope of this thesis, the review does not include micro-organisms other than Gram-positive and Gram-negative bacteria. AMR in fungi, parasites, or mycobacteria being outside the scope of this review.

The section below describes the detailed methodology adopted to conduct the systematic review.

2.2 Methods

At the time the review protocol was being developed, recent systematic reviews (51)(86)(94–96) and an expert opinion review article (7) were consulted to structure this review.

To enable streamlining the broad aim of this review the following objectives and research questions were specified to guide the search and selection process:

Objective 1: To identify quantified evidence associated with the commonly reported emergence and/or transmission risk factors of antibiotic resistance

Objective 2: To grade the quality of evidence identified in Objective 1

Objective 3: To quantify the strength of the evidence identified in Objective 1 and developing a mechanism to map this strength of evidence.

Objective 1 was developed to meet the overall aim of the first research question of this thesis regarding the identification and quantification of the drivers of AbR in humans. Simply identifying the quantified of evidence on the drivers of AbR in humans may not be enough to understand the quality of this evidence, as poorly conducted studies may incorrectly claim a causal relationship from a correlation result, thus significantly biasing the study results. Therefore, Objective 2 was deemed an essential ingredient to assessing the evidence identified in Objective 1. Finally, Objective 3 was needed to pool together the evidence in Objective 1 and assess it against Objective 2 to enable an algorithm for ranking the possible importance of one driver over another based on the quantity of good quality evidence per driver identified.

The following research questions were developed to help meet objective 1.

2.2.1 Research Questions For Objective 1

Two main research questions were developed based on the different mechanisms (i.e., emergence or transmission) via which levels of AbR are known to arise within the human reservoir as previously discussed within the Introduction of this thesis (Chapter 1). Therefore the research questions are designed to further understanding around whether and how the drivers of emergence and transmission of AbR differ. Prior meta-analyses studies (51) (86) suggested there was evidence related to the emergence of AbR due to antibiotic use. Evidence also exists on the impact of healthcare facilities and procedures (94) on the potential transmission routes of AbR. However, the evidence related to the currently quantified drivers of emergence and transmission in humans has not been assessed holistically under the umbrella of one study, which this review hopes to achieve.

The research questions to help gather richer evidence to support Objective 1 are as follows:

1. What factors impact the environment/animal/human to human emergence of antibiotic resistant bacteria and related infections? (e.g. antibiotic consumption)
    a) Which factors are more frequently quantified per reservoir type?
    b) How are factors quantified? (e.g. risk ratio, odds ratio, antibiotic resistance rates/colonisation rates)
2. What factors influence the environment/animal/human to human transmission of antibiotic resistant bacteria and associated infections? (e.g. poor infection control)
    a) Which factors are more frequently quantified per reservoir type?
    b) How are these factors quantified? (e.g. correlation coefficient, rate of transmission over time)

2.2.2 Limitations Applied In The Study Selection Process

In order to capture the most recent and relevant drivers given the current constantly changing epidemiological landscape of AbR globally, the review considered evidence published within the last 10 years (01.01.2005 – 14.02.2018). The original search was conducted on 01.03.2016. Following peer review recommendations, the review was updated on 14.02.2018.

Articles related to the impact of human antibiotic use on the emergence and spread of antibiotic resistant bacteria were extracted from 2010 onwards, due to an earlier systematic review (51) already quantifying this driver extensively in a meta-analysis.

2.2.3 Databases Searched

Keeping in line with previous systematic reviews within the area of epidemiological and observational studies in AbR in humans (51)(86)(64), the following databases below were chosen.

- Embase
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- Scopus

Since, research on 'one health' cross-reservoir drivers are more frequently published by public sector or non-profit organisations, possibly because these large organisations are in charge of collecting and disseminating the data the up to date primary data for these reservoirs were identified from grey literature searches from the following websites:

- European Centre for Disease Prevention and Control,
- Centers for Disease Control and Prevention, and
- World Health Organization

To capture any missed commonly known risk factors of AbR, meta-analyses studies were identified via a PubMed search using drug-bug specific search terms. To help select the high risk drug-bug combinations, the WHO's top priority resistant bacteria of concern were included as combination drug-bug terms for this search. Please refer to Appendix I in the thesis for these search strings.

2.2.4 Search And Selection

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol was followed for the systematic review and can be found in Appendix Table 1 Appendix I.

Four reviewers conducted the search and selection to limit bias during study selection: Anuja Chatterjee (AC – i.e., myself), Maryam Modarai (MM), Nichola Naylor (NN), and Sara Boyd (SB)). A pre-specified set of criteria was designed for each of the following categories: population, intervention, comparator, outcome, and study design (PICOS). These criteria were applied by the four reviewers in order to identify the relevant articles for data extraction for the review. Please refer to the Appendix Table 2 for the complete selection criteria. At the title/abstract selection stage the PICOS criteria were tested amongst the four reviewers using 50 abstracts. There was a 20% agreement amongst the four reviewers. Therefore, the PICOS criteria were further refined and AC went through the disagreed abstracts with each of the reviewers so the PICOS criteria were being interpreted appropriately. Following the revised PICOS criteria there was a 75% agreement between the reviewers at the title and abstract phase. Any abstracts for which AC could not reach a consensus on amongst the three reviewers were further clarified with a fifth independent reviewer (Julie Robotham).

A pre-specified data extraction form was also designed (in Microsoft Excel© 2016) guided by data fields commonly reported in previously published systematic reviews within the field of AbR and its risk factors. This form was then used for the extraction of the data for the review.

One reviewer assessed all title, abstracts, and full texts (AC = 100%), a second reviewer independently checked 50% of all title, abstracts, and full texts (MM), a third reviewer (NN), and a fourth reviewer (SB) checked the remaining 25% each of the title, abstracts, and full texts.

Following finalisation of the protocol and search criteria, the systematic review protocol was registered on PROSPERO (Registration number: CRD42016038450), to help reduce duplication of systematic review research.

The overall search strategy was guided by previous systematic reviews and meta-analyses related to antibiotic resistance (51,64,86). The search was run and fine-tuned a number of times to ensure that key important publications were being captured. The final strategy was developed in consultation with a medical librarian at Imperial College London. (Search strategy included in Appendix I)

2.2.5 Quality Assessment

To achieve the second objective of this review with regards to grading the quality of evidence identified from Objective 1 and research questions 1 and 2, an appropriate quality assessment tool was developed to grade the method and reporting of the studies.

A range of observational studies (e.g. case control, cohort, with prospective or retrospective study types) were anticipated for inclusion as part of this review. A quality assessment criterion was therefore developed to appropriately assess the different study designs. This criterion was guided by recently conducted reviews within the field of AbR and its risk factors (53) (86).

Because it is one of the more flexible quality assessment tools, with limited scope for biasing the results, the Critical Appraisals Skills Programme assessment tool for cohort and case control study designs was used to guide this part of the study. The The Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines (97) were also used in consultation when assessing these individual biases, in particular the reporting bias and the selection bias domains.

Table 1 reports the types of bias assessed for a cohort and a case control study. The method of scoring the bias domains are also reported separately. The meta-analyses studies were assessed using PRISMA guidelines (98).

Table 1: Quality assessment methodology

<table>
<tr><td>Cohort studies</td><td colspan="2">**If longitudinal data was used for the prospective cohort study design and this study scored a low risk of bias in all five bias types then this study scored an additional point and was reported as good.
Total score for cohort studies was out of 6 points</td></tr>
<tr><td>Bias type</td><td>Other details</td><td>Score details</td></tr>
<tr><td>1.Reporting Bias</td><td>(Study aim and hypothesis / Study design / Inclusion or exclusion criteria / Baseline characteristics / Source of bacteria / Study participants / Outcome measures / Method of analysis / Main findings/Conclusion)</td><td>Low risk if all 10 points are reported completely: score = 1, Potential risk: score: Score = 0)</td></tr>
<tr><td>2.Selection bias (cohort studies):</td><td rowspan="2">*Using CASP tool for cohort studies to assess low or potential risk</td><td rowspan="2">Low risk: score: = 1, Potential risk: score = 0</td></tr>
<tr><td>3.Information bias (for assessment of exposure variables)</td></tr>
</table>

4.Information bias (for assessment of outcome variables		
5.Confounding bias (for assessment of confounding effects):	If confounding factors were adjusted in a multivariate analysis, then this was labelled as low risk or else potential risk	
Case-control studies	If a case control study compared infection with resistant bacteria cases with susceptible group as well as non-infected / non-colonised controls (97,99) and the study had a low risk bias in all 6 categories this study was awarded an additional point and labelled as good. Total score for case control studies was out of 7 points	
Bias type	Other details	Score details
1.Reporting Bias	Same as Cohort study	Same as Cohort study
2.Selection bias (control selection for case-control studies)	Using CASP tool for case-control studies to assess low or potential risk	Low risk: score: = 1, Potential risk: score = 0
3.Selection bias (case selection for case-control studies)		
4.Information bias (for assessment of exposure variables)	Same as Cohort study	
5.Information bias (for assessment of outcome variables		
6.Confounding bias (for assessment of confounding effects):		

Systematic review with meta-analyses studies	PRISMA checklist(98) for meta-analysis was used to assess the quality of these studies	Total score = 27

Abbreviations: [CASP = Critical Appraisals Skills Programme assessment tool; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses]

2.2.6 Data Analysis And Systematic Mapping

Quantified evidence is often reported in a variety of ways in epidemiologic studies of risk factors of AbR. To enable collection of the most appropriate evidence for this review only statistically significant risk factors were included.

However, following the initial scoping searches which were used to guide this review, it was soon realised that data related to the cross-reservoir drivers impacting the human reservoir were primarily reported in terms of prevalence and study sample characteristics. Therefore, to avoid retrieving very limited studies from these cross-reservoir drivers, this exclusion criteria associated with statistical significance was relaxed and only applied to the human only studies.

All risk factor estimates were coded based on common attributes. These were either patient-related or treatment-related. Following this, five domains were created as umbrella terms for the risk factor codes. The results under Section 2.3.2.5 describe the domain creation in more detail.

Following data extraction of the studies, due to the variability in definitions, it was deemed important to establish a consistent definition for the *emergence* and *transmission* of AbR.

All studies mentioning that they reported on factors driving transmission AbR (e.g. healthcare worker to patient, or patient to patient infection transmission in hospitals) were taken at face value and included under the studies assessing transmission routes of AbR in humans.

Additionally, incidence or prevalence of AbR in food or beverages (e.g. food producing animal sources, retail meat and vegetables, dairy products) were assumed to be indirect sources for transmission routes to the human reservoir.

A large volume of studies did not specifically differentiate between which risk factor contributed towards emergence or transmission of AbR. Instead these studies reported outcomes measuring levels of infection, colonisation, carriage, or development of AbR. Considering this review was using secondary evidence from these studies and in the absence of a more scientific way to assess whether these factors assessed in the studies were related to emergence or transmission of AbR, these outcomes were assumed to be synonymous with emergence of AbR. Therefore, the factors reporting on increasing AbR infection levels were assumed to be factors contributing to emergence of AbR. This method of classification has been acknowledged as a limitation of this review. Therefore, given that the aim of this thesis is to inform an evidence-based bottom-up approach to policy making, in the absence of better evidence to categorise emergence and transmission routes of AbR, this classification has not been further carried forward in the final data analysis of this systematic review which is discussed further in the next paragraph below.

To pool all the evidence gathered from the studies for Objectives 1 and 2, related to the quantified evidence and the quality of this evidence on the drivers of AbR in humans, a systematic mapping method was followed.

Systematic mapping shares its roots with several disciplines, in particular the field of environmental sciences (100). The approach is often used as a scoping review prior to conducting a systematic review. Such mapping techniques help determine how the quantity and quality of evidence is distributed, highlighting where evidence is lacking and where future research should be focused.

Risk factors have also been mapped previously for various medical research and decision making purposes using evidence-based literature to create a mapping framework. (101–104). One of the largest public health issues to date that used systems thinking mapping approaches was mapping of

the factors driving childhood obesity (75,105). This project proved the suitability of assessing large volumes of evidence and presenting them within such a framework. Amongst other studies adopting systems thinking to identify risk factors of a particular public health issue, Lawton et al. (101) conducted a systematic review to identify factors that have been reported to contribute to patient safety incidents in the hospital setting. With the help of this systematic review, the authors developed a hierarchical framework to understand the immediate factors which were closest to the patient safety incident; labelled as *proximal factors*. The authors also identified *latent factors*; underlying factors attributed to systems level failures which made the proximal factors more feasible.

Lawton et al. (101) is therefore a good example of the use concepts from a systems thinking approach that guided the development of a hierarchical framework to identify factors contributing to patient safety incidents. Moreover, an understanding of the hierarchical framework helped the authors identify and recommend interventions to better target the root causes of patient safety incidents and inform policymakers about these underlying causes.

As previously discussed in Chapter 1 (Introduction), this thesis proposes to adopt the approaches from the field *systems thinking* which promotes the inclusion of the systems level issues which contribute to the causality of a particular phenomenon. This approach ties in with the evidence-based and bottom up approach to policy making which takes account of where the current evidence exists as well as acknowledging the need to identify the on the ground system level factors. The aforementioned systematic mapping processes have been used to apply a systems thinking approach to analyse and summarise the results from the systematic review.

The cross-reservoir systems maps created by the Department of Health and Social Care's analytical working group can be seen as the original scoping review which lays the foundation for a revised systematic map which will be developed as an outcome of this systematic review to inform this PhD. In particular. these previously published systems maps (described in Figure 5) will be revised and

updated by adding data identified from the systematic review. The goal of this new systems map (re-labelled as the AbR drivers map) is to showcase the balance and/or imbalance of quantified evidence on the factors which are driving AbR in humans.

2.3 Results

Overall 2,819 title and abstracts were identified from the search across the three databases and from the grey literature.

Following the title/abstract selection phase of the review, 1,883 title/abstracts were excluded from the review for not meeting the PICOS criteria. In total, 936 full texts were checked for inclusion and out of these, 565 full texts were included for data extraction.

Out of the 565 full texts, 527 were primary studies and the remaining 38 were meta-analyses. The PRISMA flow diagram in Figure 6 provides the overview of the study selection process.

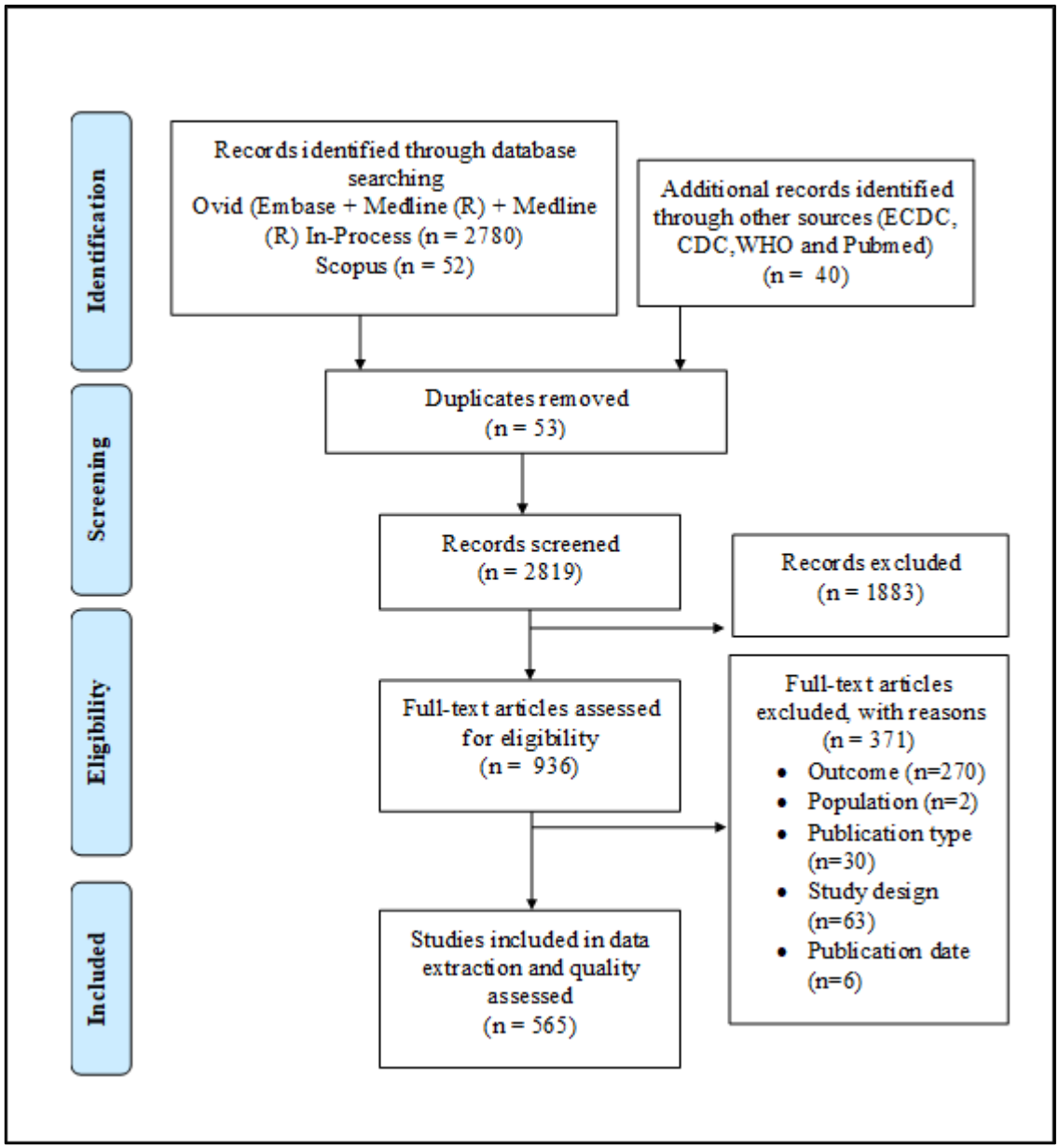


Figure 6: PRISMA flow diagram for the selection of articles

Abbreviation: [CDC = Centers for Disease Control and Prevention; ECDC = European Centre for Disease and Control;PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; WHO = World Health Organization]

Since the review identified evidence from both primary studies and pooled results from meta-analyses, the following section of the results has been divided into two parts. Part 1 will discuss the evidence retrieved from the primary studies and demonstrate how the evidence helps to meet the four objectives of the review, as well as how the evidence can be used to answer the granular research questions. Part 2 will discuss the evidence retrieved from the pooled results in the meta-

analysis studies and determine how this evidence was able to meet the review objectives and questions. As mentioned within the methods section, the meta-analyses studies were included as part of this review as a way to cross-check that the commonly known risk factors were indeed being captured in the systematic review which includes the primary studies. These primary studies will also inform the AbR drivers map. It should be noted that the meta-analysis study search was a targeted search to supplement and validate the results of the systematic review. Hence, the results have been provided separately in Part 2.

2.3.1 Part 1: Systematic Review Of Primary Studies

In total 88 key risk factors were identified from the 527 primary studies extracted that were reported to be driving antibiotic resistance in humans. Out of the 88 risk factors identified, 82 were risk factors from any reservoir, but driving AbR within the human reservoir.

Panel to understand study terminology

Risk factors related to:

- Human reservoir: Risk factor arising from within the human reservoir and which are driven by the human reservoir.
- Animal reservoir: Risk factor arising from within the animal reservoir which impact the risk of AbR in the human reservoir.
- Environment reservoir: Risk factor arising from within the environment reservoir which impact the risk of AbR in the human reservoir.

Multidrug-resistant bacteria: Bacteria which are resistant to 3 or more classes of antibiotics

Estimates versus studies in the Systematic Literature Review (SLR) results:

Study refers to one article, having one corresponding reference number (e.g. In total there are 565 studies which have been included in this systematic review)

Estimates are the number of individual quantified results identified (e.g. an odds ratio of AbR due to consumption of an antibiotic type).

There are 1000+ individual risk factors identified across all studies.

There can be multiple estimates identified from one study.

Appendix Table 4 (Appendix I.)provides a list of all the risk factors identified from these primary studies.

Out of the 527 studies, 89% reported risks related to emergence of AbR in humans whereas only 11% reported risks related to transmission of AbR. The transmission related risks were primarily arising from the animal reservoir (n = 32) and the environment reservoir (n = 21). Figure 7 shows an overview of the reservoir specific risks identified from the primary studies.

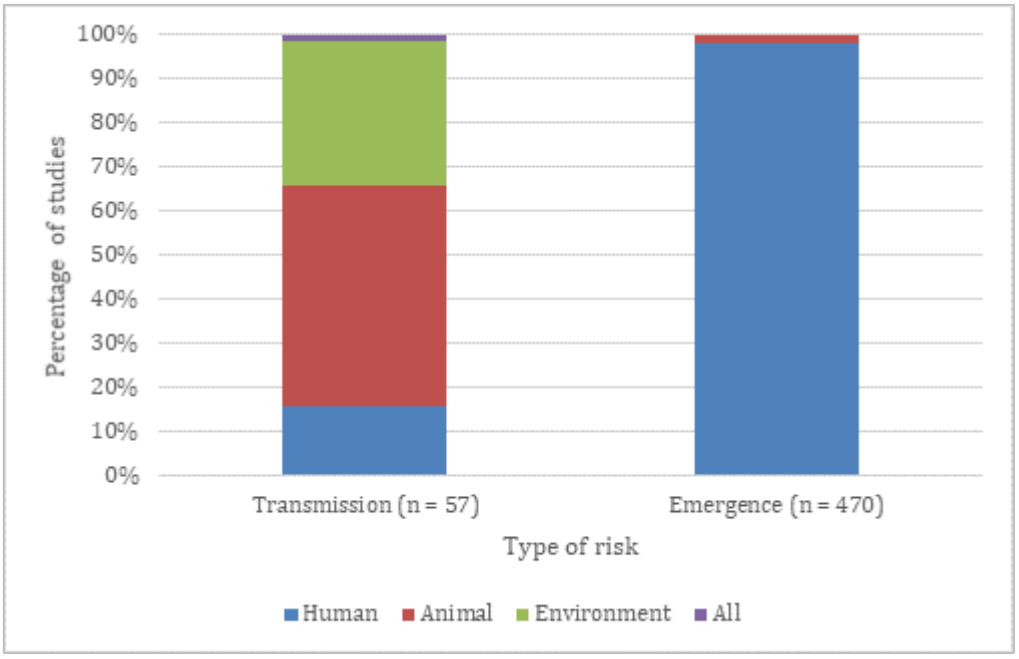


Figure 7: Overview of studies reporting on reservoirs per risk type

2.3.1.1 Organisms

A range of drug-bug combinations were identified from the primary studies. Figure 8 gives an overview of the different organisms for which quantified evidence related to their risk factors was identified. Multi-drug resistant bacteria were the most reported on organism over the past 10 years, followed by meticillin-resistant *Staphylococcus aureus* (MRSA), and antibiotic-resistant *Escherichia coli* (R-*E. coli)*. Amongst the cross-reservoir related organisms were resistant *Salmonella*, *E. coli*, and *Campylobacter*.

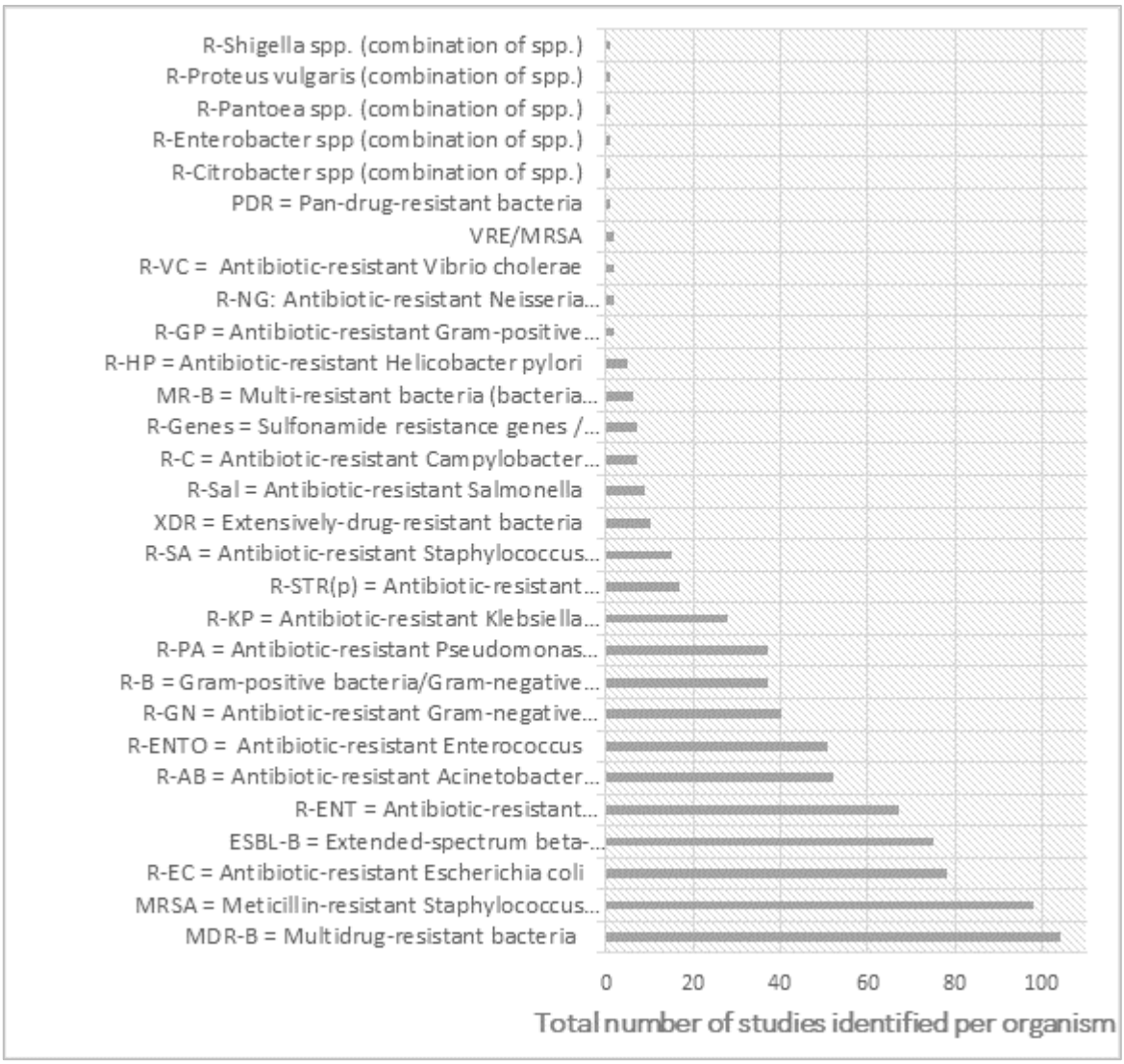


Figure 8: Overview of resistant organisms identified across the 527 primary studies

*(includes carbapenemase-producing or resistant *Enterobacteriaceae* (n = 42))
Abbreviations: [ESBL-B = Extended-spectrum beta-lactamase producing bacteria; MDR-B = Multidrug-resistant bacteria (bacteria resistant ≥3 antibiotic classes); MR-B = Multi-resistant bacteria (bacteria resistant to >1 and < 3 antibiotic class(es)); MRSA = Meticillin-resistant Staphylococcus aureus; PDR = Pan-drug-resistant bacteria; R-AB = Antibiotic-resistant Acinetobacter species; R-B = Antibiotic-resistant bacteria (combination estimates for Gram-positive bacteria/Gram-negative bacteria); R-C = Antibiotic-resistant Campylobacter jejuni (R-CJ) / Campylobacter coli (R-CC) R-Citrobacter spp (combination of spp.) ;R-EC = Antibiotic-resistant Escherichia coli; R-ENT = Antibiotic-resistant Enterobacteriaceae (includes carbapenemase-producing or resistant Enterobacteriaceae (n = 42)); R-Enterobacter spp (combination of spp.); R-ENTO = Antibiotic-resistant Enterococcus; R-Genes = Sulfonamide resistance genes sul1 and sul2 / tetracycline-resistance genes; R-GN = Antibiotic-resistant Gram-negative bacteria; R-GP = Antibiotic-resistant Gram-positive bacteria; R-HP = Antibiotic-resistant Helicobacter pylori; R-KP = Antibiotic-resistant Klebsiella pneumoniae; R-NG: Antibiotic-resistant Neisseria gonorrhoeae; R-PA = Antibiotic-resistant Pseudomonas aeruginosa; R-Pantoea spp. (combination of spp.); R-Proteus vulgaris (combination of spp.); R-SA = Antibiotic-resistant Staphylococcus aureus; R-Sal = Antibiotic-resistant Salmonella; R-Shigella spp. (combination of spp.); R-STR(p) = Antibiotic-resistant Streptococcus pneumoniae; R-VC = Antibiotic-resistant Vibrio cholera; VRE = Vancomycin resistant enterococci ; XDR = Extensively-drug-resistant bacteria]

The sections below have been split based on the original three objectives of the review, i.e., to identify, quality assess, and map the quantified evidence related to the human to human or animal/environment to human drivers of AbR.

2.3.1.2 Objective 1 and research question 1

Objective 1: Identify evidence on the commonly known emergence risk factors related to antibiotic resistance and report any additional determinants not commonly known.

Research question 1 for the emergence of AbR:

What factors impact the environment/animal/human to human emergence of antibiotic resistant bacteria and related infections? (e.g. antibiotic consumption)

a) Which factors are more frequently quantified per reservoir type?

b) How are factors quantified? (e.g. risk ratio, odds ratio, antibiotic resistance rates/colonisation rates)

HUMAN TO HUMAN:

Identification of factors

From within the human reservoir there were 80 individual risk factors that result in the emergence of AbR in humans identified from 467 studies.

The most frequently quantified (i.e., > 50 estimates) risk factors are presented in Figure 9. The top three are prior exposure to antibiotics, having an underlying disease including comorbidities, and having had an invasive procedure, such as catheterisation, during treatment at a healthcare facility. Within this top tier of quantified evidence, most of the factors were related to either healthcare related factors (e.g. invasive and surgical procedures and hospitalisation), or patient clinical history including history of antibiotic use, or patient demographic.

Figure 10 displays the next tier of studies, from which between 10-50 estimates were extracted. Apart from two quantified factors (travel abroad and transmission from family member), the

remaining factors were related to either the healthcare setting, patient demographics, or a patient's clinical history.

An additional 54 risk factors, each with less than 10 quantified estimates, were identified. These were treated as the bottom tier of (see Appendix Table 4 in Appendix I)

The overall strength of the evidence is discussed under objectives 3 and 4 below. All the risk factors identified have been used to develop a risk factor map, which is discussed under objective 3.

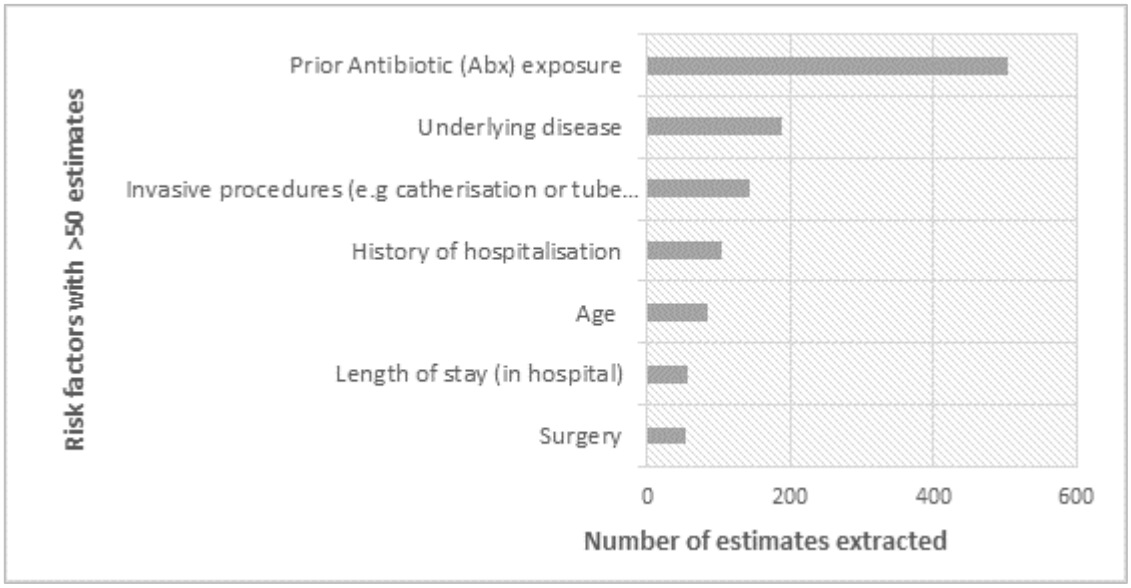


Figure 9: Frequently (>50 estimates) reported risk factors across the studies

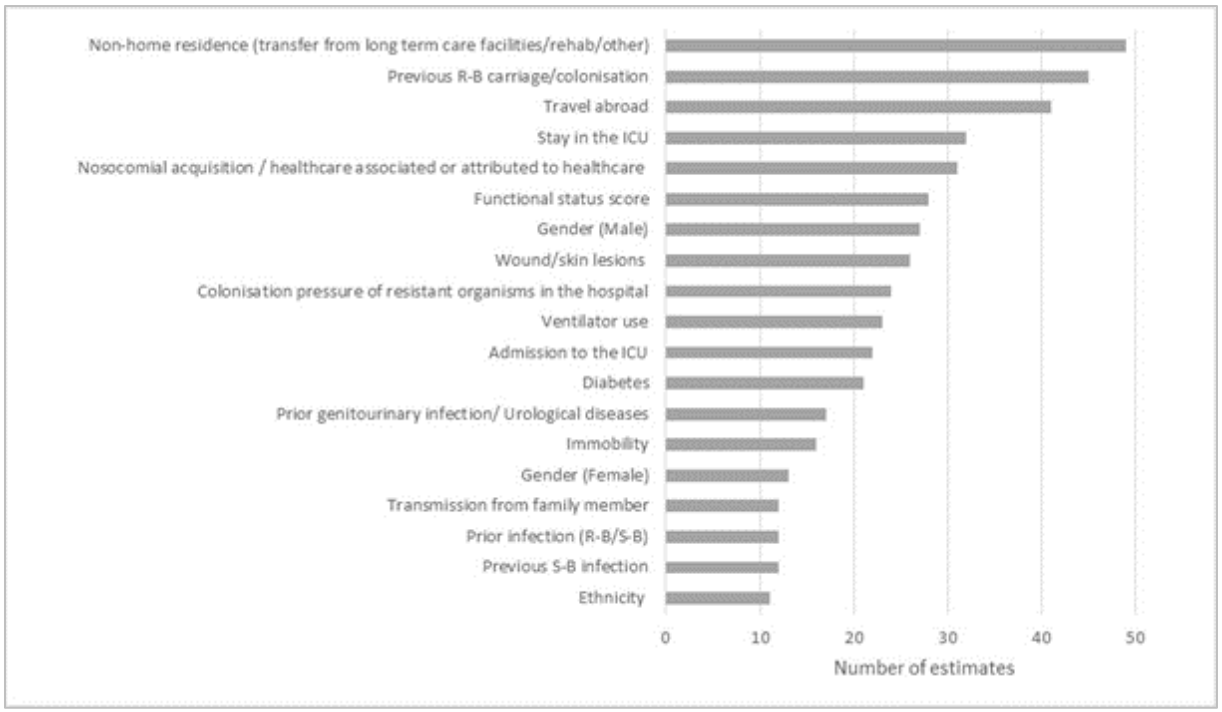


Figure 10: Less frequently (<50 estimates) reported risk factors across the studies

Abbreviations [R-B = Antibiotic resistant bacteria; S-B = Antibiotic sensitive bacteria; ICU = Intensive Care Unit]

Method of quantification

A variety (n = 12) of techniques were adopted to quantify the relationships between the risk factors and the emergence of AbR arising from within the human reservoir. In total 1,759 individual estimates were extracted from the 467 studies. Out of these 1,759 estimates, odds ratio (74%) and descriptive statistics (15%) were the main methods used to quantify these drivers.

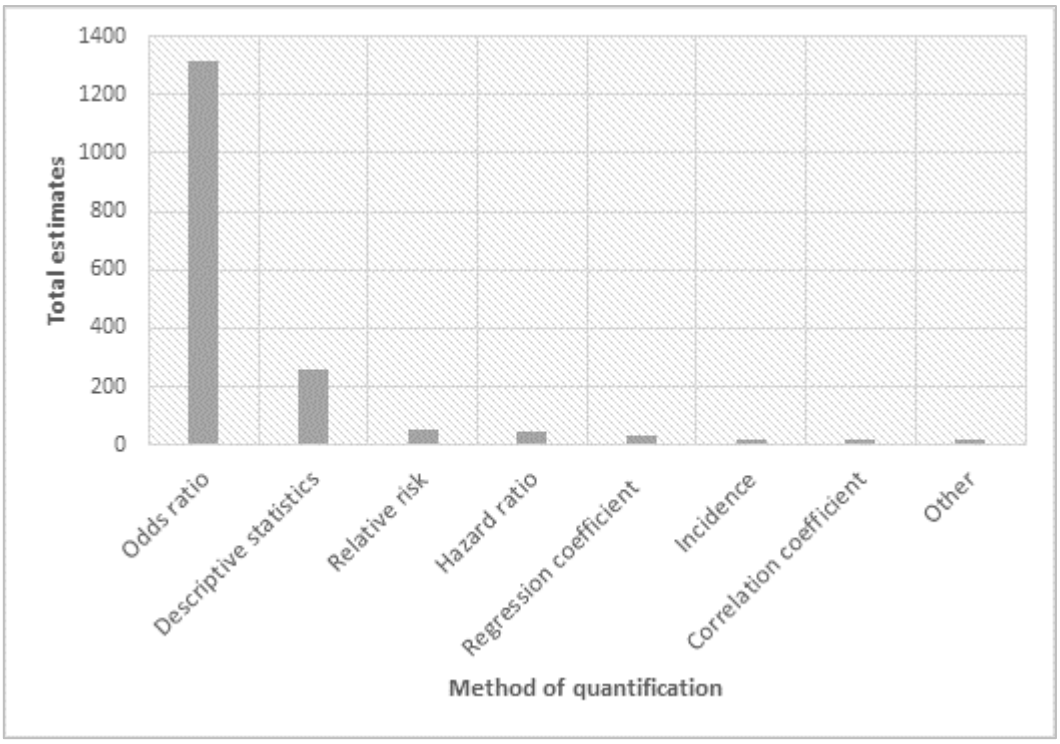


Figure 11: Methods of quantifying the drivers of AbR development in humans

Given the large number of estimates identified, it was not possible to provide odds ratios for all these risk factors without grouping them within a logical format. Therefore, Objective 3 further analyses these results by creating risk domains and reports on the estimates in greater detail.

ANIMAL TO HUMAN:

Identification of factors

Ten studies identified 5 risk factors from the animal reservoir driving the development of AbR in humans. Antibiotic use in animals, consumption of meat, eating dairy related products whilst travelling abroad, contact with animals in a domestic or occupational capacity and residing near a farm or the physical environment around a farm were the quantitatively studied risks arising from the animal reservoir. Contact with animals was quantified in 7 out of the 10 studies, with occupational exposure to poultry, cattle or pigs being the most cited risks (as shown in Figure 12).

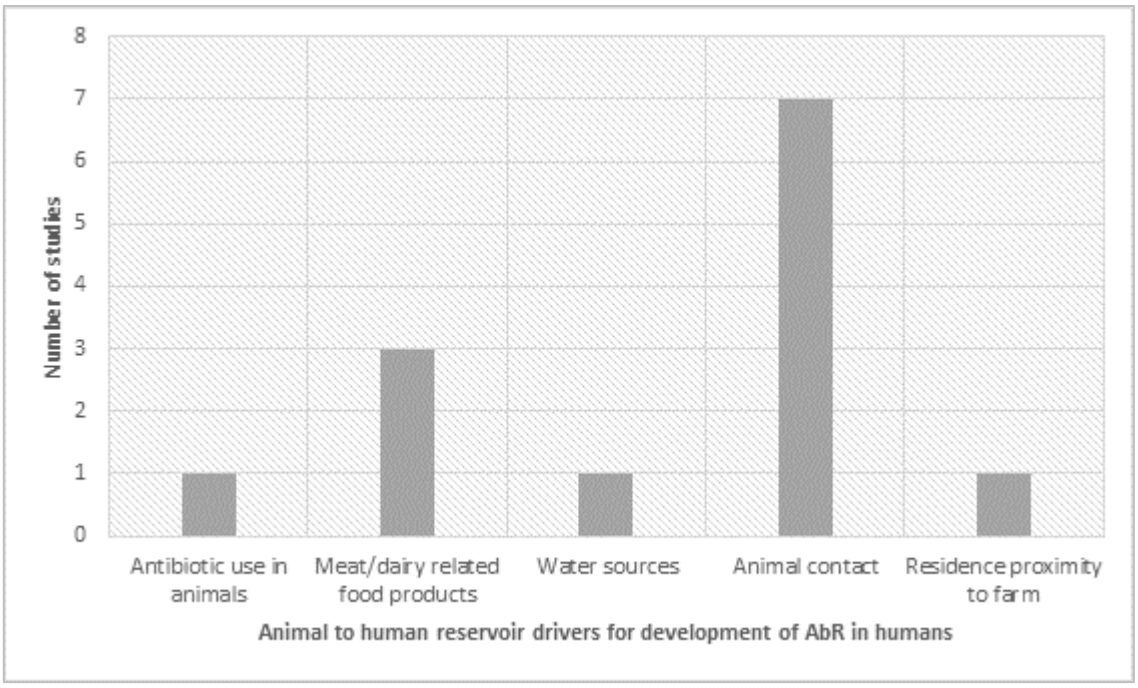


Figure 12: Drivers of AbR development in humans from the animal reservoir

*Please note one study may quantify multiple risk factors so the current Figure 12 shows 11 studies because one study quantified more than one risk factor.

The second joint ECDC / EMA and EFSA report (106) was the only study identified that quantified the potential relationship between antibiotic use in food-producing animals with AbR bloodstream infections in humans (Figure 13 and Table 2). A statistically significant relationship was reported between use of fluoroquinolones and other quinolones in animals and clinical resistance to fluoroquinolones in *E. coli* isolates found in humans. Use of tetracyclines in food-producing animals was associated with tetracycline resistance in *S. Typhimurium*, *Salmonella spp.,* and *C. jejuni* isolates in humans. A study by Barkovskii et al. (107) was able to determine a strong correlation (R^2 = 0.99) between antibiotic usage on the three farms in the study sample and incidence of tetracycline resistance genes from the direct farm environment.

Method of quantification

Out of the 10 studies, 19 estimates were extracted; with odds ratio (n = 17), correlation coefficients (n = 1), and prevalence rates (n = 1) were the three methods used to quantify the risk factors of development of AbR in humans arising from the animal reservoir. Since odds ratio was the most

frequently reported estimate, it was possible to compare these using a forest plot. Table 2 provides an overview of the risk factors for which odds ratios were reported with their respective study references.

The latest ECDC report (106) estimated the increased odds of AbR in humans due to antibiotic use in food producing animals. The relationship between fluoroquinolones use in food-producing animals and R-*E. coli* infections in humans showed the highest odds (1.12). The forest plot in Figure 13 provides an overview of these odds ratios and the associated 95% confidence intervals categorised by organism and antibiotic type. Figure 14 provides a forest plot of the other factors identified from the review for factors driving emergence of AbR in humans arising from the animal reservoir. Amongst these other factors the odds of AbR development was highest due to occupational exposure of poultry worker (OR: 33.1) compared to their community reference groups. The large confidence interval should also be taken into consideration for this estimate.

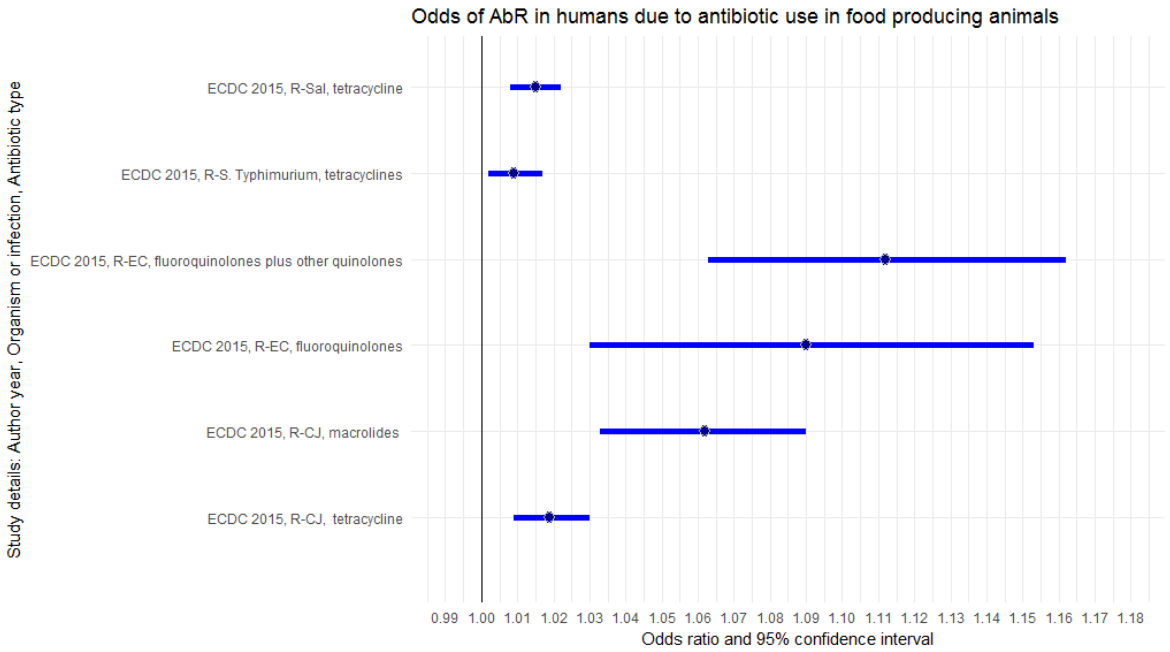


Figure 13: Odds ratio results from the European* report on impact of antibiotic use in food producing animals on antibiotic resistant isolates from human bloodstream infections

*Please refer to Figure 8 for the abbreviations
Abbreviation: [*ECDC = European Centre for Disease and Control]

Table 2: Overview of odds ratios for the development of AbR

Study detail: Resistant organism, risk factor type	Odds Ratio*	95% confidence interval Upper limit	95% confidence interval lower limit	Author year (Study reference)
R-EC, fluoroquinolones use in FPA	1.09	1.03	1.153	ECDC / 2015 (106)
R-EC, fluoroquinolones plus other quinolones in FPA	1.112	1.063	1.162	
R-CJ, macrolides in FPA	1.062	1.033	1.09	
R-S. Typhimurium, tetracyclines in FPA	1.009	1.002	1.017	
R-Sal, tetracycline in FPA	1.015	1.008	1.022	
R-CJ, tetracycline in FPA	1.019	1.009	1.03	
MRSA, Contact with cattle	8.61	1.73	42.85	Kock R. / 2009 (108)
MRSA, Contact with pigs	20.46	7.83	64.39	
Gentamicin-resistant *E. coli*, poultry workers	33.10	3.47	316	Price L.B. / 2007 (109)
MDR *E. coli*, poultry workers	5.21	1.21	23.1	
ESBL-EC, Frequent pork consumption (>=3 meals per week)	3.5	1.8	6.6	Leistner R. / 2013 (110)

* Only those odds ratios for which p-values are reported have been included, if a confidence interval included crosses over 1, i.e., includes 1 this result is not reported in the table or the forest plot, as this signifies that the odds ratio is not significant. Please refer to Figure 8 for the abbreviations, other abbreviations: FPA, Food-producing animals

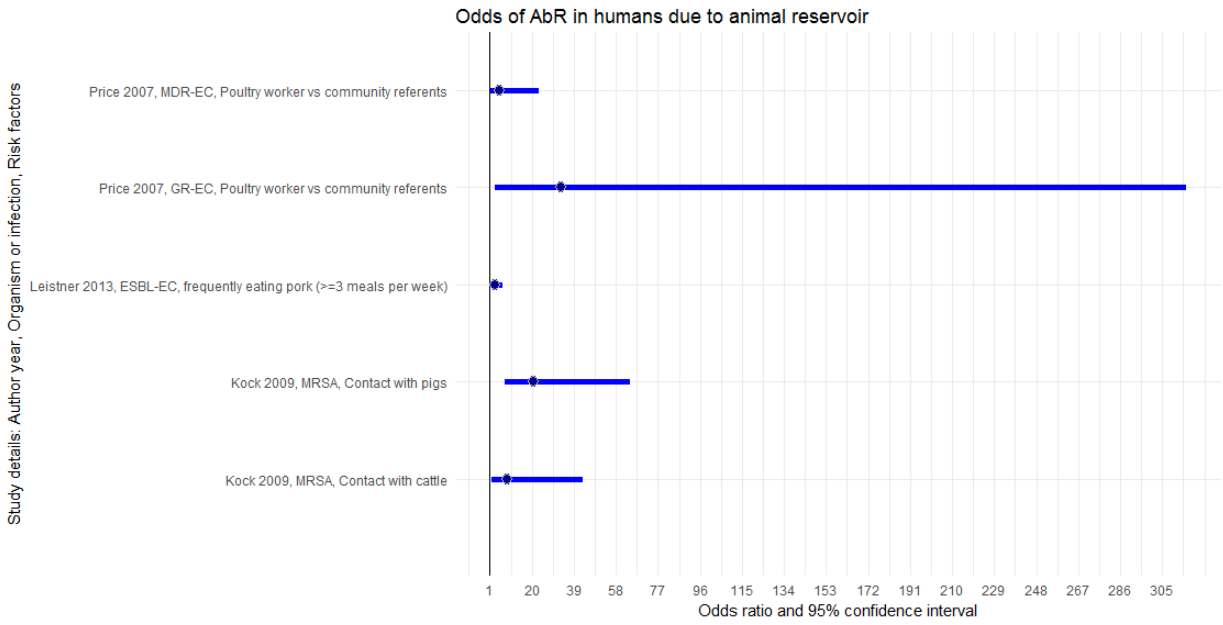


Figure 14: Odds ratio results for impact of animal reservoir on development of AbR in humans

*Please refer to Figure 8 for the abbreviations

ENVIRONMENT TO HUMAN

No factors directly related to the development of AbR in humans arising from the environmental reservoir were identified. One study(107) tested environmental samples from soil, water and feed from three farms to report the incidence of tetracycline resistance genes. The environment directly surrounding farms was considered a potential reservoir in the study for AbR for humans.

2.3.1.3 Objective 1 and research question 2

Objective 1: Identification of evidence related to the commonly known transmission risk factors related to antibiotic resistance and report any additional determinants not commonly known.

Research question 1 for the transmission of AbR:

What factors impact the environment/animal/human to human transmission of antibiotic resistant bacteria and related infections? (e.g. antibiotic consumption)

a) Which factors are more frequently quantified per reservoir type?

b) How are factors quantified? (e.g. risk ratio, odds ratio, antibiotic resistance rates/colonisation rates)

HUMAN TO HUMAN:

Identification of factors

Eleven risk factors were identified from 10 studies which identified potential risks for transmission of AbR within the human reservoir. An overview has been provided in Figure 15.

Prior antibiotic exposure and provision of type of care were the two factors most frequently quantified as transmission routes within the human reservoir. Therefore, making healthcare workers and healthcare contact a key transmission route of AbR within the human reservoir. Provision of type of care in this systematic review implies a healthcare worker helping a patient with a type of care which could include either going to the toilet, walking, or cleaning a wound.

The likelihood of the healthcare worker transmitting resistant bacteria to the patient was reported as not only dependent on the healthcare worker themselves, but also on the type of care that was being provided to a patient by a healthcare worker such as bathing or toilet assistance.

If a patient was on antibiotics or had prior exposure to antibiotics they were reported to have a higher likelihood of transmitting resistant bacteria to either another patient or to a healthcare

worker, thus making antibiotic use a risk factor for transmission of AbR as well as for emergence of AbR in humans.

Comparing the transmission routes to the factors related to the development of AbR in humans, the hospital environment can be quantified as a likely reservoir for transmission. A patient's clinical history and demographic characteristics, combined with the type of invasive procedures they might be receiving, can be hypothesized as the more established determinants of development of AbR in humans attributed to the human reservoir.

Outside healthcare related factors, the most likely transmission risk for AbR in humans within the community setting was travelling abroad. Three estimates were retrieved from one Canadian study(111), which described the increased likelihood of acquiring AbR during international travel (incl. Caribbean islands, Latin and South America and Asian subcontinent) compared to not travelling outside Canada. This study found that the method of acquiring AbR during travelling abroad was water consumption; this factor was coded under 'travel abroad' within the human reservoir rather than 'water transmission' in the environmental reservoir, since had the study participants not travelled in the first place the risk of consuming this water would not have occurred.

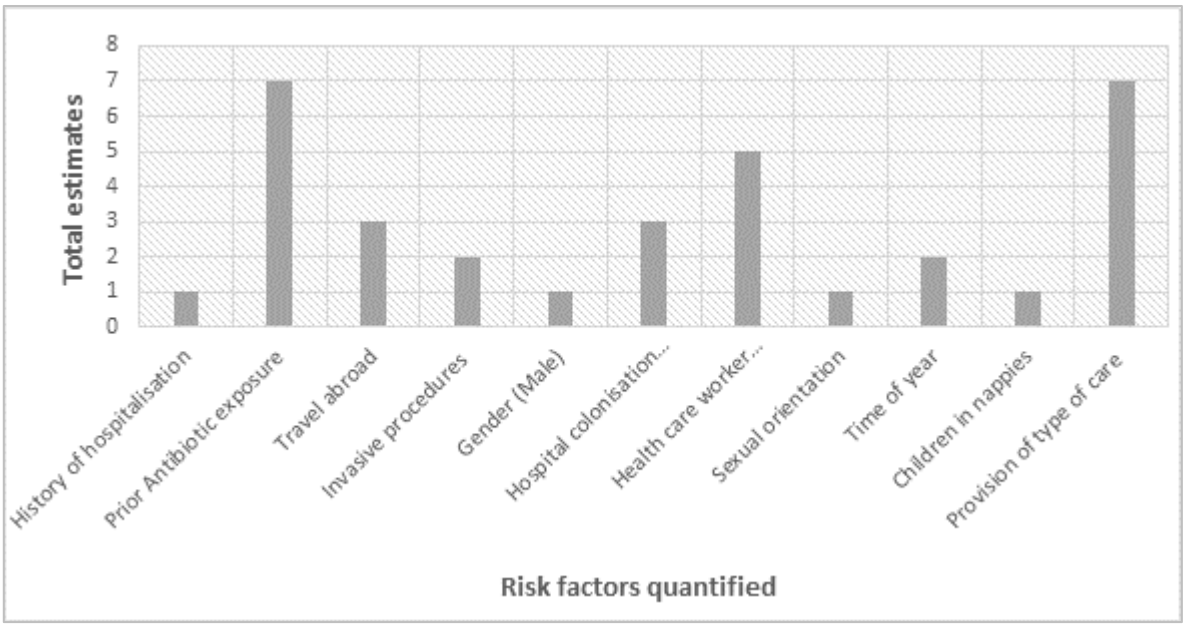


Figure 15: Risk factors related to transmission of AbR from within the human reservoir

*Please note one study may quantify multiple risk factors

Method of quantification

Figure 16 illustrates that odds ratios and prevalence rates were the two key methods used to quantify the potential risk factors for AbR transmission within the human reservoir.

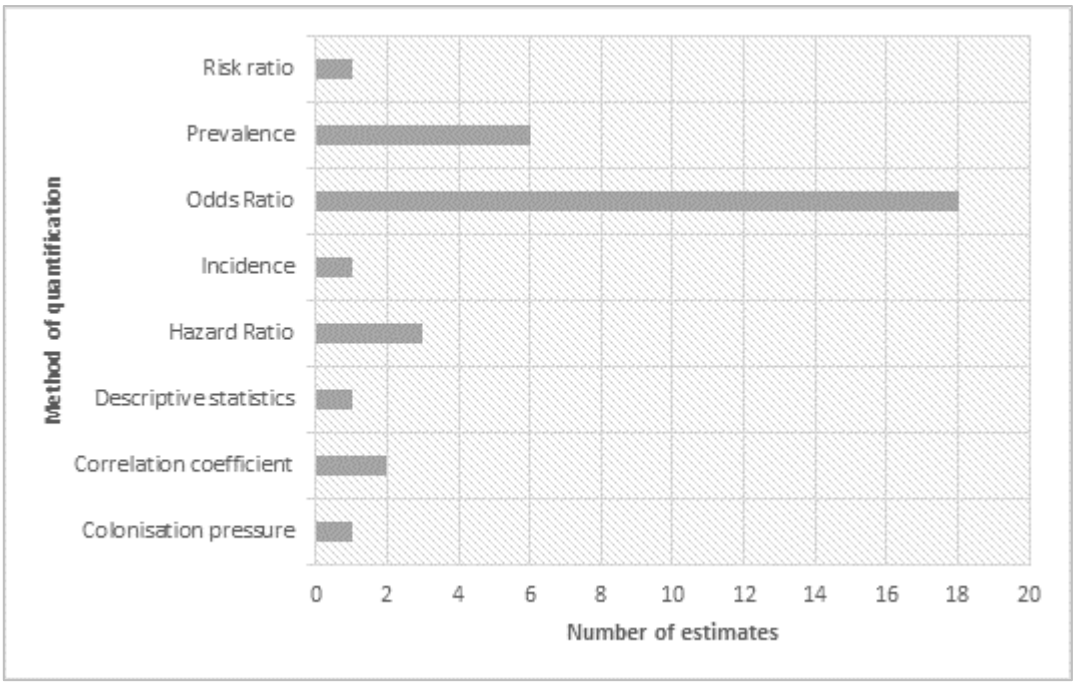


Figure 16: Methods used to quantify the within human risks of AbR transmission

ANIMAL TO HUMAN:

Identification of factors

In total 32 studies reported three potential transmission routes from the animal to the human reservoir (Figure 13). Transmission arising from food sources, primarily meat, was the most frequently quantified route. Occupational exposure to pigs, cattle and livestock, or contact with domestic pets such as dogs, were also reported as potential transmission sources from the animal reservoir. The recent ECDC 2015 report (106) was the only study which was able to establish a potential relationship between antibiotic use in food producing animals and an increased risk of AbR infections in humans. This was the first study of its kind to establish such a relationship at a European level. Therefore, food related transmission from meat products were cited as the commonly occurring transmission route of AbR from the animal into the human reservoir.

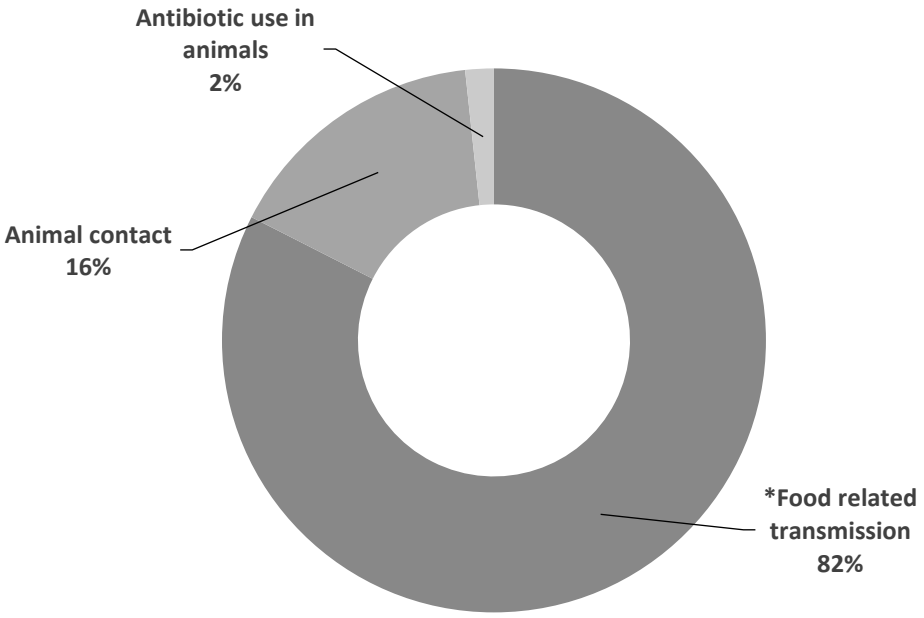


Figure 17: Total estimates (n = 177) quantifying risk factors of transmission of AbR (animal to human)

Risk factors for the human reservoir arising from the animal reservoir
*(direct) + (indirect) transmission routes: (resistant zoonotic pathogens isolated from humans) + (resistant zoonotic pathogens found in meat products + broiler meat)

Method of quantification

Unlike the factors related to the development of AbR in humans, the potential transmission routes from animals to humans were primarily quantified by establishing differences in prevalence rates (Figure 14).

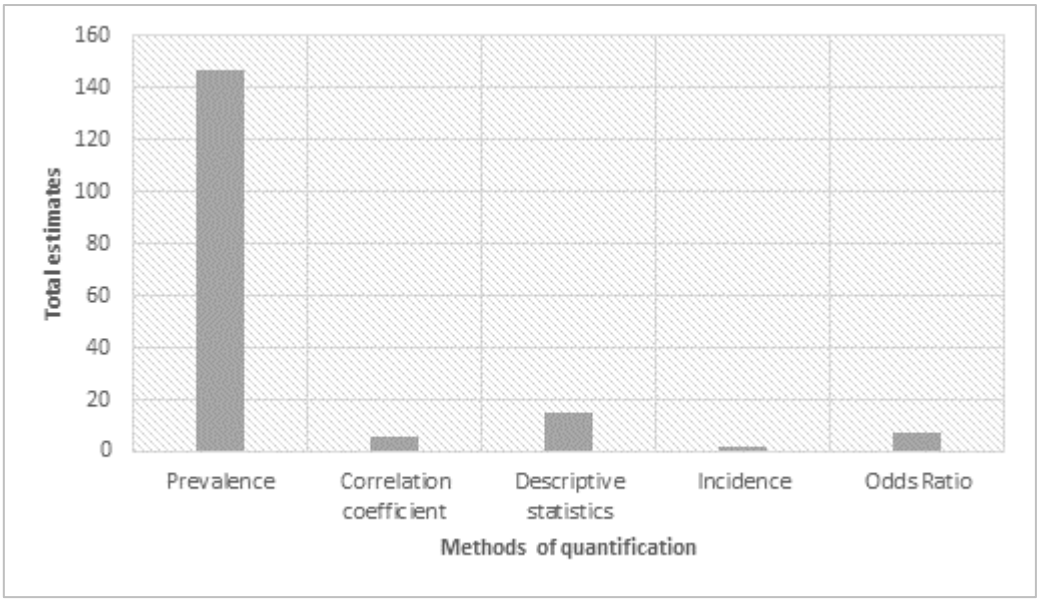


Figure 18: Methods of quantifying the drivers of AbR transmission (animal to human)

*Transmission in humans arising from the animal reservoir (n = 177)

Table 3 provides an overview of the ranges of prevalence of either resistant isolates identified from meat related food sources or zoonotic pathogens identified in humans as a result of the animal reservoir.

The overall prevalence of resistant bacteria originating from an animal reservoir isolated from humans ranged from 0.4% (out of 5,269 isolates tested) – 68.9% (out of 1,500 isolates tested). Resistant bacteria found in food sources, primarily meat and poultry, ranged from 0.9 % (out of 113 isolates tested) – 85.8% (out of 134 isolates tested). The proportion of isolates with R-CC from broiler and turkey meat were reported as the highest percentage out of all the isolates reported on from the animal reservoir.

Table 3: Prevalence rates of AbR from food or zoonotic pathogens in humans

Summary of prevalence rates from food sources including cooked and uncooked food or types of zoonotic pathogens identified in humans. Numbers in brackets are sample sizes = number of isolates tested.	
MDR-B (includes CJ / EC / Sal)	0.1% (113) to 28% (869)
MR-EC	2% (2) to 27% (12)
R-CJ	Prevalence of foodborne resistant bacteria found in humans: (0.4% (5269) - 60.2% (11,855)) Meat isolates: Meat from broilers: Total (*MSs = 3) : (0.3% (308 isolates tested) - 65.6% (308 isolates tested)) (Three EU member states were included in this study) Meat from turkeys: Total (*MSs = 2) : (1.4% (74) - 66.2% (74)) (Two EU member states were included in this study)
R-CC	Prevalence of foodborne resistant bacteria found in Humans: 1.6% (878) - 68.9% (1500); Meat isolates: Meat from broilers: Total (MSs 3) : (6% (134) - 85.8% (134))
R-EC	Prevalence of antibiotic resistant *E.coli* from food samples: 3/250 (1.2%; from minced beef) - 68/75 (90.7%; cooked meat) ; Prevalence ratio of acquiring resistant *E.coli* from handling raw meat: 1.10 (95% C.I: 1.02-1.19) - 1.32 (95% C.I: 1.03–1.70)
R-SA	Food sources: 22/39 resistant isolates Resistant profiles included: • Three or more classes (19.4% out of 39 isolates tested), • two classes (6.5%), or one class (45.2%) of antimicrobials.

	Human isolates: Out of the 125 enterotoxigenic S.aureus strains, 68.8% showed antibiotic resistance properties to at least one of antibiotics tested
R-Sal	Food producing animals: swine (4.6%; 318/6942) - Dairy cattle (28.3%; 1011/3570) ; Meat from broilers (0.4% (673) - 42.6% (674)); Meat from fattening turkeys: (0% (226) - 64.6% (226))

*European Union (EU) member States (MS): Total number of countries included in the study sample
**Please refer to Figure 8 for the abbreviations
***Zoonotic pathogens include strains of bacteria that have been transferred from animals to humans, term taken from ECDC 2015 report (106).

Occupational exposure and animals on property were two frequently reported transmission routes for resistant organisms via animal contact. Occupational exposure increased odds of carriage/colonisation of resistant bacteria in humans between 1.7 (95% C.I: 1.44-1.9)(112) to 33.1 (95% C.I: 3.47-316)(109). Risk for MRSA carriage was significantly higher for humans working on veal calf farms when compared with humans working on horticulture farms, and represented by the highest odds 591 (95% C.I: 5.1-69112.7) (113). The odds of carriage and/or colonisation with AbR due to either owning animals or livestock on the property ranged between 1.9 (95% C.I: 1.5-234)(113) - 20.46 (95% C.I: 7.83 - 64.39) (108).

Environment to human:

Identification of factors

Twenty-one studies reported on AbR transmission related factors impacting the human reservoir from the environment reservoir. Two likely factors were related to non-meat related food sources or water sources (Figure 19). Water transmission was most frequently reported across 21 studies, whereas food related sources were only reported across three studies.

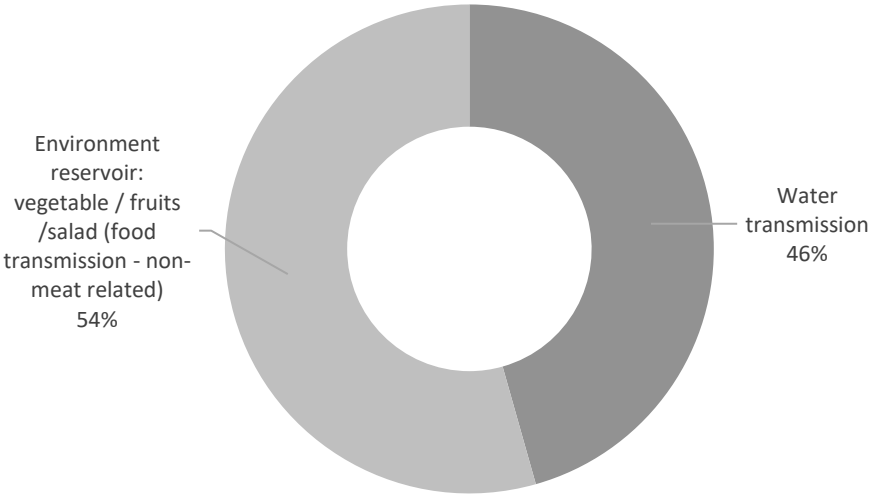


Figure 19: Risk factors related of AbR transmission from environment to the human reservoir

Method of quantification

Similar to the animal reservoir, comparison of prevalence rates was the most common method used to quantify potential transmission routes (89% out of 114 estimates reported prevalence rates), followed by descriptive statistics, odds ratios, and correlation coefficients. The prevalence of resistant bacteria identified from water sources ranged from 3% (n = 7 R- *E. faecium*) to 65% (n = 41 R- *E. faecalis*). From food related samples AbR isolates ranged from 2.6% (n = 5)(114) identified from Iceberg lettuce samples to 100% (n = 18)(115) found in salad or fruits.

2.3.1.4 Objective 2: Grade the quality of evidence

Objective 2: **Grade the quality of evidence identified under Objective 1**

Across the 527 primary studies identified, 56% were reported well according to the quality assessment criteria previously presented in Table 1 under methods, with a low reporting bias. The key areas of reporting bias shown in Figure 19 were related to lack of studies identifying: study design type (18%); baseline characteristics of the population under investigation (13%); or source of bacteria (13%). A number of studies also failed to report the original study aim/hypothesis (n = 17), complete inclusion and exclusion criteria (n = 23), the total number of participants (n = 11), a summary of the main findings (n = 7) and all the outcome measures being considered (n = 3).

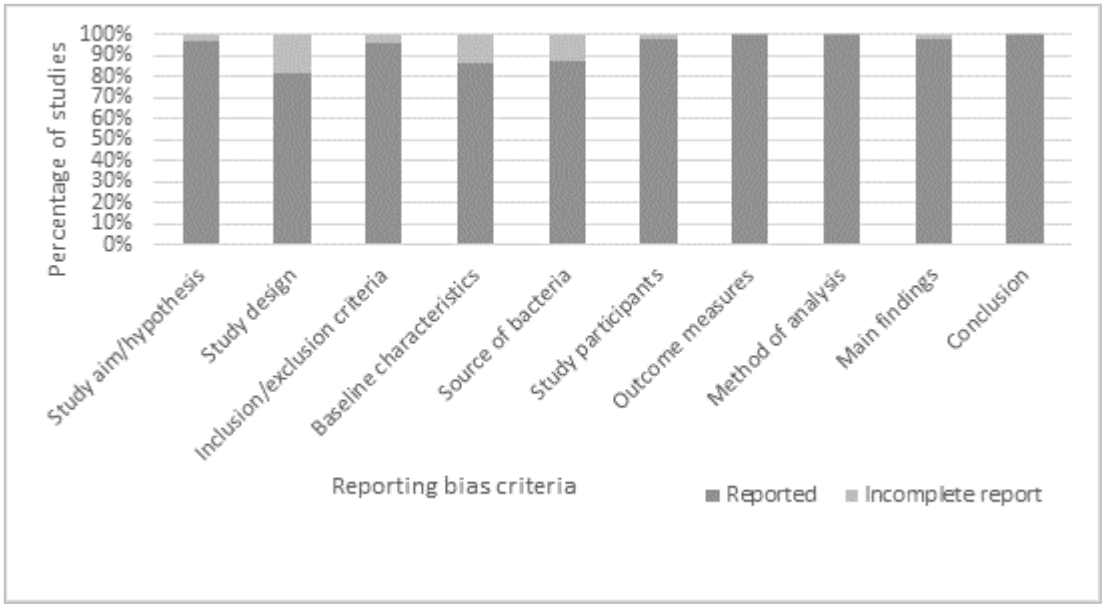


Figure 20: Overview of reporting bias results from the primary studies (n = 527)

With regards to methodological risk of bias, the main areas where studies generally had a low risk of bias were case selection and measurement of outcome. However, a large number of studies were subject to confounding bias (34%) and information bias when it came to identification of exposure variables (29%). The overall results for methodological bias are provided in Figure 21.

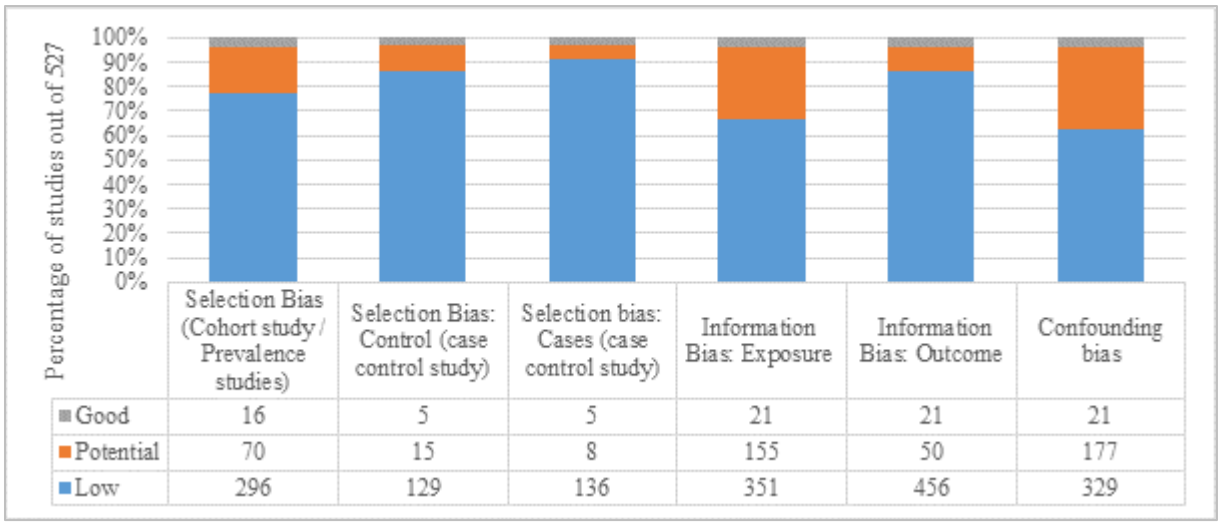


Figure 21: Overview of reporting bias results from the primary studies (n = 527)

RESERVOIR SPECIFIC STUDIES

Studies focusing within the human reservoir showed on average the highest quality score ratings (0.65 (maximum: 1; minimum: 0; standard deviation, SD: 0.19) indicating a lower risk of bias. Compared to the human reservoir studies, the other reservoirs had a higher risk of bias (average score between 0.42-0.52 (maximum: 0.86; minimum: 0.17; SD: 0.18)) (Figure 22).

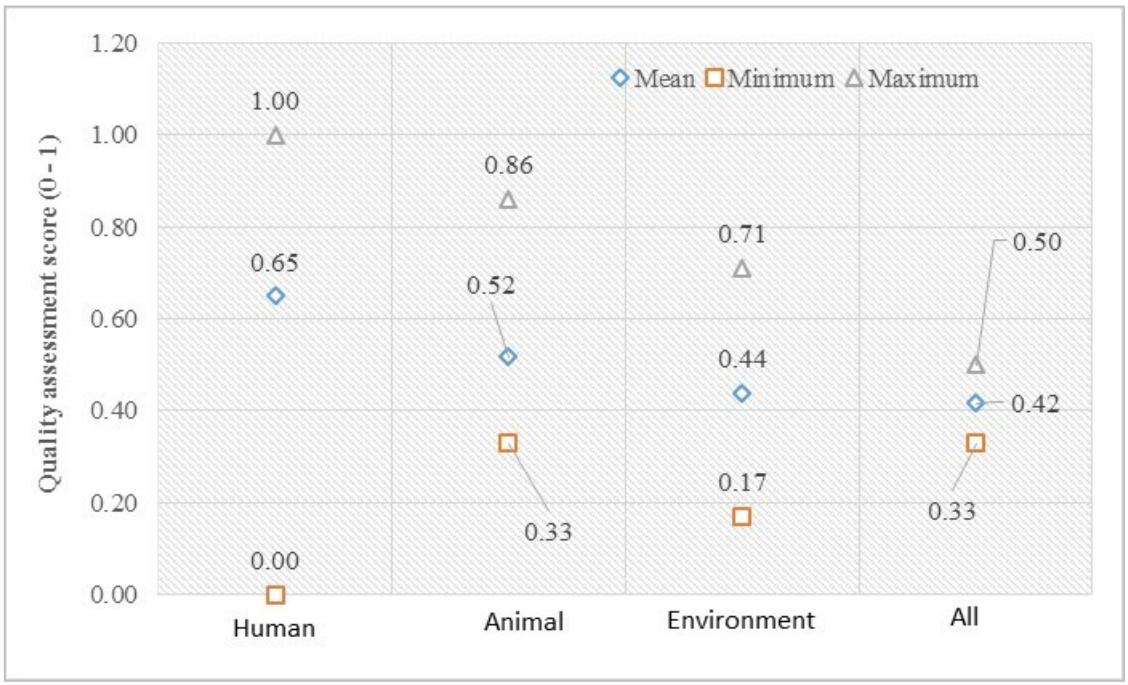


Figure 22: Reservoir specific quality assessment

2.3.1.5 Objective 3

Objective 3: **Quantify the strength of the evidence identified in Objective 1 and developing a mechanism to map this strength of evidence**

Since the majority of the evidence was reported for the emergence of AbR as shown in Figure 7, objective 3 was not separated out in terms of emergence and transmission specific risk factors of AbR.

Appendix Table 4 in Appendix I provides the complete details of the individual risk factors summarised under each of the five domains. The number of studies identified per risk factor, per domain with their respective study quality results have been detailed in this table. The type of reservoir for each risk factor and category have also been included within the aforementioned table. . Two figures (Figure 23 and Figure 24) have been developed to summarise the key results of the review.

All the 88 quantified risk factors were given separate codes. After all risk factors were coded, codes with common attributes were summarised according to these attributes. For example, if a code was regarding antibiotic use and how it increased the risk of AbR this was included under the antibiotic use risk domain. Similarly, if a risk factor was related to attending a healthcare setting or prior history of healthcare contact this was coded under the healthcare contact domain. In this way, five key domains were determined which provided umbrella terms for the 88 risk factors identified and were either patient-related or treatment-related, namely: Patient clinical history, health care contact, antibiotic use, community related factors, and demographics.

The original risk factors map presented in Figure 23 was further refined following:

- Presentations to the peer to peer AMR research groups and late stage PhD assessment at Imperial College London,
    - This group was attended by epidemiologists, junior doctors, pharmacists, research nurses, and cross discipline AMR researchers
- Advice from the peer review team (four peer reviews and one handling editor) at the journal of The Lancet Infectious Diseases, and
- Advice and guidance from Dr Julie Robotham on the final drivers map

Figure 24 is an overview of the final key risk domains and the top 5 risk factors quantified per risk domain. Figure 24 is a condensed form of Figure 23 that highlights where the majority of evidence currently exists.

Figure 24 therefore shows that based on the number of studies that quantified the extent to which a specific risk factor influenced the risk of AbR in humans, the greatest amount of evidence existed for the risk domains of antibiotic use, healthcare contact and patient's clinical history. In terms of the individual risk factors per domain, prior antibiotic exposure, followed by having an underlying disease, and having an invasive procedure during any healthcare contact were the underlying individual risk factors which have the greatest evidence currently published as identified from this horizon scan.

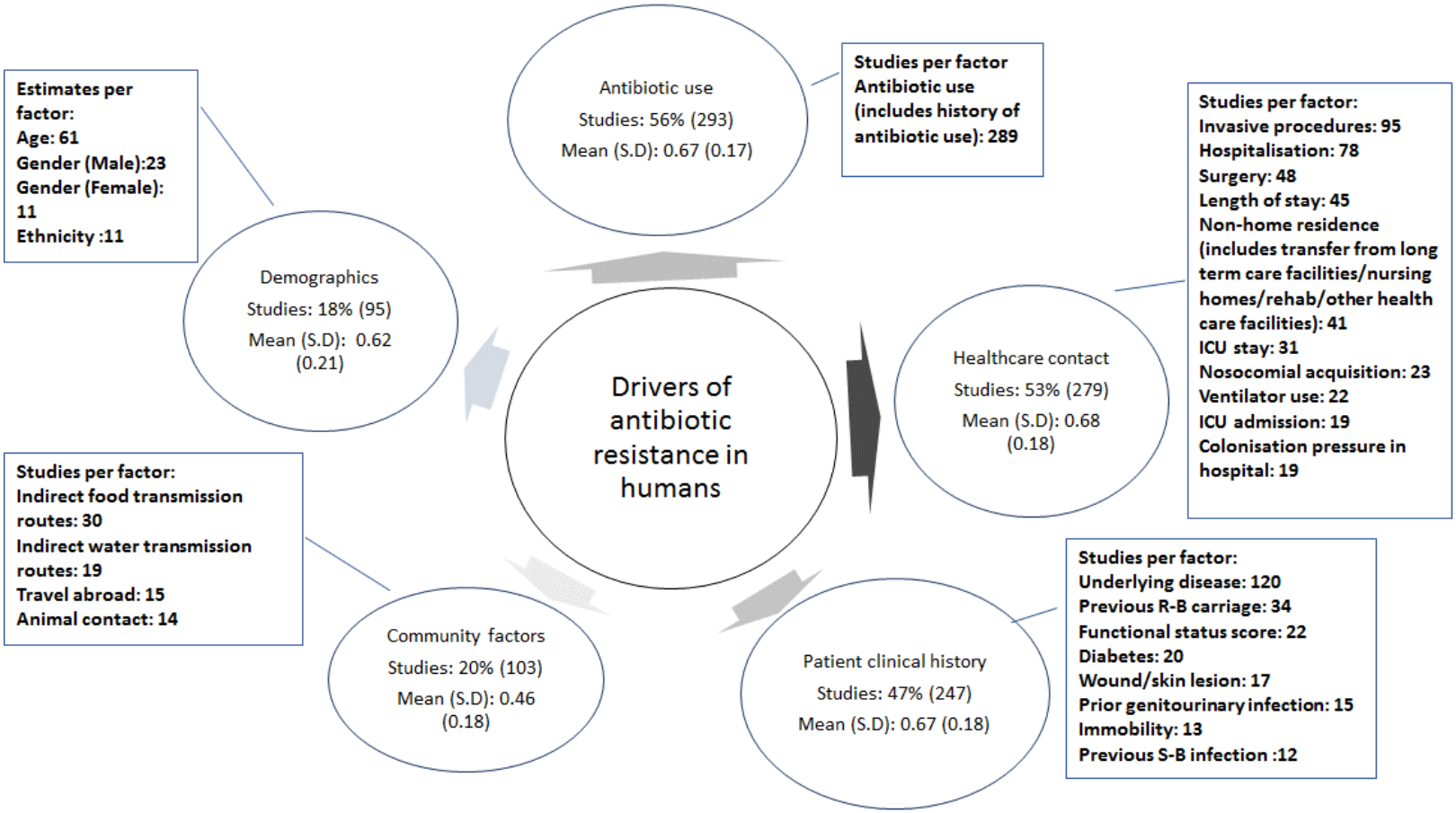


Figure 23: Overview of drivers of AbR reported in 10 or more studies

Key: The width of the arrows corresponds with the number of studies identified per risk domain. The arrow shade indicates quality of the studies identified from the risk domain: black represents the highest quality and light grey are potentially biased studies.
Abbreviations: ICU = Intensive care unit; S-B = Susceptible bacteria; S.D = Standard deviation; R-B = Resistant bacteria

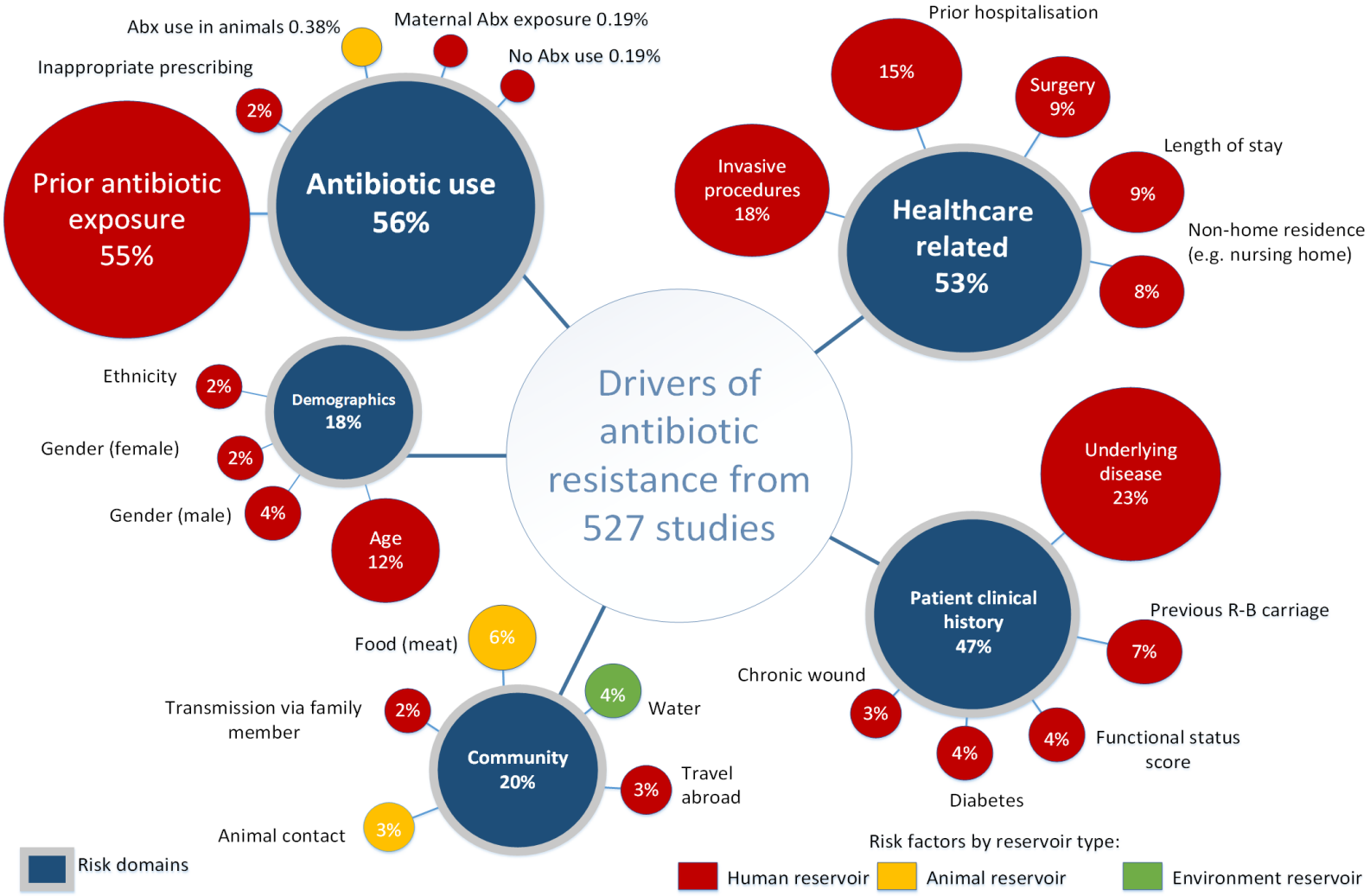


Figure 24: Top five drivers of antibiotic resistance in humans

The quality of evidence across these five domains did not vary remarkably (mean score : 0.62 – 0.68). However, evidence is currently lacking in quantity as well as quality when it comes to the community specific domain (mean score: 0.46). Thus, to meet objective 3 of this review, to rank the importance of the evidence in terms of quantity, antibiotic use followed by healthcare and patient history are the top three respective risk domains that can be ranked as important when it comes to tackling AbR in humans.

As discussed previously in section 2.2.6, a systematic map is especially useful in identifying the imbalances in the current evidence horizon, showing where research is currently lacking rather than where the greatest risk of AbR is. This analysis found that the community setting lacked the most evidence.

To determine the strength of the evidence, it was necessary to summarise the estimates which were used to quantify the risks of AbR. Since odds ratios were the most frequent quantification method identified, a sub-analysis was conducted using only data from studies which had conducted a multivariate analysis of the risk factors of AbR. Multivariate analysis was used as a method to quality control the analyses against the risk of confounding bias. It was therefore possible to conclude with a degree of certainty that the risk factor identified contributed to the increased risk of AbR, while concurrently taking account of all other factors which had been included within the analysis.

If a study reported only the odds ratio without the confidence interval or the statistical significance level, these studies were not included in this analysis, as the degree of uncertainty surrounding this specific risk factor could not be determined simply based on the odds ratio itself. There were also some studies which included 1 within the confidence interval yet claiming a significant p-value which was an incorrect statistical result. In these instances, the study was not included within the sub-analysis.

Table 4 is an overview of all the studies which were included for the five domains, along with the range of odds ratios elicited from these studies together with an indication of the quality of these

studies. The antibiotic use risk domain, along with the community factors domain, showed the largest OR ranges, with the community domain having the lowest quality studies, supporting the previous analysis.

Table 4: Multivariate analysis results

Overall outcomes	No. of studies	OR Range	Mean quality score (SD)
Patient clinical history	147	1·05 to 87·17	0.74 (0.15)
Healthcare contact	184	1·01 to 147·30	0.75 (0.15)
Antibiotic use	189	1·04 to 361·18	0.74 (0.15)
Community-level factors	34	1·27 to 591·00	0.62(0.18)
Patient demographics	54	1·03 to 30·50	0.74(0.15)

Abbreviation: [OR = Odds ratio; SD = Standard deviation]

The odds ratio of AbR in humans was between 2 to 4 times higher given exposure to one of the risk factors across the five domains compared to if the human was not exposure to these risk factors. Table 5 provides a heat map overview of the number of studies identified per odds ratio range. Risks identified from community level factors were much more variable compared to the other domains. However, since the quality of these studies were also low compared the other domains the variability in risk should be interpreted with caution.

Table 5: Heat map of odds ratio estimates from the primary studies

Overall	OR >1 - <2	OR ≥2 - <3	OR ≥3 - <4	OR ≥4 - <5	OR ≥5 - <6	OR ≥6 - <7	OR ≥7 - <8	OR ≥8 - <9	OR ≥9 - <10	OR ≥10 - <12	OR ≥12 - <14	OR ≥14 - <16	OR ≥16 - <18	OR ≥18 - <20	OR ≥20
Patient clinical history (n = 147)	16%	34%	22%	15%	7%	8%	8%	3%	5%	3%	3%	4%	2%	3%	5%
Health care contact (n = 184)	24%	35%	27%	20%	12%	7%	6%	4%	3%	5%	4%	2%	4%	1%	9%
Antibiotic use (n = 189)	15%	32%	20%	13%	16%	7%	10%	3%	4%	5%	7%	4%	1%	2%	8%
Community level factors (n = 34)	21%	29%	29%	12%	12%	9%	3%	9%	0%	3%	3%	3%	3%	6%	15%
Patient demographics (n = 54)	28%	37%	19%	11%	6%	2%	4%	0%	2%	2%	4%	4%	0%	0%	2%

Colour scheme: Green depicts where the largest amount of evidence (in terms of n = number of studies) was identified. Red depicts where the least evidence was identified.

SUMMARY OF PRIMARY STUDIES

In summary, from the systematic review on primary studies reporting on the risk factors of AbR in humans, 527 studies were identified. Out of these studies, 91% (477) reported on risk factors arising from within the human reservoir only. Eleven percent (59) reported on cross-reservoir risk factors impacting AbR in humans arising from either the animal (8%, 42) or environment (4%, 21).

Amongst these 527 studies, bacteria resistant to 3 or more classes of antibiotics (i.e., multidrug-resistant bacteria) was the most frequently reported AbR organism. Antibiotic resistant *E. coli* was the most frequently organism reported for the cross-reservoir risk factors.

In total 88 risk factors were identified which empirically quantified a relationship between the risk factor and AbR in humans. Four of these risk factors were specific to the animal reservoir (i.e., food (meat/dairy) related products, animal contact, antibiotic use in food-producing animals, and residence proximity to a farm), and two were specific to the environment reservoir (i.e., water and non-meat related food).

The bulk (470/527) of the studies reported on the increased risk of emergence of AbR in humans. Eighty-two risk factors were from within the human reservoir. The top 3 quantified were related to prior antibiotic use, underlying disease, and history of invasive procedures. Five factors reported on risk from within the animal reservoir, with animal contact being the most frequently quantified.

A smaller (57/527) proportion of studies reported on risk factors for transmission of AbR in humans. Ten of these studies were only specific to within-human reservoir factors. Transmission during healthcare contact either due to healthcare worker or type of care received during the patient's length of stay were the most frequently reported. Out of the 32 studies reporting on animal reservoir factors leading to transmission of AbR in humans, 3 risk factors were reported, all of which were also identified under emergence of AbR in humans. Food meat related potential transmission routes were the most frequently reported, followed by animal contact, and antibiotic use in humans. Twenty-one studies reported on environment to human reservoir AbR transmission routes, with two risk factors namely water and food related transmissions.

The estimates related to the transmission of AbR should be treated with caution as the studies reporting on prevalence of AbR in food and water sources were assumed as potential indirect transmission routes of AbR; a direct transmission route was not established. For example, the

consumption of a food product with AbR resulting in AbR infection in a human was not reported in this study, only the prevalence of AbR organism in a food or water item.

Objective 1 of this review was therefore met, and factors related to emergence and/or transmission of AbR in humans were identified. The key factors related to the emergence of AbR from within the human reservoir are related to antibiotic use, underlying disease, and invasive procedures. For transmission of AbR in humans, the risks are primarily from the animal reservoir and related to food transmission.

With regards to Objective 2, the quality assessment of the 527 studies concluded there was a low risk of bias. The key areas of bias were related to confounding bias when assessing the methods, thus making the validity of the correlation determined between the risk factors of AbR questionable. Compared to the other reservoirs, the human reservoir reported the highest quality of evidence, although there was also high variability in quality.

To establish a suitable method to meet objective 3, five risk domains were created, based on the risk factors extracted from the 527 studies. Antibiotic use, followed by healthcare contact, patient clinical history, community factors, and demographics had the greatest amount of evidence respectively. The present strength of evidence in terms of both quality and quantity lies with the risk factors reporting on healthcare contact factors contributing to AbR in humans. Community level factors had the poorest quality of evidence compared to the other four domains. However, this was the only domain where risks arising from all 3 reservoirs were identified.

2.3.2 Part 2: Targeted Review Of Meta-Analyses Studies

Out of the 88 risk factors identified from the primary studies, 26 were retrieved from the meta-analyses studies with pooled estimates. In addition, the meta-analyses studies identified three risk factors which were more granular versions of previously identified risk factors from the primary studies. These risk factors included: overall impact of nursing staff versus medical staff on AbR acquisition, transmission of MRSA from healthcare workers to environment objects in healthcare

facilities (116), and the non-hospital environment surface contamination (e.g. natural/built environment in the community) (117). Four meta-analyses studies reported on cross-reservoir drivers from the animal to human reservoir. No meta-analyses reported on risk factors from the environment to human reservoir.

Since very few studies were identified for the cross-reservoir risk factors impacting the human reservoir, the sections below (Section 2.3.2.2 and Section 2.3.2.3) have not been split further into human-human and animal-human as they were in Part 1 for the primary studies.

2.3.2.1 Organisms

Out of the 38 meta-analyses studies retrieved, MRSA followed by a combination of carbapenem resistant organisms (CRO) (CRO = carbapenem resistant (CR) *Pseudomonas aeruginosa* + CR-*Enterobacteriaceae* + CR- *Klebsiella pneumoniae*) were the most frequently quantified AbR organisms. Figure 25 provides the distribution of organisms identified from the meta-analyses studies alone.

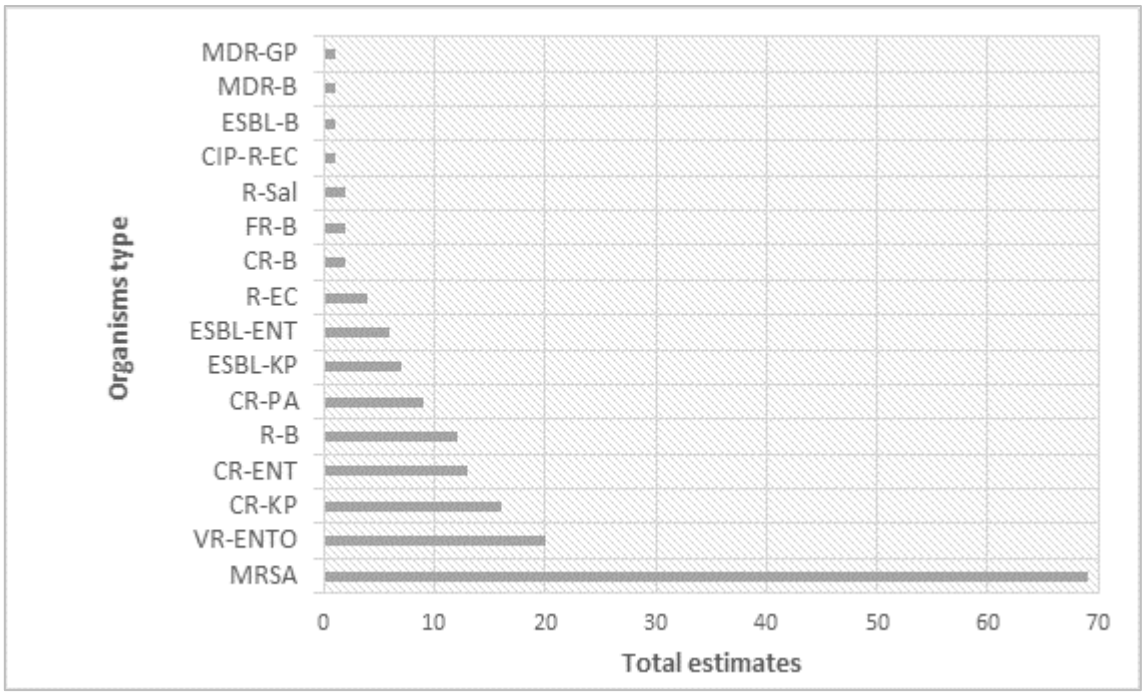


Figure 25: Resistant organisms overview from the meta-analysis studies

Please refer to Figure 8 for the abbreviations

2.3.2.2 Objective 1 and research question 1

Objective 1: Identify evidence on the commonly known emergence risk factors related to antibiotic resistance and report any additional determinants not commonly known.

Research question 1 for the emergence of AbR:

What factors impact the environment/animal/human to human emergence of antibiotic resistant bacteria and related infections? (e.g. antibiotic consumption)

a) Which factors are more frequently quantified per reservoir type?

b) How are factors quantified? (e.g. risk ratio, odds ratio, antibiotic resistance rates/colonisation rates)

Thirty-two meta-analyses studies were retrieved which reported on the within-human reservoir (human-human) risk factors of AbR. The top five risk factors most frequently summarised in the meta-analyses studies were similar to the factors identified from the primary studies: Prior antibiotic exposure and underlying disease. However, prior history of AbR carriage or colonisation were more commonly summarised as a key risk of AbR followed by history of hospitalisation and invasive procedures. In comparison invasive procedure was the third most commonly reported risk factor in the primary studies. This top tier of evidence where currently the greatest quantity of evidence was retrieved is shown in Figure 26. This top tier of evidence from the meta-analyses studies gives an indication of where the evidence on the key drivers of AbR in humans currently are.

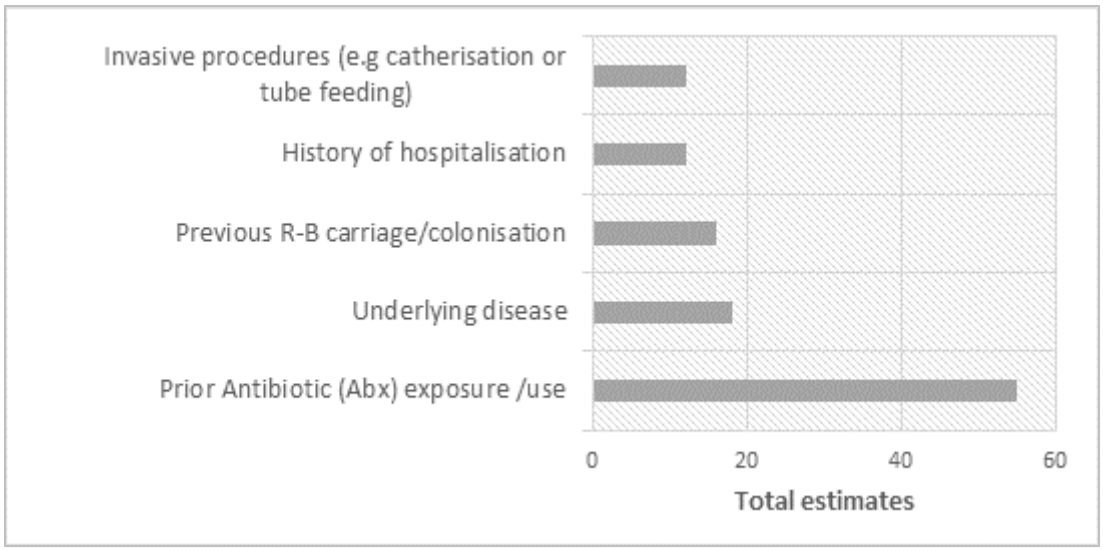


Figure 26: Top five most frequently quantified risk factors of AbR in humans (meta-analysis studies)

Abbreviation: [R-B = Antibiotic resistant bacteria]

Only one meta-analysis study was retrieved that reported on the animal to human reservoir risk factors of emergence of AbR. In this meta-analyses study, Tang et al. (118) identified evidence related to the impact of a reduction in antibiotic use in food producing animals and absolute reduction in AbR in humans. Therefore, indicating that in fact it is the impact of the human reservoir on the animal reservoir which is giving rise to AbR in humans. In other words, the human use of antibiotics in food producing animals is ultimately driving AbR in humans according to these meta-analyses which has pooled evidence from 81 studies. As previously indicated, no meta-analysis was retrieved in relation to pooled risk estimates for the environment to human reservoir.

Odds ratio was the most frequent method to report the pooled risk estimates followed by risk ratios (Figure 27).

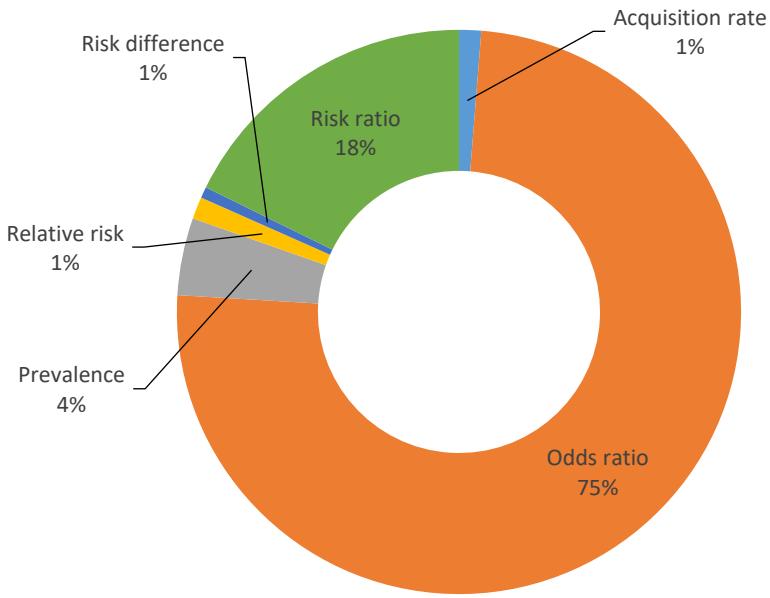


Figure 27: Quantification methods identified from (n=32) meta-analyses studies

2.3.2.3 Objective 1 and research question 2

Objective 1: Identification of evidence related to the commonly known transmission risk factors related to antibiotic resistance and report any additional determinants not commonly known.

Research question 1 for the transmission of AbR:

What factors impact the environment/animal/human to human transmission of antibiotic resistant bacteria and related infections? (e.g. antibiotic consumption)

a) Which factors are more frequently quantified per reservoir type?

b) How are factors quantified? (e.g. risk ratio, odds ratio, antibiotic resistance rates/colonisation rates)

In total five meta-analyses studies were retrieved which reported on potential transmission routes of AbR in the human reservoir. Two of these studies were related to the within-human reservoir. Three were related to the animal to human reservoir and none were identified related to the environment reservoir.

The two studies related to the within-human reservoir risk factors reported on transmission routes occurring from within the healthcare facility setting (116) or within the community setting (not related to water or soil related transmission routes) (117). Odds ratios were the most frequently quantification method to quantify these studies on within-human reservoir transmission routes.

Out of the animal to human reservoir studies, food related transmission sources were the only risk factor reported. Indirect transmission routes arising from animal milk sources, slaughtered food producing animals, and meat products were reported across these studies. The highest prevalence (17%) was reported for resistant *Salmonella* spp. identified from slaughtered food producing animal sources.

Pooled prevalence rates were the only quantification method used to summarise these meta-analyses results for the quantified evidence on AbR transmission routes from the animal to the human reservoir. Since only prevalence rates were elicited, the relationship was labelled as indirect, as baseline factors would not have been adjusted for these studies, hence making a causal inference from these results would incur biasing any conclusions made from this review.

2.3.2.4 Objective 2

Objective 2: **Grade the quality of evidence identified under Objective 1**

On average the methodological and reporting quality of these meta-analyses study were good. The average quality score out of 27 was 24 (90%), thus the majority of the meta-analysis studies were reported well with limited bias. The key reporting issues identified were due to studies failing to specify a prior study protocol or the complete search strategy used for the systematic review.

2.3.2.5 Objective 3

Objective 3: **Quantify the strength of the evidence identified in Objective 1 and developing a mechanism to map this strength of evidence**

Maintaining consistency in the methodology used in Section 2.3.1.5, the risk factors identified across the 38 meta-analysis studies were grouped into five domains. Similarly, to the primary studies these domains were: patient clinical history, healthcare contact, antibiotic use, community factors, and demographics. Table 6 reports the overview of all studies identified per domain, with their respective mean quality scores and standard deviation of these quality scores.

Antibiotic use was reported as the key risk factor of AbR in humans across the largest number of meta-analyses studies (n = 20). In terms of the quantity of evidence, prior antibiotic use could be ranked as an important determinant of AbR in humans. Given the higher mean quality score and the lower variability in the quality score assessed by the standard deviation across the quality scores, the quality of evidence was more robust, for healthcare contact risk factors across the studies when compared to antibiotic use.

Table 6: Quantity and quality of evidence identified from meta-analyses studies

Domain	No. of studies	Mean quality score	Standard deviation of quality score
Patient clinical history	17	0.907	0.0366
Healthcare contact	18	0.924	0.0631
Antibiotic use	20	0.907	0.0802
Community factors	5	0.8294	0.1385
Demographics	2	0.926	0.0524

An overview of the strength of evidence has been provided in Figure 28. The breakdown of odds ratios per domain are provided in Figure 29 to Figure 31. The most frequently estimated overall odds of AbR in humans due to clinical history, demographics, and healthcare contact was between 2 to 3-fold (Figure 28). The odds of AbR due to antibiotic use was more variable at 2 to 5-fold higher depending on the organism and the setting of the study (Figure 31). Compared to antibiotic use (Figure 31) and patient clinical history (Figure 29), the variability (in terms of odds ratio ranges) in the odds of AbR in humans due to healthcare contact was smaller (Figure 30). Smaller odds ratio ranges could be considered an indication of the robustness of the estimates identified from the healthcare contact domain when compared to the other risk domains.

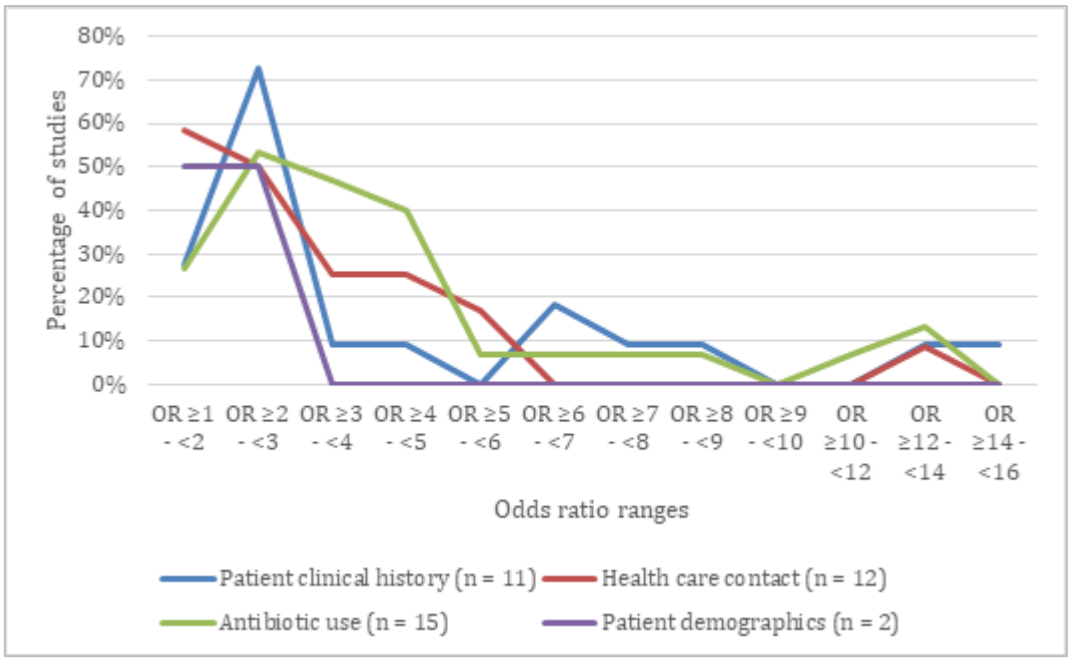


Figure 28: Distribution of odds ratios per risk domain from the meta-analyses studies

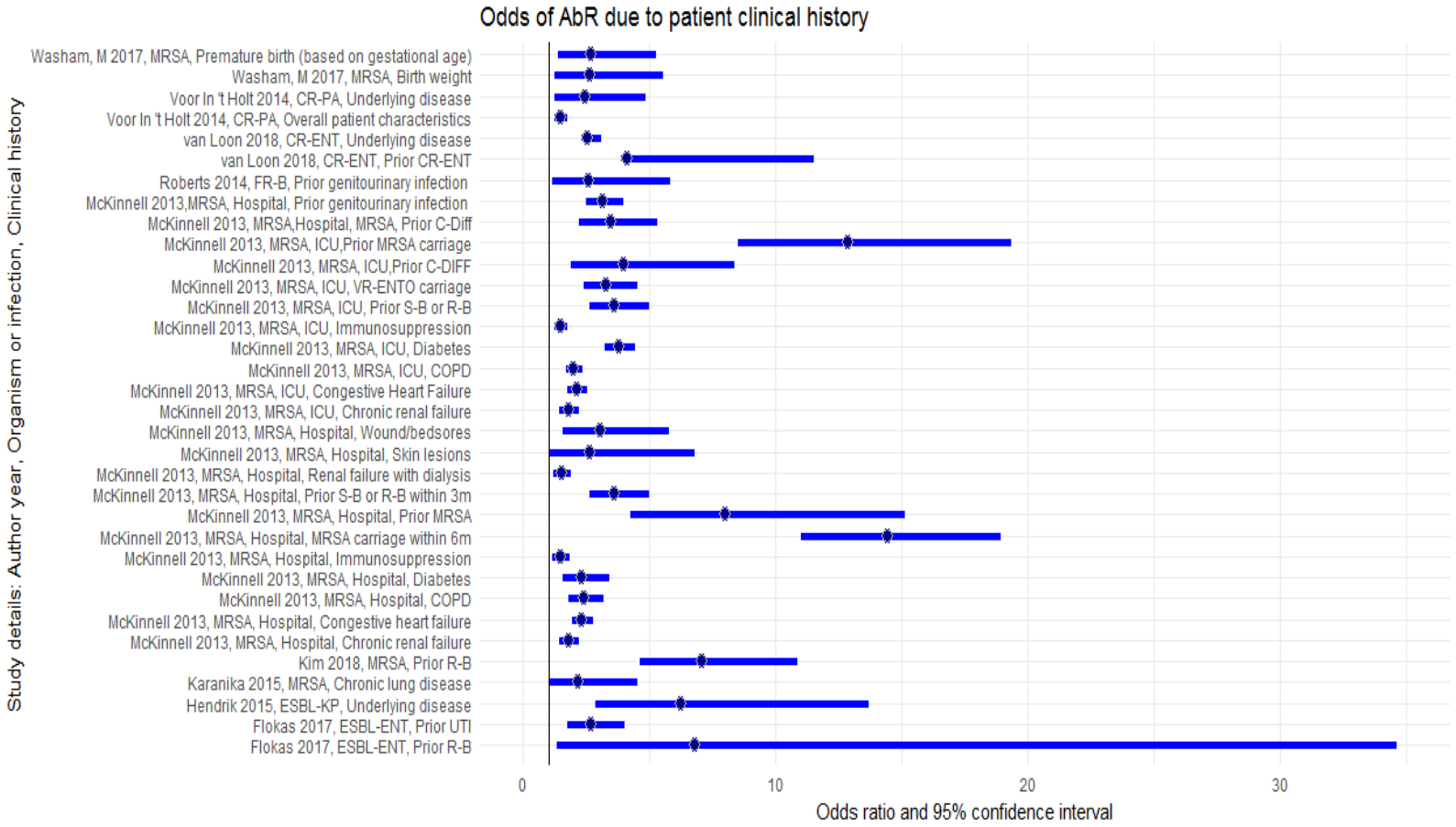


Figure 29: Distribution of odds ratios reporting on the patient clinical history domain as a risk factor of AbR in humans

Abbreviations: [COPD =Chronic Obstructive Pulmonary Disease; ICU = Intensive Care Unit; UTI = Urinary Tract Infection; 3M = within the last 3 months; For drug-bug combinations please refer to Figure 8]

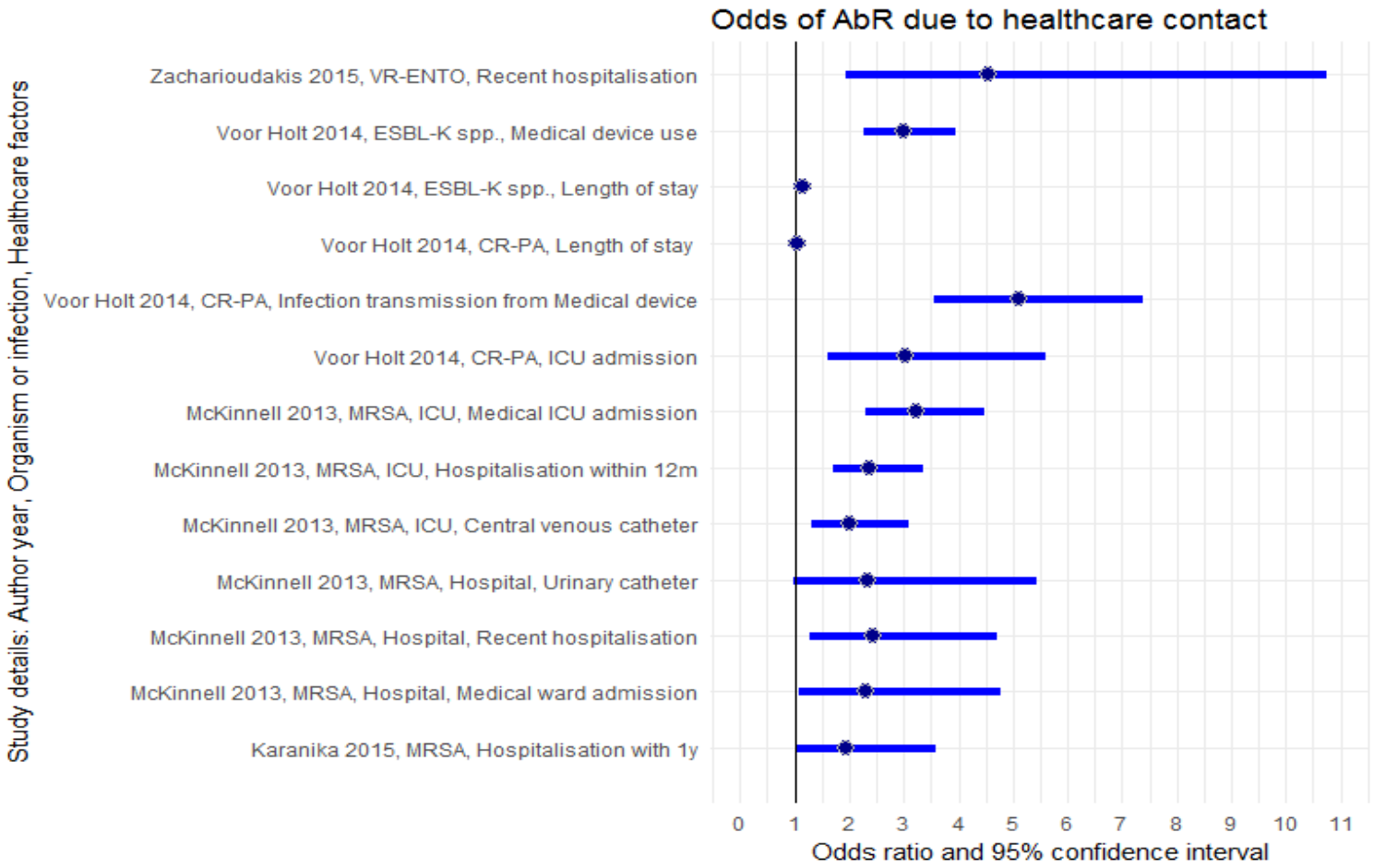


Figure 30: Distribution of odds ratios reporting on the healthcare contact domain as a risk factor of AbR in humans

Abbreviations: [ICU = Intensive Care Unit; 12M = within the last 12 months; For drug-bug combinations please refer to Figure 8]

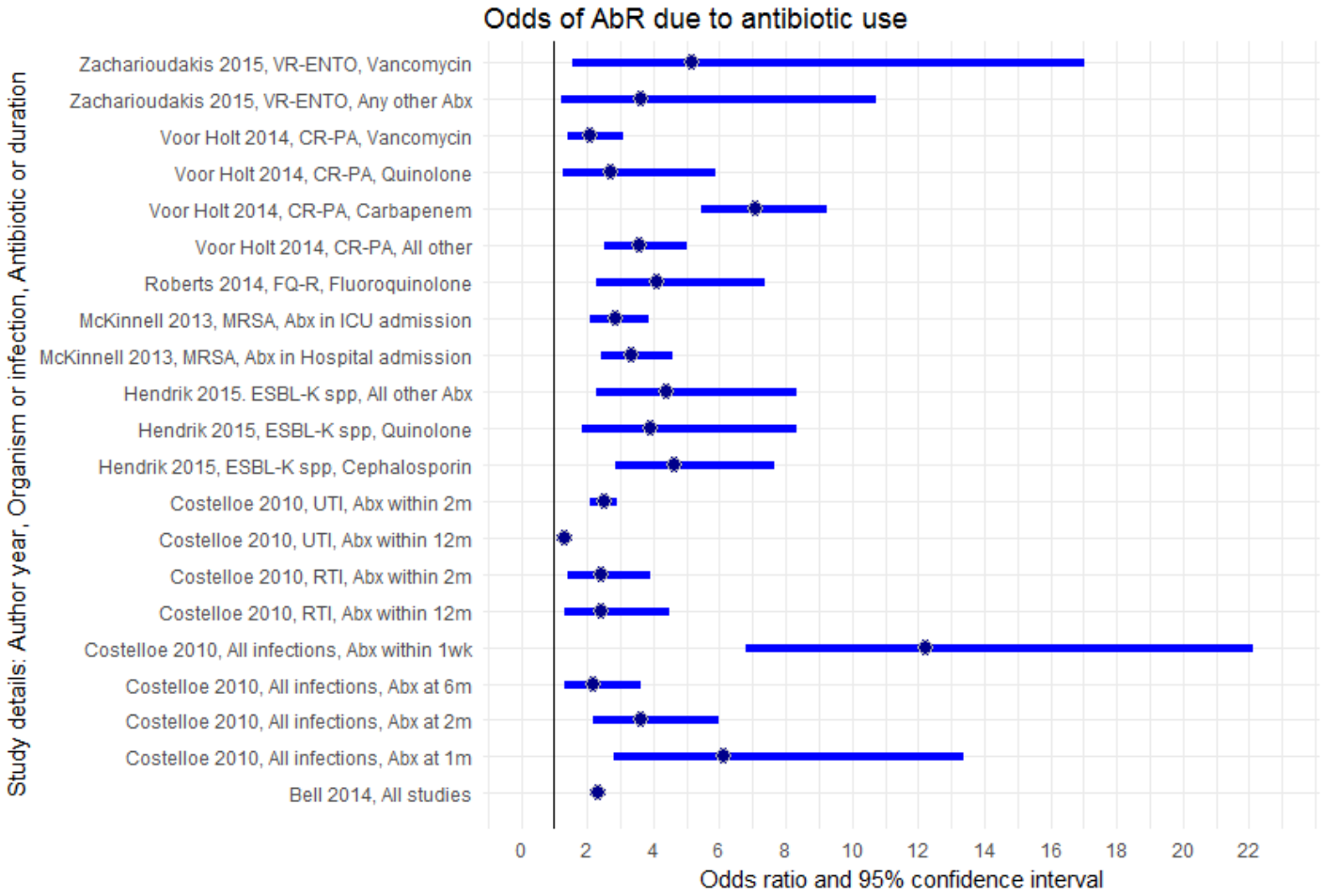


Figure 31: Distribution of odds ratios reporting on the antibiotic use domain as a risk factor of AbR in humans

Abbreviations: [Abx = Antibiotic treatment; ICU = Intensive Care Unit; m = months; RTI = Respiratory Tract Infection; UTI = Urinary Tract Infection; wk = weeks; For drug-bug combinations please refer to Figure 8]

2.3.2.6 Summary of meta-analyses studies

In summary, 38 meta-analyses studies that pooled evidence on the risk factors of AbR in humans were retrieved from the targeted review. Thirty-three of these studies were related to within-human reservoir specific risk factors and 5 were related to the cross-reservoir factors from the animal reservoir. No meta-analysis study reported on factors from the environment reservoir impacting humans.

MRSA was the organism which had the greatest number of studies reporting on it. Twenty six risk factors were identified from these 38 meta-analyses studies. Out of these 26 risk factors, 3 risk factors were more granular versions of those previously identified from the primary studies. For example, in the primary studies healthcare workers were identified as a risk factor for carriage or transmisison of AbR to patients, however, one meta-analysis specifically reported on the impact of nursing staff versus medical staff on AbR acquisition; another reported on healthcare staff seen as a risk factor for transfer of AbR to surfaces of objects in the hospital settings.

In terms of the quantity of evidence, antibiotic use, underlying disease, and prior colonisation (with AbR organisms) were the top three factors driving the emergence of AbR in humans arising from the human reservoir. The top 2 risk factors were therefore the same as those identified from the primary studies. However, invasive procedures were more frequently quantified under primary studies compared to prior AbR. Antibiotic use in food producing animals was the only factor identified from one meta-analysis study to have an impact on the emergence of AbR in humans.

Out of the 5 studies reporting on animal to human cross-reservoir factors, 4 reported on indirect transmission routes from the animal to human reservoir. These links were specific to either food, including meat and dairy sources, or contact with animals due to occupational exposure or from owning domestic animals.

Only two within-human reservoir studies estimated factors of transmission of AbR. These were specific to healthcare worker transmission of AbR, or community settings in terms of the type of natural built environment created by humans.

When looking at the pooled data in terms of the five risk domains, most of the quantified evidence supports antibiotic use as the key driver of AbR in humans. The quality of studies are better for the healthcare contact domains. Subsequently, this is reflected within the narrower odds ratio ranges (within a reasonably small confidence interval) from these studies reporting on healthcare contact.

The results identified from the meta-analyses studies resonate with the results from the primary studies, with antibiotic use, followed by healthcare contact and patient clinical history, showing better quality evidence. In comparison, patient demographics and the community setting had limited quantified higher quality evidence. The impact from the animal reservoir was the most frequently quantified cross-reservoir driver. Evidence from the environment reservoir has not been pooled in any recently conducted meta-analysis study at the time this review was conducted.

2.4 Discussion

When comparing the AbR drivers framework developed from this systematic review and the hierarchical framework of factors driving patient safety incidents previously discussed in the Introduction of this chapter, the Lawton et al. (101) paper was an example of a public health concern which had a well-defined boundary of the hospital setting. When it comes to AbR, it is a public health issue which spans settings. With the community setting encompassing a heterogenous group of stakeholders and reservoirs across the globe. Therefore, identifying all the root causes and the multiple causal factors driving AbR was more challenging to capture as precisely as Lawton et al's research piece did for patient safety incidents. In particular the literature surrounding these underlying factors (described as latent factors in Lawton et al.) driving the key risks (described as proximal factors in Lawton et al.) is still immature for the case of AbR. A large number of risk factors

were identified from this systematic review, however, the causal relationship between one risk factor and another was challenging to grasp based on the evidence identified. The concept of proximal and latent factors have also been utilised for a periodontal risk factor mapping exercise using a narrative review to inform this framework (103). In this paper, the identification of these latent underlying factors was highlighted as being challenging, as the further one moves away from the core problem the causal factors contributing to the core problem become increasingly difficult to identify.

The AbR drivers map developed here was able to rank the quantity and the strength of the current evidence and highlight the key proximal factors, here termed 'domains', (i.e., antibiotic use, healthcare contact, patient clinical history, community factors, demographics). Some proximal factors (antibiotic use, healthcare contact, and patient clinical history) are at present summarised more often across most AbR risk factor studies.

Given the vast boundaries of AbR, there still remain gaps in our knowledge regarding the importance of the underlying causal factors driving the key proximal factors such as antibiotic use and community level factors. The granularity in evidence on the risks driving these two proximal factors still requires further exploration. (Please note that Chapter 6 discusses some recent research, published since this systematic review was conducted and then published in 2018, which aim to address this gap.)

Thus, it can be concluded the strength of the evidence currently lies with what can be quantified from patient records such as records related to prior antibiotics, clinical history and type of procedures being carried out during healthcare contact. The weakness in the quantified evidence lies with the factors which cannot be easily measured, for example evidence outside of the routinely collected hospital data. Hence, very limited evidence was identified from factors related to the immediate hospital specific factors (e.g. importance of inadequate infection control measures impacting transmission of AbR), or the factors related to the community setting, or the impact of cross-reservoir drivers; factors which could be considered the latent underlying drivers of AbR.

To successfully obtain better quality, reliable evidence to identify underlying risks of AbR outside of routine hospital records naturally requires resources in terms of time, money, and staff to design a study tailored to such niche evidence identification. From the review, some attempts to collect this type of evidence were identified however unfortunately the quality of these studies was low. For example, even though evidence exists on the potential underlying transmission routes of AbR from the animal and environmental reservoirs to the human reservoir, this evidence is much less robust. At present the evidence related to cross-reservoir drivers are primarily from cross sectional studies which have an increased risk of selection, misclassification, and confounding bias, thus reducing the reliability of the risk estimates identified. When comparing the quality scores, the cross-reservoir factors from the animal and environment reservoir scored 0.52 and 0.44 respectively versus the human reservoir which scored 0.65. The following section provides some recommendations based on the results of this systematic review to help identify these underlying factors of AbR.

2.4.1 Limitations

Since this review attempted to conduct a horizon scan of the current literature landscape of the drivers of AbR, it was not able to capture all the risk factors across all drug-bug combinations. However, it was still able to provide an indication of where majority of the evidence currently lies and where future research investment efforts need to be focused.

The coding of the domains and the risk factors was conducted by one researcher, there remains a potential for researcher bias. However, the risk domains were discussed within Peer to Peer research meeting at Imperial College London, assessed at the late stage assessment with an internal and an external examiner. Last of all, the systematic review went through a peer review process prior to publication which included four external peer reviewers and the handling editor.

2.4.2 Recommendations From The Review

Based on the results of this review and the gaps identified from the evidence-based systematic mapping of the drivers of AbR, the following recommendations can be made to AbR researchers and policymakers who are interested in reducing the increasing burden of AbR.

This systematic review was able to give policymakers an idea of what the key proximal factors are which are driving AbR with the help of a risk factors domain map. Firstly, this domain map could be used to design future data collection protocols for research studies focusing on identification of risk factors of certain AbR causing organisms. Specifically, this research piece allowed identification of areas where little evidence exists and therefore where more research may be helpful. Conversely, preventing studies duplicating evidence where a large quantity already exists. Better risk factor identification protocols could be designed with the AbR risk domains map in future case-control and cohort studies.

Secondly, qualitative research in terms of interviews or focus groups may help identify the underlying factors which are not captured within the quantified evidence. More in-depth qualitative studies should therefore be combined with the routinely collected data to identify ground-level and organisational level factors contributing to risks of AbR. Such further risk identification efforts could enable novel areas for policy targets to be uncovered. Underlying local level and country specific factors influencing the established commonly quantified proximal factors need to be highlighted to potentially raise the efficacy of existing public health interventions and to achieve sustainable long term gains from such interventions. Thus, future research could aim to use the systematic mapping framework as a starting point to decipher the cumulative impact of these domains and how one domain may impact the other when it comes driving AbR in humans within their individual settings. Hopefully such an effort would also lead to addition of further domains and better identification of the key risks with the help of future evidence sources.

Last of all, there is a lack of uniformity in the definition of what type of risk of AbR is being quantified. The systematic review identified a large number of outcomes in terms of carriage, colonisation, infection, acquisition, transmission, or development of AbR; often the definitions were variable. More clarity in what factors are driving emergence of AbR and transmission of AbR from the risk factor studies could better inform future interventions and policy targets.

The above three recommendations should also enable future risk factor studies within the field of AbR to tackle the biases identified from the quality assessment stage of this review. Namely, a better understanding of the underlying causal factors will limit the confounding and information bias commonly identified across these risk factor studies. These two types of bias might make certain risk factors seem more important than they are. For example, it might be that system level factors within a hospital are promoting the increased risk of healthcare worker transmission of AbR infections. Ideally the system level factors should be tackled to gain long term sustainable control over the AbR infection transmission within the hospital setting. Or, it might be, that within the community setting, it is in-fact the socioeconomic and demographic background of a particular group of individuals which is increasing their risk of antibiotic misuse or awareness rather than the GPs prescribing behaviour. Improving awareness and education and reducing the socioeconomic disparity in the community might be the long term policy target rather than solely focusing on clinician behaviour to sustainably address the increased risk of AbR in the community setting. However, without better quality reliable evidence, one can only speculate what the key underlying system level factors are which are driving AbR and policymakers would only address the key visible proximal factors highlighted in current research.

2.4.3 Implication Of Chapter In The Thesis

Taking forward the key risk domains identified from this review, the next chapter (Chapter 3) aims to map the current interventions in terms of public policy objectives against these key evidence-based risk domains identified from this review. This should help to answer the second goal of this thesis, regarding how the key drivers of AbR are currently being tackled.

CHAPTER 3.

3 POLICIES, INTERVENTIONS AND DRIVERS OF ANTIBIOTIC RESISTANCE

3.1 Introduction

So far in this thesis, Chapter 1 has highlighted the need for an evidence-based bottom-up framework to AbR policy making. To inform this framework, Chapter 2 has focused on where the current evidence lies related to the key risk factors which are driving AbR in humans. Chapter 2 found that majority of the evidence related to risks driving AbR relates to antibiotic use, healthcare contact, and the heterogeneity in a patient's clinical history. To effectively inform the evidence-based bottom-up approach to AbR policy making, a level of knowledge is needed to understand how the key evidence-based risks of AbR may or may not be targeted by current policy measures and interventions. This Chapter therefore aims to map the key policy measures being taken to tackle the key evidence-based risks identified from Chapter 2.

Following a detailed rationale for the studies proposed in Chapter 3, the overall aim, research questions and methodology of this Chapter are provided below.

3.2 Rationale For Study

Many stakeholders are involved in tackling the public health crisis of antibiotic resistance (AbR), each trying to tackle AbR in their own way to achieve their own objectives. These stakeholders span the globe and their priorities involve not only preventing AbR in humans but also reducing the impact, on humans, from the animal or environmental reservoir. Stakeholders include policy level institutions from a global (e.g. United Nations (UN) / World Organization for Animal Health (OIE)) to a national (e.g. European Union (EU) / European Food and Safety Authority (EFSA)) and local level (e.g. secondary care – hospital specific policies).

Following the UN political declaration signed by leaders around the globe to collectively tackle AbR, the World Health Organization (WHO) have developed five key policy objectives to tackle AbR. These objectives are known as the Global Action Plan (GAP) for AbR. Subsequent to the formulation of the GAP, the various stakeholders who are involved in tackling AbR have also based their individual policy objectives on this GAP set by the WHO. However, there is some degree of variability in how each organisation is prioritising each of these objectives (58,119).

As discussed within the Introduction (Chapter 1), since there are so many stakeholders responsible for AbR health policy making and implementation, the problems of collective bargaining and mismatch of incentives are likely to occur. Within a recently published article, Hoffman *et al*., 2015 (38), highlighted this issue of collective bargaining further concluding that the involvement of many stakeholders may give rise to conflicting motivations and that different stakeholders may work on different timescales to achieve the single goal of controlling AbR in humans. A simple example could include the stakeholders tackling AbR in humans within a clinical setting. These clinicians' key priorities would be to save their patient's lives within the limited window of time they are presented with. However, these clinicians may not share the same interests as those working within the agricultural industry trying to limit bacterial infection spread across the food producing animal settings.

Wernli et al. (46) conducted a recent review of the global objectives set by these various stakeholders tackling AbR. Within this review five key mechanisms were identified which were driving these policy objectives. This review further added to the argument of multiple policy incentives which were driven by the stakeholders' individual priorities. Following the review of current AbR policy objectives, Wernli et al. (46) subsequently concluded that at present there remains a lack of a holistic framework which binds these individual policy objectives together.

Within the introduction of this thesis (Chapter 1), the two policy implementation methods often adopted were briefly discussed. These included the top down and the bottom up approach to policy

implementation. Where the top down approach includes a central organisation creating the policy objectives and ensuring that the policy implementers on the ground level implement the policy objectives as envisioned by the central organisation. For a top down policy approach to be successfully implemented, the policy problem at hand needs to have some key features. These include at the very least a central organisation who have clear objectives along with implementers on the ground who have appropriate incentives to be motivated enough to implement these policy measures. As highlighted by Hoffman and Wernli, the current AbR policy landscape needs a central organisation and aligned policy objectives. Therefore, a bottom-up approach to policy implementation is currently more suited for AbR policy. A bottom-up approach requires policymakers to consider the role of the policy implementers on the ground and the process-level barriers associated with implementing a particular policy.

This chapter therefore proposes to provide policymakers (tackling AbR) with frameworks to inform a bottom-up approach to AbR policy making. As a first step to inform this framework, the evidence identified from Chapter 2 regarding where the drivers of AbR currently lie will be mapped with what the current policy landscape of AbR is proposing. This mapping process will give policymakers a holistic understanding of what policy objectives are being prioritised and whether these prioritised policy areas match with the key evidence-based drivers of AbR identified in Chapter 2.

A holistic understanding of where policy is being prioritised does not however tell the policymaker whether the implemented measures are actually working as initially intended by the policy maker. Therefore, a second step is needed to inform the framework for a bottom-up approach to AbR policy-making. This second step will identify how the current policy measures have been implemented in terms of ground level AbR interventions. Subsequently, this step will also report on how effective these interventions have been so far in terms of tackling AbR.

Overall, setting policy objectives, mapping the relationship between evidence for these objectives and interventions, and understanding if these interventions are effective is also necessary for

streamlining public resources aimed at addressing the public health threat of AbR. Therefore, enabling policymakers identify better investment opportunities.

The Panel below provides an overview of the terminology used in this chapter. Section 3.3 discusses the general aim of this Chapter, Section 3.4 discusses the methods, Section 3.4.2.3 discussed the study limitations, Section 3.6 describes the results, and Section 3.6 discusses the results.

Panel to understand study terminology

'Objectives' refers to the individual objectives being set by the respective stakeholders listed in literature as tackling antibiotic resistance.
'Effectiveness' refers to clinical effectiveness of interventions. Clinical effectiveness is focused on since it can be directly mapped onto the risks the interventions are aiming to minimise.
'Primary care' refers to the community setting, such as general practitioner services.
'Secondary care' refers to the hospital setting.

3.3 Overall Aim

Chapter 3 proposes to meet the second objective of this thesis, subsequently addressing the research question of *how are the key quantified factors driving AbR in humans being targeted*?

This Chapter aims to answer the research question using a two-step approach which is described below.

Step 1: Policy objectives overview

Firstly, the key policy objectives to tackle AbR that are being recommended by key stakeholders globally will be reviewed from literature (38,46). Secondly, the evidence-based risk domains of AbR created in Chapter 2 will be mapped against the global objectives set out by stakeholders responsible for tackling AbR. Section 3.4.1 will provide the scope and methods overview for the identification and mapping of the policy objectives.

Step 2: Effectiveness of interventions

To be able to understand if the interventions currently implemented are effective, the highest quality of clinical evidence from meta-analyses and randomised controlled trial (RCT) studies will also be explored to identify the clinically effective interventions currently targeting the risks domains identified from Chapter 2. Section 3.4.2 provides the scope and methods overview for this targeted search for clinical evidence.

3.4 Methods

Figure 32 is an outline of the key methods being used to meet the overall aim of this Chapter mentioned in Section 3.3. Further details on the methodology adopted in Steps 1 and 2 are provided in Sections 3.4.1 and 3.4.2 respectively.

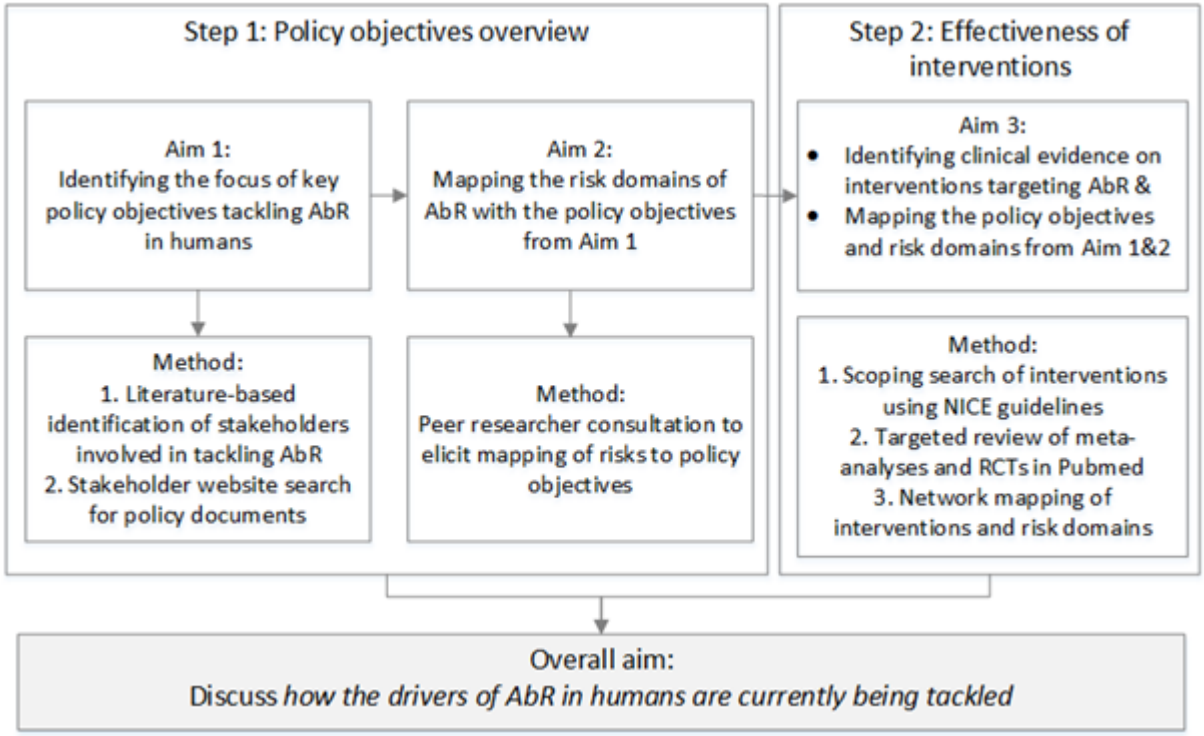


Figure 32: Overview of aims and methods used in this Chapter

Abbreviations: [AbR = Antibiotic resistance; NICE = National Institute of Health and Care Excellence; RCTs = Randomised controlled trials]

3.4.1 Step 1: Policy Objectives Overview

3.4.1.1 Rationale and scope:

Given the need for global solutions to tackle AbR, transnational and national organisations and institutions have made a concerted effort to create a coherent AbR strategy. However, prior policy mapping exercises have not yet mapped the evidence of the risk of AbR with the policy strategies and objectives (38,46,58,119). This research aims to provide an overview and highlight where there might be a policy and risk mismatch e.g. a risk which is unaddressed by a policy.

3.4.1.2 Methods overview

Utilising prior AbR policy identification techniques (37)(38)(46), the latest global policy strategies were identified from policy document searches from the websites of the global organisations involved in tackling AbR Following identification of relevant policy documents, it was determined that all the respective stakeholder policy documents included in our Study sample were developed based on the WHO GAP objectives. Therefore, how often a WHO policy objective was being included in the respective stakeholders' AbR policy plans were used as a proxy to determine where institutions were focusing their efforts to tackle AbR. For example, one of the WHO GAP is to improve infection prevention control measures to tackle AbR by helping to reduce the spread of such AbR related infections. Certain stakeholder organisations such as the ones representing the secondary care hospital settings primarily included this objective in their AbR policy objective, so this is assumed as the policy priority for this specific stakeholder organisation.

A similar technique has been previously adopted by the International Coordination Group for Antimicrobial Resistance (IACG) for a selective number of stakeholder organisations (58). However, in Chapter 3, unlike the mapping work done previously, the risk factor domains identified from Chapter 2 have been overlaid onto the WHO policy objectives to identify gaps in strategy recommendations.

To help reduce researcher bias, eight researchers in the Health Protection Research Unit in AMR and Healthcare Associated Infections at Imperial College London, each working in the field of AMR, were contacted to anonymously elicit how they would map the risk domains identified from Chapter 2 with the WHO GAP objectives. According to the level of agreement over which objectives should be mapped to which risk domains, the mapping procedure was split into direct and indirect objectives. Directly mapped objectives therefore represent where a high degree of agreement was attained across the 8 researchers. Indirectly mapped objectives are a result of lower degree of agreement between the researchers. If the same number of researchers mapped more than one risk domain to an objective, then both were assumed to be 'directly' mapped to that WHO GAP objective. If at least one researcher mapped a risk domain to the WHO GAP objective, then an 'indirect' relationship between the risk domain and the objective was assumed. This mapping process therefore enabled a framework for gaps in intervention targets to be identified.

3.4.2 Step 2: Effectiveness Of Interventions

3.4.2.1 Rationale and scope

Due to the expanding research interest in the field of AbR, a number of systematic reviews are currently being conducted to determine the effectiveness of global AbR policy implementation and similar behaviour change policies tackling AbR in Low and middle income countries (LMICs) (120,121). The protocols for these systematic reviews have been published so it has been assumed that research is currently ongoing.

A recent scoping review has also been published on interventions tackling antibiotic use in LMICSs (122). Within another expert opinion review on the current AbR policy plans and their efficacy it was also highlighted that at present there is limited data to determine whether the AbR policy plans have worked or not (78).

To avoid an overlap with on-going research and make the best use of current published literature, this Chapter will conduct a step-wise hierarchy of evidence search which will be guided by the NICE

clinical evidence search guidelines (123). A targeted reviewing search approach will therefore be employed to identify the evidence on the efficacy of interventions tackling antibiotic resistance in humans. This proposed targeted review in Chapter 3 will therefore not be looking at the evidence that exists for AbR policy but instead at the individual interventions which have been implemented. Since previous studies has been unable to identify sufficient evidence to determine whether these AbR policy plans are working or not and since a current systematic review protocol also exists where researchers are trying to determine the effectiveness of AbR policy, looking into the efficacy of ground-level interventions was deemed a more sensible approach.

There is current evidence suggesting that despite the existence of national and international action plans, there is a degree of heterogeneity in how these are being adopted and implemented at ground level (78,124). Therefore, this chapter will also be able to determine how policies aiming to tackle AbR is being translated into ground-level interventions.

As previously mentioned within the scope of this thesis in Chapter 1, there are a number of ways to tackle AbR. These include investing in new antibiotics or investment in the prevention and control of AbR. However, given the potential of bacteria to develop novel survival mechanisms to new antibiotic classes, it was highlighted that investment in prevention and control of AbR would provide a more longer term solution to tackling AbR as opposed to investment in new antibiotics. Therefore, the investment focus of this thesis in on prevention and control of AbR as opposed to development of new antibiotics. The efficacy of new drugs in Phase I-III trials are as a result beyond the scope of the targeted review in this Chapter.

The next section discusses the methods used to identify the evidence on the effectiveness of interventions tackling AbR to inform Step 2 and this Chapter.

3.4.2.2 Methods overview

Figure 33 is a schematic of the step-wise evidence identification method that has been utilised to identify the relevant, up-to-date and highest quality evidence on the effectiveness of interventions targeting AbR in humans.

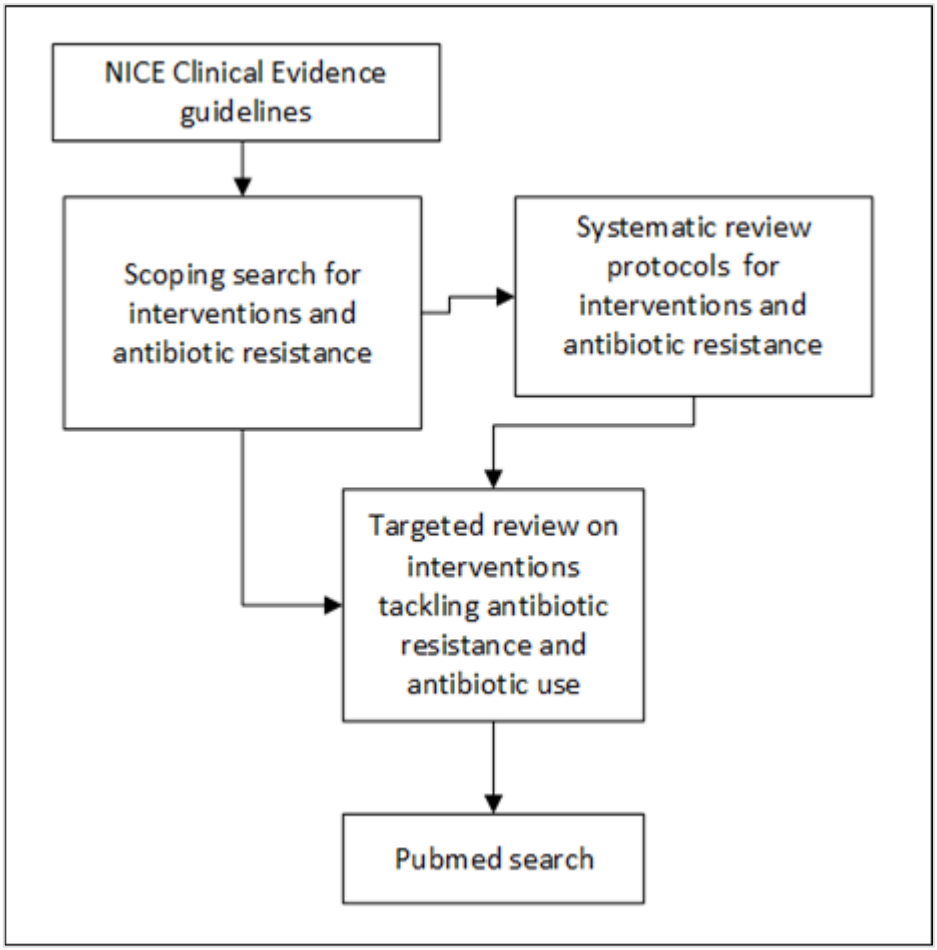


Figure 33: Targeted review methods overview

Abbreviation: [NICE = National Institute of Health and Care Excellence]

Utilising the NICE guideline manual recommendations for a step-wise identification of studies stratified by a hierarchy of study designs (e.g. meta-analysis of randomised controlled trials versus case-control versus observational study), studies providing data on effectiveness of interventions were identified (123).

Following the NICE guidelines, an initial scoping search was conducted to identify the most recent meta-analyses and systematic reviews evaluating interventions targeting a reduction in antibiotic resistance in humans. The initial scoping search identified published systematic review protocols on assessing the effectiveness of AbR policy and behaviour change related interventions in LMICs (120)(121). The protocols for these systematic reviews identified from the scoping search were used to inform the targeted review search for studies reporting clinical effectiveness data of interventions tackling AbR in primary and secondary care settings.

3.4.2.3 Assumptions to support methodology

Since the scope of this PhD only includes antibiotic resistant bacteria, the population outcomes for infection control strategies in hospitals were restricted to AbR organisms. Within the initial scoping search it was determined that the key efficacy measure most often reported in the primary care setting was antibiotic use and these intervention assessments were not specific to a drug-bug combination. Therefore, no population-specific (e.g. bacteria or viral infections) restrictions were made for interventions in the primary care setting. Antibiotic prophylaxis strategies or strategies which involved increased and/or promotion of antibiotic use in either primary or secondary care are not within the scope of this targeted review.

To determine the effectiveness of interventions from the highest quality and most recent evidence, this Study has been limited to the past 10 years and the top tier of the evidence quality hierarchy where the study designs include systematic reviews of meta-analyses studies, meta-analysis studies, and randomised controlled trials.

3.4.2.4 Research questions

The research questions for the targeted review on intervention effectiveness are:

1. What is the clinical effectiveness of antibiotic stewardship programmes or other interventions targeting reduction of:

a) antibiotic resistance in humans,

b) antibiotic prescribing

c) duration of antibiotic exposure in either a primary or secondary clinical care setting

2. What is the clinical effectiveness of infection control programmes targeting reduction of antibiotic resistance in hospital settings?

3.4.2.5 Search, selection, and result dissemination

The search strategy is described in the Appendix II.

Outcome measures describing clinical effectiveness could differ from one study to another (e.g. outcomes could be related to reduction in antibiotic use or reduction in infections caused by AbR organisms), therefore a number of 'outcomes' identified from the clinical effectiveness studies were used to map across to the policy objectives in Step 1 and the risk domains of AbR identified in Chapter 2.

To help facilitate the mapping process of the clinically effective interventions with the risk domains identified from Chapter 2, an adapted version of network maps was used. Network maps are a common tool used in a network meta-analysis which analyses data across separate clinical trials. In network maps, the comparators from one randomised controlled trial are mapped with another randomised controlled trial where the baseline population of patients are comparable. Thus, the common comparator (e.g. placebo or intervention A) can be mapped with the intervention arms of different trials. Here, network maps are used to present the results of all the different interventions identified from the targeted review with quantified clinical evidence supporting the efficacy of the intervention against either reducing antibiotic resistance or curbing antibiotic use. The baseline population across all trials may not necessarily be the same, therefore, only the 'visual concept' has been borrowed from the network maps commonly seen in network meta-analysis studies. The network maps were developed using Microsoft Visio (version 2016).

Any additional assumptions with regards to the results of the mapping process are discussed under the results section.

Table 7: Population Intervention Comparator Outcome Study design criteria

Criteria	Inclusion	Exclusion
Population	Interventions targeting; 1. Community interventions: No population restrictions; 2. Hospital interventions: Population restricted to antibiotic resistant bacteria	TB / viral / parasites / fungi
Intervention	Interventions targeting antibiotic use in the community	Antibiotic use as the intervention such as for treating/preventing surgical site infections (e.g. prophylaxis)
	Interventions targeting antibiotic use and infection control in the hospital to reduce antibiotic resistant infections	Interventions for healthcare associated infections overall and not primarily evaluation of antibiotic resistant infection transmission or emergence
		Interventions including AMS evaluating antibiotic allergy outcomes rather than reduction of antibiotic use or antibiotic resistance. Antibiotic prophylaxis to prevent MRSA not included.
	Interventions that have evidence of reducing resistance to antibiotics, improving appropriate prescribing or	

Criteria	Inclusion	Exclusion
	reducing inappropriate use (i.e., concordant with guidelines), or decreasing overall prescribing of antibiotics	
	Decontamination/decolonisation (patient level and hospital environment level) to prevent AbR infections	Primary outcome to evaluate susceptible-healthcare associated infections
		randomisation of hypothetical patient cohorts on decision tree analysis/cost effectiveness modelling studies
Comparator	Control group where no interventions have been implemented to target antibiotic use in the community or hospital, or infection control in the hospital, or usual care	
Outcome	Changes to antibiotic prescribing (reduction or control) in community or hospital	Risk factor studies
	Changes to incidence of infection/colonisation with antibiotic resistant bacteria	Not reporting outcomes for an intervention's evaluation
	Result of AMS programmes related to incidence of infection/colonisation with antibiotic resistant bacteria	Result of AMS programmes / interventions targeting antibiotic use / IPC programmes - decolonisation/selection/decontamination related to incidence of

Criteria	Inclusion	Exclusion
		infection/colonisation with *Clostridium difficile* or any other susceptible infections
	Study is either providing an overview of studies measuring quantitative difference in one intervention versus usual care or efficacy of an intervention	
Studies	Systematic reviews of meta-analyses, if no systematic reviews of meta-analyses then meta-analysis, meta-regression from systematic reviews	Qualitative, surveys, non-randomised, observational, prospective, retrospective, case study, case report, review not systematic (e.g. targeted / realist / scoping)
	RCTs if no meta-analysis exists	Quantitative results from systematic reviews and meta-analysis will be included: If duplicate studies are retrieved the quantitative results from these duplicate studies will be excluded
		RCTs already included in meta-analysis results
		Systematic review already included in Cochrane systematic review of systematic reviews
Limits	10 years (2008-2018) English full texts	

Abbreviations: [AMS = Antimicrobial stewardship; TB = Tuberculosis; MRSA = Meticillin resistant *Staphylococcus aureus*; RCTs = Randomised controlled trials]

3.5 Results

3.5.1 Step 1: Policy Objectives Overview

In total 49 stakeholder organisations were selected by combining the ReACT and Hoffman et al. (38) stakeholder lists. Out of the 49 stakeholder organisations, 44 were selected to be included in the study as they were within the scope of AbR; there were some organisations specifically dealing with Human Immunodeficiency Viruses, Acquired Immune Deficiency Syndrome, or malaria, which are outside the scope of this PhD. The 44 stakeholder organisation websites were searched in detail to identify their policy objectives for AbR; 32 specifically included tackling AbR within their organisational mission or objectives, backed by policy documents detailing the steps that they were taking to achieve this goal.

Table 8 presents the outcome of the identification of objectives of key stakeholder institutions who are tackling AbR at an international level. The complete stakeholder list and the policies extracted from these stakeholder policy documents have been provided in Appendix Table 7 to Appendix Table 10 in Appendix II.

Most objectives and activities from the sample of stakeholders focus on Objectives 2: *Surveillance and research* and Objective 4: *Optimising antibiotic use (antibiotic use / diagnostic to aid effective antibiotic use)* from the WHO GAP.

In addition to the five GAP objectives, three additional objectives or activities were identified which relate to how stakeholders are increasingly involved in cross discipline collaborative efforts across the one health economy. As previously discussed in Chapters 1 and 2, 'one health' refers to the inter-relationship between the different reservoirs where AbR may emerge or transmit from; currently known reservoirs of AbR include humans, animals, and the environment. In summary, surveillance and research (Objective 2) and optimising antibiotic use (Objective 4) have the greatest number of stakeholder policy objectives associated with them. Surveillance has the greatest number of stakeholders engaging with the policy objective.

Table 8: Overview of mapping GAP objectives with stakeholder objectives

WHO Global Action Plan Policy objectives for National Action Plans around the globe	**Individual policy objectives / activity**	**Total stakeholders or declarations signed by collective stakeholders**
1. Awareness	34	22
2. Surveillance and research	50	26
3. Infection prevention and control (Infection control)*	29	21
4. Optimising antibiotic use (incl. Antibiotic use / diagnostic to aid effective antibiotic use) • (Antibiotic use)*	50	23
5. investment/new antibiotics, vaccines, diagnostics	26	16
Other objectives/activities identified not specific to the Global action plan objectives		
Interdisciplinary cooperation	36	17
Helping other stakeholders with frameworks/ implementation	43	19
Governance/regulation/financial incentives	13	9

*Objective 3 will be referred to as infection control and Objective 4 will be referred to as antibiotic use from this point on.

The results of the expert elicitation process described above are provided in Table 9 and Table 10

Table 9: Results of elicitation of mapping conducted by eight researchers

	*Researcher number identifier (ID). and domains to which they mapped each objective.							
.	ID: 1	ID: 2	ID: 3	ID: 4	ID: 5	ID: 6	ID: 7	ID: 8
WHO GAP – Objectives (1-5)	Risk factors A-E*							
1.Awareness	B, D	A, B, C	A, B, C	A,D	A,B,D,E	A,B	A,B	A,B
2. Surveillance	A, B, E	E, D	A, B, C, D, E	C,E,A	A,B,C,D,E	A, B, D	A,B,C	C,D,E
3. Infection Control	A, B, C	A, B, D	B, C, D	B,C,A,E	B,C,E	A, B, D	B,C,E	B
4. Optimising antibiotic use	A, B, C, E	A, C	A, B	B,C,A,E	A,B,C,E	A, B, C, D,E	A,B,E	A
5.Investment in antibiotics	A, C, E	A, B, D	A, B, C, D, E	A,D,E	A,D,E	A, B, C	D	A,B

The researchers (ID: 1-8) mapped the WHO objectives (1-5) onto the risk factor domains (A-E)

Risk factors: *A =Antibiotic use, B = Healthcare contact, C= Patient clinical history, D = Community factors, E = Patient demographics; WHO GAP = World Health Organization Global Action Plan, Objective no. 1 = Awareness; 2 = Surveillance and research; 3 = Infection prevention and control; 4 = Optimising antibiotic use (Antibiotic use / diagnostic to aid effective antibiotic use); 5 = investment/new antibiotics, vaccines, diagnostics

Table 10: Mapping the risk domains against the five WHO objectives

WHO GAP - Objective	Risk domains															
	A: Antibiotic use		B: Healthcare contact		C: Patient clinical history		D: Community factors		E: Patient demographic		*Directly mapped to*	*Indirectly mapped to*
Awareness	7		7		2		3		1		*A&B*	*all*
Surveillance	6		5		5		5		6		*A&E*	*all*
Infection Control	4		8		5		3		3		*B*	*all*
Optimising antibiotic use	8		6		5		1		5		*A*	*all*
Investment in antibiotics	7		4		3		5		4		*A*	*all*

WHO GAP Objective no. 1 = Awareness; 2 = Surveillance and research; 3 = Infection prevention and control *; 4* = Optimising antibiotic use (Antibiotic use / diagnostic to aid effective antibiotic use)*; 5* = investment/new antibiotics, vaccines, diagnostics. The numbers under the risk domains represent the number of researchers who mapped the WHO objectives with the respective risk domains
Colour coding: Green dots indicate highest agreement between the researchers, red dots indicate lowest agreement between the researchers, orange dots indicate a mid-level agreement.
Abbreviation: [GAP = World Health Organization's Global Action Plan]

Using the consensus gathered from the eight peer researchers, Figure 34 shows an overview of the mapping of WHO Gap objectives to risks.

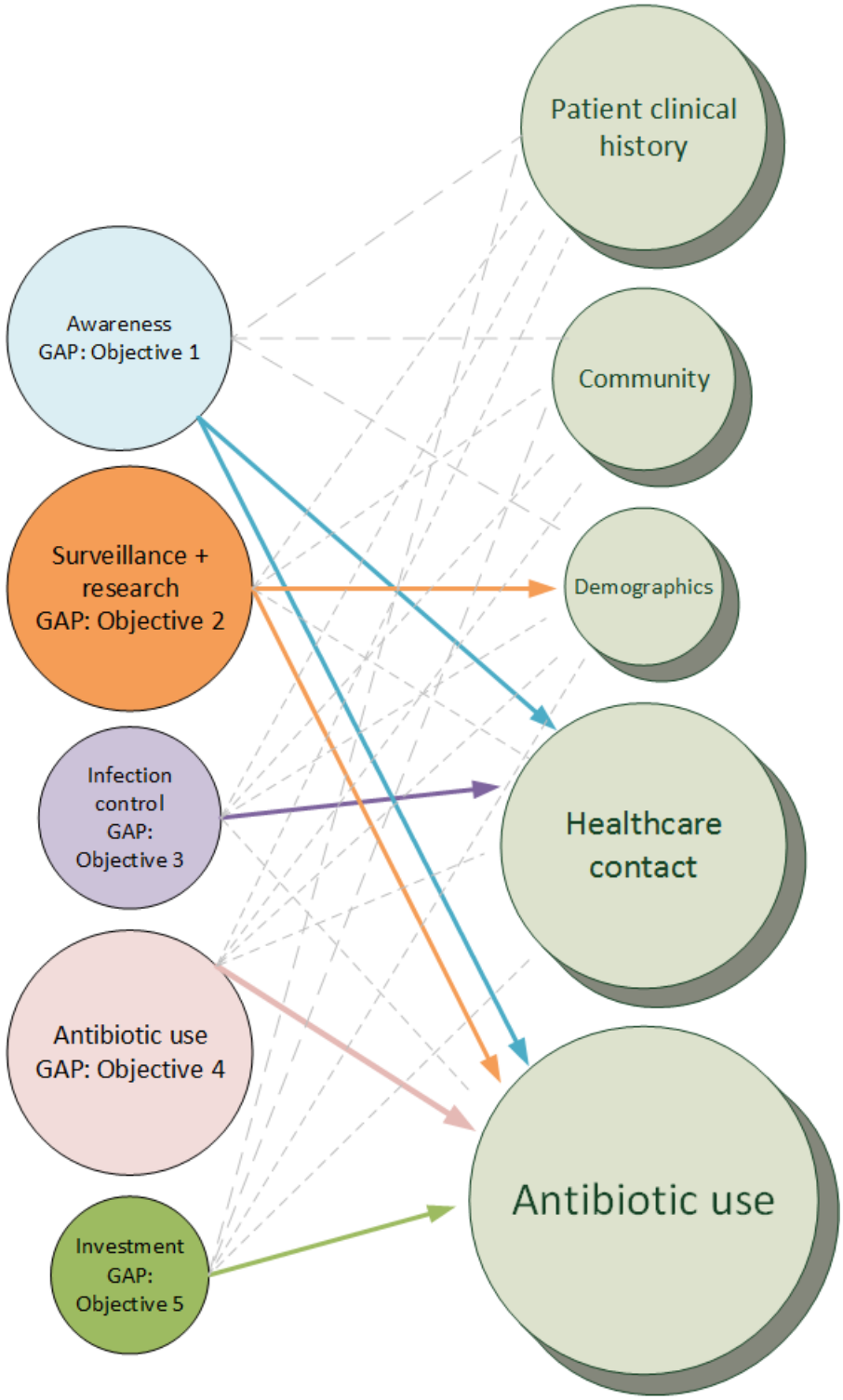


Figure 34: Mapping the World Health Organization Global Action Plan objectives with the risk domains identified from the systematic review

Abbreviation: [GAP = World Health Organization's Global Action Plan]
The bubble size for the WHO GAP objectives indicate the number of policies addressing each objective, as identified in Table 8. Similarly, the bubble size for the risk domains indicates the strength of evidence in terms of the quantity of data which was retrieved per risk domain (from Chapter 2). The grey lines

represent the potential indirect effect that each objective may have on each of the risk domains. The coloured lines indicate a potential direct relationship between the objective and the risk domain.

Apart from Objective 3 (Infection Control) and Objective 1 (Awareness), all the WHO objectives target antibiotic use directly. Although patient clinical history was identified as the third most quantified driver of AbR, none of the WHO GAP objectives directly address this risk domain. From Figure 34 it can be concluded that majority of the policies are targeting antibiotic use, the most frequently quantified risk factor of AbR. Other equally commonly quantified risk domains (i.e., patient clinical history and healthcare contact) have limited policies targeting these domains specifically, therefore few policies from a global policy level can be seen to address the highly quantified risks of AbR, apart from antibiotic use.

Thus far, these findings have focused on how the WHO GAP objectives map alongside the key risk domains, followed by which WHO GAP objectives are being prioritised at a global scale by the various stakeholders cited in literature. The next part of this chapter delves deeper into the detail of the interventions that are actually being implemented, and how they match with the policy objectives and key risk domains identified in Chapter 2.

3.5.2 Step 2: Effectiveness Of Interventions

To identify the clinically effective interventions from the highest quality of evidence available in literature, a targeted literature search was conducted in PubMed. Figure 35 provides the results schematic for the total articles identified and included in Step 2 of this Chapter.

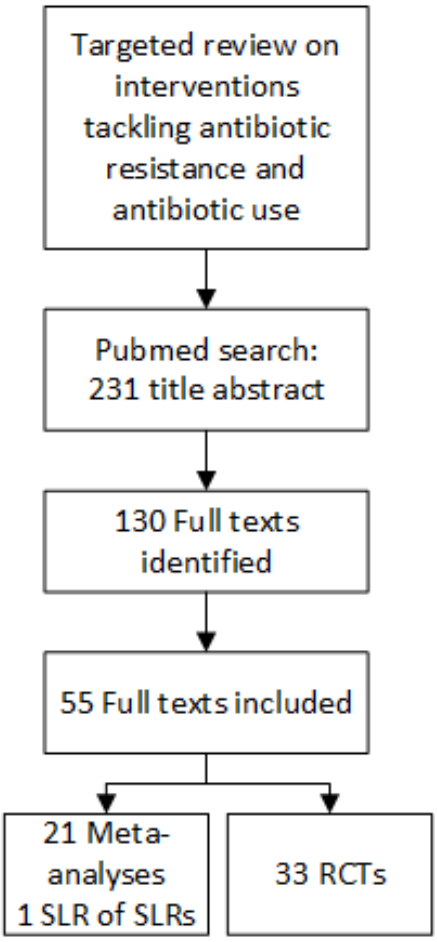


Figure 35: Results of targeted review

Abbreviations: [RCT = Randomised controlled trial; SLR = Systematic literature review]

In total, 231 title and abstracts were retrieved. Out of the 231 title abstracts, 21 meta-analyses were included in the analyses. After checking for any duplicate RCTs that may have also been included in the meta-analyses studies, 33 RCT studies were also identified and included in this analysis, the results from this search has been provided in Section 3.5.2.2.

3.5.2.1 Meta-analysis studies:

Twenty-one meta-analysis studies were extracted that identified various interventions targeting either antibiotic use in the community or hospital, or infections in hospitals.

The eight key outcomes identified, their associated efficacy measures, and range of values are listed in Table 11. The last two columns include the WHO GAP objective that these clinical outcomes relate to and the target AbR risk domain.

WHO's GAP Objective 3 (related to curbing antibiotic use) and 4 (related to appropriate infection control measures) were the only two objectives which could be directly mapped with any clinically effective interventions identified from the targeted review. Therefore, the associated risk domains with these WHO objectives: antibiotic use and healthcare contact were the only two risk domains that could be mapped against any clinically effective interventions. Out of the 8 outcomes, 4 were related to antibiotic use; the remaining outcomes were related to reduction in infections, length of stay related to infection, mortality related to infections, or adverse events in terms of symptom severity.

Table 11: Overview of outcomes measuring clinical effectiveness from meta-analysis studies

Clinical effectiveness outcomes related to:	No. of meta-analyses (References)	Measure used (Range)	Translation of interventions into WHO GAP objectives	Target risk domain
Antibiotic use				
Reduction in antibiotic use	8 (125–132)	% reduction in consumption (-9.74% to -19.9%) % reduction in consumption of restricted antibiotics (-26.6%) Odds Ratio (0.02 – 0.88) Risk Ratio (0.46 – 0.75)	Objective 4: Antibiotic use	Antibiotic use
Appropriate antibiotic use	1 (133)	Pooled Relative risk = 1.49	Objective 4: Antibiotic use	Antibiotic use
Cost of antibiotics	1 (131)	Pooled percentage change decrease in antibiotic cost = - 33.9%	* Objective 4: Antibiotic use	*Antibiotic use
Duration of antibiotic exposure	3 (128,132,134)	Difference in days (mean) = -2.4 Decreased duration (in days) = - 2.36 to – 4.19 Odds ratio difference = -1.23 to - 3.02	Objective 4: Antibiotic use	Antibiotic use
Other outcomes				
Infection (In hospital/secondary care setting)	8 (131,135–140)	Absolute risk difference (of being infected versus not infected by an AbR organism = -24% to -68% Incidence ratio (of infection due to AbR organism) = -31% to -66% Odds ratio: No significant difference to 0.33 Rate ratio = 0.01 – 0.38	Objective 3: Infection control	Healthcare contact

Clinical effectiveness outcomes related to:	No. of meta-analyses (References)	Measure used (Range)	Translation of interventions into WHO GAP objectives	Target risk domain
		Pooled risk ratio = 1.84 – 2.5		
Mortality (In secondary care setting)	4 (129,131–133)	Relative risk ratio reduction = No significant effect to - 56%	± Objective 3: Infection control	±Healthcare contact
Adverse event	1(141)	Relative risk ratio reduction = -55%	N/A	N/A
Length of stay (In secondary care setting)	2(131,133)	Pooled percentage change = -8.90% Pooled relative risk = No significant effect	$ Objective 3: Infection control	$ Healthcare contact

Abbreviations: [GAP = Global Action Plan; N/A = Not applicable; WHO = World Health Organization]
Guide to Table 11
* A reduction in the cost burden of antibiotics is assumed as impacting Objective 4 and the antibiotic use risk domain ; ± A reduction in mortality rate in the secondary care setting due to AbR organisms is assumed as impacting Objective 3 and the healthcare contact risk domain ; $ A reduction in length of stay in the secondary care setting due to AbR organisms is assumed as impacting Objective 3 and the healthcare contact risk domain

Overall thirty-five interventions implemented to tackle AbR in primary and secondary care settings were retrieved from the meta-analysis results. Interestingly, when comparing the clinical efficacy outcomes of the interventions and their intended targets, it was realised that there was a difference in what the intervention was aiming to target and how this outcome was being measured. Thus, there were some interventions which were aiming to influence patient's health seeking behaviour such as 'Video in waiting room' or 'Leaflet/poster/book' which were intended to target awareness of AbR and thus also impact antibiotic use, but it was only possible to measure 'antibiotic use' as the clinical efficacy outcome for these interventions rather than 'awareness'.

Therefore, to provide a fuller picture of both *intended* intervention targets (labelled as Intended focus) as well as the outcomes which were finally *targeted* (labelled as outcome successfully measured) (Table 11), the WHO GAP objectives, as well as the risk domains were also mapped to the actual interventions in Table 12.

For ease of the visualising the data presented in Table 12, the interventions, their comparators, and the corresponding risk domains of AbR are presented in Figure 36

Table 12: Intervention, comparator, target stakeholder list, mapped risk domains

Network map number	Intervention	Comparator	Target stakeholder	Intended focus	Outcome successfully measured	Target risk domain
Bundled interventions						
Antibiotic stewardship (ASP) bundle						
1	ASP bundle	Usual care Bundle of hand hygiene and contact precaution (STD Before ASP bundle implementation	Clinicians / Healthcare Professional	Antibiotic use	Antibiotic use	Antibiotic use
2	Stewardship and patient-clinician communication bundle	Usual care	Clinicians / Healthcare Professional + Patient	Antibiotic use Awareness	Antibiotic use	
Infection Control Bundles						
3	STD + Environmental cleaning (ENV)	Bundle of hand hygiene and contact precaution (STD)	Clinicians / Healthcare Professional	Infection control	Infection control	Healthcare contact
4	STD + Decolonization (DCL)	STD				
5	STD + Source control (SCT)	STD				
6	STD+ENV+SCT	STD				
Stewardship and infection control bundles						
7	STD+ASP+ENV+SCT	STD	Clinicians / Healthcare Professional	Antibiotic use and Infection control	Antibiotic use and Infection control	Antibiotic use and Healthcare contact
8	STD+ASP+ENV	STD				
9	STD+ASP+DCL	STD				
10	STD+ASP	ASP				

Network map number	Intervention	Comparator	Target stakeholder	Intended focus	Outcome successfully measured	Target risk domain
11	ASP + HH	ASP				
Individual Interventions						
Diagnostics						
12	C-Reactive Protein (CRP) test	No CRP test	Clinicians / Healthcare Professional	Antibiotic use	Antibiotic use	Antibiotic use
13	Procalcitonin-guided algorithms of antibiotic therapy (PCT)	No PCT guided Abx therapy				
Information Technology						
14	Decision support	Before decision support	Clinicians / Healthcare Professional	Antibiotic use		
Prescribing Related / Antibiotic Use Behaviour Related						
15	All clinician-patient communication	No intervention	Clinicians / Healthcare Professional + Patient	Antibiotic use Awareness		
16	Audit/Feedback on antibiotic prescription rates (APR)	No intervention	Clinicians / Healthcare Professional	Antibiotic use		
17	Bedside consultation	Usual care	Clinicians / Healthcare Professional	Antibiotic use		
18	Clinician targeted intervention	No intervention	Clinicians / Healthcare Professional	Antibiotic use Awareness		
19	De-escalation of therapy based on culture activities	Usual care	Clinicians / Healthcare Professional	Antibiotic use		
20	Delayed prescribing	No intervention	Clinicians / Healthcare Professional	Antibiotic use		

Network map number	Intervention	Comparator	Target stakeholder	Intended focus	Outcome successfully measured	Target risk domain
21	Delayed prescribing with watchful waiting and book for patients	Usual care	Clinicians / Healthcare Professional + Patient	Antibiotic use		
22	Discontinuation of empirical treatment based on no evidence of infection	Usual care	Clinicians / Healthcare Professional	Antibiotic use		
23	Guideline for infection (e.g. Respiratory Infection) / Empirical therapy according to guideline	No interventions / Usual care	Clinicians / Healthcare Professional	Antibiotic use Awareness		
24	IV to oral switch	Usual care	Clinicians / Healthcare Professional	Antibiotic use		
25	Leaflet/poster/book	No interventions	Clinicians / Healthcare Professional + Patient	Antibiotic use Awareness		
26	List of restricted antibiotics/formulary restrictions	Usual care	Clinicians / Healthcare Professional	Antibiotic use		
27	Patient targeted intervention	Usual care	Patient	Antibiotic use Awareness		
28	Therapeutic drug monitoring activities	Usual care	Clinicians / Healthcare Professional	Antibiotic use		
29	Training for communication between patient and clinician	No interventions	Clinicians / Healthcare Professional + Patient	Antibiotic use Awareness		
30	Video in waiting room	No interventions	Patient			

Network map number	Intervention	Comparator	Target stakeholder	Intended focus	Outcome successfully measured	Target risk domain
31	Externally imposed bans and reductions/Organic interventions/Self-labelled antibiotic-free, pasture, or free-range/Voluntary reduction or withdrawal in antibiotic use	No interventions	One Health			Antibiotic use Community-related factors (Infection levels in the general population)
Infection control related						
32	Contact precaution	Usual care	Clinicians / Healthcare Professional	Infection control	Infection control	Healthcare contact
33	Decolonisation (selective oral decontamination (SOD) or selective digestive decontamination (SDD))	Usual care				
34	Hand hygiene measures	Usual care				
35	Selective digestive decontamination (SDD)	SOD				

Abbreviations: [APR = Antibiotic prescription rate; ASP = Antibiotic Stewardship Program; Abx = Antibiotic treatment; CRP = C-Reactive Protein; DCL = Decolonisation; ENV = Environment cleaning; HH = Hand hygiene; IT = Information technology; n = Number of meta-analysis studies; Patient comm = Patient communication; PCT = Procalcitonin Testing ; SCT = Source Control; SDD = Selective Digestive Decontamination ; SOD = selective oropharyngeal decontamination ; STD = Standard care]

Panel for terminology in Table above

The 'implemented antibiotic stewardship (ASP) bundle' varies and includes a range of restrictive, persuasive, and structural interventions such as antibiotic cycling, formulary restriction, prior-approval, automatic stop orders, computer-assisted management programmes, audit and feedback, education guidelines, and academic interventions. The efficacy of these interventions was measured together and not as individual interventions.

'Environmental cleaning' applies to cleaning and disinfection of all patient-care areas (e.g. bedrails, bedside tables, commodes, doorknobs, sinks, surfaces and equipment in close proximity to the patient) and medical equipment/instruments/devices.

'Decolonization' applies to treatment of colonized persons with a specific regimen consisting of non-absorbable antimicrobial agents administered as an oral paste and/or digestive solution (selective oral decontamination and selective digestive decontamination, respectively).

Interventions targeting animal antibiotic use include externally imposed bans and reductions / organic interventions / self-labelled antibiotic-free, pasture, or free-range / voluntary reduction or withdrawal in antibiotic use

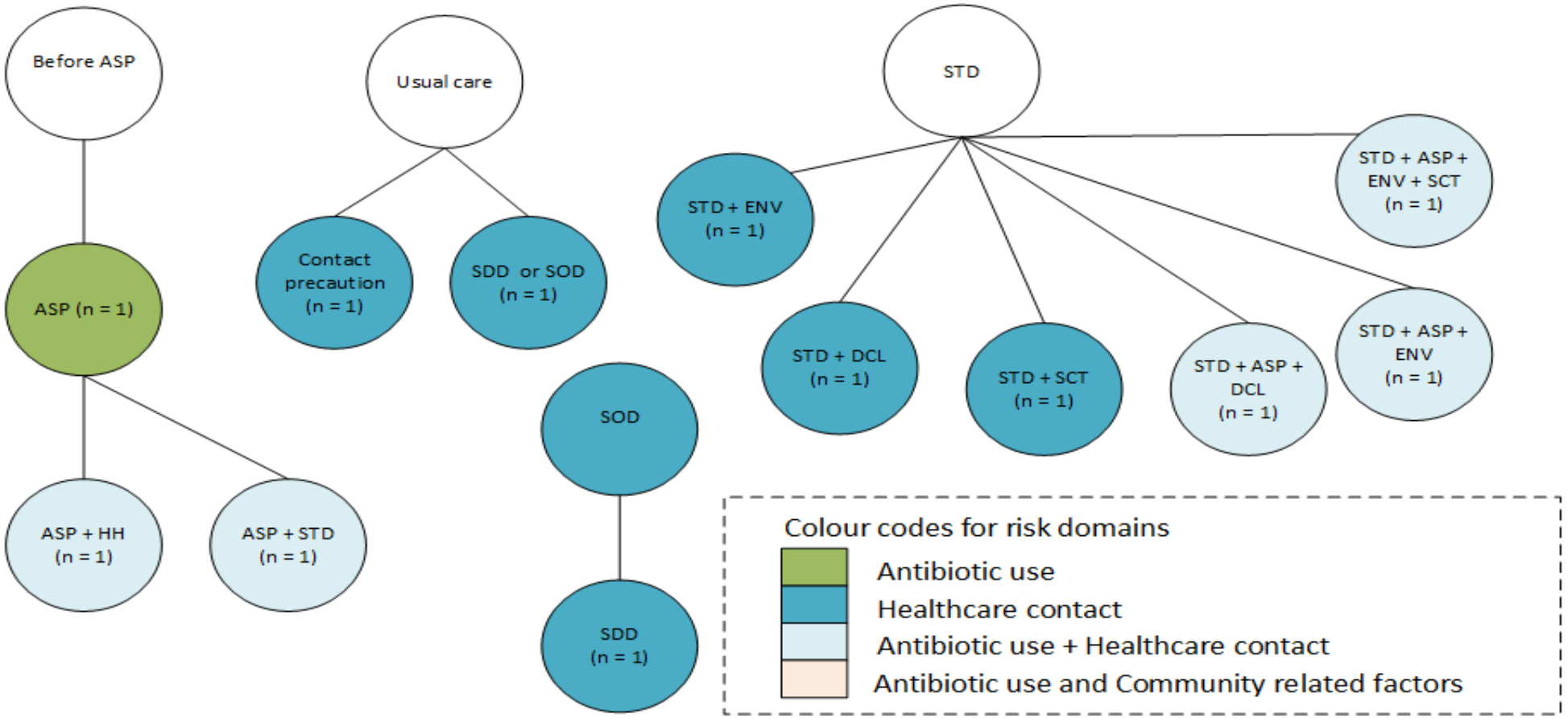
'Source control' includes interventions such as daily bathing or showering or whole-body washing with chlorhexidine.

Network map of key interventions and risk domains:

To gain a clearer understanding of how the clinical efficacy of interventions was determined in terms of what the intervention was actually being compared to, Figure 36 provides network maps for these interventions. The risk domains from Table 12 above have also been mapped across into these network maps using the colour codes as displayed in Figure 36.

Based on the clinical efficacy results Procalcitonin Testing (PCT) guided therapy was found to be a clinically effective intervention in reducing antibiotic use across four different meta-analysis studies, while antimicrobial stewardship bundles were found to be effective in reducing antibiotic use in three different meta-analysis studies. Within a secondary care setting, infection control combined with stewardship efforts were concluded to have increased clinical efficacy compared to stewardship efforts alone (142).

From Figure 36, the risk domain mapping exercise shows that antibiotic use and healthcare contact were the dominant risk domains being targeted by the currently implemented interventions. The only other risk domain that was seen to be targeted was community-related factors, where the impact of external ban of animal antibiotic use on AbR infections in humans was reported in one meta-analysis (143). However, the primary target of this intervention was also curbing mis-use of antibiotics within the animal reservoir.


Before ASP
ASP (n = 1)
ASP + HH (n = 1)
ASP + STD (n = 1)
Usual care
Contact precaution (n = 1)
SDD or SOD (n = 1)
SOD
SDD (n = 1)
STD
STD + ENV (n = 1)
STD + DCL (n = 1)
STD + SCT (n = 1)
STD + ASP + DCL (n = 1)
STD + ASP + ENV (n = 1)
STD + ASP + ENV + SCT (n = 1)
Colour codes for risk domains
Antibiotic use
Healthcare contact
Antibiotic use + Healthcare contact
Antibiotic use and Community related factors

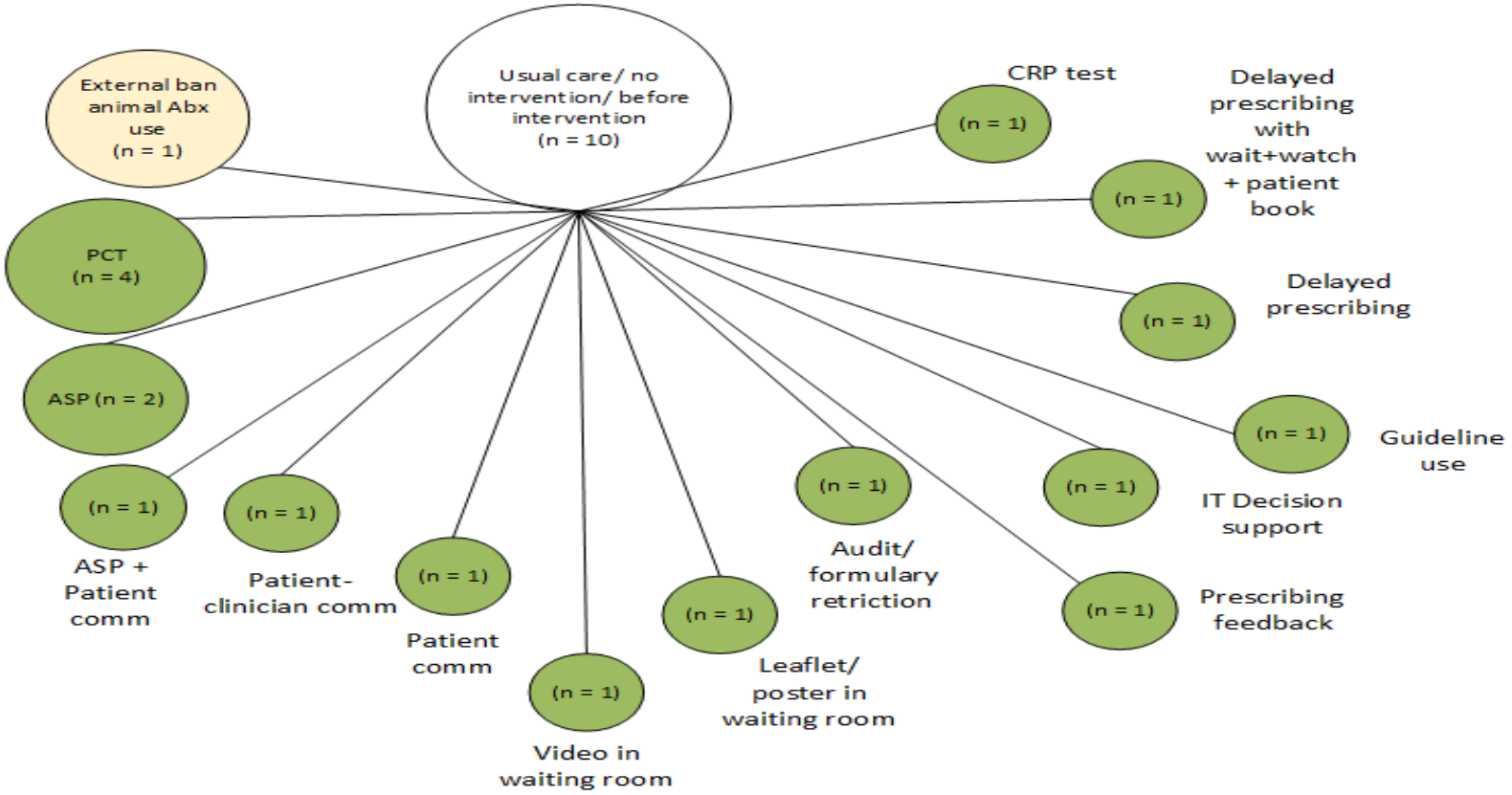


Figure 36: Network map comparing interventions with their control groups mapped to risk domains of antibiotic resistance

Abbreviations: [ASP = Antibiotic Stewardship Program; CRP = C-Reactive Protein; DCL = Decolonisation; ENV = Environment cleaning; HH = Hand hygiene; IT = Information Technology; n = Number of meta-analysis studies; Patient comm = Patient communication; PCT = Procalcitonin Testing ; SCT = Source Control; SDD = Selective Digestive Decontamination ; SOD = selective oropharyngeal decontamination ; STD = Standard care]
Please note Usual care is different from standard care, as standard care included additional infection prevention control measures (see Table 12) which studies reporting usual care as the comparator did not include/mention.
Bubble size represents the number of meta-analysis identified per intervention type, bubble colour represents the risk domain the intervention is targeting based on the efficacy outcome reported in the trial.

Mapping interventions with WHO GAP objectives and risk domains

In Figure 37 the key targets of the interventions have been mapped onto the policy objectives. ASP bundles primarily target antibiotic use and therefore meta-analyses focused on these interventions were mapped to GAP objective 4 'antibiotic use'. Decolonisation-related interventions primarily targeted prevention or control of infections, therefore these interventions have been mapped to GAP objective 3 'infection control'. Some interventions were also mapped to multiple objectives, such as 'ASP+HH' which were targeting both Objective 3 and Objective 4.

A handful of interventions targeted GAP objective 1 'raising awareness of antimicrobial resistance', which were primarily related to communication and training with patients. The main aim of these initiatives was curbing antibiotic use; hence these have also been mapped against the antibiotic use risk domain.

As seen in Figure 36. only one meta-analysis study reported on interventions aiming to curb antibiotic use in animals and measure the impact on AbR infections in humans. This study can be considered a good example of the indirect links which were mentioned by the researchers who conducted the WHO GAP Objective and risk domain mapping exercise. Impact of curbing antibiotic use in animals (in the community setting) and the indirect link to infections in humans (community and hospital settings combined) can therefore be linked to objective 3 'infection control', consequently having an impact on antibiotic use as well as community-related factors identified in Chapter 2.

The WHO GAP objectives do not have a specific objective for government bodies to implement legislation surrounding misuse of antibiotics in the animal reservoir. However, within the interventions identified from this meta-analysis study, some measures could be mapped against current regulatory procedures also being put in place in some countries (143).

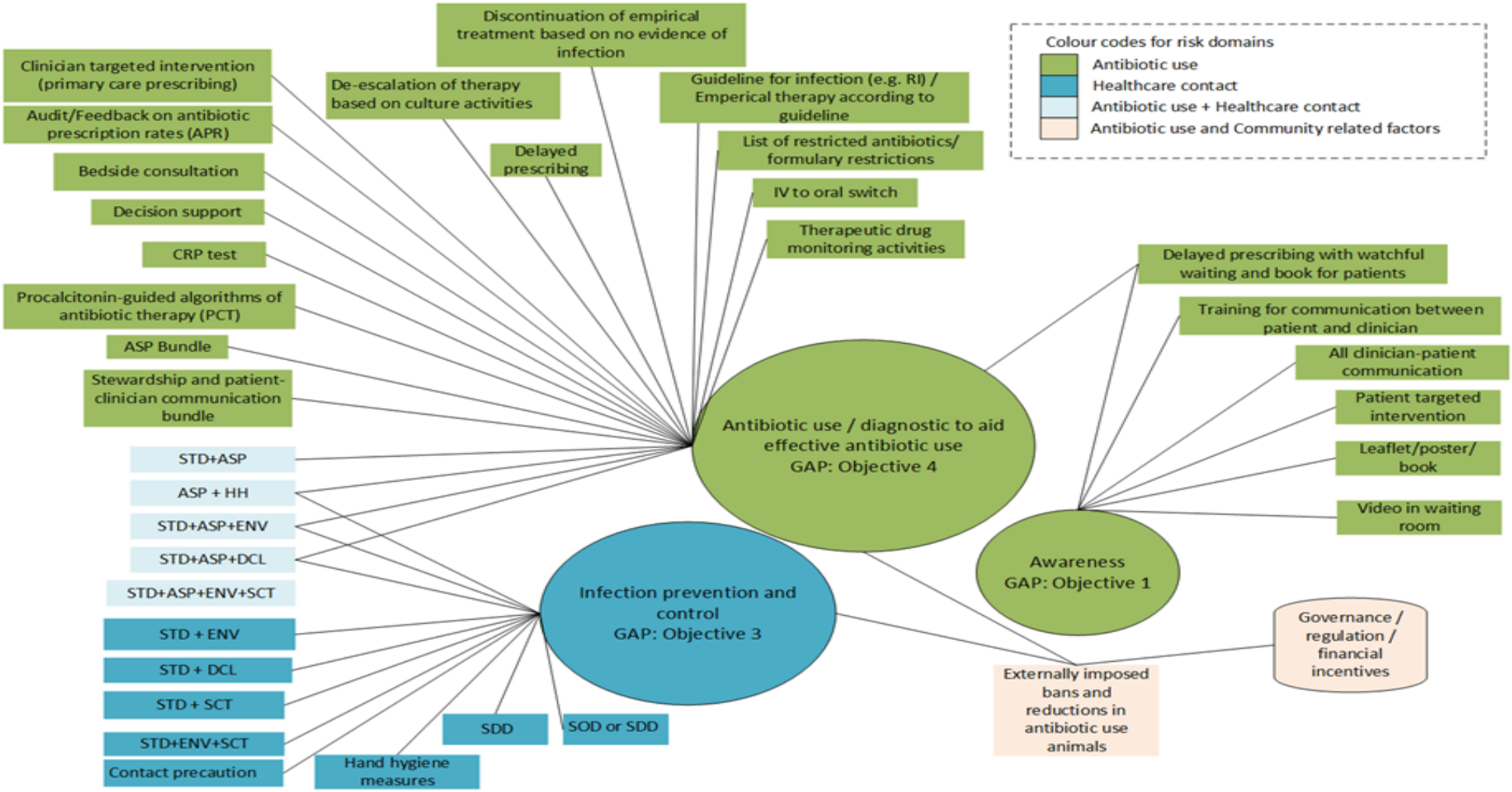


Figure 37: Mapping interventions, policy objectives, and risk domains of antibiotic resistance

Abbreviations: [ASP = Antibiotic Stewardship Program; CRP = C-Reactive Protein; DCL = Decolonisation; ENV = Environment cleaning; GAP: World Health Organization's Global action plan; HH = Hand hygiene; IT = Information Technology; n = Number of meta-analysis studies; PCT = Procalcitonin Testing ; SCT = Source Control; SDD = Selective Digestive Decontamination ; SOD = selective oropharyngeal decontamination ; STD = Standard care].
The size of a GAP objective bubble indicates the number of different clinically effective interventions identified which are targeting that particular objective. Governance/ regulation / financial incentives do not share the same shape as GAP objectives, because it was an objective identified outside of the WHO five objectives from the stakeholder websites search. (See Table 8)

In summary, it can be seen that the interventions with the highest quality evidence on clinical effectiveness target objective 4 (antibiotic use), objective 3 (infection control), and objective 1 (awareness of AbR). Although Objective 2 (surveillance and research) has the greatest number of stakeholders and stakeholder policies associated with it (See Figure 34 and Table 8), it is a challenging objective to quantify from a clinical effectiveness perspective.

When comparing how intervention efficacy data matches with the WHO objectives and the drivers of AbR (Figure 36-Figure 37), we can see that the intervention efficacy results only map with three WHO GAP objectives (1,2, and 4).

From the pooled results of the meta-analysis studies, antibiotic use and healthcare contact were the only two risk domains which were ultimately the primary targets for the identified interventions which in turn had clinically effective interventions targeting them.

As concluded from Table 8 and Figure 34, a limited number of stakeholders focus on the infection control policy objective, and limited policy objectives aim to address healthcare contact as a key risk domain of AbR. However, despite, the infection control policy GAP objective not being a primary policy objective for many of the stakeholders tackling AbR (see Table 8), there are a large number of 'on the ground' interventions targeting this policy objective (see Table 12). Step 2 of the targeted review in this Chapter shows that the large volume of clinically effective interventions targeting AbR are in fact infection prevention control measures within secondary care hospital settings. One can speculate that since every secondary care setting has its own policy guidelines, and patient safety

regulations, infection control is maintained as the key priority in these settings by the policy implementers on the ground. Thus, even if healthcare contact is not prioritised via the stakeholder policy objectives, it is prioritised as a key risk domain at a local ground-level setting. This phenomenon further supports the bottom-up approach to policy making which gives policy implementers the flexibility to prioritise policy focus on areas they feel are a priority. In this case, the clinicians and Trust board members in secondary care settings maintain infection control as a key policy to help reduce the emergence and spread of AbR related infections.

In summary, based on the targeted review results from the highest quality of pooled clinical evidence from meta-analyses studies shows that the majority of the clinically effective interventions are currently targeting the two key evidence-based risk domains of AbR identified from the systematic review in Chapter 2. However, patient clinical history, also identified as a key risk domain, is neither a key objective focus for global policymakers nor is there substantial evidence on any clinically effective intervention focusing on targeting this risk domain.

3.5.2.2 Randomised controlled trial studies

Apart from the intervention effectiveness evidence identified from the meta-analysis studies, an additional 34 randomised controlled trials (RCTs) were identified from the targeted review which were not previously included in the meta-analyses studies. Most of these RCTs were either from China or the United Kingdom and were conducted within the primary care setting. Out of the RCTs identified from the targeted review, the primary infection focus of the interventions was respiratory tract infections.

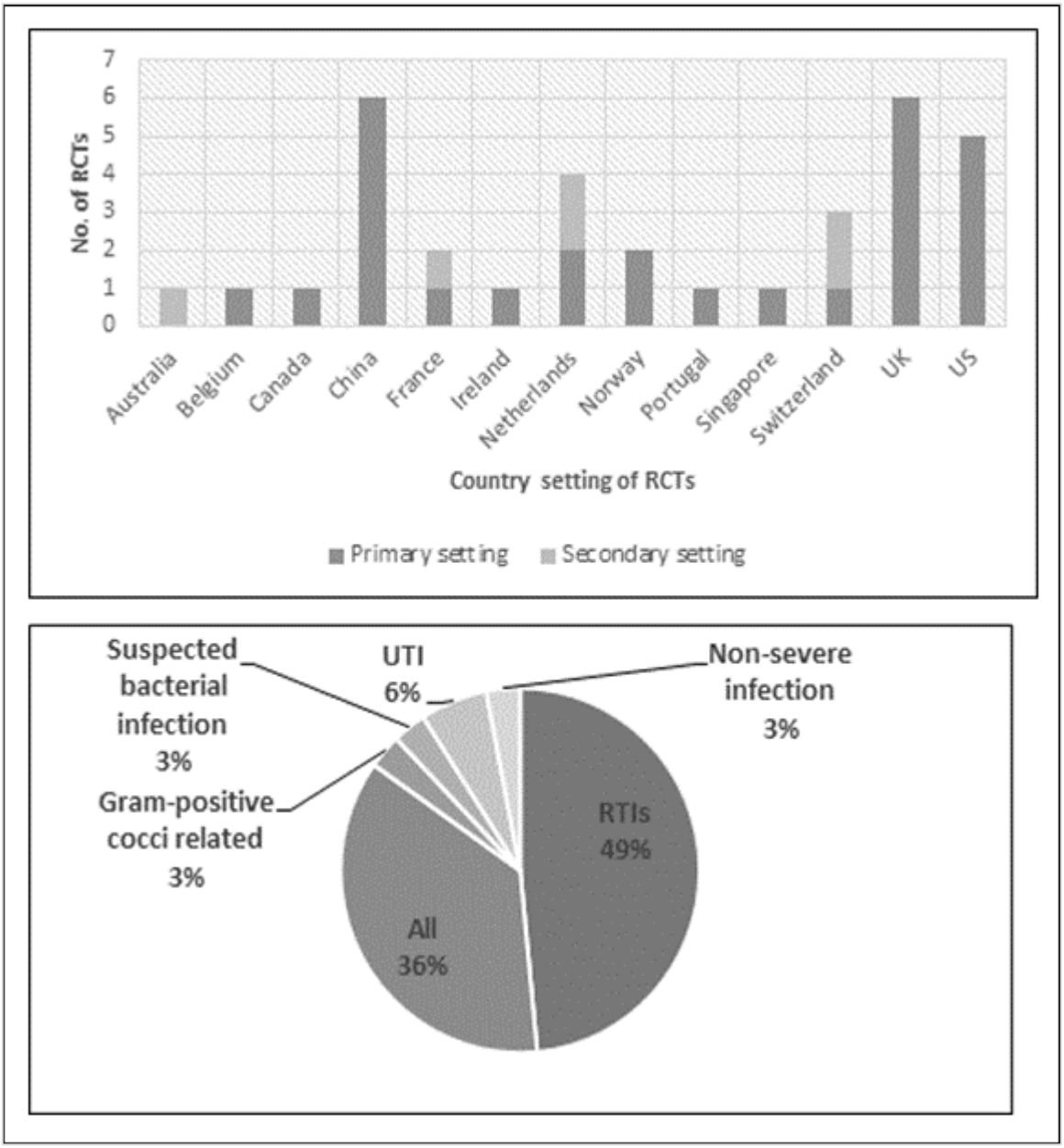


Figure 38: Top: Randomised controlled trial (RCT) results: Country and setting overview; Bottom: Infection overview from the RCT

Abbreviation: [RCT = Randomised controlled trial; RTI = Respiratory Tract Infection; UTI = Urinary Tract Infection]

Similar to Table 11 and Table 12 for the meta-analysis studies, Appendix Table 11 in Appendix II reports on the interventions identified from the RCTs in the targeted review, along with their

corresponding efficacy outcomes, mapped with the WHO GAP objectives and the risk domains from Chapter 2.

Comparison between meta-analysis results

From the results of the RCT studies identified in the targeted review, three additional interventions were not previously identified from the meta-analyses. These included a procalcitonin and pyuria-based algorithm for clinical decision making (144), education intervention workshops such as outreach visits to highlight the importance of appropriate antibiotic use (this included workshops related to the Treat Antibiotics Responsibly, Guidance, Education, Tools developed in England, and printed decision support and checklists for clinicians) (145–147)

Similar to the meta-analyses results, what emerges from the RCTs identified from the targeted review is that reductions in antibiotic use were the key outcome assessed. This reduction was also assessed in terms of quality indicators such as appropriateness of antibiotics based on guideline adherence or culture test results. Reduction in macrolides was the most commonly reported antibiotic across these studies (ranging from 7% - 9% reduction in use) (148–150)

Interestingly, one study which targeted interventions around patient education leading to conservative antibiotic use was able to identify a difference in health-seeking behaviour based on the ethnic group the patient belonged to (151). In this particular case, the intervention helped influence patients who were from an Indian ethnic background and impact their health-seeking behaviour towards antibiotic use. Therefore, this particular intervention was an example of an intervention which was able to influence the 'Demographics' risk domain identified from Chapter 2 which was not thus far the key target of any of the interventions identified from the meta-analysis studies.

Most interventions incorporated some form of audit and feedback of antibiotic related prescribing data to inform the clinicians about their own prescribing practice by comparing to other clinicians in

their unit or providing aggregated results for the practice areas. Audit and feedback were provided in a number of ways, including: systematic post-prescription review (152), public reporting of prescribing data (153), and electronic dashboard of quality indicators which included prescribing data (154).

The common adverse events or unintended consequence of an intervention recorded included severity of infection, future consultations, mortality rate and increased length of stay. Interventions that were only focused on targeting patients rather than the clinicians did not retrieve significantly different results when compared to usual care or no intervention. Decision support and diagnostic tests were more clinically effective in terms of reduction in antibiotic use when they were compared to delayed prescribing (155).

The follow up time frame for majority of the RCTs was between 6 to 12 months. The RCT that provided intervention impact data beyond the second year showed a decline and insignificant overall efficacy of the audit and feedback intervention following its success in the first year (150). In 2016 Van der Velden et al. (150), however, found a 4.6% reduction in prescribing compared to a 2% increase in prescribing in the control group in the 2nd year following the bundled intervention implementation, although the 1st year reduction was 7.6% in the intervention group compared to -0.4% reduction in the control group.

In comparison to the results of the meta-analysis studies, since the intervention settings were primarily within primary care, antibiotic use was the main risk domain which was the intended target of the interventions identified from these RCT studies.

3.6 Discussion

3.6.1 Key Findings

Study overview

This is the first study that has combined systematically identified evidence related to risk factors of AbR with the WHO GAP objectives proposed to target AbR at a global level. This chapter described how policy objectives of the key stakeholders tasked with tackling AbR map against firstly the overall WHO GAP policy objectives, secondly the risks of AbR, and finally the clinically effective interventions currently implemented to tackle AbR in humans. This step-wise mapping process helped meet the overall aim of this Chapter and the second research question of this thesis to understand how the drivers of AbR are being tackled.

Based on the targeted reviews conducted in Chapter 3, some key findings are summarised below that will help inform and guide the framework for the evidence-based bottom-up approach to AbR policymaking.

Key quantified risks, policy objectives, and interventions

In terms of the key policy objectives, this Chapter found that *surveillance and research* was the main policy focus across majority of the stakeholders (26 of the 32 stakeholders). When comparing the key policy objectives and interventions being implemented at practice level (i.e., ground level interventions) with the key risk domains from Chapter 2, this Chapter found that the key risk domain of AbR, antibiotic use, was the primary target of majority of the policy objectives set out by 23 of the 32 stakeholders as well as the interventions identified in Step 2. Healthcare contact, the second most evidenced risk domain of AbR, was not a major policy focus amongst the 32 stakeholders, although infection control measures were a key intervention implemented to control and prevent AbR infections within secondary care settings. This might be the case because at a ground level, the risks

of AbR arising from prior antibiotic exposure and healthcare contact are the most explored areas of research as identified from Chapter 2. Therefore, the interventions are more aligned with the current risk factor evidence. It may be assumed that since evidence-based medicine is the backbone of current clinical practice, the interventions are closely aligned with the current evidence on the risk factors of AbR. Direct interventions aiming to target the patient clinical history, community-related factors and patient demographics risk domains were limited.

One of the issues previously highlighted in Chapter 2 was that if underlying risks are not identified and quantified appropriately the interventions may not be developed to tackle these risks. Within this Chapter (Chapter 3) using a mapping framework we were able to show that in practice this is the case. Only interventions with the key quantified evidence are currently being targeted at a high policy level and subsequently at a ground intervention level

Clinical effectiveness of interventions

When investigating the clinical efficacy and types of interventions being implemented on the ground, the interventions targeting antibiotic use were similar across the primary and secondary care settings. The key targets of these interventions were either related to changing prescriber behaviour by audit and feedback of their antibiotic prescribing history or raising awareness of AbR amongst both clinicians and patients, or enabling clinicians to make quicker more accurate decisions related to prescribing with the help of point of care decision support tools.

There were some differences noted between the interventions targeting antibiotic use across these two settings. Within the primary care settings, the GP or the patient were the key stakeholders who were targeted via these interventions. The patient focused interventions were targeted towards influencing health seeking behaviour by raising awareness with the help of leaflets, books, or videos. Therefore, within primary care, the interventions were primarily related to raising awareness of the use and misuse of antibiotics by targeting both the clinician and the patient and were more related to the persuasive classification of interventions targeting antibiotic use. Within the secondary care

settings, the interventions required involvement of multidisciplinary teams. These teams consisted of microbiologists and pharmacists who played an essential role in enabling successful and appropriate antibiotic prescribing by the clinicians. The interventions focused on antibiotic use within secondary care settings were also supplemented by infection prevention control measures. These interventions were usually a combination of infection prevention and control techniques and restrictive, persuasive, and structural interventions targeting antibiotic prescribing. These bundled interventions were also highlighted within a recent Cochrane systematic review on antibiotic prescribing related interventions in hospital inpatients (156,157). The persuasive interventions nudge clinicians to make better prescribing decisions. Restrictive interventions limit access to some types of antibiotics to help curb their use. On the other hand, structural interventions, include point of care testing tools to help clinician decision making. Thus, the interventions in secondary care settings, were more complex bundles targeting multiple stakeholders (i.e., microbiologists, pharmacists, junior doctors, or registrars) compared to the primary care settings (where the patient and the prescriber were the key targets).

Overall, this Chapter identified a number of interventions in both primary and secondary care settings tackling antibiotic use and AbR. The evidence from the secondary care settings were most commonly summarised within large global meta-analysis studies of RCTs. The evidence supporting the clinical efficacy of primary care setting specific interventions were commonly identified from single centre and single country RCTs. Therefore, at the time the targeted review was conducted, the quality and quantity of the evidence supporting the clinical effectiveness of interventions implemented within secondary care settings were better than those identified for the primary care settings.

3.6.2 Limitations

Firstly, one of the key limitations of this Chapter is that the research conducted to identify interventions of AbR and their efficacy was via targeted literature review rather than a systematic

literature review. Only one researcher searched, selected, and data extracted the information to inform the study. Therefore, there remains the possibility of researcher bias within the results. However, since a step-wise approach was taken to first identify meta-analyses studies followed by RCTs, this should have limited inclusion of extensive researcher bias, since meta-analyses studies aim to collect information in a systematic and unbiased way.

Additionally, since only one systematic review of systematic reviews was identified for the primary care setting rather than a meta-analysis of RCTs, there remains the possibility of missed RCTs from this setting.

Secondly, antibiotic use and reduction in infection levels were the key outcome measures most often reported to measure the clinical efficacy of an intervention. However, awareness of AbR or increasing surveillance may have been the intended focus of policy or ground-level interventions. Therefore, in theory, policy targets like surveillance and research focus may indirectly help address risk domains such as patient clinical history, patient demographics, and community factors identified from the systematic review in Chapter 2. However, efficacy of broad policy measures such as surveillance and awareness may not be easy to capture or quantified within one outcome measure within short follow-up timeframes often seen across most RCTs in the targeted review. Thus, this Chapter cannot conclude with any degree of certainty whether these risk domains are being targeted effectively.

Lastly, for the majority of the cases the policies set out by the stakeholders were primarily if not solely influenced by the WHO GAP objectives. The stakeholder websites do not report the ground level initiatives these stakeholders are carrying out (if any) in relation to the policies described on their respective websites without detailed research and evaluation. Therefore, there may be a multitude of granular interventions which are currently being implemented on the ground, the clinical efficacy of which is not being reported across peer reviewed literature databases. Since, the method used in this Chapter was solely reliant on peer reviewed evidence on the clinical efficacy of

the current ground level implemented interventions, capturing all the current ground level interventions and their associated clinical efficacy not published in peer reviewed high quality evidence bases was outside the scope of this Chapter. However, the UN-via their Interagency Coordination Group on Antimicrobial Resistance (IACG) task force is currently in the process of identifying and cataloguing all the initiatives being taken across the globe related to tackling AbR. Objectives 2 and 3 of the IACG's work plan in particular are focusing on compiling stakeholder activities and assessing their efficacy to identify gaps and overlaps. The proposed work plan is expected to be for the time period of May 2017 to September 2019. The end product of Objectives 2 and 3 of this work plan should help achieve the missing link between stakeholder policy objectives and the ground level interventions implemented which was outside the scope of the methods of this Chapter.

3.6.3 Recommendations

Currently the interventions are directly targeting where the majority of evidence related to drivers of AbR have been quantified, i.e., towards reduction of antibiotic use and limiting transmission of AbR within healthcare settings. Better understanding of the granularity in drivers of AbR could potentially give rise to greater granularity in the design and targets of interventions, improving the clinical efficacy and evaluation of interventions tackling AbR.

The community related factors risk domain is an ideal example of where the lack of identification of underlying risks has limited the scope of current interventions being implemented. The present scope of community specific interventions lies within the primary care setting and involves better diagnosis of viral and bacterial infections alongside improving awareness of antibiotic prescribing best practices. The stakeholders usually involve either the clinician prescribing the antibiotic or the patient attending the primary care setting. Therefore, the interventions are far less complex than those seen in secondary care settings. The patients, range of stakeholders and environments within which care is delivered in the primary care setting is much larger than the secondary care setting.

Therefore, the interventions in the primary care setting need to be more thoughtfully designed to reach out to and effectively target the community population. The current evidence on interventions in primary care therefore do not necessarily reflect this complexity.

It should be taken into consideration that implementing and measuring efficacy of interventions within the community setting often face a two-fold barrier. The first barrier is identifying and reaching out to the general community population to influence their health seeking behaviour. The second barrier is implementing tools to measure whether this intervention has been effective. Within the primary care setting the GPs only have a limited amount of time (e.g. In the UK, average time spent with a patient is about 9 minutes) to prescribe and convince their patients of the repercussions of misusing antibiotics. Additionally, the evidence regarding the efficacy of current interventions incorporated in the primary care are less extensively catalogued, with limited RCTs being carried out, compared to the secondary care setting.

Therefore, the first recommendation from Chapter 3 combined with the evidence from Chapter 2, is that there is a greater need to identify policy targets within the community setting and quantification of the clinical efficacy of interventions within this setting. Future research investment should focus across the community setting to help identify granular policy targets. AbR policymakers should also invest in identifying measures to enable quantification of the clinical efficacy of interventions within this setting. With respect to filling a research gap, there is a need for a meta-analysis to pool the results of all the RCTs currently conducted and published within the primary care settings across the globe. Currently, only one Cochrane systematic review pools together data from previous systematic reviews conducted in primary care. However this Cochrane review does not summarise the efficacy of these interventions from the RCTs within a single measure via a meta-analyses to identify the clinically effective over the ineffective interventions.(158)

The evidence within the secondary care settings is far richer, both in terms of intervention targets and measuring the clinical efficacy of these interventions. A number of meta-analysis studies have

pooled results of interventions currently targeting AbR in the hospital and acute care settings (139)(131). So, within the secondary care researchers and policymakers have an overview of where certain interventions may or may not work. This overview is still needed for the community setting.

The second recommendation is related to the current policy frameworks which are in place to tackle AbR. The WHO GAP objectives were developed over a number of years, based on expert consultations and input from experts from around the world. As an overall initial framework, the objectives indirectly address the evidence-based risk domains identified from the systematic review in Chapter 2. However, since these GAP objectives are at present being used to formulate national action plans across the world, there may be a need to tailor them for country and setting specific requirements. The Center for Disease Dynamics, Economics & Policy is already conducting similar work around the Asian sub-continent (specifically in India) in terms of a country specific situational analysis. The risk domains framework from Chapter 2 could be incorporated within such situation data collection protocols to rank the importance of these domains at an individual country level, and also add to the risk domains where necessary. Such a systematic method by which to identify intervention targets may improve the long-term efficacy of the interventions currently targeting AbR and its established risks. Thus, enabling an evidence-based bottom-up approach to identify policy targets for AbR across the globe.

The third recommendation is related to how clinical efficacy outcomes are being measured for the interventions tackling AbR. From the clinical efficacy results extracted from the meta-analyses and RCT studies, it was evident that measuring the clinical effectiveness of an intervention within the field of antibiotic resistance is very different to other areas of health economics to inform policy, where it is possible to take account of the direct impact of an intervention. There remains a need to identify a comprehensive metric for measuring the clinical efficacy of interventions targeting AbR to enable policymakers gain a better understanding for the 'bang for their buck' when it comes to investing in prevention and control of AbR. In particular, this metric is needed for the community

setting, since in the secondary care setting, apart from antibiotic use, patient's length of stay and mortality, or monitoring overall AbR infection levels in the hospitals already serve as essential metrics to measure the clinical effectiveness of interventions.

The final recommendation from this Chapter is regarding the follow up times for RCTs of interventions tackling AbR. Measuring the short term (6-12 month) impact of antibiotic use and reduction in infections may not be enough to understand the true clinical efficacy and in turn the cost-effectiveness of interventions tackling AbR. As a short-term solution, researchers and policymakers should be planning long term clinical trials lasting more than the commonly identified 12 month timeframe.

3.6.4 Implications for the thesis

To help inform the evidence-based bottom-up framework to AbR policy making, the next Chapter brings together the highest quality of evidence gathered from the systematic review in Chapter 2 for the risks which increase the rate of AbR in humans and the clinical effectiveness evidence from the interventions identified from this Chapter. The evidence is being brought together within a case study of *E. coli* from an English healthcare perspective. The results from RCTs in primary care in England (145–147)(155) and the overall meta-analyses of the efficacy of interventions for secondary care (131,139) will be applied from this Chapter. Combining the efficacy of interventions, the top three risk factors (with the most evidence) from Chapter 2, namely prior antibiotic use, healthcare contact, and underlying comorbidities will be utilised to inform a mathematical decision analyses framework to project the cost effectiveness of interventions tackling AbR across hospital and community settings.

CHAPTER 4.

4 MODELLING THE NHS ENGLAND PERSPECTIVE OF ANTIBIOTIC RESISTANCE

4.1 Introduction

The thesis has so far explored where the most evidence lies towards the risks of antibiotic resistance (AbR) in humans, as well as the policies, interventions, and both their current effectiveness on curbing the threat of AbR in humans.

This Chapter aims to answer the penultimate research question of this thesis which is to assess *where policymakers should focus investment decisions to tackle AbR*. To be able to meet this aim the Chapter will bring together and quantify some of the key aspects of AbR from an English perspective. Quantifying this vast context of AbR requires an inclusive framework, which allows for enough flexibility to make assumptions in the absence of concrete quantified evidence.

A primer on decision models

Decision modelling or 'decision analysis' is an example of one such framework which provides a systematic approach to quantifying a complex problem. For example, within such decision modelling frameworks, a clinical problem can be formulated and explored from the health-care provider (e.g. physician) as well as the health-care payer's (e.g. public health policy) perspective. Such modelling techniques allow decision makers to assess clinical problems while considering the (often numerous) uncertainties surrounding it, for example the efficacy of a particular treatment option. At the early stages of applying decision modelling to a clinical problem, the decision maker can assess where data is lacking, where reasonable assumptions are needed to address the data gaps, and how the decision problem can be framed from various perspectives. Therefore, such modelling techniques act as a tool for decision makers to examine the impact of various policy targets in a controlled setting at a relatively low cost. They enable policymakers to make an informed decision using the best available

current evidence in literature and build upon past assumptions and analysis. If data gaps result in uncertain model results, then these models can also provide insight into targets for future research to decrease this uncertainty.

Health economic models such as cost-effectiveness analyses are a prime example of such systematic approaches to modelling a clinical problem and can be seen to fit the strictest definition of a decision analysis model. For a meaningful cost-effectiveness analysis, which helps policymakers make reasonable population-level decisions, there needs to be sufficient data to support the model structure and parameters, for example the epidemiology of the disease (i.e., the clinical problem) under study, as well as reasonable data on the clinical efficacy of the interventions being assessed versus either the standard of care, or other intervention alternatives.

Decision model in the context of this Chapter

Within the context of this Chapter, decision modelling is being used as an umbrella term for modelling a disease pathway which encompasses both health economic models as well as mathematical transmission models. A model is a representation of what reality could be in the future. Within the world of theoretical modelling whether that be mathematical, statistical, or health economic, a famous quote is quite often used "Essentially, all models are wrong, but some are useful." (159). Therefore, it is the hope of every mathematical modeller to improve the usefulness of these decision models, with the help of better quality evidence as and when they become available.

An overview of previous mathematical disease transmission models

Over the past 15 years there has been an increased focus on modelling AbR. A large number of models with varying complexity can be seen from literature. Two recent reviews (160,161), have discussed in depth the type of models being published and the strengths and limitations of these models. The reviews highlighted the epidemiological complexity surrounding modelling antibiotic resistance. As evidence suggests from Chapter 2, the prevalence and incidence of AbR in humans may vary depending on several different setting specific factors. The evidence from Chapter 2

suggests that prior antibiotic use and patient specific factors (e.g. underlying disease) are currently the most evidenced factors identified across all settings. To further add to the epidemiological complexity discussed in the two reviews, Chapter 2 also identified that different drivers of AbR may vary depending on whether we are assessing colonisation levels or infection levels. In terms of setting specific factors, the impact of the healthcare setting also plays a role, as was also commonly highlighted from Chapter 2. The secondary-hospital / healthcare environment may act as an easy breeding ground for transmission of resistant bacteria, thus accelerating the acquisition rates of antibiotic resistance.

Furthermore, some of the models have also looked at evaluating and forecasting the impact of interventions targeting antibiotic resistance. Assessments of interventions are more abundant within the hospital setting compared to the community settings.

Therefore, modelling antibiotic resistance is becoming an increasingly important policy tool as it gives rise to a better understanding of where information is needed to better understand the underlying causes of antibiotic resistance.

Complexity of modelling the AbR pathway in humans

As learning points from previous models, it can be concluded that decision modelling the pathway of antibiotic resistance development in humans is complex. Firstly, heterogeneity in human-attributable risk factors exist. Secondly, heterogeneity also exists given the different drug-bug combinations which can be found in the community and / or the hospital settings. The risk of a human being infected by a certain AbR related infection may differ depending on the type of drug-bug combination under study.

Considering the heterogeneous drivers of antibiotic resistance in humans, differences across populations and complexities of bacterial transmission and evolution, it is often challenging to incorporate all these different aspects within one model framework. Combining the patient to patient heterogeneity with the community and hospital setting specific difference, makes such

models tricky to parameterise. As also reported in the reviews (160,161), the parameters are often not clearly discussed or described thus making these models difficult to believe when it comes to policy level decision making.

Gaps identified from previous mathematical transmission models

Both the reviews mostly discuss models which focus on a particular setting or a particular cohort of the population. A large number of the models have also specifically focused around either the hospital or the community setting to capture the setting specific drivers of AbR and their impact on future AbR rates. In addition, only a handful of models show a relationship between the hospital and the community setting together. With regards to the impact of the effectiveness of an intervention, the models only report on impact of a community intervention on the community setting and vice versa for the hospital setting.

There remains an unmet need to assess the impact of interventions across both hospital and community settings using a modelling framework to inform policymakers of where potential investment decisions might be cost-effective when tackling AbR.

Rationale and scope for the decision model being used in this Chapter

Type of bacteria and data availability

Based on the complexities surrounding modelling antibiotic resistance and the quality and type of evidence currently available and identified from Chapters 1-3, in this Chapter the rising levels of *Enterobacteriaceae* are being modelled in detail. Specifically, the problem of antibiotic resistant *Escherichia coli* (*E. coli*) within an England healthcare setting is being modelled. In England, between 2010 and 2014 the rate of bloodstream infections caused by *E. coli* increased by 15.6%. Between 2014 and 2015 the number of cases continued to increase by a further 4.6%. The UK 5 year AMR

strategy team have therefore prioritised reducing gram-negative infections with a particular focus on *E. coli*.

Given the increasing focus on bloodstream infection due to *E. coli* and the mandatory surveillance systems in place to collect data on these infection types, the quantity and quality of the data is good. Apart from the prevalence and incidence data collected through mandatory surveillance, the quality of evidence at a population level is also good with recent epidemiological, economic burden, and mortality estimates derived using the routinely collected national data sources available for this species of bacteria. Therefore, modelling this bacterial species seemed the most appropriate, relevant, and also useful from an English healthcare policy perspective given both public health concern and potential to develop a data-driven model.

Model dynamics:

Links to Chapter 2

From the results of the systematic review in Chapter 2 healthcare contact, antibiotic use, and patient characteristics were concluded as being the key drivers of AbR in humans. Therefore, the model aimed to incorporate these key factors within the model dynamics.

Firstly, the hospital setting represents the importance of patient history of prior healthcare contact as a driver of AbR as identified from the systematic review. Secondly, antibiotic use in humans was identified as a key driver of AbR and since majority (70% in the English setting) of antibiotics in humans are prescribed within the community, it was necessary to model the community setting as well as the hospital setting. In particular, understanding what impact this burden of prescribing (the primary identified driver of AbR) might have on the hospital setting is an ideal application of decision modelling methods.

Lastly, infection and colonisation were the two most commonly quantified outcomes related to antibiotic resistance in humans identified from the review in Chapter 2. Healthcare factors were primarily quantified as the risk factors for infection whereas patient clinical history was mainly

quantified to be driving colonisations. Within patient clinical history, underlying disease had the greatest amount of quantified evidence supporting an increased risk of colonisation. Moreover, colonisation is often considered a better indicator of bacterial dynamics than infection, since colonisation only leads to infection in a small group but contributes significantly to the epidemiology of bacteria (162). Therefore, the model aimed to incorporate the dynamics of changing colonisation levels and their impact on infection levels.

Links to Chapter 3

Chapter 3 identified the landscape of the current clinical effectiveness evidence of stewardship and infection control programmes on reducing prescribing rates and infection levels respectively. In particular, Chapter 3 concluded that stewardship programmes have been effective in reducing antibiotic use in both hospital and community settings. On the other hand, infection control measures have been successful at reducing infection rates within the hospital settings. The efficacy of these interventions is difficult to quantify in terms of the impact they may have on the underlying colonisation levels; hence, the efficacy of these interventions was primarily measured in terms of either antibiotic use or infection levels. Therefore, understanding the impact of an intervention on colonisation of resistant bacteria followed by on the infection caused by this resistant bacterium is currently not available from literature sources. Modelling this relationship between the impact of interventions tackling AbR on colonisation levels would provide a more wholesome picture to policymakers of the epidemiology of bacterial resistance.

Therefore, the aim of this chapter is to predict the potential impact of interventions on changes to antibiotic resistant colonisation and infection levels using a decision model.

4.2 An *E. coli* Transmission Model

4.2.1 Aim

This model aims to evaluate the impact of antibiotic stewardship and infection control measures to control antibiotic resistance at a population level in England. The model aims to simulate the potential impact of interventions tackling antibiotic resistance. The clinical efficacy of the interventions will be scaled up and down to see how this may impact on the incidence and prevalence of colonisations in the community and hospital settings. By applying an infection rate to the total number of colonisations in the community and hospital setting helps to estimate the link between AbR and its economic burden on the NHS.

The primary aim of this transmission model is to evaluate the colonisation, infection and, total cost impact (from an NHS England perspective) of interventions targeting AbR in the community and hospital settings using antibiotic resistant *E. coli* as a case study.

4.2.2 Method

4.2.2.1 Model development process

The theoretical transmission model was based on a previous model developed by Knight et al. (162). The original model (162) aimed to evaluate where colonisation with Extended Spectrum Beta-Lactamase-producing- (ESBL) *E. coli* is primarily acquired from an NHS England perspective.

The deterministic core model structure was used where 100,000 individuals colonised with susceptible bacteria (e.g. we all carry gut bacteria, so we are all colonised with susceptible bacteria) were simulated over time (daily basis) through the community and hospital setting. Out of the 100,000 individuals being simulated, a proportion of these individuals had an increased likelihood of either being colonised by a resistant bacteria, or infected by a susceptible or resistant bacteria. Individuals could acquire a resistant bacteria inherently due to antibiotic exposure or via transmission from another individual who has been infected by a resistant bacteria.

The three key contributions of the new model developed as part of the PhD are as follows:

Firstly, to assess the impact of the two key factors identified driving AbR, underlying disease and antibiotic use on colonisation and infection levels were assessed as part of the model. To take account of the impact of underlying disease and antibiotic use, the model was developed such that the population was stratified according to comorbidity, allowing for variability in prescribing rate based on comorbidities to be modelled using secondary data from a recently published large data analysis specific to the English primary care population (163). Shallcross et al. (163) established variability in prescribing practices given the number of comorbidities an individual might have. Therefore, the relationship between antibiotic use and comorbidities in the community setting in England was used to inform the heterogeneity in antibiotic use in the community within the model.

Secondly, the original model was expanded to include *E. coli* bacteraemia (will be referred to as an *E. coli* infection) enabling modelling of the costs of treating a resistant and susceptible *E. coli* infection in the community and hospital setting from an NHS England perspective.

Thirdly, the model parameters have, wherever possible been updated to use the highest quality, most recent, and setting specific evidence, to model transmission and control of resistant *E. coli* in England.

Lastly, following the development of the new model with the aforementioned three changes, using the clinical efficacy estimates of current implemented interventions to tackle AbR from Chapter 2, the impact of interventions on colonisation and infection rates in the community and the hospital setting was also evaluated. The results of these interventions were presented in terms of costs savings attributable to infections avoided within the community and the hospital settings.

4.2.2.2 Model description:

Model simulation across settings

To summarise the overall model structure, within the model 100,000 people in both hospital and community populations together are hypothetically simulated; the cycle length of the model is one day. The model assumes everyone is colonised with susceptible bacteria in the community (Cs) and hospital (Hs). Antibiotic resistance is acquired due to antibiotic use or due to transmission from a colonised person who has previously been prescribed antibiotics. The rate of transmitting a resistant bacteria is higher in the hospital setting compared to the community. People move in and out of the hospital at the rate of hospitalisation and inverse of average length of stay in England respectively. The people colonised with resistant bacteria are decolonised in the community setting at a rate of clearance. Individuals colonised with susceptible bacteria do not have a clearance rate because it has been assumed that everyone modelled will be colonised by susceptible bacteria (e.g. healthy gut bacteria). On the other hand, individuals colonised in the hospital do not have a rate of clearance applied to them due to the short period of time they are in the hospital. A proportion of the colonised people will get infected at rate estimated from the national mandatory surveillance data (164,165)and recent literature sources (166,167), a proportion of the infected population will die at a death rate applied based on the most recent estimate of attributable mortality (168). An overall background death rate is applied to the population to take account of all-cause mortality (169). In order to maintain the population level, the proportion of people who die are replaced by individuals colonised by susceptible bacteria. Community related and hospital related costs are applied to those who are infected but have not died in the model. The model equations are provided in the Appendix III.

The original model using R was provided by Dr Gwenan Knight. This model in R was then further updated with additional lines of code to ensure the entire susceptible population cohort in the community setting was split into a comorbid cohort and a non-comorbid cohort. In addition the

antibiotic prescription rate specific to each population cohort in the community was also added to make up the average antibiotic prescribing rate in the community. Appendix Table 17 in Appendix III provides an overview of the equations used in R from the original model. The sections highlighted in yellow in the table was updated to fit the comorbid population and update the inputs.

Model fitting with English setting specific infection levels

The model was fitted to the infection levels calculated from England specific sources (see Appendix III). This method of calibrating the model to fit the England specific *E. coli* infection level also allowed to determine the ratio of infection per individual colonised per year. The community onset and hospital onset infections were calculated using multiple recent literature sources and an adjustment factor was applied to the infection rates to provide a cost break down based on where infections were acquired. A more detailed explanation has been provided in Section 4.2.2.3 and in Appendix III. These estimates were used to compare the results of the baseline model (which assumes the infection levels reported within the mandatory surveillance report) with the results of the model following the evaluation of the interventions. Section 4.2.2.6 discusses how results from Chapter 3 have been modelled within the framework of this transmission model to enable evaluation of interventions tackling AbR.

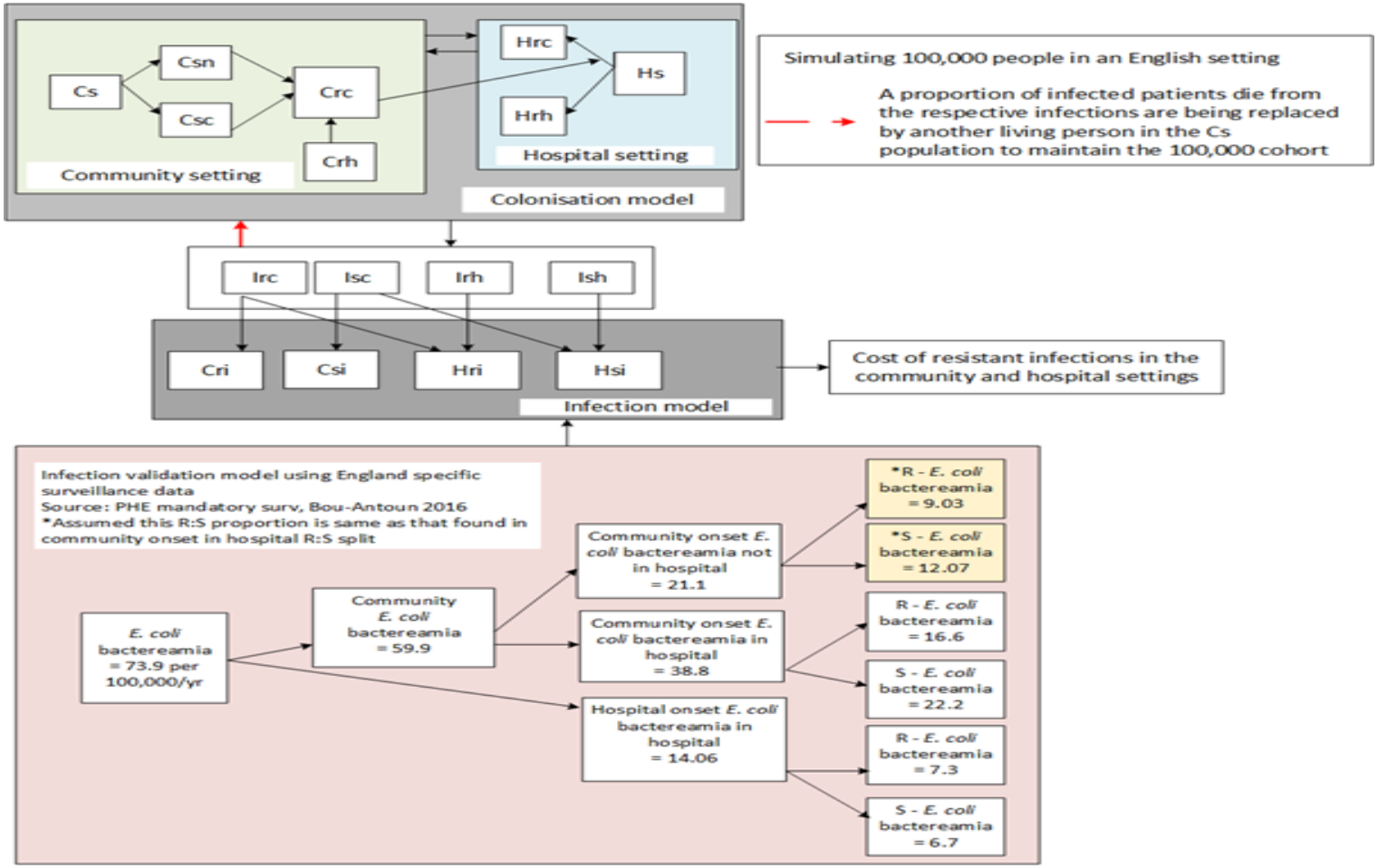


Figure 39: Overview of model structure

Abbreviations: [Please see Table 13; Values fitted from England specific surveillance data on *E. coli* to the model infection rates are: Cri = Resistant infections in the community; Csi = Susceptible infections in the community; Hri = Resistant infections in the hospital; Hsi = Susceptible infections in the hospital]

The key assumptions of the model are as follows:

- Infection can only occur if individual has been colonised
- Transmission can only occur from colonised patients previously treated with antibiotics

4.2.2.3 Parameterisation

The distribution of setting specific (i.e., community onset and hospital onset) *E. coli* rates (i.e., resistant and susceptible) from publicly available mandatory surveillance data and literature sources were incorporated to reflect the recent setting-dependent susceptibility patterns of *E. coli* (167,170–172). Using secondary data from a recent modelling study and a molecular biology study, the per day transmission rates have been updated in the model (173,174).

To be able to evaluate the impact of interventions in the community setting the clinical efficacy results from the most recent English primary care randomised controlled trial studies (145–147) have been incorporated from Chapter 3. For the interventions in the hospital, the evidence from the meta-analyses studies (142,175) identified in Chapter 3 have been incorporated to determine a threshold (i.e., a minimum and maximum efficacy interval based on the highest quality of evidence available) for the clinical efficacy of tackling AbR.

Since the original model was not incorporating the community onset and hospital onset infections which were calculated from using multiple recent literature sources, an adjustment factor was applied to the infection rates to calibrate the model's infection levels to the current per year *E. coli* incidence levels estimated in England. The model was therefore fitted so that 73.9 infections per 100,000 were generated per year from the model (2016/17 rates), so that the infection levels reflected the setting specific current *E. coli* infection levels in England per 100,000 per year.

The proportion of community specific versus hospital specific infections used were from estimates reported within recent England specific literature on *E. coli* infection levels (166,167). The sources

also presented the resistant versus susceptible infection split per setting. These proportions were extrapolated to the mandatory surveillance data. A weighted average approach, using the total infection level as a weight was applied to avoid overestimation of the community and hospital infection proportions.

Please refer to Appendix Table 12 in Appendix III to see how these parameters were derived from literature. The calculations to estimate the setting onset specific infection levels has been provided in Appendix Table 13 - Appendix Table 16 in Appendix III.

4.2.2.4 Epidemiological parameters

The complete list of model outputs and the parameter list with the sources of data has been provided in Table 13 and Table 14 respectively. The total number of setting specific colonised and infected individuals categorised by their antibiotic resistance profiles were the key outputs from the model. An infection rate was applied to these colonised individuals to derive the resistance profile and setting specific infection levels, which were the secondary outputs derived from the colonisation rates.

The baseline model was fitted with the infection levels: These are the parameters from Irc to Irh in Table 13 which were elicited by combining the mandatory surveillance on *E. coli* infections with recent sources of evidence (167).

Table 13: Overview of model output

Model outputs generated by the model	Description
Cs	Susceptible population in community
Csn	Susceptible population in community without comorbidity
Csc	Susceptible population in community with comorbidity
Crc	Population in community colonised by resistant *E.coli*
Crh	Population in community colonised by resistant *E.coli* in hospital
Hs	Susceptible population in hospital
Hrc	Population in hospital colonised by resistant *E.coli* in community
Hrh	Population in hospital colonised by resistant *E.coli*
Irc	Population infected with resistant *E.coli* in community
Isc	Population infected with susceptible *E.coli* in community
Irh	Population infected with susceptible *E.coli* in hospital
Irh	Population infected with resistant *E.coli* in hospital

Table 14: Overview of model inputs

Model inputs	Description	Value	Source
N	Total population size = 100%	100,000	Simulation of 100,000 people from an English population perspective
N_h	Percentage of the total population in hospital	N*0.24%	(176)
N_c	Percentage of the total population in the community	N*(1-N_h) = N*99.76%	(176)
α	Rate at which those in the community enter the hospital	8.02 x 10^{-4} per day	(177)
l	Rate at which those hospitalized return to the community	0.20 per day	(178)
b (bdr)	Background death rate	3.38 x 10^{-5}	(169,179)
ε (eps)	Proportion that acquire resistance during each antibiotic treatment	0.0667 per treatment	(160) (179) (180)
ω_c	Rate of antibiotic exposure in community	0.0018 per day	(163)
ω_h	Rate of antibiotic exposure in hospital	0.24 per day	(179)

Model inputs	Description	Value	Source
ncomo	Proportion of susceptible population (Cs) who have no comorbidities	Nc*0.653	(163)
como	Proportion of susceptible population (Cs) with comorbidities	Nc*0.347	(163)
ω_{cn}	Rate of antibiotic exposure in community for individuals without any co-morbidities	0.0013 per day	(163)
ω_{cc}	Rate of antibiotic exposure in community for individuals with any co-morbidities	0.0028 per day	(163)
β_h	Transmission rate in the hospital	0.05	(173)
β_c	Transmission rate in the community	0.0053	(174)
c	Rate of clearance of resistant bacteria in community	(1/401.5) per day	(181)
i_c	Rate of infection in England (*E. coli* bacteraemia)	73.9 per 100,000	(165)
Inf_c	Rate of infection in community	V1* i_c	(165)
i_h	Rate of infection in the hospital	V2* i_c	(165)
V1	Multiplier for decreased rate of infection in community	0.16	(165)
V2	Multiplier for increased rate of infection in hospital	2.5	(165)

Model inputs	Description	Value	Source
r_{inf}	Multiplier for decreased rate of infection by resistant organisms.	0.973	(182)
μ_r	Proportion of infections with resistant bacteria that result in death	16.07%	(168)
μ_c	Proportion of infections with susceptible bacteria that result in death	14.33%	(168)

Please refer to Appendix Table 12 in Appendix III for details of these sources

4.2.2.5 Cost parameters

Two clinicians at Imperial College London NHS Trust were consulted to determine the type of costs that can be associated with *E. coli* infections. Costs for a hospital setting have been estimated from the most recent patient length of stay study for England, estimates from this preliminary unpublished study have informed the NHS Improvement tool estimating cost impact of *E. coli* bacteraemia by Trust in England (168). Based on clinician advice, outpatient cost using NHS reference costs have been applied for the community setting (183).

To ensure that the cost impact of a change in infection levels as a result of the interventions modelled were being accurately reflected, a weighted average approach was applied. The baseline infection levels generated from the model is being used as a weight to determine the relative change in community onset and hospital onset infection levels compared to the baseline community onset and hospital onset infection levels following evaluation of an interventions. This method ensures that the setting specific cost savings are not overestimated.

Table 15: Baseline cost

Resource use					**Cost**				
Symbol	**Parameter description**	**Value**	**Unit**	**Reference**	**Parameter**	**Value**	**Unit**	**Year**	**Reference**
Clr	Length of stay resistant *E. coli*	4.63	Total days per spell	Unpublished thesis (168) Excess length of stay compared to non-infected controls *E. coli* bacteraemia resistant to at least one antibiotic: 4.63 (4.12,4.95) *E. coli* bacteraemia susceptible to all tested antibiotics 3.71 (3.52,3.89)	Excess Bed day cost	313	£	2016/17	**NHS reference cost Reference cost V 2016/2017** (183)
Cls	Length of stay susceptible *E. coli*	3.71	Total days per spell						
Cc	Community cost	1	Per visit	Clinician recommendation	Outpatient attendance	120	£	2016/17	
Total cost = Hospital cost for resistant + Hospital cost for susceptible + Community cost for *E. coli* in the community **Total cost = (lr*infhr) + (ls*infhs) + (c*infc)**									

*We assume that one infection acquired in the hospital from the transmission model represents the whole patient pathway and is a proxy for 1 spell to which we apply the cost of an excess length of stay for 1 spell in terms of excess bed days.

**"Reference costs are the average unit cost to the NHS of providing defined services to NHS patients in England in a given financial year. They show how NHS providers spend money to provide healthcare to patients."

4.2.2.6 Modelling and evaluation of the effectiveness of current interventions

Interventions identified from Chapter 3

To be able to model the best available evidence on the effectiveness of interventions targeting antibiotic resistance in an English healthcare setting, the highest quality evidence has been incorporated from Chapter 3.

The results gathered from Chapter 3 identified two key types of interventions which are currently implemented in practice (in the community and hospital setting). The first type of intervention targets reduction in antibiotic use. The second type of intervention targets infections within the hospital setting with the help of infection control practices.

Interventions targeting a reduction in antibiotic use

The interventions targeting reduction in antibiotic use identified from Chapter 3 did not report any unintended consequences or adverse events in terms of increased mortality or infection levels as a result of these interventions. Therefore, it is assumed that the reduction of antibiotic use in the community or hospital settings only result in improving prescribing outcomes and have no consequences on any other variable in the transmission model. Within a recently published interrupted time series analysis (184), the impact of the quality premium financial incentive as an intervention to improve antibiotic prescribing practice within a primary care setting in England reported positive outcomes which have been included within the evaluation of the interventions.

Within the interventions being evaluated, the community prescribing, and hospital prescribing correspond to antibiotic stewardship efforts being carried out in the community and hospital settings.

With the help of the targeted review search, a relationship between universal government strategies could be measured in terms of prescribing rate changes. These prescribing rate changes were then be applied within this transmission modelling framework.

Interventions targeting antibiotic resistant related infections

When it came to changes in infection control practices and their impact on reduction in infection levels in the hospital setting (142), there was little point in reporting a x% reduction in infections. If the clinical effectiveness studies provided how infection control practices had an impact on transmission rates in the hospital, this would have been a more interesting scenario to model by changing the 'transmission rate' parameter in the transmission model. Moreover, transmission in the community is not being tested as an intervention since limited evidence was available with regards to transmission rates and routes within the community setting.

In summary, only prescribing rate changes due to for example universal stewardship strategies were modelled across the community and hospital settings. The impact of these prescribing changes on colonisation, infection, and costs were reported as main outcomes of the model to guide policymakers on investment strategies to tackle AbR.

Incorporation of intervention effectiveness and other scenarios

The effectiveness of interventions were incorporated by changing the community and hospital prescribing rate parameters. Within the model the ω_{cn} and ω_{cc} parameters represent community prescribing rates for an individual with and without comorbidities respectively. The targeted review did not identify interventions which reported changes in prescribing levels split by comorbidities, therefore the ranges identified for overall prescribing level reductions from the review were used to reduce these prescribing rates in the community setting. Within the hospital setting the ω_h parameter represents the hospital prescribing rates, therefore a reduction in hospital prescribing levels to show the effectiveness of interventions was evaluated by modelling reductions in the ω_h parameter.

To enable policymakers to understand the repercussions of not being able to effectively target current antibiotic use levels, the model also evaluates increases in prescribing levels. Therefore the ω_{cn}, ω_{cc}, and ω_{h} parameters have also been utilised to evaluate the increase in the prescribing levels across both community and hospital settings.

Table 16 provides a range of the intervention effectiveness rates over a 1 year time horizon which was identified from the results of Chapter 3. Within an English specific community setting, a 0 to 7.7% reduction in antibiotic use on average over a one year time frame was reported.However, in other country settings a 0 to 15% reduction in antibiotic use was reported on average in the community setting. Within a hospital specific setting, better quality data was available from meta-analysis studies. Between 0 to 19.1% pooled reduction in antibiotic use was reported within the community setting within these meta-analysis studies. Based on the results of Chapter 3, the prescribing parameters in the model were varied between 0 to 20% to show a lower and upper limit of the clinical effectiveness of currently implemented interventions to tackle AbR.

Therefore, overall the prescribing parameters were varied by a lower limit of 0, i.e., no change from baseline to 20%. For example, a 20% increase evaluated the impact of not being able to curb antibiotic use, whereas a 20% decrease evaluated the impact of effective interventions from baseline levels. To show the impact of granular in changes in prescribing levels, the rates were assessed in 5% increments or decrements.

Please note that the increase and decrease in prescribing levels will be referred to as scenarios.

Table 16: Overview of intervention evaluation and scenarios.

Parameter for scenario	% variation identified from Chapter 3	Sources	England specific interventions
ω_{cn} (prescribing rate in the community for population without a comorbidity)and ω_{cc} (prescribing rate in the community for population with a comorbidity)	England specific setting: 0% - 7.7% reduction Other country settings: 0% - 15% reduction	(145–147)	TARGET Quality premium Education + feedback
ω_{h} (prescribing rate in the hospital)	0% - 19.1% reduction	(170,175)	Pooled meta-analysis result

Extrapolation to reflect impact on overall English population

Cumulative colonisation incidence levels over a one year period were used to calculate the change in colonisation levels and subsequently the rate of change in infection levels over a 1 year period, which were in turn used to calculate the impact of prescribing levels on NHS cost consequences.

Since the model inputs were in terms of 100,000 person years, this has been extrapolated to the entire English population for a year to calculate total colonisations avoided and the total infection

prevented. The cost results are therefore reflective of England following a 1 year period of the implementation of the intervention.

4.3 Result

4.3.1 Comparison Of Baseline Results Of The Original Model To The Enhanced Model

The results in Panel A and Panel B of Figure 40 present the results from the baseline model, with the parameter updates to the Knight et al. model (179) and the split of the community population to incorporate the prescribing differences in the comorbid and non-comorbid population.

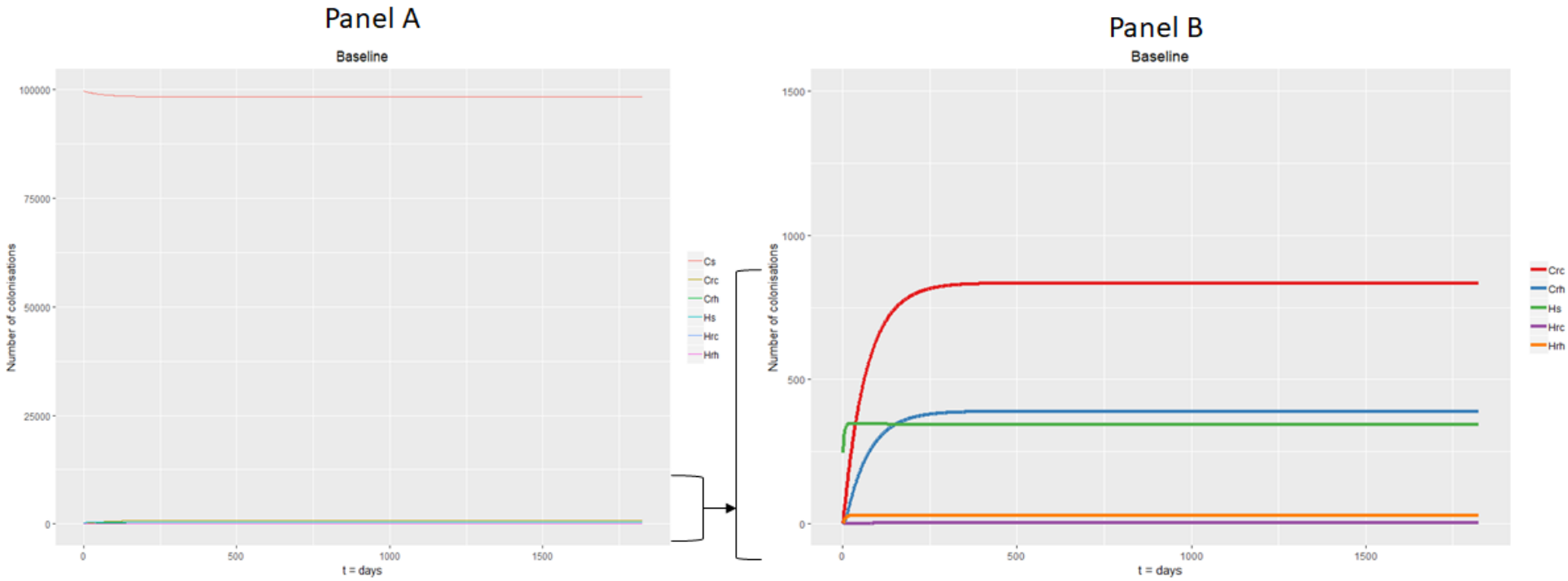


Figure 40: Results following simulation of the baseline model

Legend: Cs: Susceptible population in community, Crc: Resistant population in community, Crh: Resistant population in community from hospital, Hs: Susceptible population in hospital, Hrc: Resistant population in hospital from community, Hrh: Resistant population from hospital in hospital

Panel A shows all the populations modelled including all the susceptible individuals in the community (Cs), as shown by the highest line nearing 100,000. Panel B is a granular version of Panel A without the Cs population. Panel B therefore shows that the new model with the aforementioned changes, provides similar results in terms of colonisation levels to the Knight et al. model. The main take home message across both models being that majority (~80%) of the resistant colonisation occur in the community. As can be seen from the Crc population which is above all the other resistant colonised populations in Panel B in Figure 40.

Following the introduction of heterogeneity of comorbidities in the general community population leading to heterogeneity in prescribing, as would be expected there was no change in the total number of colonised individuals in the community compared to the original model structure (179). Therefore, the sense check demonstrated that the structural change has not altered the main model outcome that colonisations with resistant infections are primarily due to the community setting. The addition of the comorbidity split was incorporated purely to enable assessment of the differential impact in terms of prescribing differences seen between individuals with and without comorbidities and the impact of reducing prescribing levels across these two populations (via antimicrobial stewardship) in the community setting.

4.3.2 Prevalence And Cost Of Infections Across Community And Hospital Settings

4.3.2.1 Infection prevalence and incidence levels

After fitting the mandatory surveillance infection levels to the transmission model, the total number of setting and susceptibility specific infections over the simulation period of 1 year have been provided in Figure 41. For year 1 of the model per 100,000 individuals per year are similar but not identical to those estimated from the mandatory surveillance data. Table 17 provides a comparison

of the results of the baseline model infections with a column comparing the infections levels which were estimated from the mandatory surveillance sources from 2016/17.

The primary burden of resistant infections is in the hospital setting, however, when separating out the onset of infections, the burden is higher for infections from the community in the hospital (77% for susceptible infections and 69% for resistant infections).

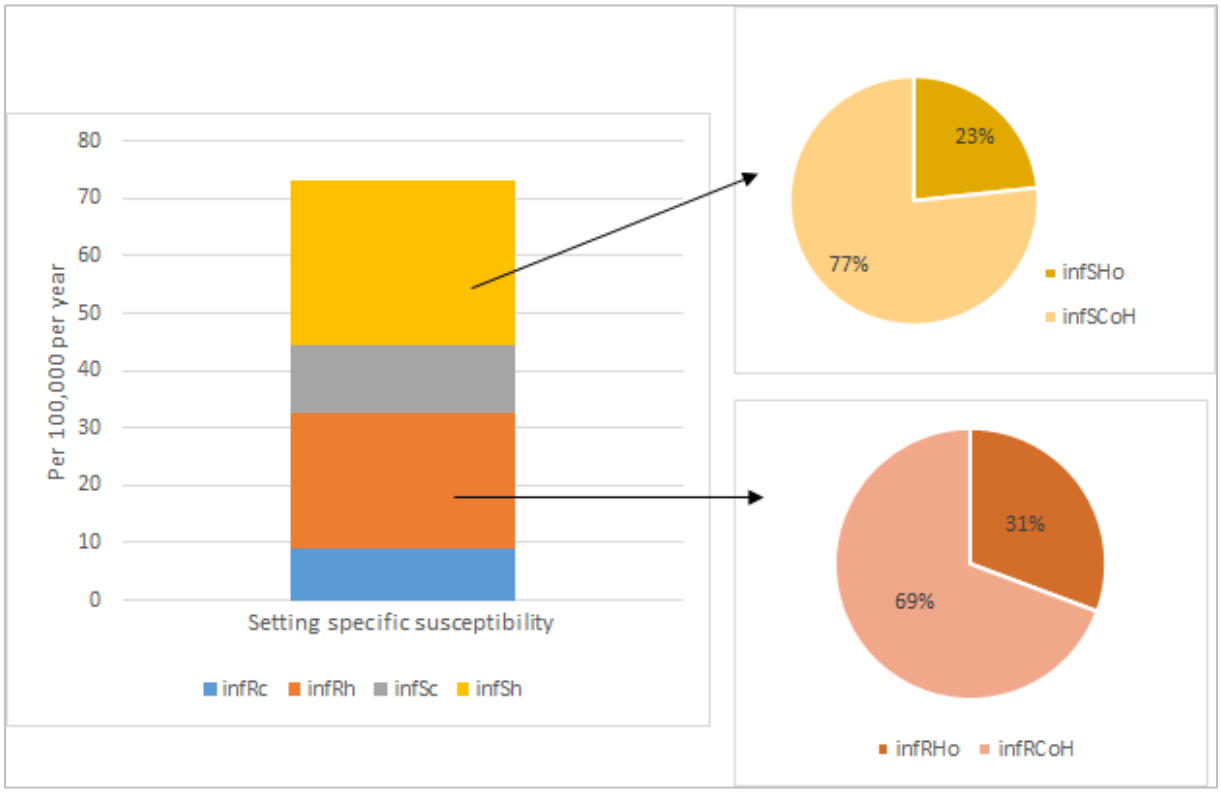


Figure 41: Total Infection prevalence – baseline model

Legend: infRc: Resistant infection population in community, infRh: Resistant infection population in hospital (infRHo: Hospital onset resistant infection population in hospital, infRCoH: Community onset resistant infection population in hospital), infSc: Susceptible infection population in community, infSh: Susceptible infection population in hospital (infSHo: Hospital onset susceptible infection population in hospital, infSCoH: Community onset susceptible infection population in hospital)

4.3.2.2 Costs due to infections

After applying the setting specific unit costs it was possible to indicate the overall burden of *E. coli* split by setting onset and susceptibility. The hospital burden of infection is substantially higher when compared to the community setting. However, the costs of hospital infections due to the community onset infections are also a lot higher compared to the hospital onset infections (Figure 42).

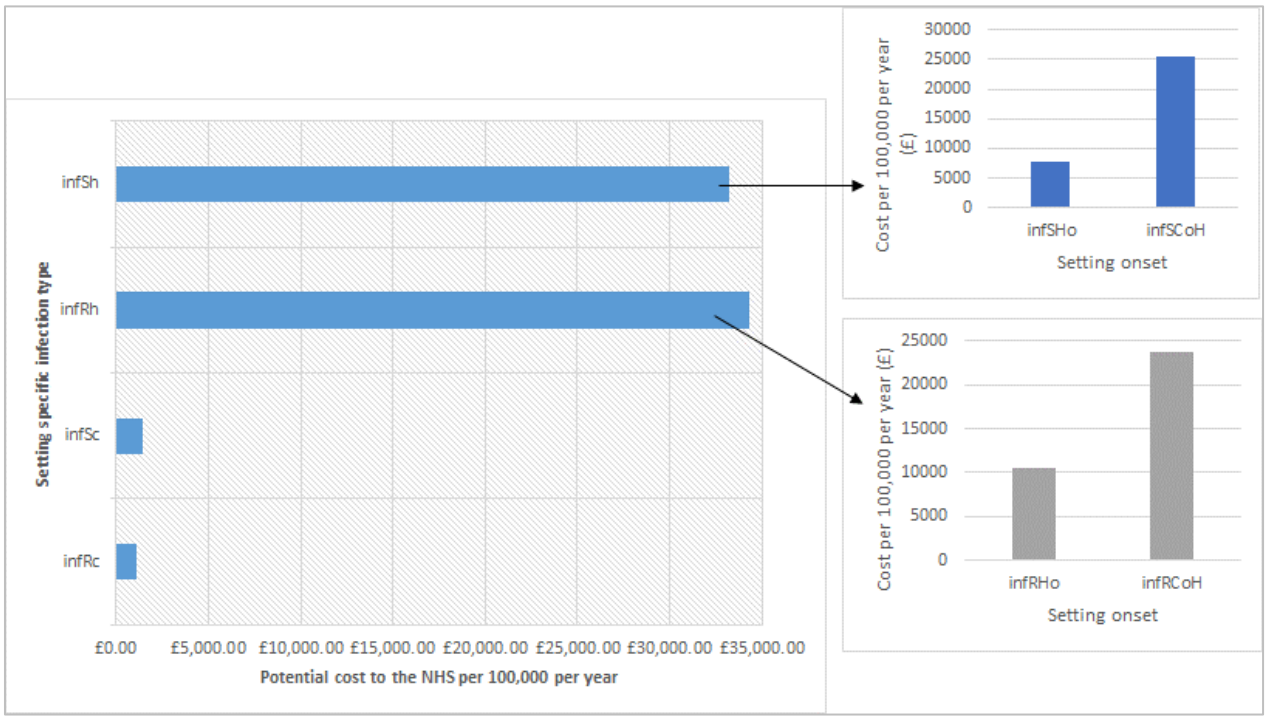


Figure 42: Setting and susceptibility specific cost of *E. coli* bacteraemia in England

Please refer to the legend of Figure 41 for abbreviations

4.3.2.3 Infection rates estimated from the baseline model

The total infection levels and the colonisation prevalence levels by setting (community/hospital) and susceptibility (resistant/susceptible) is provided in Table 17. The majority of susceptible and resistant colonisations are in the community, whereas majority of the infections (susceptible and resistant) are within the hospital setting.

Table 17: Modelled infections and colonisations

Model output in terms of infections per 100,000 per year		
Infection type categorised by community and hospital setting	Results from the model of total infections per year per 100,000	Comparison to mandatory surveillance estimates
infEC*	73.45	73.90
infRc	8.94	9.03
infRh	23.66	23.90
infSc	11.94	12.07
infSh	28.64	28.90
Model outputs in terms of colonisation levels per year		
Populations in which infections occur	Total colonisations per year	
Cs+Crc+Crh+Hs+Hrc+Hrh		100,000
Resistant colonisations acquired in the community (Crc+Crh)		10527.23
Resistant colonisations acquired in the hospital Hrc+Hrh		67.05
Susceptible population in the community (Cs)		89095.20
Susceptible population in the hospital (Hs)		310.52

*Overall *E. coli* bacteraemia in England per 100,000 per year (2016/17)
Please refer to Table 13 and Figure 41 for abbreviations

Figure 43 show the infection rate per colonised individual in each setting (i.e., colonisations acquired in the community or the hospital setting) and by susceptibility (i.e., resistant or susceptible). The total resistant colonised proportions are higher in the community setting since the model predicts that majority of resistant colonisations occur in the community. Although, in comparison the number the resistant colonisations are lower in the hospital setting, as the hospital setting is only a small fraction of the overall population. However, it should be noted that, the rate of infection per colonised individual is nearly three times higher in the hospital when compared to community settings. Therefore, in the baseline model the rate of progression from colonisation to infection is a driver of infections in the hospital setting.

Figure 43: Setting specific Infection rates and total colonisations

Intervention evaluations

Figure 44 provides an overview of the percentage change in the prevalence of resistance infections due to community acquisitions and due to community acquisitions, which have resulted in hospitalisation.

The entire population modelled is colonised with *E. coli*, whether this be susceptible or resistant (with a portion of each of these resulting in an *E. coli* related infection). The overall population size is set to 100,000, and in all scenarios the colonised susceptible (Cs) population size greatly exceeds the resistant population size.

As such, the colonisation and infection prevalence levels for the susceptible population have not been shown. Since the only change in the number of Cs is as a result of changes in the number of colonised resistant individuals and the background mortality rate from either infections or other causes, the susceptible population is effectively inflated/deflated to maintain the population at 100,000 per year. So, the impact of an increase or decrease in antibiotic use on the colonised resistant population would be balanced out in the model by increasing/decreasing the number of people in the susceptible cohort in the overall model population. To avoid over/underestimating this

susceptible population and its subsequent impact on the other cohorts in the model, the model was adjusted to assume no changes across the susceptible population. Since the focus of this study is the impact of interventions on resistant infection levels, the results focus only on the resistant population. (Appendix III includes results of both the susceptible and resistant population for the non-adjusted and adjusted model using the impact of antibiotic use in the community population as an example in Figure 64).

From the targeted review in Chapter 3, the clinical effectiveness of prescribing changes in the community or hospital setting were reported for a 6 to 12 month follow-up period. Therefore, the results reported in this chapter are for a 1 year timeframe following intervention implementation, and are therefore reflective of published evidence from clinical trials in England. The reduction in prescribing levels reported from the studies identified from the targeted review, as summarised in Table 16, have been used to assess the impact these prescribing changes could have on the number of resistant colonisations and subsequently the number of infections in either the community or the hospital setting. Within the best case scenario, prescribing would be reduced by 20% over a 1 year period and in the worst case prescribing would be reduced by 1% over a 1 year period.

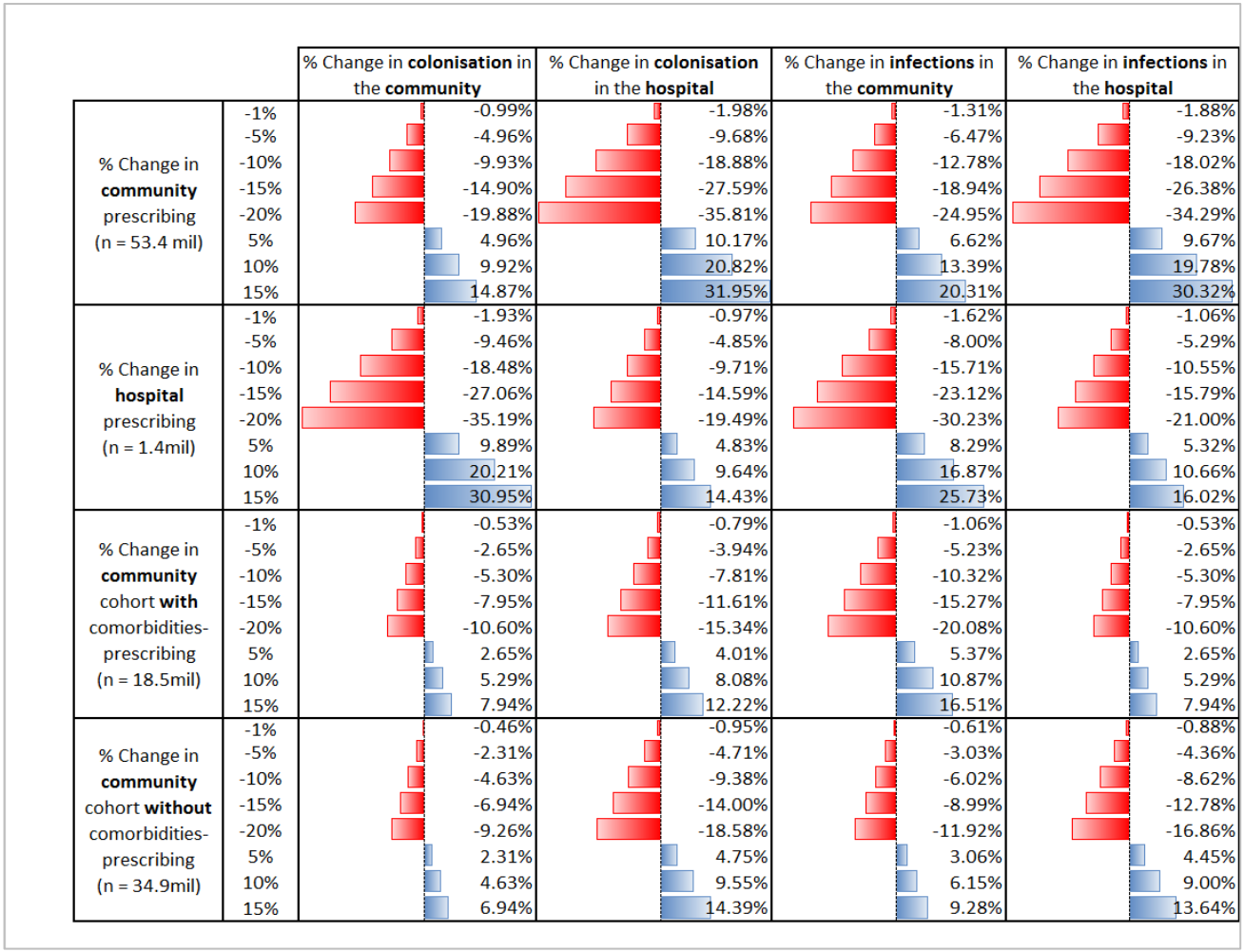
4.3.2.4 Change in antibiotic use in the community and hospital settings

Figure 45 shows the overall impact of changes in both community and hospital prescribing levels on colonisations and infections incidence levels in both the community and hospital settings. Changing prescribing levels in the community had a larger impact on colonisation and infection incidence levels in the hospital setting compared to colonisation and infection incidence levels community setting. A decrease in community prescribing resulted in 50% more colonisations being avoided when averaging across the 1% to 20% reduction in prescribing which were evaluated as part of the model. A similar inverse trend was seen when assessing the impact of increase in prescribing levels.

This difference was smaller when comparing the number of infections where on average across all the scenario for prescribing reductions assessed around 34% more infections were prevented or added in the hospital setting compared with the community.

When analysing the impact of changes in prescribing in the hospital setting, a reverse but symmetrical relationship was predicted. A higher number of colonisations (~49%) and infections (~34%) were prevented or added in the community setting compared to the hospital setting.

Within the community setting, when comparing the impact of a change in prescribing rates in the comorbid and non-comorbid population, reductions in comorbid population prescribing results in larger reduction in the community colonisations compared to change in prescriptions in the non-comorbid population. However, reduction in non-comorbid population in the community has a larger impact on hospital colonisation levels. This is most likely because the non-comorbid population is a much larger share of the community population, therefore, any little change within this population will results in larger widespread impact on the English population as a whole. A similar pattern is also seen with infection levels in the community and hospital settings.



		% Change in **colonisation** in the **community**	% Change in **colonisation** in the **hospital**	% Change in **infections** in the **community**	% Change in **infections** in the **hospital**
% Change in **community** prescribing (n = 53.4 mil)	-1%	-0.99%	-1.98%	-1.31%	-1.88%
	-5%	-4.96%	-9.68%	-6.47%	-9.23%
	-10%	-9.93%	-18.88%	-12.78%	-18.02%
	-15%	-14.90%	-27.59%	-18.94%	-26.38%
	-20%	-19.88%	-35.81%	-24.95%	-34.29%
	5%	4.96%	10.17%	6.62%	9.67%
	10%	9.92%	20.82%	13.39%	19.78%
	15%	14.87%	31.95%	20.31%	30.32%
% Change in **hospital** prescribing (n = 1.4mil)	-1%	-1.93%	-0.97%	-1.62%	-1.06%
	-5%	-9.46%	-4.85%	-8.00%	-5.29%
	-10%	-18.48%	-9.71%	-15.71%	-10.55%
	-15%	-27.06%	-14.59%	-23.12%	-15.79%
	-20%	-35.19%	-19.49%	-30.23%	-21.00%
	5%	9.89%	4.83%	8.29%	5.32%
	10%	20.21%	9.64%	16.87%	10.66%
	15%	30.95%	14.43%	25.73%	16.02%
% Change in **community** cohort **with** comorbidities-prescribing (n = 18.5mil)	-1%	-0.53%	-0.79%	-1.06%	-0.53%
	-5%	-2.65%	-3.94%	-5.23%	-2.65%
	-10%	-5.30%	-7.81%	-10.32%	-5.30%
	-15%	-7.95%	-11.61%	-15.27%	-7.95%
	-20%	-10.60%	-15.34%	-20.08%	-10.60%
	5%	2.65%	4.01%	5.37%	2.65%
	10%	5.29%	8.08%	10.87%	5.29%
	15%	7.94%	12.22%	16.51%	7.94%
% Change in **community** cohort **without** comorbidities-prescribing (n = 34.9mil)	-1%	-0.46%	-0.95%	-0.61%	-0.88%
	-5%	-2.31%	-4.71%	-3.03%	-4.36%
	-10%	-4.63%	-9.38%	-6.02%	-8.62%
	-15%	-6.94%	-14.00%	-8.99%	-12.78%
	-20%	-9.26%	-18.58%	-11.92%	-16.86%
	5%	2.31%	4.75%	3.06%	4.45%
	10%	4.63%	9.55%	6.15%	9.00%
	15%	6.94%	14.39%	9.28%	13.64%

Figure 44: Impact of change in colonisations and infections due to prescribing changes

*n = total target population size e.g. the community population consists of 53.4 million people and the hospital consists of 1.4 million people.

		Results in terms of colonisations avoided				Results in terms of infections avoided			
		Total colonisations avoided	Colonisations avoided in the community	Colonisations avoided in the hospital	CP	Total infections prevented	Infections prevented in the community	Infections prevented in the hospital	IP
% Change in community prescribing (n = 53.4 mil)	-1%	9055	8714	341	0.02%	311	65	246	0.001%
	-5%	44837	43166	1671	0.08%	1529	320	1209	0.003%
	-10%	88579	85317	3262	0.17%	2993	632	2360	0.006%
	-15%	131223	126449	4774	0.25%	4391	937	3454	0.008%
	-20%	172766	166561	6206	0.32%	5724	1234	4490	0.011%
% Change in community cohort with comorbidities-prescribing (n = 18.5mil)	-1%	4701	4683	18	0.03%	166	34	132	0.001%
	-5%	23390	23298	92	0.13%	823	171	652	0.004%
	-10%	46492	46307	185	0.25%	1628	341	1288	0.009%
	-15%	69304	69027	277	0.37%	2414	508	1907	0.013%
	-20%	91827	91457	370	0.50%	3182	673	2510	0.017%
% Change in community cohort without comorbidities-prescribing (n = 34.9mil)	-1%	4346	4187	159	0.01%	145	30	115	0.000%
	-5%	21740	20951	789	0.06%	720	150	571	0.002%
	-10%	43504	41943	1561	0.12%	1427	298	1129	0.004%
	-15%	65292	62975	2316	0.19%	2119	445	1674	0.006%
	-20%	87102	84048	3054	0.25%	2797	590	2207	0.008%
% Change in hospital prescribing (n = 1.4mil)	-1%	11116	10924	192	0.81%	219	80	139	0.02%
	-5%	54792	53834	959	4.00%	1089	396	693	0.08%
	-10%	107600	105688	1912	7.86%	2159	777	1382	0.16%
	-15%	158398	155537	2861	11.56%	3212	1144	2068	0.23%
	-20%	207161	203356	3805	15.12%	4246	1496	2750	0.31%

Figure 45: Colonisations and infections prevented per intervention group

Abbreviations: [CP, Colonisations prevented per head = Total colonisations prevented / Total interventions target population; IP, Infections prevented per head = Total infections prevented / Total intervention target population] Colonisation heat map: Blue to red = most colonisations avoided to least colonisations avoided. Infection heat map: Green to red = most infections prevented to least infections prevented, *n = total target population size

The absolute number of colonisations avoided, and infections prevented has been provided in Figure 45. For the worst case scenario, where the prescribing rate was reduced by only 1%, the model predicted that between 4,346 and 11,000 colonisations could be prevented in England over a one year timeframe after the intervention was implemented.However, in the best case scenario, where the prescribing rate was reduced by 20%, the model predicted between 87,102 and 20,7161 colonisations could be avoided. For all prescribing reduction scenarios, fewer colonisations were avoided in the hospital setting compared to the community. When comparing reductions in prescribing rate in the community and hospital target populations, changes in hospital prescribing prevents the largest share of colonisations, primarily in the community setting. Which is similar to the relationship described in Figure 44.

Between 145 and 311 infections are prevented due to a 1% reduction in prescribing levels in the community, and between 2,797 and 5,724 infections are prevented in England over a one-year time frame in the best case scenario of a 20% reduction in prescribing rates. Similar to Figure 44.the largest number of infections prevented were due to reductions in community prescribing, with reductions in the comorbid population preventing more infections than targeting the non-comorbid population. In terms of total colonisations and infections prevented per head of the target population, the hospital settings prevent the largest numbers of colonisations and infections per head, followed by the comorbid population.

4.3.2.5 Cost consequences

Cost savings due to reductions in community prescribing

Figure 46 shows the results of the impact of a reduction in community prescribing translated into cost savings made as a result of infections being prevented, in the worst-case scenario a 1% reduction in prescribing predicted a saving of around £357,000 a year in England. The best case scenario, where community prescribing was reduced by 20%, resulted in a large reduction in yearly colonisations of over 172,000 and a resulting 5,700 infections were prevented which translate into cost savings of over £6 million a year in England. On average across the 5 community prescribing interventions assessed (-1% to -20%) around 97% of the cost savings arise due to reduction in hospital infections driven by curbing prescribing in the community setting.

It should be noted that the interventions assessed (see Table 16) in the English setting showed prescribing reductions of up to 7%. Therefore, the 20% reduction should be evaluated as the best case scenario. Based on current efficacy levels a 10% reduction in community prescribing resonates closely with was is seen in England based on current published data.

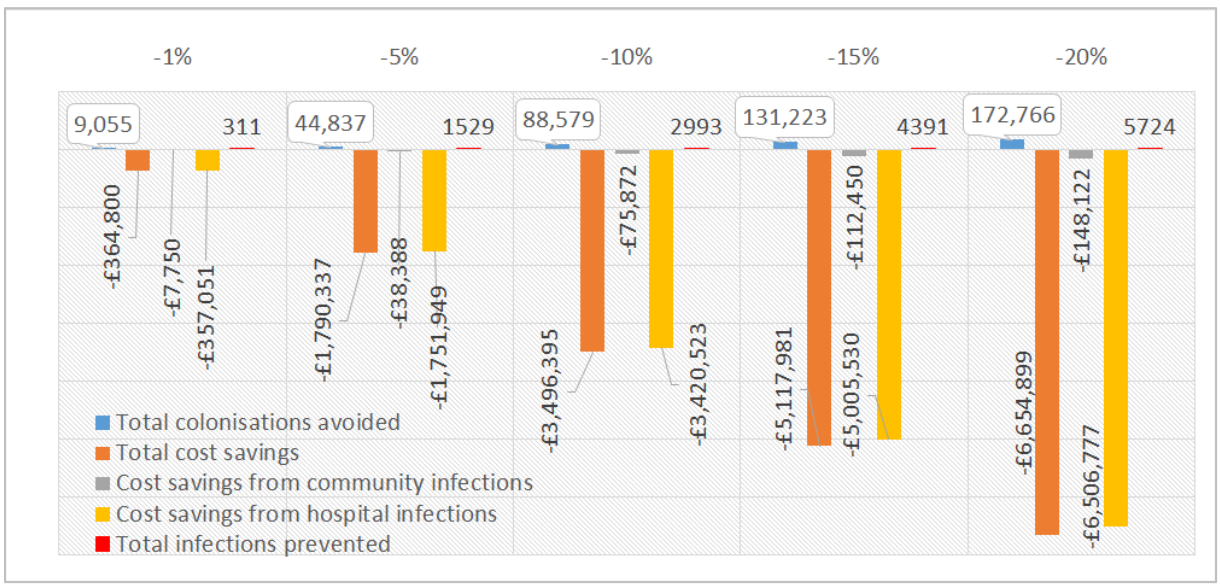


Figure 46: Impact of percentage change in community prescribing (-1% to -20%)

Figure 47 provides an overview of the impact of non-comorbid and comorbid community cohort specific prescribing rates. In the worst case scenario with 1% reduction in prescribing levels, £170,000 was saved when targeting only the non-comorbid population, whereas £194,000 was saved when targeting only the population with comorbidities. However, in the best case scenario £3.2 million and £3.7 million were saved by targeting the population without a comorbidity and with a comorbidity respectively. Thus, greater cost savings were predicted when targeting the cohort with comorbidities compared to the overall population with no comorbidities. These savings were driven by the lower number of infections in the hospital due to reduction in prescribing levels in the community.

Figure 47 demonstrates the cost savings predicted by the transmission model because of reducing prescribing levels for each of the individual comorbid and non-comorbid populations.

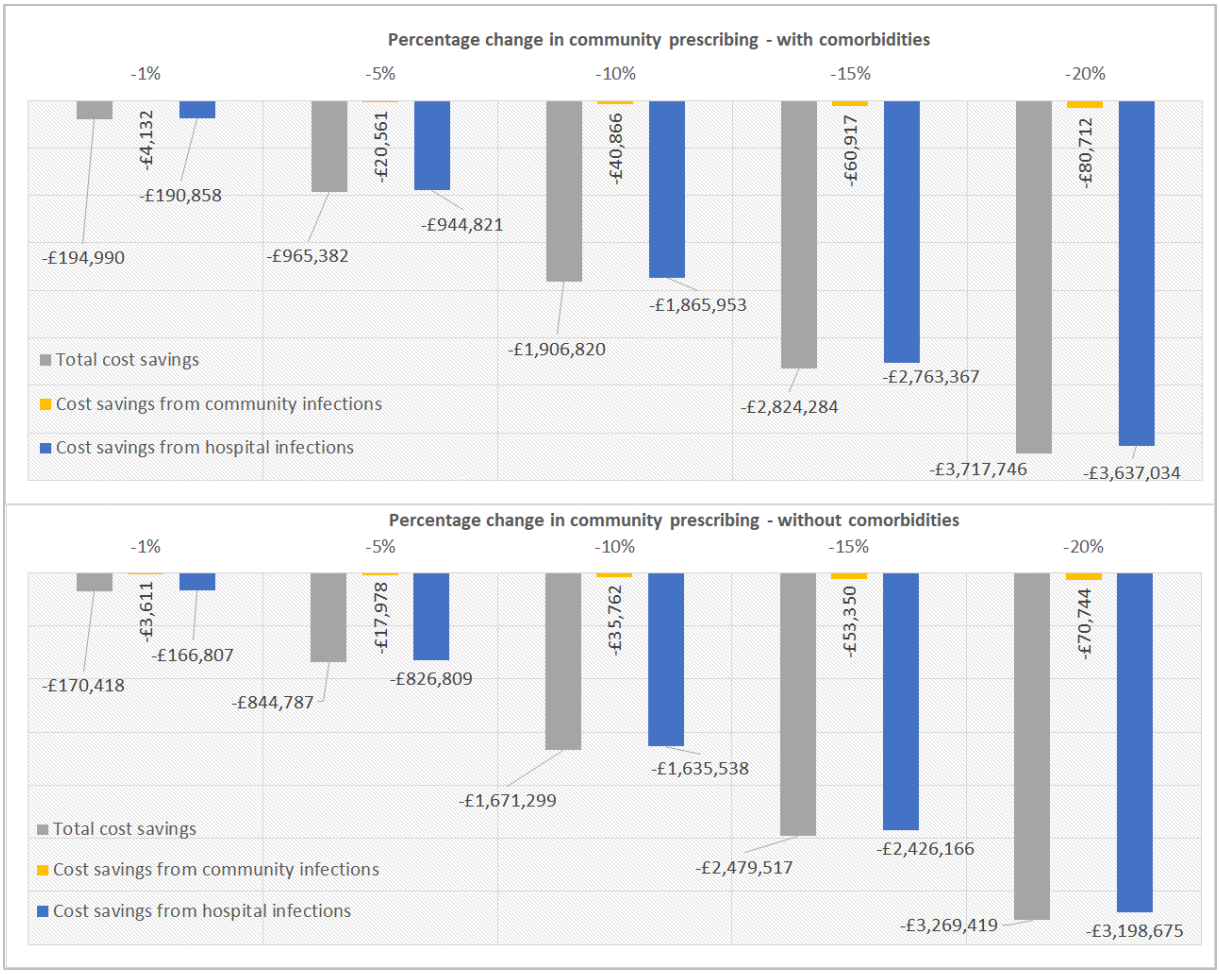


Figure 47: Cost savings due to changes in comorbid (Top) and non-comorbid (bottom) population prescribing

Cost savings due to reductions in hospital prescribing

The model predicted that reductions in hospital prescribing over a 1 year period in England were able to save between £210,000 and £3.9 million when assessing the worse and best case scenarios respectively. Similar to the community prescribing scenario, over 90% of the cost savings were due to the hospital infections being prevented.

When comparing the impact of reductions in hospital prescribing (see Figure 48) with reductions in prescribing across the comorbid and non-comorbid community cohorts, targeting hospital

prescribing levels were predicted to save more costs than targeting individual population cohorts in the community setting. Although, targeting the overall community setting as a whole (comorbid and non-comorbid together) compared with the hospital setting is able to save on average 67% more costs over a one year period. Seventy-three percent and 60% more costs were saved in the hospital setting compared to the community setting with a 1% (worst case scenario) and 20% reduction in prescribing respectively.

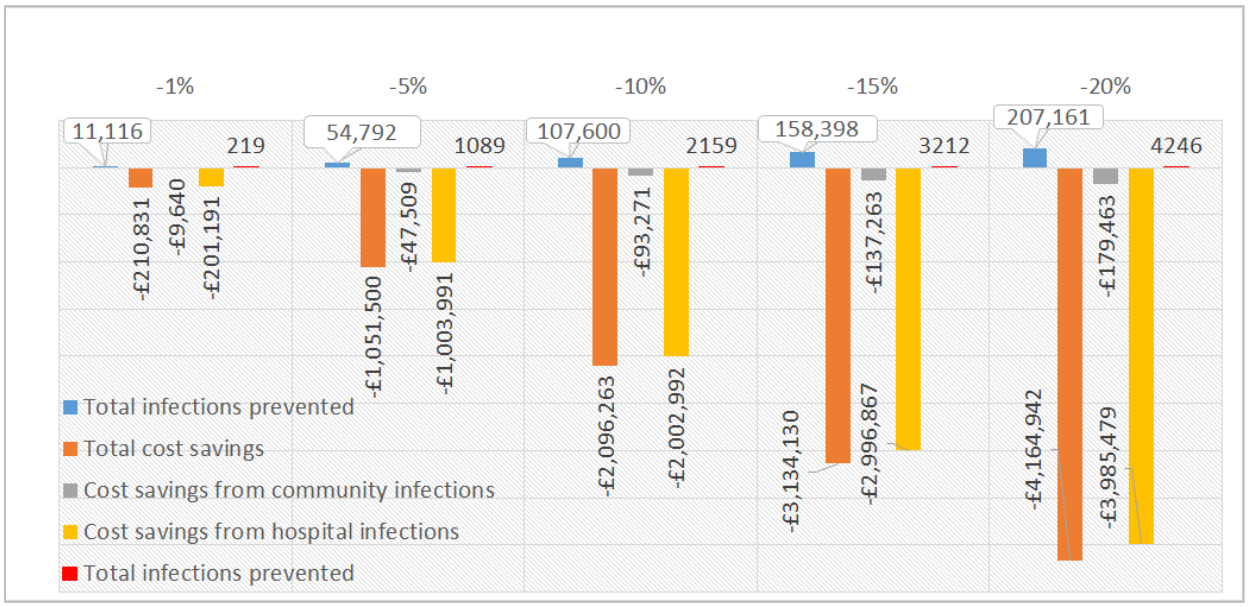


Figure 48: Cost savings due to changes in hospital population prescribing

4.3.3 Results Overview

Utilising the 1 year timeframe commonly used as a follow up period to measure the clinical effectiveness of antimicrobial stewardship interventions as identified from Chapter 3, this model was able to show the potential cost consequences for reductions in colonisations and infections from an English healthcare perspective.

Applying current *E. coli* infection levels from England and estimated costs of treating these infections, this model was able to provide a predictive framework of the potential relationship between

reduction in antibiotic prescribing and its impact on acquisition of resistant *E. coli* colonisations and infections and resulting savings to the NHS.

The model predicted that reductions in community prescribing had the potential to substantially impact colonisation levels both in the community and hospital settings (i.e., due to fewer colonised individuals entering the hospital setting from the community and then impacting transmission of infections within the hospital setting). On average across all the community prescribing interventions evaluated, compared to baseline colonisation levels, colonisation levels were reduced between 0.99% - 36% when assessing the worst (-1%) and the best case (-20%) scenarios respectively. Although, 38% of the prevented colonisations were in the community setting only. As a result, given the lesser force of infection within the community as opposed to the hospital setting, therefore having less of an impact on numbers of infections. Thus, in turn, fewer cost consequences. Only 0.74% of the colonisations in the community are predicted to result in community resistant infections, whereas around 70% of the colonisations from the community that enter the hospital have the potential become resistant infections.

Targeting individual comorbid and non-comorbid population cohorts did not prevent as many colonisations or infections compared to targeting both cohorts together, or the hospital setting alone. Compared to targeting the community setting overall, reductions in hospital prescribing did not have a substantial impact on colonisation levels in either settings. The hospital setting showed the highest colonisation and infections prevented (up to 35% reduction in colonisation and infection levels) across all the interventions evaluated which targeted reductions in prescribing levels in the community. Moreover, these infection preventions in the hospital setting as a result of reduction of prescribing levels in the community resulted in cost savings of up to £6.6million. Furthermore, the largest impact that reduction in hospital prescribing had was on colonisations in the community which were initially acquired in the hospital (~93%). However, the infection levels, in particular in the hospital setting, were sensitive to any change in prescribing in the hospital. Therefore, the results

arising from changes in hospital prescribing should be interpreted with caution, firstly since the per person rate of prescribing is higher and secondly the force of infection is higher. Even though, these two factors reflect the reality of the secondary care setting, it makes the results coming from this model framework particularly sensitive to the hospital prescribing parameter (wh). Thus, this could lead to a substantial overestimation of how many infections may be prevented simply by reducing prescribing only in the hospital setting.

4.4 Discussion

4.4.1 Limitations

The two key limitations of this model are the limited data that was identified from literature to parameterise the transmission and acquisition of bacteria with various susceptibility profiles and the way the model handles the susceptible colonised population.

The linear relationship between the changes in colonisation and prescribing rate may not be reflective of the real world outcomes. Firstly, the parameter 'eps' that incorporates the rate at which bacteria may acquire resistance as a result of antibiotics being prescribed, was highlighted as a sensitive parameter in the Knight et al. model. This rate may vary considerably given an individual's past clinical history, or their lifestyle and socioeconomic factors, including their travel history, which are examples of a few heterogeneous factors identified from the systematic review in Chapter 2. This acquisition rate is also dependent on the bacterial species and its ability to mutate or acquire inherent resistance to the antibiotic as a result of these heterogeneous factors.

The second limitation was in the way the model handled the susceptible colonised population. Since the model aims to keep the population balanced at 100,000 individuals, in the absence of granular parameters in terms of the clinical effectiveness of interventions to inform the model, it was challenging to assess the true impact of a reduction in community prescribing on the resistant population in the hospital due the way the susceptible population was being handled in the model

framework. A reduction in the community resistant population was effectively translated as an increase in both the community and hospital susceptible populations, which had the potential to bias results, by underestimating the true impact of how many resistant colonisations were prevented. Therefore, an adjustment was incorporated in the model so the rate of community to hospital susceptible colonisation and infection levels were dictated by the baseline colonisation and infection levels. With better real world evidence on the clinical effectiveness of interventions and the link between how much a unit reduction in antibiotic use has on preventing colonisation levels, this ratio of colonisation to infection rate can be better parameterised.

As stated within the introduction, all models are wrong, but some are useful. This transmission model was able to predict the potential impact a reduction in community prescribing on colonisation and/or infection levels in the hospital setting. Therefore, in the absence of better real world evidence, this transmission model helps to inform the policymaker on the cost-effectiveness of antimicrobial stewardship interventions. It clearly highlights that interventions targeting prescribing should consider the potential impact community prescribing may have in preventing infections in both the high-cost incurring hospitals as well as the potentially low cost community settings.

4.4.2 Policy implications and recommendations

I would like to draw the reader and the policymakers attention to one of the interesting results which should be further investigated using linked primary and secondary care data. The model predicted the potential for colonisations in the community to become infections in the hospital setting. The model was able to show that in both the best case and worse case community prescribing reduction scenarios, preventing community colonisations, and consequently preventing them from entering the hospital, could lead to large cost savings due to fewer infections in the hospital setting. Therefore, this link between the community and hospital should be further supported by data analysis projects to further convince policymakers that changes in the community could result in a

substantial impact on cost savings, in particular in terms of the cost savings from a hospital's perspective.

A second interesting result from the model was the impact of comorbidities on prescribing and prescribing reduction interventions, and potential to address the increased prescription levels within this cohort of the community population. Despite the target cohort of people in England with comorbidities being lower than people without comorbidities, a change in prescribing levels in the comorbid population led to a much larger reduction in colonisation and infection levels across both community and hospital settings compared to baseline levels. Unfortunately, within a recent study supported by routinely collected individual level prescribing data (185), the study did not find a high rate of inappropriate and/or overuse of antibiotic prescribing within this cohort of patients with comorbidities. Therefore, achieving a high level of reduced prescribing within this cohort of population may not be achievable and could have the potential for unintended consequences in terms of not prescribing antibiotic appropriately for those who actually do need them. However, preventing individuals entering the comorbid population could be reinforced as a potential overarching policy measure. Currently, the Department of Health and Social Care emphasize the need for a healthier population and highlight the threat of comorbidities such as diabetes that could be preventable. The link between increased need for antibiotics due to preventable comorbidities could be an area to further investigate to gain long term benefits from antimicrobial stewardship programmes in the community.

Thus, antibiotic resistance should be treated as a whole health system issue. Only challenging inappropriate prescribing within hospitals would resolve part of the issue. Given the impact of community prescribing levels on the hospital population, tackling community prescribing has the potential to reap long term benefit. Likewise, investment to achieve a healthier population within the community could also play a role in reducing the economic burden of antibiotic resistant infections. In light of the results from the model, in the long run the investment strategies to tackling antibiotic

resistance should consider longer term solutions to curb antibiotic use within the community setting. It is possible to implement cheaper interventions within the community and reap the benefits overtime by infections preventions in the hospital setting. The hospital setting still remains a high cost incurring setting, in the short term stewardship practices and infection control measures should be maintained to prevent high cost burden of infections spreading within this setting.

PART B QUALITATIVE SYSTEM THINKING APPROACH TO POLICY

CHAPTER 5.

5 PROCESS-LEVEL FACTORS INFLUENCING HOW ABR IS CURRENTLY BEING TACKLED

A LOCAL TRUST PERSPECTIVE

5.1 Introduction

So far in the thesis to inform a bottom-up policymaking approach to tackling antibiotic resistance, quantitative secondary sources of literature based evidence was utilised. This Chapter aims to delve deeper into a setting specific perspective of AbR and elicit primary data to address the final objective of this thesis which is to understand the *process-level barriers to tackling AbR*. The sections below will touch upon the rationale for this objective previously discussed in the Introduction in Chapter 1 and highlight the importance of this objective in light of the results gathered from Chapters 2-4.

5.1.1 Rationale For Study Aim

AbR and the secondary healthcare setting

The results from the systematic review in Chapter 2 identified contact with healthcare setting as the second most frequently reported reason for the development and transmission of AbR globally, after antibiotic use. Chapter 3 identified a large number of complex interventions being implemented within the secondary care setting to protect patients against antibiotic resistant organisms. Clinical efficacy data from recent meta-analysis studies from secondary care settings (131,139) specifically reported the added advantage of reinforcing hand hygiene and infection control measures alongside stewardship programmes to reduce the acquisitions of antibiotic resistant infections. Finally, Chapter 4 shows the increased risk of transmission of resistant organisms further adding to the cost burden of tackling AbR.

Burden of tackling AbR in England and the importance of the secondary healthcare setting

Compounding the current national funding issues in the NHS, hospitals have had to continually fight against healthcare associated infections which are either introduced from the community or harboured within the hospital environment, or from both settings. One NHS Trust in England reported that tackling an outbreak of Carbapenemase-producing Enterobacteriaceae resulted in costs of over £1million (22). Majority of the direct healthcare costs of AbR compromise of costs associated with inpatient length of stay. Recent literature[6] (8,22,186) has however suggested that there is large variation of cost burden of AbR from the healthcare payer perspective between hospitals.

Importance of effective interventions to tackle AbR in the secondary care setting

The results of the modelling study in Chapter 4 that incorporated estimates from recent literature and from Chapter 2 and 3 shows that the short-term cost consequence of AbR in a secondary care hospital setting outweigh the costs reported in community settings. Furthermore, Chapter 4 also shows firstly the cost impact of a high risk of transmission of resistant infection in the hospital setting and secondly a higher colonisation to infection risk primarily seen in the hospital setting compared to the community setting. Chapter 4 therefore highlights the importance of ensuring effect interventions are consistently being adopted to tackle AbR within the secondary setting.

Linking the policy implementers to the policymakers

The problem of AbR therefore adds to the complexity of delivering safe, effective, and high-quality care in secondary care settings. In order to target these life-threatening infections effectively and inform future policy, it is essential to understand the challenges of introducing interventions and innovations to tackle AbR, in such a resource constrained environment as the NHS, and determine how costing and resource allocation decisions are being made and what factors influences them. A better understanding of these ground-level factors only seen by the policy implementers could then

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[6] https://improvement.nhs.uk/resources/preventing-gram-negative-bloodstream-infections/ (Date accessed: 10/03/2019)

potentially help policymakers identify more informed policy targets. Subsequently facilitating implementation of bottom-up policies to tackle AbR.

Current strategies in place to tackle AbR in England

As concluded in Chapter 2, research identifying factors driving the emergence and transmission of AbR is wide-ranging and hard to interpret. In light of the complex public health issues of AbR, the Department of Health and Social Care in England introduced a five year strategy in 2013 to introduce interventions to tackle AbR (187). As part of this five year strategy, a number of measures have been put into place to tackle AbR in England. Some of these measures include curbing antibiotic prescriptions in the secondary (hospital) settings by introducing financial initiatives via the Commissioning for Quality and Innovation (*CQUIN)* framework. The CQUIN framework is a method via which the NHS can monitor the quality of the services being delivered across the Trusts in England. If individual Trusts meet the targets set out within the CQUIN framework they are provided a financial incentive in return. The 2017/18 CQUIN framework included the 'Reducing the impact of serious infections (Antimicrobial Resistance and Sepsis)' initiative which for example required Trusts to submit data on antibiotic prescribing and the decisions (e.g. using blood culture results) which had led up to prescribing antibiotics using the start smart and then focus prescribing algorithm.[7]

Moreover, due to rising levels of Gram-negative resistant bacteria across England, an ambition to halve Gram negative bloodstream infections nationally by 2022 has been an added measure, with a particular focus on *E. coli* bloodstream infections. Clinical Commissioning Groups (CCGs), NHS and Foundation trusts in the secondary care setting[8] (referred to as 'Trusts' from this point on) around England are currently adopting the five year strategy's recommended measures and interventions,

[7] https://improvement.nhs.uk/resources/reducing-impact-serious-infections-antimicrobial-resistance-and-sepsis-cquin/ (Link accessed: 26/05/2019)

[8] Secondary care setting in the context of this chapter refers to the hospital setting which includes intensive care units, major trauma centres, accident and emergency (A&E), specialist centres based within this hospital setting.

although individual trusts have some choice over what to adopt. It is therefore important to understand how Trust-specific financial, organisational, and other socioeconomic factors influence these decisions.

A recent nationwide survey attempted to collect information on what initiatives Trusts and CCGs in England have adopted to tackle AbR (124). This survey provided a holistic overview of the initial attempts by Trusts at tackling AbR. However, since the survey was conducted in 2014, a number of key initiatives like the Gram-negative ambition and the CQUIN antibiotic prescribing targets have been introduced. Therefore, the aim of this chapter is to develop a deeper understanding of what Trusts are doing on the ground. This includes better knowledge on the type of risks which may be giving rise to the increased emergence and spread of infections that are commonly discussed within Trusts, the barriers they may be facing when it comes to tackling AbR, including the impact of resource constraints on the approval of new investments.

In summary, Chapter 4 concluded the community setting should be targeted to gain long term cost effective from interventions tackling AbR. Chapter 4 also showed the high cost impact of AbR in the hospital setting, with majority of the savings arising from reduced length of stay costs from the hospital setting. From the community setting perspective, Chapter 2 identified a lack of in-depth understanding of the drivers of AbR in the community. Potentially due to this lack of understanding of the granular drivers of AbR in the community setting, Chapter 3 identified fewer effective interventions in the community setting compared to the hospital. An important component of a long term solution may therefore be to firstly identify the key drivers in the community followed by targeting interventions at these key drivers to tackle AbR not only in the community but also the knock on impact on hospitals. However, within the short term, there is a need to maintain the efficacy of current interventions to control AbR in the high cost and high risk (in terms of increasing emergence and transmission of AbR organisms) hospital setting. Moreover, the health impacts of AbR such as AbR attributable death rates are also most likely to occur in the hospital setting

compared to the community setting. The clinical efficacy of current interventions can generally be improved either by changing the current interventions in place altogether or by addressing the implementation issues which are restricting the intervention from being as effective as was intended. Therefore, to identify and influence the implementation barriers of current interventions or to develop newer intervention options to tackle AbR in the secondary setting, an understanding is needed of the process-level factors which influence the stakeholders who are in-charge of implementing policy on the ground, i.e., in the hospitals. Thus, helping to inform the bottom-up approach to policy making as highlighted in the introduction (Chapter 1) of this thesis.

5.1.2 Overall Aim

The primary aim of this Chapter is to investigate the final research question of this thesis, *the process-level factors influencing how AbR is being tackled.*

To meet this aim, two approaches are taken. First, an overview of the key challenges to tackling AbR in the secondary care setting context in England is undertaken. Second, given the resource-constraints currently faced by the NHS hospital setting, the study also explores how decisions are made when it comes to adopting and implementing an AbR related intervention. The overall aim of this Chapter was primarily met via semi-structured interviews at a large NHS Trust in England. These data were supported by a document analysis of published, publicly available resources from sixteen Trusts in England.

5.2 Methodology

5.2.1 Rationale For Methods

The systematic review conducted in Chapter 2 was only able to determine limited quantified evidence with regards to the ground-level factors driving AbR within secondary care settings. The majority of the studies identified in Chapter 2 that investigated the drivers of AbR from a hospital

perspective utilised routinely collected patient level data and were therefore unable to reflect the different stakeholder perspectives within a complex hospital setting.

Within the targeted review on interventions tackling drivers of AbR, Chapter 3 identified a large number of meta-analysis studies summarising intricate hospital interventions which required a variety of stakeholders for implementation. Therefore, given the involvement of various stakeholders responsible for tackling AbR in the hospital setting, there is a need to understand the process-level factors which may be facilitating or introducing barriers to tackling AbR. A qualitative study using an inductive exploratory approach was deemed an appropriate technique to identify these factors

The aforementioned approach had the advantage of enabling a breadth of perspective from a wider range of stakeholders to be gained, which would be otherwise difficult to capture from quantitative literature sources. Understanding the problem of AbR in healthcare provider organisations enables deeper insight and new avenues of policy and practice to control and prevent AbR within this high risk and high cost setting.

Qualitative research methods are increasingly becoming popular within the field of medical research due to their usefulness for understanding underlying behaviours driving complex phenomena such as the challenges of tackling AbR. Combining qualitative research methods with the systems thinking approach introduced in Chapter 1 could add further insight into the complexity surrounding the interactions between various stakeholders involved in the implementation of interventions tackling AbR as discussed in Chapter 3. Moreover, the linkages between interventions are potentially made more transparent (188). Visually presenting underlying factors driving the challenges of tackling AbR in causal loop diagrams is a methodology rarely utilised but potentially a beneficial tool for policymakers within this field of AbR. The following sections discuss the theory behind qualitative research and the applicability of a systems thinking approach, further adding to the rationale behind utilising them as research tools to help answer the fourth research question of this thesis.

5.2.1.1 Qualitative research versus quantitative research and medical research:

Prior to the appreciation of in-depth qualitative research methods informed by principles of grounded theory principles[9], the positivist approach using quantitative methods was the primary methodology adopted within medical / scientific research (189). Quantitative studies, using 'rigorous' scientific methodology to facilitate 'unbiased' data collection and analysis to generate generalisable laws and scientific facts, were often viewed as the only appropriate method of conducting research. It was assumed that such methods were able to produce quantitatively collected facts that represented the 'reality', and which could not be altered on a non-factual basis such as with a difference in opinion, views, or perspectives.

Post-positivist approaches using qualitative research techniques promote collection and interpretation of the same data in a variety of ways. Such approaches were not initially seen as a scientific method of doing research, primarily due to the lack of reproducibility of these studies and the high level of researcher bias which could be attached (189,190). However, critiques of the positivist approach often raised concerns about the varying nature of a human's behaviour, driven by culture, gender, context amongst other factors (190), which unlike 'objects in nature' (e.g. metal, atoms, water etc.) could challenge the generalisability of these '*facts*' and '*laws*' that dictate the notion of '*reality*' developed using a positivist approach. It is a challenge for the current positivist methods to account for the impact of non-quantifiable elements such as 'feelings' or 'attitudes' generated as a result of the changeable nature of human behaviour.

Glaser and Strauss's book on how to conduct rigorous qualitative research using a grounded theory approach (191) raised the profile of doing research using qualitative methods (189). The importance of understanding human behaviour and its interaction with key issues under study or that form the premise of a qualitative research question, to facilitate new theory development, is the rationale

[9] Grounded theory principles in the sense that the researcher maintains an open minded and inductive approach to analysing the results of the research.

underlying most grounded theory studies. One of the key advantages of qualitative research, in particular those grounded in theory, proposes the idea that in certain circumstances a setting specific theory (*substantive theory*) can be extrapolated to a more generalisable theory (*formal theory*) applicable to a wider audience than where the data was collected from (189).

The principle behind a grounded theory approach is to maintain an open minded inductive approach and eventually generate new 'theory' which is 'grounded' in the data that is being collected (192). The aforementioned principle helps conduct the data analysis without inclusion of any preconceived hypothesis. Therefore allowing only the data guide the answer to the research question. Amongst the seven key guidelines (189) set out by Glaser and Strauss, one of the guidelines also recommended was to not bias one's data analysis process by conducting a review of the literature to determine a hypothesis for the research question. As a result allowing for key themes to emerge from the data in an iterative manner.

Sbaraini et al. (192) has published one of the few research articles that acknowledge the variability and the similarities across all these different strands of grounded theory and provide a step by step guide to using grounded theory in medical research. This paper has helped guide the methods of this Chapter and in particular the intensive interviewing part of this chapter.

Please note that the aim of this study is to conduct an inductive exploratory analysis to identify the main themes from the interviews.

5.2.1.2 Qualitative research in medical literature and antibiotic resistance:

Within the field of health economics and health services research, patient reported outcomes and metrics to measure the well-being of a patient in terms of 'Quality of life' or 'Quality adjusted life years' have their initial roots in qualitative research. These are designed to render cost and resource allocation decisions by policymakers and managers more 'human'. The field of medicine, and in particular the problem of antibiotic resistance, has required both quantitative and qualitative

research to identify solutions. In particular, within the field of antibiotic resistance, the prescribing behaviour of clinicians, for example surgeons (193), the reasons behind the success or not of stewardship programmes (194) or the behaviour surrounding compliance with infection prevention practices, in particular for hand hygiene (195) have been studied in great detail using qualitative research methods.

Given the complexity identified in Chapter 3 surrounding the variety of stakeholders involved in a secondary care settings tackling antibiotic resistance, individual responsibilities and team dynamics, culture, behaviour, experience and expertise (196), a qualitative research methodology was deemed a suitable approach to identify solutions to the issue of AbR in this setting.

Previous studies have focused on identifying challenges of implementing stewardship programmes at a ground level, i.e., on the front-line in hospital settings, including in England (67,197). The hierarchical team dynamics of surgeons or junior doctors and their prescribing behaviour were highlighted as key front-line factors which could be barriers to effectively implementing stewardship programmes to reduce antibiotic use in secondary care. At present, Charani et al. are also conducting and have published more in-depth qualitative research within this field in England and across the globe (67,198,199). Contextual factors such as peer influence, specialty of the prescriber, patient needs, and methods of antibiotic usage surveillance were commonly reported to influence the antibiotic prescribers' decision. The stakeholders included in these studies have solely been from a healthcare worker and clinician perspective. Studies focusing on the whole system perspective looking at the wider organisational structure are currently lacking in the field of AbR. Stakeholders in charge of managing the Trust could be responsible for making crucial end level investment decisions and can include non-clinical and finance focused stakeholders in a secondary care setting. Decisions made by both clinical and non-clinical stakeholders could result in long term financial commitments which could have a sustainable impact on the efficacy of interventions tackling AbR. Since both clinical and non-clinical stakeholders at the organisational level are involved in making the final

decisions about where to allocate resources, such a whole system perspective could provide insights into improving existing interventions as well as identifying long term solutions to tackling AbR.

5.2.1.3 Systems thinking, secondary care, and antibiotic resistance:

Often complex systems are difficult to interpret given the range of actors, and variability and unpredictability of causes and effects driving a system at different scales and time points (188,200). The phenomenon being seen at a whole system level may be dictated by underlying individual factors or systems. Therefore a systems thinking approach is often needed to determine the underlying causal factors driving the system as a whole.

A primer on systems thinking

From a theoretical perspective the definition of 'systems thinking' has varied over the years. A recent literature review looking at the various definitions proposes the following definition:

"Systems thinking is a set of synergistic analytic skills used to improve the capability of identifying and understanding systems, predicting their behaviours, and devising modifications to them in order to produce desired effects. These skills work together as a system." (201) (summarised in Figure 49):

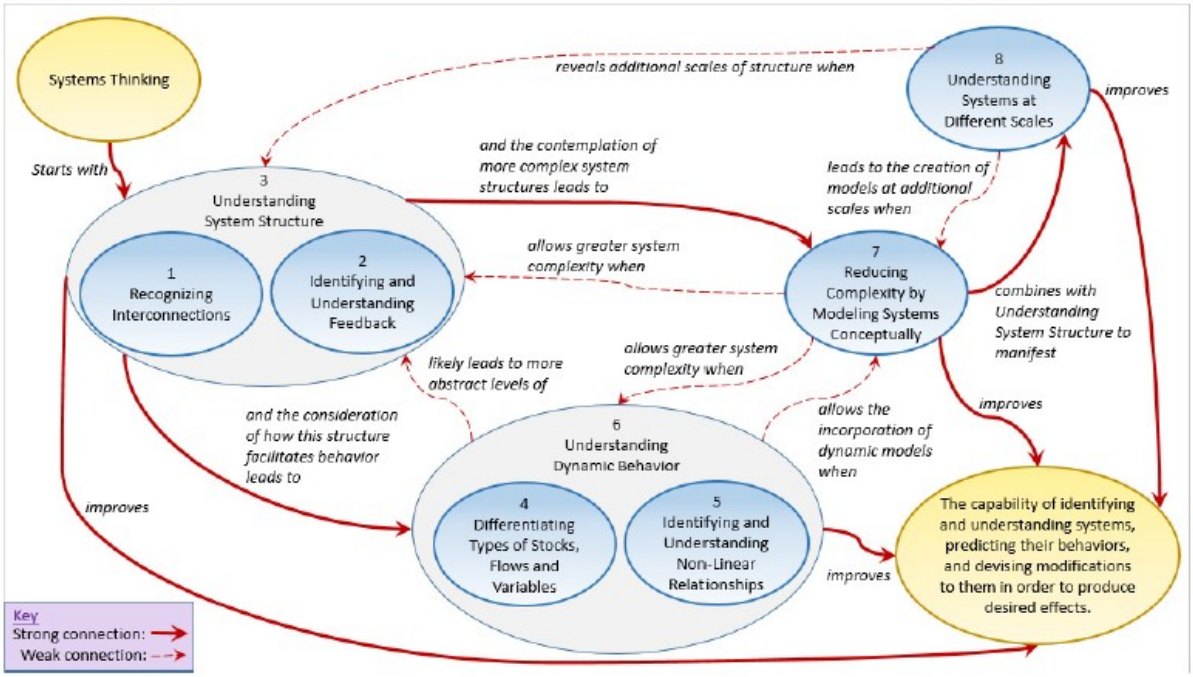

Figure 49: Overview of the concept of system thinking[10]

Source: (201)

From a practice and implementation perspective, a systems thinking approach is a management technique commonly adopted to identify solutions for an on-going business or corporate problem (202). The common features of this business problem usually have the attributes of a big, well-known issue, that has been a problem for some time, and where past solutions have not been ineffective. When looking at the complexity surrounding the challenges of controlling and tackling AbR within a single Trust, it is possible to draw parallels with the typical business problem often tackled using a systems thinking approach.

The philosophy of systems thinking is to start by understanding how the system within which the problem is being studied works, and gain perspective of the problem from a variety of stakeholders

[10] The figure is being reused from the Source (201) under the Creative Commons Attribution-Non Commercial No Derivatives 4.0 International (CC BY-NC-ND 4.0)

https://creativecommons.org/licenses/by-nc-nd/4.0/ (Date accessed: 01/06/2019)

(188,203). Another essential part of the systems thinking philosophy is not to 'assign blame' to any one person or team and to be open minded about the problem. The approach of being open minded resonates with our inductive exploratory approach for conducting interviews with stakeholders at the secondary care setting.

This systems thinking approach to understanding a particular problem takes into account the role of time in explanations of phenomena by suggesting that a process has a beginning and middle and an end. It encourages the possibility of incorporating feedback, which is where a 'fix' can be applied, to resolve an underlying problem in a certain part of a system, but that will result in a set of changes that will result in the system's behaviour evolving into another state over time.

As a first step of systems thinking, it is important to know the state of the system for making decisions. This approach to identifying solutions to a problem allows the researcher to look at a complex problem systematically and to understand the relationships between the key issues of the problem (200,202).

Tools to apply a systems thinking approach: Causal loop models

A causal loop model is a systems thinking tool that is adopted as the first step towards finding a solution to the problem at hand. Such a model also allows for non-linear relationships in the system (188,203,204). The loops that are created are the reality experienced from the perspectives of the stakeholders, perhaps elicited through interviews and analysis of documentary material (203,204). This reality may not necessarily apply to other settings and should be treated as *substantive* or setting specific theory, as it's the story which was identified from *this* particular system.

Balancing and reinforcing loops

A causal loop model links individual systems and components of systems by using 'positive' and 'negative' feedbacks in the system, creating 'balancing' and 'reinforcing' loops to explain the individual system level behaviour over time (203). Within the field of systems thinking research, balancing loops imply that all else remaining constant, a particular behaviour within the system will

balance out over time in the system. On the other hand, a reinforcing loop implies, that all else being constant, a particular behaviour within the system will keep escalating a part of the system over time, unless an intervention is introduced to bring the system back to its equilibrium state (72,200).

The supply and demand curves commonly used in macroeconomics can be used as a simple example of balancing and reinforcing loops. The higher the price of a good (e.g. aspirin brand X) the lower the demand (assuming consumers choose to switch to another alternative aspirin brand Y – where demand is commonly known to be '*elastic*' in nature). The lower the demand for a product, the supplier will have excess supplies, so the price of the good will need to be reduced by the supplier until an equilibrium price is reached where the market will clear. Alternatively, there are examples of products where a consumer cannot switch to an alternative product; the oncology drug market being a good example. Within the pharmaceutical market, the demand for a particular oncology drug could be '*perfectly inelastic'*. A consumer might be willing to pay at times an infinite amount of money to get access to a life-saving drug. In this case the suppliers could keep increasing the price, causing a reinforcing loop, until regulatory bodies (e.g. the National Institute of Health and Care Excellence in England) intervenes to introduce price ceilings such as the willingness to pay threshold commonly used in health economics to bring this reinforcing loop to an equilibrium level.

Complex systems in secondary care settings and AbR

A large acute Trust in London that may include more than one A&E department, trauma and speciality units, as well as general wards, all covering an extensive catchment area, is a well-suited example of a complex environment to which a systems thinking approach could be applied to understand a particular phenomenon such as tackling AbR. Systems thinking has therefore been used in healthcare and clinical policy research to guide policy recommendations (200) – mapping the causes of obesity is one example of use of a systems approach to tackle a health policy issue (105).

This Chapter therefore intends to ***understand the system underlying the secondary care setting using a single Trust in England as a case study – to gauge the process-level factors impacting how AbR is being tackled.***

5.2.2 Overall Method

The frequently adopted data collection tools commonly used by qualitative researchers include interviewing participants, conducting focus groups, or following cohorts of participants within ethnography studies. The results from these tools are quite often corroborated using a method known as document analysis (205). For the purpose of this study, it was decided that an overarching document analysis using publicly available resources across representative Trusts in England would be a suitable starting point to understand:

1) the overall key challenges Trusts are facing,
2) additional information on challenges related to IPC, antibiotic use and AbR, and,
3) common interventions being put in place to tackle AbR and antibiotic use.

Thus, the document analysis was deemed necessary to help generalise the issues commonly facing the secondary care healthcare providers when tackling AbR. The method in which representative Trusts were chosen has been provided in Section 5.3.1.1. Following the document analysis, a more in-depth interviewing study in one Trust was conducted, to illustrate an example of the whole system issues of tackling AbR. Using systems thinking approaches and causal loop diagramming tools, drawing on qualitative data from the interviews and documentary analysis, the complexity of decision-making in relation to the issue of tackling AbR was modelled. The rationale behind the case study was to understand the organisational level challenges of AbR from a range of stakeholders' perspectives, all of whom are involved in the smooth running of Trust activities. To capture a wider range of perspectives, an ethnography type data collection technique was not considered suitable, since it would only be possible to closely and intensively follow a cohort of stakeholders, as

commonly done in ethnography studies, compared to interviewing a wide range of stakeholders. The data would have been richer using ethnographic tools, but for the purpose of incorporating systems thinking methods, it was more important to gather a wider range of perspectives as opposed to concentrating on a particular cohort of stakeholders tackling AbR.

In summary, the data corpus of this qualitative study includes:

1) A document analysis of reports from 16 Trusts:
    - Data sources: Annual report, Infection prevention control report, Care Quality Commission report.
2) Semi-structured interviews with clinical and non-clinical stakeholders from a case-study Trust:
    - Trust board meeting notes and business cases reports related to AbR from this case-study Trust.
    - Peer to peer research presentation of the results of the interviews.
    - One to one consultation with two key IPC stakeholders to discuss the results, and structure of the final causal loop models.

To improve transparency of qualitative research study results, the reporting guidelines for qualitative research recommended on the Equator research method website and associated publication (206) have been followed. The reporting guideline results have been provided in Appendix IV.

5.3 Part 1: Documentary Analysis

This document analysis was conducted to understand the overall challenges related to AbR from a representative sample of English acute Trusts. Acute Trusts in England were chosen as the study

sample as they are a perfect example of a resource constrained and high AbR risk setting, where AbR can further add to costs and resource consumption.

The detailed methods used for this analysis are provided in Section 5.3.1, explaining how and why the Trusts were chosen, followed by what data types were included in the analysis. Section 5.4 provides the results of the document analysis, including significant illustrative quotes, along with an overview table with the key results related to the overall challenges all Trusts are facing and the unique interventions they are currently implementing apart from the common ones identified across all the Trusts.

5.3.1 Documentary Analysis Methods

5.3.1.1 Trust selection criteria

To help create a representative sample out of the 135 acute non-specialist and 17 acute specialist Trusts in England[11], selection criteria were applied. Trusts were chosen based on three key factors: form of Trust funding, location , and MRSA rates:

1. Based on the mechanism of funding, Trusts can either be considered 'Foundation Trusts' (FT) or 'NHS Trusts'.
    a. This selection criteria are important since FTs are accountable to a local governing body rather than the central government and have some freedom over practice level policies from the Department of Health and Social Care.[12]
2. The location of Trusts is based on the clinical commissioning group (CCG) within which the acute Trusts are situated. The CCG classification currently splits England into London, Midland, South, and North of England.

[11] http://www.nhsconfed.org/resources/key-statistics-on-the-nhs (accessed 21/10/2018)
[12] https://www.nhs.uk/using-the-nhs/about-the-nhs/nhs-authorities-and-trusts/ (accessed 26/02/2019)

    a. It was felt to be important to cover a geographical range of Trusts because antibiotic use and AbR related infection levels have been reported to vary across different geographical locations across England. Therefore, different Trusts may be facing individual challenges which need to be accounted for.

3. To help maintain the infection control standards in England, each acute Trust and CCG needs to submit their quarterly MRSA rates as a mandatory requirement. These are summarised within an online AMR surveillance database – The PHE Fingertips tool within the Public Health Profiles database.

    a. These data provided a consistent indication of the range of pressures related to AbR facing Trusts across England.

Thus, we were able to identify a sample of acute Trusts that should represent the range of challenges faced in the control of AbR. Figure 50 below describes the selection criteria used to identify the appropriate data for this document analysis. Specialist Trusts such as those only including orthopaedic /eye hospitals were not included, as rates of infection are disproportionately higher (based on the data in the PHE Fingertips tool).

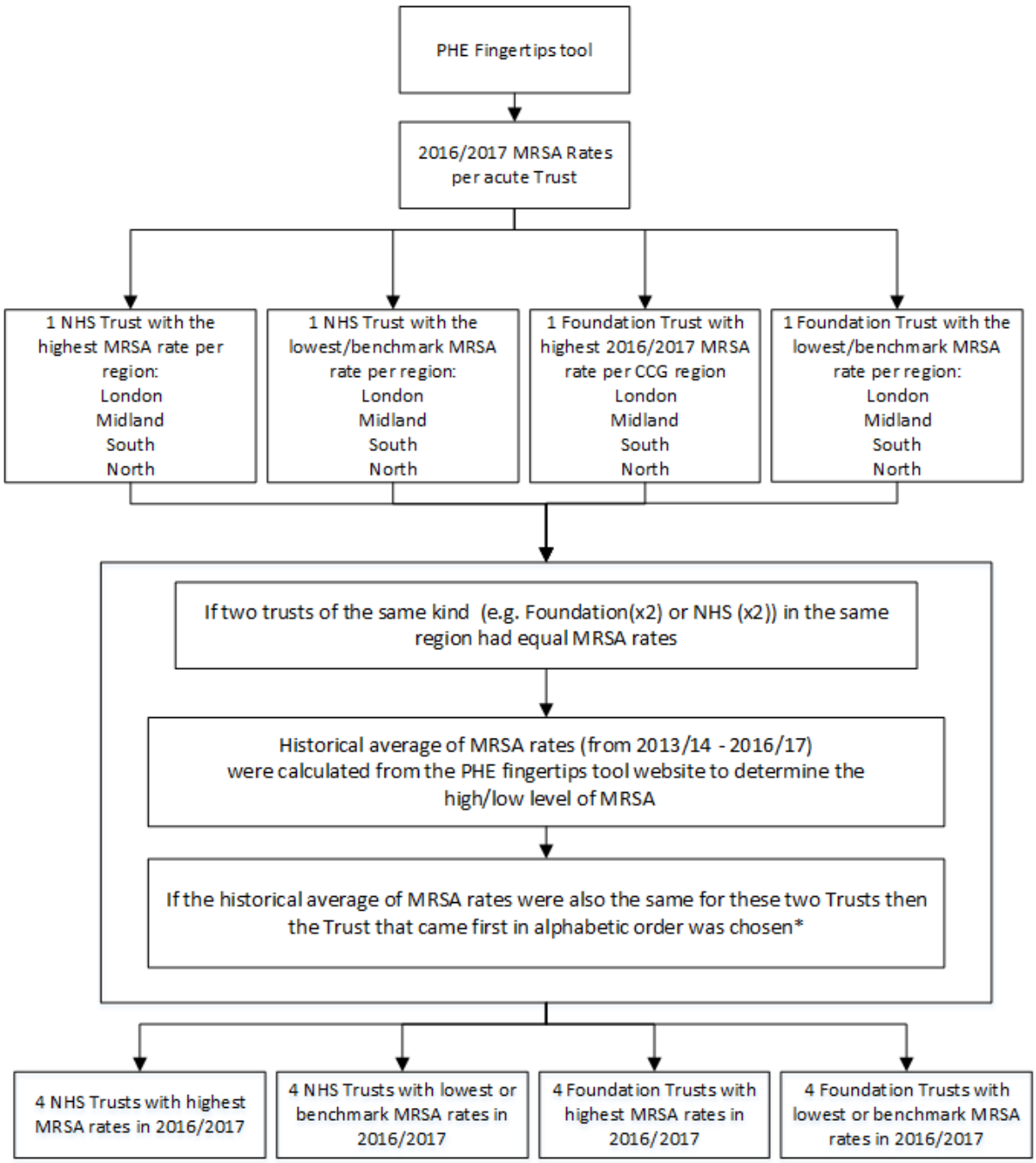

Figure 50: Selection process to identify the 16 Trusts for the document analysis

*If two Trusts had the equal historical average, then only the Trust that came first by alphabetical order was chosen, so the sample of that Trust category would not be over-represented (e.g. In the case of the region of north of England - two foundation Trusts, Barnsley and Harrogate, both had lowest MRSA rate for 2016/17 and overall same history average. If both were chosen, Foundation Trusts, north of England, and Trusts with a lower MRSA rate would be over represented, therefore to avoid the risk of selection bias Barnsley was chosen instead of Harrogate.

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5.3.1.2 Data selection criteria

There is a large volume of information recorded monthly from Acute Trusts in their Trust board meeting minutes, which is summarised within the annual reports, quality reports and the infection prevention control reports. Due to this rich source of frequently documented information, recently researchers have turned to analysing board meeting minutes in NHS England. Board meeting minutes have either been used as standalone secondary sources of evidence(207), or have been triangulated within mixed methods studies where primary evidence has also been gathered from stakeholder interviews or board meeting observations (208,209). To be able to identify evidence across all the Trusts, publicly available resources were used from their respective websites. The rationale for choosing the data types is described below.

Trusts have a statutory responsibility to be compliant with the Health and Social Care Act 2012[13]. A requirement of this Act is for the Board of Directors to receive an annual report from the Director of Infection Prevention and Control (DIPC). Therefore, Infection Prevention and Control (IPC) reports were identified for all Trusts. Annual reports were also identified when searching for IPC reports and since they provided an overview of the Trust's performance and future plans they were deemed an appropriate source of information in this study.

Since the IPC and annual reports are from the Trust perspective, the evidence provided in these reports may be subject to a degree of reporting bias. To help triangulate the evidence identified from these two types of reports, the Care Quality Commission (CQC) reports on their Trusts were included into the data corpus.

CQC are an independent regulatory body that assesses the safety and security of the patient care pathway being provided by Trusts in England. The five main questions asked and assessed in these reports include: 1. Are they safe? 2. Are they effective? 3. Are they caring? 4. Are they responsive to

[13] https://www.gov.uk/government/publications/health-and-social-care-act-2012-fact-sheets (Date accessed 10/03/2019)

people's needs? 4. Are they well-led? The CQC reports then provide a detailed position of the Trust and the key concerns identified from their inspection.

The overall dataset in this study therefore included evidence for Annual, IPC, and CQC reports for each of the selected Trusts.

5.3.1.3 Search method

To be able to select data in the most unbiased way possible the following search terms were selected to identify the best quality evidence.

Search terms: "infect" or "MRSA" or "resist" or "antibio" or "E.coli" or "CPE" or "carbapen" or "risk" or "challeng"

Outcome of interest

1. Any information surrounding the search terms or related to antibiotic resistance.

2. Categorising the information based on:

a) Risks which increase the incidence of AbR.

b) Measures being taken to control or prevent the emergence or transmission of AbR.

c) The barriers to implementation of measures (including Challenges at Trust level).

d) Overall challenges of the Trust that impact IPC and AbR.

3. Identifying themes across a) Trust types (NHS versus Foundation) b) risks of AbR c) interventions implemented d) barriers to implementation.

Following the identification of the three reports across the 16 Trusts, these were retrieved and uploaded into NVIVO 11 for the coding and document analysis.

5.4 Document analysis Results

From the 16 Acute Trust websites and 45 sources of evidence were included for document analysis in NVIVO 11.

The overview of the Trusts chosen based on Acute Trust type (NHS Trust / Foundation Trust), location in England, and MRSA rates is provided in Table 18.

Table 18: Study sample of Acute Trusts

Trust Type	**NHS Trust location**			
NHS TRUST	**London**	**South**	**Midland**	**North**
Low / at MRSA benchmark rate	Lewisham and Greenwich NHS Trust	Northern Devon Healthcare NHS Trust	Wye Valley NHS Trust	North Cumbria University Hospitals NHS Trust
High / above MRSA benchmark	London North West Healthcare NHS Trust	Dartford and Gravesham NHS Trust	Mid Essex Hospital Services NHS Trust	Leeds Teaching Hospitals NHS Trust
FOUNDATION TRUST	**London**	**South**	**Midland**	**North**
Low / at MRSA benchmark rate	St George's University Hospitals NHS Foundation Trust	Royal Devon and Exeter NHS Foundation Trust	Papworth Hospital NHS Foundation Trust	Barnsley Hospital NHS Foundation Trust
High / above MRSA benchmark rate	Kingston Hospital NHS Foundation Trust	East Kent Hospitals University NHS Foundation Trust	Heart of England NHS Foundation Trust	Bradford Teaching Hospitals NHS Foundation Trust

The evidence identified varied depending on how much information was provided in the IPC and annual reports. Apart from Papworth Hospital NHS Foundation Trust (2014 inspection report found) all Trusts had a recent (either 2017 n = 7 or 2016 n = 8) CQC inspection. The CQC reports provided a more impartial view of the status of the Trust to corroborate the evidence in the annual and IPC

reports. However, the IPC reports were very detailed and often raised similar issues to those identified in the CQC inspections.

Table 19 is an overview of the key results identified from this study. The panel below Table 19 explains the type of information extracted. The challenges discussed were more general and some were specifically related to AbR and infections. The five main challenges reported across all 16 Trusts were the annual financial deficit and funding issues, increasing demand for services with limited capacity, meeting performance targets such as the accident and emergency (A&E) 4 hour target, recruiting staff across all levels but primarily maintaining senior staff balance, and lastly maintaining IPC compliance and consistent application of IPC measures. Box 1 provides illustrative quotes extracted from the Trust reports on these issues. The 'word cloud' in Figure 51 provides an overview of the key terms which were commonly extracted when the challenges were discussed.

In terms of individual Trust level challenges, financial constraints and the impact of rising demand on services stood out. Also common were the quality of IT infrastructure and lack of leadership. The quality of the estate was an additional challenge faced in some Trusts that had an impact of IPC level risks. One Trust specifically outlined some of the issues they were facing when it came to antimicrobial stewardship (AMS), not identified in any of the other Trust reports.

BOX 1: Challenges across Trusts

"For 2017-18, the Trust again faces a significant financial deficit and a number of financial risks and challenges going forward."

(Barnsley Hospital NHS Foundation Trust – Annual report 2016-17)

"The balance of delivering care and treatment whilst maintaining good financial and operational performance has continued to be challenging through 2016/17."

(East Kent Hospitals University NHS Foundation Trust – Annual report 2016-17)

"*There continue to be significant challenges within the management of unplanned care at the Trust*. *We did not meet the 4-hour emergency access target of 95% consistently, nor did we meet the annual trajectory target…. The CQC also reported that the Trust should ensure that staff consistently follow guidance related to the prevention of healthcare associated infections with specific regard to hand hygiene* "

(**St George's University Hospitals NHS Foundation Trust - Annual report 2016-17**)

"*Challenges with regards to antimicrobial stewardship in a Trust such as MEHT are similar to that elsewhere, and these include limited resources, paucity of antimicrobial education, reduced face to face time, lack of electronic prescriptions and increasing complexity of patients along with the changing demographics*."

(**Mid Essex Hospital Services NHS Trust – Infection Prevention Control Report 2016-17**)

Figure 51: Word cloud related to the challenges across the 16 Trusts

Key: The words included in the word cloud were the ones which were frequently associated with the challenges the Trust was facing

The most common interventions being carried out with regards to antibiotic resistance were: formation of an antimicrobial stewardship group or committee, who are in charge of conducting regular audits on antibiotic prescribing practices. IPC audits in terms of hand hygiene practices and general decontamination are also mentioned in these reports. In addition, as of 2017 all Trusts were aiming to roll out electronic prescribing, however, the sample Trusts were at different phases of this roll out.

Similar to the results of the survey conducted by Ashiru-Oredopeu et al. (124), there was a degree of variability in what interventions are being implemented. Interventions range from simple behaviour change exercises like adding a sticker to medical charts to remind the prescriber of the need for 48 hour antibiotic review, to more complex interventions, including the adoption of decision support tools such as mobile applications to guide the prescriber. Ward rounds to check patients who are on antibiotics were not mentioned for all the Trusts, which does not mean that they do not conduct

them, but they were not highlighted as a key part of their stewardship process. Text box 2 provides illustrative quotes relating to interventions introduced by Trusts and Figure 52 provides an overview of the key intervention terms commonly identified from the reports related to antibiotic use and AbR.

BOX 2: Interventions being implemented across Trusts

"There had been antibiotic audits of documentation, stop dates, appropriate use and induction. The Trust had found a 50 – 75% improvement in prescribing practices"

(Bradford Teaching Hospitals NHS Foundation Trust – CQC report 2016)

"The Antibiotic Management Group (established in February 2013) continues to promote excellence in antimicrobial prescribing." **(Kingston Hospital NHS Foundation Trust – IPC report 2016-2017)**

"The Trust Antimicrobial Stewardship Committee met with most of the bed-holding CSUs in 2016/17 to review and support their work. This has helped to deliver the four elements of the Antimicrobial Stewardship CQUIN on reducing antibiotic consumption compared to the baseline from 2013/14 and improving the review of "best-guess/empiric" antibiotics within the first three days."

(Leeds Teaching Hospitals NHS Trust – Annual report 2016-2017)

"*One of the Consultant Microbiologists has been working over the last year as the antimicrobial stewardship lead, along with other colleagues**…** Regular stewardship meetings have been established with the core members (Microbiology and Pharmacy); aiming to expand the team to include senior sisters***"**

(Mid Essex Hospital Services NHS Trust – Infection Prevention Control Report 2016-17)

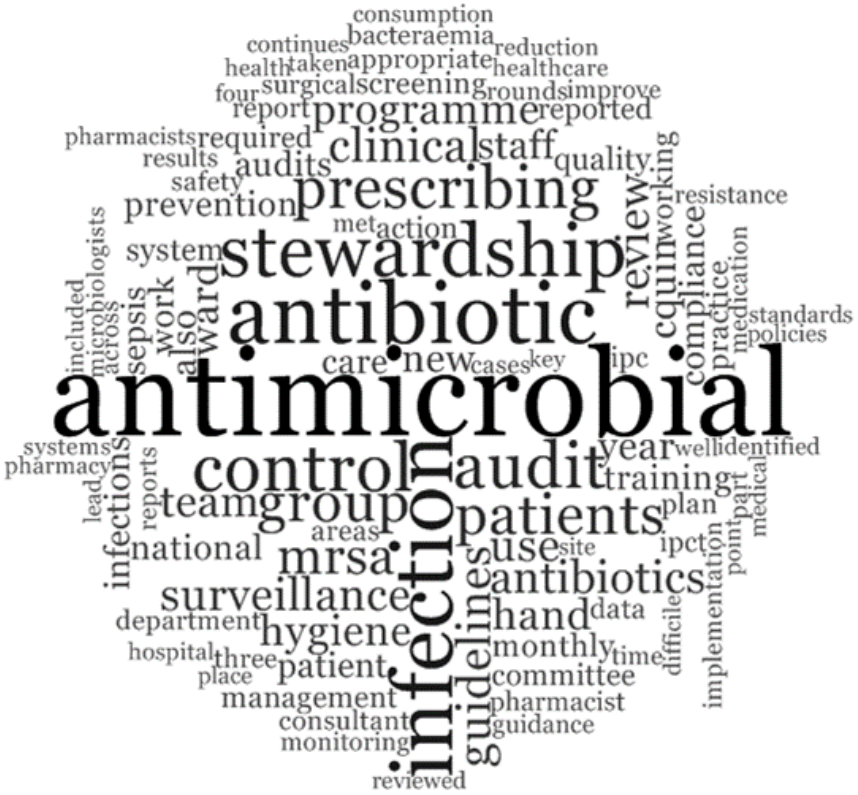


Figure 52: Word cloud of the interventions most frequently reported across the 16 Trusts

Factors that increase the risk of AbR were only discussed within a handful of Trust reports. These risks were usually identified following a root cause analysis following identification of an AbR related infection such as MRSA.

Amongst these risks, the risk of community carriage of Carbapenemase-producing Enterobacteriaceae (CPE) brought into the hospital setting was discussed. Prompt identification and decolonisation of MRSA patients, IV line or urinary catheters, hand hygiene compliance, movement of high risk patients in the Trust, inconsistencies in IPC practice and policy and IPC team's response times were also mentioned as areas of concern when it came to contributing factors that were increasing the risk of AbR in the Trust. See word cloud in Figure 53.

Figure 53: Word cloud of the risks of AbR

In summary, these publicly available documents contained little information that is specific to the *barriers* of tackling AbR. However, a general sense of the daunting overarching challenges the acute Trusts are facing in England can be concluded from this document analysis study. These include struggling to meet current NHS targets such as A&E waiting times, increasing financial deficits, and balancing unplanned care with limited resources.

A large number of interventions being incorporated in each Trust were also identified from this document analysis. This shows the increasing awareness by Trusts of significance of AbR and their will to prevent and control it. However, the range of interventions and contexts within which they are being deployed also makes quantifying their clinical effectiveness challenging. Measuring which interventions are more effective over others, to help policymakers better allocate resources, is therefore a challenging task within the field of health economics, which largely relies on clinical effectiveness data (see Chapter 3).

The increasing threat of AbR and the pressure to meet the antibiotic use targets in the CQUIN were often discussed as additional performance targets on top of the existing difficult to meet targets. The general sense of pressure to meet performance targets overall was also reported as a key challenge across all the Trusts (see Box 1).

A more in-depth analysis into a single Trust is needed to explore these issues further, analyse the relationships between factors influencing decisions about interventions to adopt, prioritisation of targets and barriers to implementation ranging across organisational and wider system levels.

Table 19: Overview of the sixteen Trust study

Trust name	Trust type / Location / MRSA rate	Overall key common challenges	AbR related interventions implemented	Unique challenges commonly reported	Additional Interventions
Lewisham and Greenwich NHS Trust	NHS Trust/ London/ Low/at benchmark	• Financial deficit[14] • Demand for services • Staffing issues • NHS Performance targets • IPC inconsistencies • Record management (e.g. incident reporting)	• Antibiotic audits • IPC audits • Antimicrobial stewardship team/Antibiotic working groups[15] • Implementation of electronic prescribing	• Water quality • Lab merger • IPC workload due to new initiative • IPC compliance issues • Merger with Queen Elizabeth hospital related challenge (impacting smooth running of day to day activity)	• Video promotion of antibiotic stewardship in Trust intranet
London North West Healthcare NHS Trust	NHS Trust/ London/ High/above benchmark			• Cyber security issue • Old estate • Water quality • Merger and leadership • Hand hygiene compliance	• 'Right Wipe, Wipe Right' IPC project pilot • Broad spectrum antimicrobials ward rounds

[14] Northern Devon Healthcare NHS Trust reported a financial surplus to invest back into the trust, Papworth Hospital NHS Foundation Trust reports financial surplus for 2016/17, but deficit for 2017/18 is planned which will need cost improvement plans

[15] Wye Valley NHS Trust does not mention having an antimicrobial stewardship team only antimicrobial pharmacist who is currently dealing with the CQUIN targets for antibiotics

Trust name	Trust type / Location / MRSA rate	Overall key common challenges	AbR related interventions implemented	Unique challenges commonly reported	Additional Interventions
St George's University Hospitals NHS Foundation Trust	Foundation Trust / Low/at benchmark			• Low morale among theatre staff and consultant surgeons • Colonisation and infection due to a virulent and antibiotic resistant Enterobacter cloacae (intermittent episodes) • Estate related challenges – regarding water quality, re-location of departments	• Composite score-card system to flag wards with AbR organisms + other IPC performance measures e.g. Hand hygiene score • Stewardship programme also includes dedicated antimicrobial stewardship champion
Kingston Hospital NHS Foundation Trust	Foundation Trust / High/above benchmark			• Leadership issues • Expensive residential area for staff (lack of staff recruitment / capacity issues)	• Education + training for nurses/pharmacists • Close collaboration with community (Pharmacists/GPs) • IPC software package ("*ACME*") installation for better surveillance • Hand hygiene training unit • Infection Control Core Elements Audit Tool • IPC training + skills day
Northern Devon Healthcare NHS Trust	NHS Trust/ South/ Low/at benchmark			• IPC issues in emergency department • Maternity care (including IPC issues during surgical procedures) • Data record management: including meeting increased IPC workload to meet the Gram-negative targets • Outbreaks (norovirus)	• Mobile/intranet: Electronic application (app) to check antibiotic prescribing guidelines: • "RxGuidelines" • Voluntary post-discharge surveillance of infections following a surgery
Dartford and Gravesham NHS Trust	NHS Trust/ South/ High/above benchmark			• Population expansion near hospital (misalignment of payment from commissioners)	• MRSA Ward-Acquired Check List • Hand hygiene competency assessment

Trust name	Trust type / Location / MRSA rate	Overall key common challenges	AbR related interventions implemented	Unique challenges commonly reported	Additional Interventions
				• Incident learning and feedback issues (unaddressed IPC issues) • Leadership issues	
Royal Devon and Exeter NHS Foundation Trust	Foundation Trust/ South/ Low/at benchmark			No additional IPC related challenges were recorded apart from the ones already included under 'Overall key common challenges'	• Mobile/intranet: Electronic application (app) to check antibiotic prescribing guidelines: • "RxGuidelines" • Compliance related to AMS reported on IPC dashboard • (includes: compliance with indication / duration / documentation)
East Kent Hospitals University NHS Foundation Trust	Foundation Trust/ South/ High/above benchmark			No additional IPC related challenges were recorded apart from the ones already included under 'Overall key common challenges'	• Poster antibiotic management and prescribing in critical care units. • Checklist included to be utilised daily, on ward round to prompt best practice • F1 junior doctors' stewardship training • Microguide antibiotic prescribing guideline app (smartphone / tablet / computer) • IT system to refer patients (on antibiotics) to pharmacist • Ward rounds
Wye Valley NHS Trust	NHS Trust/ Midland/ Low/at benchmark			• Recently removed from 'special measures requirement for quality'	No unique interventions were reporting other than the ones mentioned under 'AbR related interventions implemented'

Trust name	Trust type / Location / MRSA rate	Overall key common challenges	AbR related interventions implemented	Unique challenges commonly reported	Additional Interventions
				• Lapses in care related to antibiotic prescribing and environment contamination • Risk of infection during maternity care	
Mid Essex Hospital Services NHS Trust	NHS Trust/ Midland/ High/above benchmark			• Norovirus / MRSA outbreaks (leading to transmission within the Burns unit) • Legionella / *Pseudomonas aeruginosa* risk • AMS related challenges	• Measures to tackle Surgical site infection (including within the Gynaecology department) (Surveillance, training, audit, IPC precautions)
Papworth Hospital NHS Foundation Trust	Foundation Trust/ Midland/ Low/at benchmark			No additional IPC related challenges were recorded apart from the ones already included under 'Overall key common challenges'	• "Infection Control Link Group" with clinical champions across the Trust • Ward focused stewardship rounds (surgery, cardiology, critical care) • Stickers on drug-charts for 72 hour review of antibiotics
Heart of England NHS Foundation Trust	Foundation Trust/ Midland/ High/above benchmark			• Vancomycin-resistant *Enterococcus* colonisations	Quality Dashboard metrics to monitor antibiotics
North Cumbria University Hospitals NHS Trust	NHS Trust/ North/ Low/at benchmark			• Higher than expected SSIs in Orthopaedic unit • Antibiotic shortage leading to change in guidelines	• Mobile/intranet: Electronic application (app) to check antibiotic prescribing guidelines: "RxGuidelines"
Leeds Teaching Hospitals NHS Trust	NHS Trust/ North/ High/above benchmark			• Pathology IT system issue • Outbreaks (MRSA / Multi-resistant *E. coli*)	• IPC champion in every ward • Sticker/sign post reminder on medical noted for >3day antibiotic review

Trust name	Trust type / Location / MRSA rate	Overall key common challenges	AbR related interventions implemented	Unique challenges commonly reported	Additional Interventions
					• Ward Health check audits displayed on patient safety boards in wards (incl. antibiotic review data) • Screensaver displays for lessons learnt from outbreaks • Ward rounds following recruitment of locum infectious disease specialist • HPV decontamination • Plan, Do, Study, Act (PDSA) cycles of focused IPC training
Barnsley Hospital NHS Foundation Trust	Foundation Trust/ North/ Low/at benchmark			• IT/Electronic system issues • Pay issues with commissioners: • Issue with 7 day funding with CCG • CPE screening (lack of capacity)	• Weekly stewardship ward rounds • Display of appropriate antibiotic use posters
Bradford Teaching Hospitals NHS Foundation Trust	Foundation Trust/ North/ High/above benchmark			• Policy update inconsistencies • Mandatory training compliance	• Patient acuity monitoring dashboard • Twice weekly stewardship war rounds • Selective reporting of susceptibility of key organisms

Abbreviations: [AbR = Antibiotic resistance; AMR = Antimicrobial resistance; AMS = Antimicrobial stewardship; F1 = Foundation year 1; GPs = General Practitioners; HPV = Hydrogen peroxide fogging; IPC = Infection prevention and control; IT = Information technology; MRSA = Methicillin-resistant Staphylococcus aureus ; NHS = National Health Service]

Panel: terminology to understand the table above

Overall key common challenges: The common challenges related to smooth running of Trust operations which were discussed in either the annual or IPC report across all 16 Trusts. If there are any exceptions these are reported within the footnotes.

AbR related interventions implemented: The measures being taken to tackle antibiotic use or IPC related to AbR mentioned in either the annual report or the IPC report across all 16 Trusts. These are additional measures above the standard of care infection prevention and control measures which legally need to be embedded according to the Health and Social Care Act. If there are any exceptions these are reported within the footnotes.

Unique challenges commonly reported: Challenges apart from the common ones discussed across all 16 Trusts, which were mentioned in at least the annual/IPC or the CQC reports which have an impact on 1) IPC, 2) preventing or controlling AbR, 3) antibiotic use 4) smooth running of day-to-day operations

Additional interventions: The measures being taken to tackle antibiotic use or IPC related to AbR mentioned in either the annual report or the IPC report apart from the common AbR interventions implemented.

5.5 PART 2: Case Study Trust: Semi-structured Interviews

The two main aims of chapter 5 are to firstly further understand the challenges of tackling AbR within a large and complex NHS Trust and secondly to determine how resource allocation related decisions are being made within a resource constrained environment. The approach is to apply a narrower lens into the day-to-day challenges of tackling AbR that cannot be achieved by the study of peer reviewed published data (Chapter 2), previously published surveys of NHS Trusts, or from an in-depth document analysis into publicly available resources in 5.3 above.

The selected Trust Imperial College Healthcare NHS Trust (ICHCNT) includes a large number of services ranging from a major trauma centre, to two accident and emergency units, and a renal and haematology ward focused centres. ICHCNT was chosen for two reasons. Firstly, it is one of the largest NHS Trusts in England, serving over 1 million patients every year; it currently employs around 11,000 staff. Secondly, my PhD research centre was based within this Trust which gave me the appropriate links and contacts to aid the research approval and data collection process. Hence, it was hoped that this would potentially retrieve higher response rates and enable obtaining a richer quality of data, which is crucial for making any theoretical conclusions from qualitative research studies.

5.5.1 Ethics

The ethics board at Imperial College London was first consulted to check if full ethics might be required for this study. Since the study was from an organisational perspective, and no patient or patient related data would be included, even though NHS staff were being interviewed, I was informed that no ethics approval would be needed [Email correspondence provided in Appendix IV]. However, the study would need to be registered as a service evaluation at the Trust and would need approval from the internal audit team at the Trust. A service evaluation protocol was therefore

formalised and submitted which was approved by the internal audit team at the Trust [Approved study protocol provided in Appendix IV].

5.5.2 Case Study Methods

Following the approval of the service evaluation, the aims and objectives of the service evaluation were presented at a weekly IPC meeting which included the IPC manager, IPC data analysts, the Director of Infection Prevention and Control, and the Chief of Nursing. At this meeting two business cases related to AbR were brought to my attention.

The first regarding an '*on-site HPV / UV (hydrogen peroxide / Ultra violet) hybrid decontamination service*' to enable quick identification of decontamination of CPE outbreaks the Trust had been dealing with over the past two years. The second was regarding a 'Surgical site infection' (SSI) surveillance programme again to enable quick identification and control of SSIs.

It was decided to include discussion of these two business cases within the semi-structured interviews with the stakeholders. In this way the business cases could be used as example scenarios during the interview process, to understand how different stakeholders made decisions based on the evidence provided within them. Additionally, these business cases would help with understanding of how the objectives of the business cases weigh up against the other priorities in the Trust, if at all.

5.5.2.1 Semi-structured interview schedule

The two main research questions this interview study was aiming to answer were as follows:

1. What are the challenges of controlling and preventing AbR at the Trust?
2. How are decisions being made related to investment/resource allocation related to the control and prevention of AbR at the Trust?

To facilitate appropriate answers for these two research questions and to create a more open discussion to enable richer data collection, a Topic guide was created drawing on the results from the 16 Trust study.

The Topics included the following:

- Risks of AbR in a healthcare setting
- Interventions implemented to target AbR (included additional IPC measures)
- Challenges:
    - At an overall Trust level which impact AbR as well as specific to AbR
    - Related to implementing interventions at a Trust level, which impact AbR as well as specific AbR level interventions
- Decision making related to resource allocation of Trust finances (specific to IPC and AMR)

Open-ended questions were framed to elicit both subjective views and personal stakeholder opinions as well as a positivist view (e.g. facts rather than opinions) approaches (see Section 5.2.1.1 for explanation). For example, when it came to questions regarding the risks, interventions, and challenges of tackling AbR, a positivist line of questions was adopted where the facts related to sequence of events, the behaviours of different stakeholders were asked to enable a more open conversation with the stakeholders.

Please see Participant Sheet in Appendix IV for an example of questions and order of questions which were asked to each participant.

5.5.2.2 Stakeholder selection and contact

A stakeholder was someone who was involved in either:

- Making a decision on implementing an intervention related to AbR or,

- Proposing to adopt, implement, currently Implementing, or helping to implement an AbR related intervention at the Trust

Using the Trust board meeting reports, a shortlist of stakeholders (i.e., participants for the interview study) involved at a functional and an operational level, and who would be involved in IPC and AbR decision making processes, was created. This shortlist was then discussed at the Trust IPC meeting, where further suggestions on potential interviewees from different stakeholder groups were made.

All potential stakeholders were contacted via email. If the stakeholders agreed in writing via email to be interviewed, then a copy of the service evaluation protocol was sent to them and a date and location was arranged.

5.5.2.3 Data collection

All interviews were recorded and then outsourced to an external professional transcription agency (www.Rev.com) to be transcribed. Following the transcription, the scripts were checked against the recording when any discrepancies were identified. Initial data coding took place soon after the interviews had been transcribed and this helped inform the conversation in subsequent interviews. For example if a particular challenge the Trust was facing was identified (e.g. financial constraints) within one interview, this was also subsequently discussed and added to the Topics with the next interviewees. In parallel to the interviews, a reflective journal of how the interviews were going was also kept. As a result, this reflective journal helped to some extent maintain an objective approach when coding the interviews, so as not to mix what I 'thought' versus what the stakeholder actually said.

Within such qualitative interviewing studies, it is the norm to stop data collection once thematic saturation has been reached. However, in the case of this study, I aimed to interview all possible stakeholders who were available and willing to be interviewed to gain a holistic overview from as many stakeholders as possible.

5.5.2.4 Data analysis

The inductive coding methodology recommended in Charmaz 2006 and Sbaraini *et al*., 2011 was used to guide the data coding process (189,192,203). This coding methodology usually takes a two-step approach, initial coding followed by the focused coding, both of which are described in more detail below. Bearing in mind the coding methodology introduced by Glaser and Strauss (Section 5.2.1) when conducting qualitative research, the interview transcript coding methods of this chapter are anchored around these guidelines.

Initial coding:

As a first step I read the entire transcribed interview, correcting for any discrepancies between the recording and the transcriptions. The reflective journal was closely consulted when checking for any inconsistencies between the replies to the questions being asked from the transcribed script. Reading the entire interview script helped me gauge an understanding of the stakeholder's core messages and their general and personal stance on the questions that were asked.

An initial line by line open coding of the individual interviews was conducted as this was a more efficient way to code the data collected from these interviews. Line by line coding also increased the chance of coding within the context of the stakeholders' reply to the questions. In rudimentary terms line by line coding means reading an answer given by the interviewee and categorising it every sentence at a time, the categorising is called 'coding' within qualitative research.

The interviews were transcribed and coded immediately after they were conducted. I aimed to code the data as soon as the transcriptions were made available and while I was still conducting the interviews rather than waiting till all the interviews were completed. This method of coding is recommended to allow for incorporation of any new concepts emerging from the interviews within open-ended questions of the preceding interviews. Adopting this method of coding, supplemented by the notes from the reflective journal, also helped to highlight any issues with the way the open-ended questions were being structured or delivered to enable a more richer data collection process.

As a result of this immediate transcribing and coding technique I was able to provide stakeholders (in particular, the non-clinical stakeholders) with better examples of Trust specific terminology relating to AbR which they might be more familiar with (e.g. “the CPE outbreak”, “MRSA” as opposed to more generic “antimicrobial resistance” terms which they might be less familiar with).

Additionally, I realised that questions related to ‘resource allocation’ or how decisions were being made with regards to the business cases were not being understood or perceived very well by the clinical stakeholders. These questions were therefore slightly rephrased from ‘*What resource allocation related factors have you had to consider when making a decision on the recent AbR related business cases*’ to be a lot more open-ended (e.g. I started with opening questions such as: Have you been involved in making decisions surrounding a business case previously?). If the answer was a yes, then I asked further about *how they would decide on whether the business case was a cost-effective option*, followed up with *what factors they would consider help in making this decision?*

In terms of additional lines of questions or introduction of new concepts, no unforeseen concepts were explored apart from the questions related to the business cases that were identified following the study protocol presentation to the IPC team as mentioned previously.

Focused coding:

After all interviews were complete and initial line by line open ended coding was complete, focused coding was conducted. All the initial codes were compared:

a) with the data (i.e., the quotes or what the stakeholders were saying in the transcribed script) and

b) across all the stakeholders.

The similar initial codes were then grouped to identify the more frequently occurring initial codes (frequent in this case refers to two stakeholders being coded under the same initial code). Following the grouping of these initial codes the focused codes were developed and labelled appropriately to reflect and define what was happening in the data. During and after the data analyses stages, the

codes and emerging themes were discussed with my supervisors to arrive at a consensus about their meaning. Figure 55 provides the results of the initial codes followed by the focused codes. Each theme will be discussed in detail in Section 5.5.3.

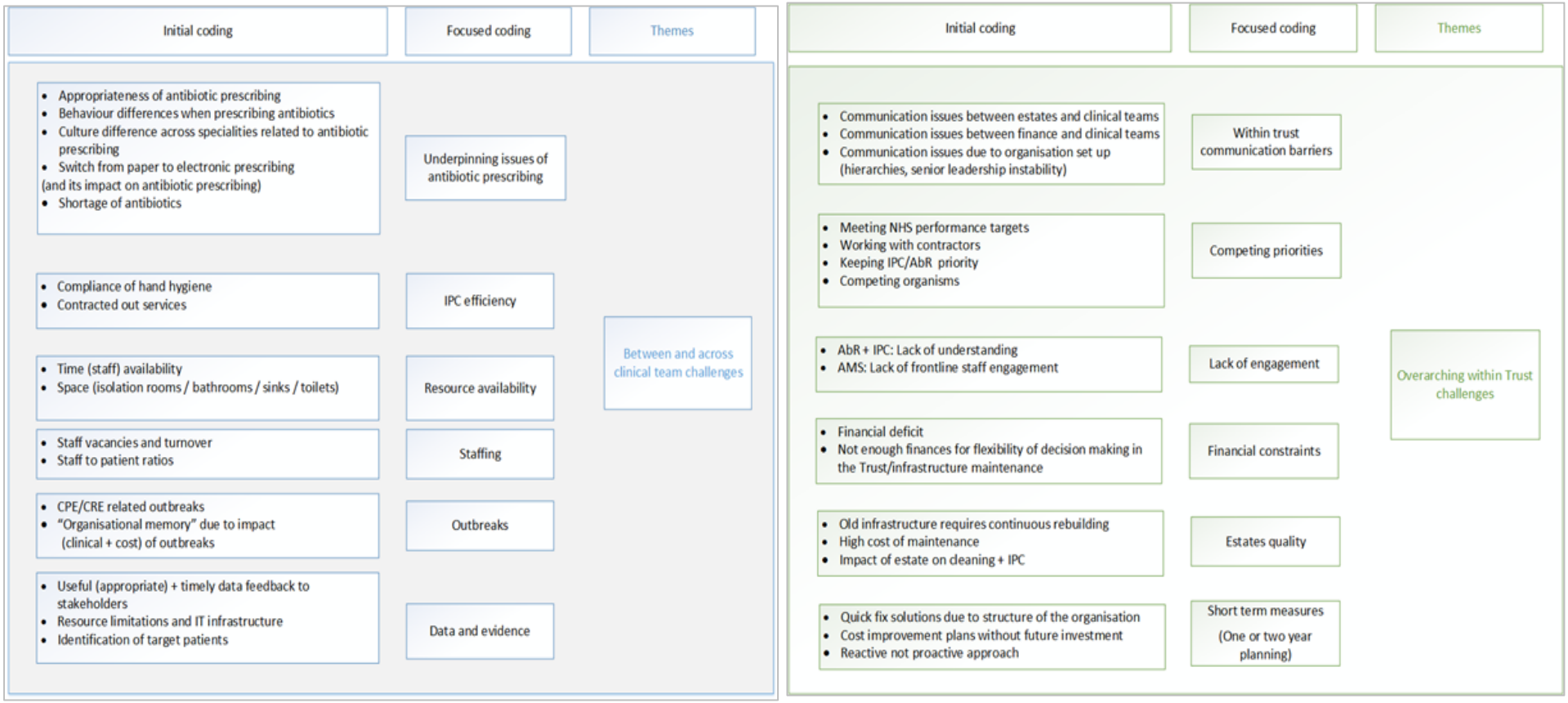


Figure 54: Themes highlighting the challenges of tackling AbR at a National Health Service Trust (1/2)

Abbreviations: [AbR = Antibiotic resistance; AMS = Antimicrobial stewardship; CPE/CRE = Carbapenemase producing/resistant Enterobacteriaceae; IPC = Infection prevention control.]

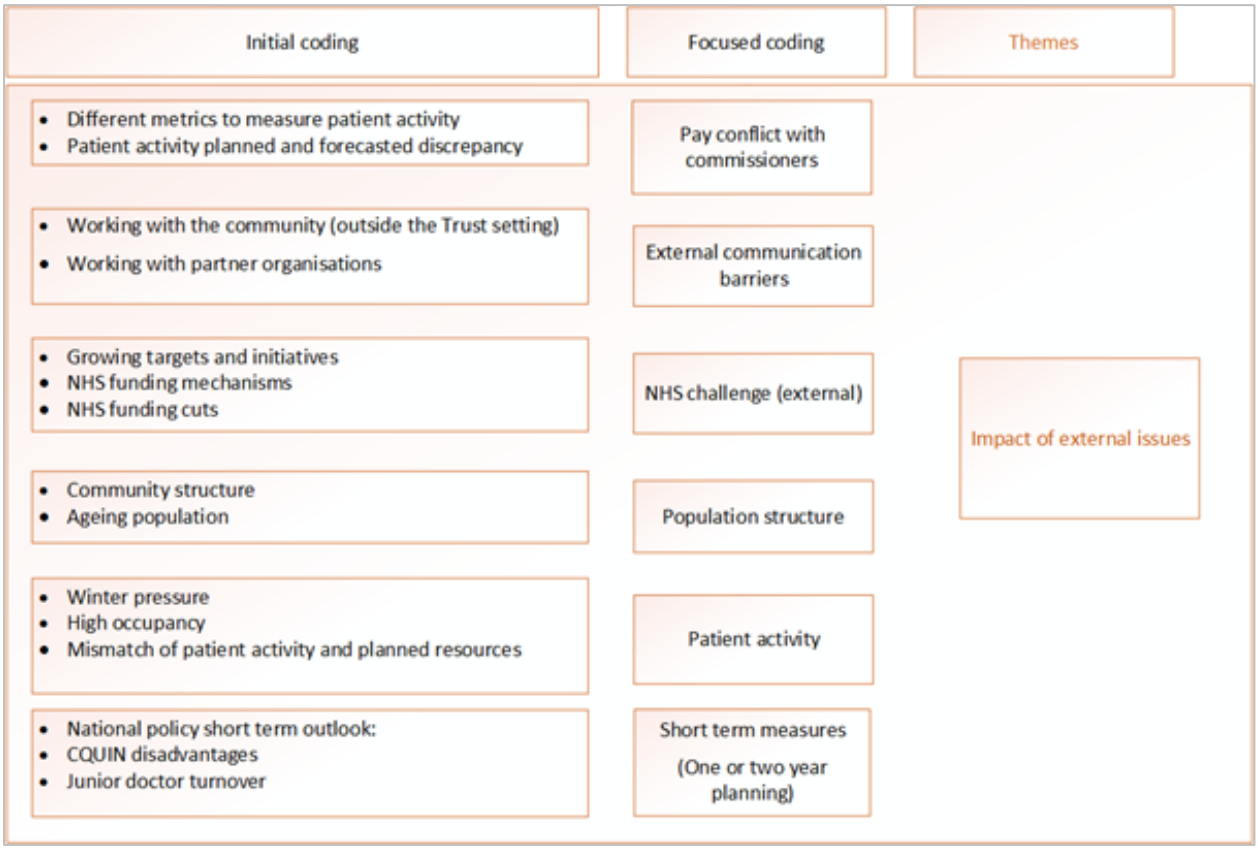


Figure 55: Themes highlighting the challenges of tackling AbR at a National Health Service Trust (2/2)

Abbreviations: [CQUIN = Commissioning for Quality and Innovation (framework for AbR); NHS = National Health Service.]

With regards to the first research question related to the challenges of tackling AbR in the Trust, the challenges could be split into frontline, clinical-specific challenges and overarching Trust level strategic and operational challenges. To bring all the codes together to understand the overarching Trust level issues, an overarching framework was constructed guided by the axial coding methodology. This methodology helps to bring the association between the themes together in a systematic manner (192). Charmaz et al. (189) do not discuss the need for an axial coding framework, but for the purpose of this particular research study, an axial coding framework was felt to be a useful tool to answering the multifactorial research question of the challenges of tackling AbR in such

a complex setting, as well as streamlining the interview codes to help fit them within a systems thinking approach as discussed previously in Section 5.2.1.3.

Axial coding, systems thinking, and causal loop mapping:

To help bring together the individual open codes, researchers often prefer to use the axial coding framework to categorise the data (open codes) in terms of a model that seeks to explain (189):

1) The *causal* relationships between the open codes potentially impacting the central problem (or research question).

2) The core issue(s) possibly driving the open codes (or the research question overall).

3) The *strategies* adopted in terms of how these are impacted as a result of the:

- *context* of the study setting and
- *conditions* being experienced by the stakeholders

6) The *consequences* of the strategies being adopted by the stakeholders when dealing with the central phenomenon identified from the interviews or the research question.

Axial coding brings together the open codes for all the research questions in the study, to create an understanding of the relationship between each of the open codes within the overarching context of the study setting. It helps create a framework to identify the cognitive distances (188) between the various themes which are grounded in data from the interviews.

Axial coding is not a technique necessarily always adopted by all qualitative researchers and quite often the qualitative study is discussed only in terms of the open codes (initial and focused codes) and the overall themes are deemed sufficient to answer the research question under study. However, as previously mentioned, considering the complexity of the challenges of tackling AbR with the various system level and ground level drivers of AbR, it was necessary to understand how the themes might inter-relate to one another, what these causal links between the themes may or may

not be, and if there was a central phenomenon driving the themes(204). Figure 56 below shows the overview of the framework that was created following application of the concepts discussed so far. Section 5.5.5 discusses this framework is greater detail below.

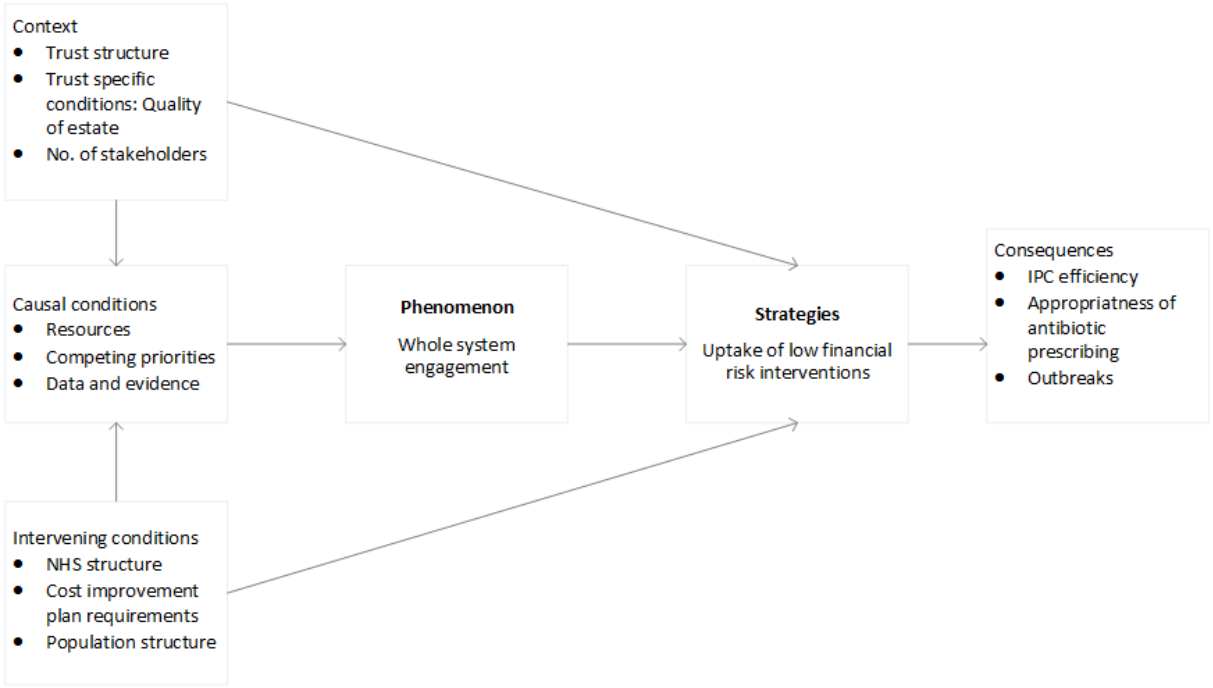


Figure 56: Axial coding framework to understanding the challenges of controlling and preventing AbR in the Trust

Looking at the codes in terms of the research question on the potential challenges of tackling AbR helps identify the phenomena underlying the disjointed issues identified from the interviews and thus enables policymakers to identify the root causes to guide effective interventions. One can thus draw parallels (204) between axial coding techniques in qualitative studies and causal loop models commonly developed in the field of 'qualitative' systems thinking approach (Part 3 of this chapter), as discussed in Section 5.2.1.3.

5.5.3 Case Study Results

Out of the 27 stakeholders contacted via email with an overview of the service evaluation, 23 agreed to take part in the interview. The interviews were conducted over a 6 month period (October 2017-April 2017) following internal audit approval from the ICHCNT audit team.

Table 20: Sample overview and characteristics

Speciality	Sample size (%)	Workplace type/Profession	Case numbers
Directly Involved in patient care (Case number starts with 'A') - Will be referred to as '*clinical* stakeholders '	15 (65%)	Infection prevention control (IPC) team IPC nursing team Non-IPC nurse team Pharmacist Microbiologist Medical directors (at variable capacity: incl. executive team/ board member/ IPC team) Quality and improvement team IT team (included clinicians)	Case A001 – A015
Not directly involved in patient care (Case number starts with 'B') Will be referred to as 'non-clinical' stakeholders	8 (35%)	Estates and facilities Finance team Executive team Business development team IT team (did not include clinicians)	Case B001-B008

Participants who did not respond (n=4/27) included: 3 from patient focused and 1 from non-patient focused roles in the Trust. The non-responding stakeholders or their personal assistants were contacted two to three times over the consecutive months. However, following a third attempt to either re-schedule or schedule an appointment, the stakeholders were not contacted any further.

5.5.3.1 Topic 1 – Overview of risks of AbR

The first Topic that was discussed in the interviews with stakeholders at the Trust was related to the risks of AbR at the Trust that the stakeholders objectively see during everyday practice. . The stakeholders directly involved in the patient care pathway were able to understand and respond to the questions surrounding the risks of AbR at the Trust in greater depth than the stakeholders who were not involved directly involved in the patient care pathway.

Starting with the answers received from the non-clinical stakeholders, these were more specific to infection control and issues highlighted by the IPC teams during Trust board meetings. Therefore, the non-clinical stakeholders' knowledge of risks of AbR were gained mainly through the clinical teams

The key overall theme in the answers gathered from both the clinical and non-clinical teams was with regards to the current state of the estate, and how the secondary care environment acts a key transmission route for AbR. The increasing risk of CPE outbreaks within the Trust was common knowledge across both these teams and the need for intensive cleaning such as the use of HPV decontamination was most often brought up by the non-clinical teams.

Box 3 below provides a number of quotes from stakeholders involved within the patient care pathway which gives a brief summary of how and why the hospital environment can escalate and spread that one resistant infection which may have been brought into the hospital from the community. One stakeholder describes the hospital environment as an optimal pathway for transmission of these AbR infections. Another describes how antibiotics are used differently in hospitals to the primary care setting, which help facilitate the development of resistance. These points closely resonate with some of the findings from Chapter 4 regarding the role of the community as well as the national level challenges identified and discussed from the document analysis of the Trusts around England. The high levels of unplanned care which is affecting the number of beds to staff, toilet and general hospital resource ratio are also mentioned to be impacting the risk of AbR. One stakeholder discusses the issue of competing priorities when it comes

to junior doctors. The stakeholder states that due to high demand for services Junior doctors have to choose between for example the immediate safety of the patient or following hospital protocol and waiting for blood cultures prior to prescribing antibiotics.

Increased risk of AbR across certain units such as renal and haematology were identified by some stakeholders. Patients within these units are more vulnerable compared to the general ward of the hospital, for example they often have underlying comorbidities and are immunocompromised. These factors were also identified within the Systematic review in Chapter 2, where underlying disease was a commonly reported risk factor for AbR.

Some stakeholders also discussed a recent phenomenon that at the time of the interviews was starting to become an issue at the Trust. At the time the interviews were being conducted a number of antibiotic shortages at a global level was impacting clinicians' ability to prescribe certain antibiotics. One stakeholder in particular discussed how this had an impact on their ability to restrict carbapenem use at the Trust. Limiting carbapenem use was a restrictive policy being implemented to preserve the antibiotic since it is a last-line antibiotic needed to treat infections caused by certain resistant bacteria which cannot be treated with other antibiotic classes. In summary, the risks commonly identified from the stakeholders related to either the hospital environment itself, transmission within the healthcare setting due to other patients being colonised by an AbR organism (e.g. for CPE), underlying patient conditions and admission to wards where more vulnerable and immunocompromised patients may be admitted (e.g. the renal and haematology wards), intensity of antibiotic use, the current limitations on resources due to patient flow increasing the level of unplanned care, and antibiotic shortages.

BOX 3: Risks of AbR

"I think also we've had a massive impact from antibiotic shortages recently that have made it quite difficult to restrict our carbapenems use as we would like due to a shortage of other antibiotics." (Case A007)

"secondary care in general I think because we are a bit of a hub for developing resistance. High acts [activities] of patients come in ... They are more likely to be more sick or having resistant bugs but I mean we've also got an environment where it encourages development of resistance so lots of antibiotics are being used. We're using them in different ways to primary care. We're also moving patients quite a bit ... we've got, it's a very warm, good breeding ground for bacteria in general." (Case A008)

"But the doctors in training are ... you know, they're stretched very thinly. They know the right thing to do. But actually the safe ... Sometimes the safe thing to do is not to spend the time getting the samples [cultures to identify what organism it is for appropriate prescribing]. It's to give the antibiotics because they actually have to go and see somebody else in five minutes. So ... And there aren't enough of them to delegate some of those tasks to other people and say, "Could you take those samples? I need to go and see the other person."" (Case A004)

"But I just wanted to mention about pathways because we have designed admission pathways that are the perfect, perfectly engineered systems for the maximum transmission of organisms. So you admit people to a holding area, an admission area, largely with very little isolation and then you move them all over the place. So you've designed a place and a pathway for maximal transmission and then what you do you move people around……. So we have people shoving more and more beds into bays and there's still only one toilet for all those people and it's an enteric organism …….So the whole issue about enteric pathogens and pathways and toilets and care around that in terms of the environment, personal hygiene and also best practice on the wards is a major challenge. And the other thing is you need to remember that whilst we can criticise and we need to improve practice continuously that will always be compromised if you have inadequate staffing ratios.." (Case A010)

"And also in the areas where we have identified problems, say, renal and haematology, the intensive care unit and the vascular units. And those happen to also be the same units that get the increased rates of CPE. So conveniently the two kind of go together. They're also the patients who have the biggest challenges." (Case A007)

Abbreviations: [CPE, Carbapenemase-Producing *Enterobacteriaceae*]

It is a challenge to comment on what was deemed the most important risk from the interviews with the stakeholders because not all stakeholders were aware of what these risks might be. Different risks were highlighted by different stakeholders. The most commonly mentioned theme was related to the current unplanned care pressure which could be impacting the transmission of AbR organisms.

5.5.3.2 Topic 2 – Overview of interventions

The second Topic discussed in the interviews was the types of interventions that were being implemented in the Trust to tackle AbR. Similar to the results from Topic 1 (for risks of AbR), the stakeholders who are involved in the direct patient pathway (the clinical stakeholders) were better able to understand and answer this question with some degree of granularity.

The non-clinical stakeholders primarily described the standard infection prevention and control interventions which are in place in the hospital, in line with what the Health and Social Care Act recommends and holds the Trust accountable for. In particular, cleaning (e.g. in terms of surgical instruments) and hand hygiene targets were most often discussed. It can be speculated that these stakeholders felt under pressure to mention IPC related interventions since I was a researcher looking into AbR. These were interventions they may have been were aware of that should be implemented in the Trust, but they may not have had any personal experience with implementation or execution of these interventions.

However, the business cases briefly discussed under Section 5.5.2 were also discussed as examples of AbR related interventions by the non-clinical stakeholders. Following a CPE outbreak the externally contracted HPV decontamination procedure was the most prominent intervention highlighted, apart from the standard hand hygiene related interventions. Therefore, it can be assumed the occurrence of a CPE outbreak had greatly increased the organisation's awareness of the repercussions of AbR organisms and the extent of infection control required to tackle such infections. Additionally, MRSA

had previously raised the profile of hand hygiene in particular as discussed in one of the quotes by a non-clinical stakeholder.

Antimicrobial stewardship or control of antibiotic use was not identified as an intervention by the non-clinical stakeholders. However, the clinical stakeholders primarily focused on appropriate antibiotic use and current antimicrobial stewardship programmes that were implemented at the Trust. One stakeholder who was involved with the Trust's stewardship programmes, provided a good overview of the programmes and its four elements.

The more granular interventions[16] discussed by the clinical stakeholders were in line with the 16 Trust study. Antibiotic audits, formulation of an antimicrobial stewardship team to guide audits, guidelines and education and awareness, IPC audits, and implementation of electronic prescribing were the key interventions that were talked about when Topic 2 was discussed with the stakeholders. Within the Trust the ward rounds surrounding patients who were on antibiotics formed a key part of the interventions strategy and was discussed by some stakeholders.

In summary, there appeared to be a different level of awareness regarding interventions related to AbR between the clinical and the non-clinical stakeholders. The clinical stakeholders were more aware of the ground-level details of stewardship programmes tackling antibiotic use and AbR. On the other hand, the non-clinical staff especially within the Estates and Facilities and Finance departments, were more aware of the overarching infection control and outbreak related interventions.

Overall it should be noted that themes identified from this particular Topic were not extensive, there was a lot of repetition from non-clinical stakeholders who either focused on IPC measures or the HPV intervention.

[16] Granular interventions mean interventions that fall under the overall antibiotic stewardship programmes or infection prevention and control such as hand hygiene

BOX 4: Interventions and AbR

"the stewardship program within the organization, and that in my own head, has four key elements. One is a clinical element, one is an education and training element, one is a surveillance and epidemiology consumption of antibiotics and how we use those antibiotics effectively. Then the fourth domain is the research domain and how we can collaborate with various institutions on various technology innovations, et cetera." (Case A012)

"Other than that, the interventions, I mean obviously hand washing is always one. It's always up there. Hand washing. I wouldn't say I'm necessarily aware of any other specific interventions. Certainly MRSA and C. Diff are what I would now call just routine." (Case B003)

"So, we have to have a separate pool of instruments for high-risk surgery for patients that are having surgery. So, we have to now have a separate pool of coloured instruments." (Case B004)

"So in the last three years, for example, I briefly mentioned that I've seen two business cases. One was around surgical site infection ….HPV business case, which has not come to DSP [Decision support panel] just yet." (Case B001)

"So there was one that came yesterday ... it came to Decision Support on Monday and we had a further discussion with them at the Capital Steering Group yesterday. Around ... is it HPV? So this was [redacted] *business case that* [redacted] *brought, where we currently have a cleaning service internally that is provided by an external company but done on an ad hoc basis." (Case B006)*

Abbreviations: [DSP = Decision support panel; HPV = Hydrogen peroxide fogging]

5.5.3.3 Topic 3 – Challenges of tackling AbR including overarching Trust challenges

The penultimate Topic discussed within the interviews was related the challenges the Trust was currently facing including AbR and the difficulty of tackling AbR. The bulk of the interview time spent per stakeholder comprised of the Topic on challenges of tackling AbR and overarching system level challenges faced by the Trust.

Following the opening Topics 1 and 2 regarding risks of AbR and interventions implemented to tackle AbR in the Trust, it seemed the stakeholders were more comfortable discussing the challenges across the Trust and did not feel under pressure to answer questions in a more restrictive and reserved manner as was noted for Topic 1 and 2. Therefore, the overall aim of this Chapter was to identify the process-level factors which policy implementers may face on the ground during implementation of a particular intervention or tackling AbR and related infections in general was successfully discussed with all stakeholders.

Following the initial coding of the interviews, 48 initial codes were developed from the stakeholders' answers. These 34 initial codes were then condensed into 18 focused codes. From these 18 focused codes, 3 key themes were identified which could be seen to drive the current challenges the Trust was facing, some were related to AbR specifically and some were interlinked with AbR and the overall Trusts' system level factors.

Figure 55 previously presented in Section 5.5.2.4 provides a detailed overview of the initial codes condensed into the focused codes and finally the three themes which arose from the interviews analyses which were driving the AbR specific challenges the Trust was facing at the time of interview, Appendix Table 18 in Appendix IV includes the overview of these initial and focused codes with some exemplar quotes which helped shaped the initial, focused codes, and the theme.

The first theme was related to the challenges the clinical teams are facing, the second theme was specific to the overarching Trust specific issues. The third theme was related to the pressures the Trust is facing from outside of the Trust, so the external pressures from the immediate surrounding community and from a national perspective.

Starting with the first theme 'Between and across clinical team challenges', this theme was most relevant for the AbR related challenges that the Trust was facing. The behaviour, culture, adherence to prescribing guidelines surrounding antibiotic prescribing was discussed by a number of stakeholders. The implemented infection prevention control measures were seen as a particular problem at the Trust. In particular the clinical teams' relationship with the contracted-out services who were in charge of cleaning was highlighted a number of times. Lack of time to think differently about tackling AbR was highlighted by one stakeholder. A lack of resources was discussed as a key barrier to tackling AbR. The following examples were provided when it came to the lack of resources, staff availability, time to complete tasks, and availability of isolation rooms for CPE patients were reiterated as an increasing issue at the Trust. The year before the interview, the Trust had suffered a number of CPE outbreaks. Therefore, the stakeholders emphasised the repercussion of a CPE

outbreak on ward closures and increasing costs of tackling the CPE outbreaks at a time when the Trust was already facing financial setbacks. Last of all, the drawbacks of a lack of efficient data and evidence dissemination within the Trust was mentioned by a number of stakeholders. Specific to AbR, the need for an efficient IT structure to enable clinical teams to audit patients on antibiotics more efficiently was discussed. One stakeholder discussed how it is not possible to review all patients on an antibiotic seven days a week. Another stakeholder emphasised that a list of high priority patients who needed early review could be a better method of conducting ward rounds (related to antimicrobial stewardship) at the Trust rather than trying to identify such patients one by one. However, one stakeholder stood out in particular with their view on how data and evidence could be used more effectively to feedback prescriber behaviour from the already implemented electronic patient record system. Therefore, usage of data for measuring improvement rather than purely regulation was highlighted as a current barrier to tackling AbR.

BOX 5: Underpinning issues of antibiotic prescribing

"That data should be playing back to us so that you could send them back to me and say out of the nine consultants, I'm the eighth good at it [prescribing practice related], and actually I could be given support and help to improve and get better. When does anybody ever give me that data? They don't. They report it up centrally. People ask for action plans and action plans don't turn into action. We have to measure for improvement. This is so incredibly important and so deeply cultural. The culture of data in this country is they use it for regulation and for commissioning purposes and what we want to do is to use it to measure it for improvement and give the data to local teams…….over the year, we've had an electronic patient record. We still have no data from there to tell us and support us in our work." (Case A001)

"…think one of the challenges is then to get them [AbR + AMS related messages] filtered back down, to the people who are doing the prescribing. And so I think that you probably need to target multiple levels at the same time….
I'm not convinced that appreciation is there, at the lower level of the people who are prescribing….. and if you aren't a clinician who's been involved in an outbreak, why would you think that you doing that IV to oral switch is so important." (Case A007)

Abbreviation: [AbR = Antibiotic resistant; AMS = Antimicrobial stewardship]

The second theme 'Overarching within-Trust challenges' was related to challenges the Trust was facing at a broader level which also included AbR. These broader Trust level challenges were also impacting some of the challenges identified within theme one, such as resource availability and the

efficiency of IPC measures. One of the key challenges which all stakeholders unanimously spoke about was related to the quality of the estate at the Trust. The majority of the Trust level challenges hinged on the quality of the estate. Therefore, other challenges such as financial constraints were further being aggravated as a result of the quality of the estate. Under theme 1 (on clinical team level challenges), the quality of the estate was mentioned, particularly related to how it has been impacting IPC efficiency and resource availability. Following quality of the estate, the second Trust level challenge all stakeholders discussed was related to the financial deficit that the Trust was currently in and had been since the previous year. Cost improvement plans were developed to generate additional income to overcome the financial deficit. Some stakeholders described the primary goal of cost improvement plans to create efficiency within the boundaries of the resource constraints the Trust was facing. In other words, making the most of the current resources available at the Trust. A number of stakeholders also discussed how the current financial position of the Trust was limiting the Trust's ability to make long term financial commitments. With most financial commitments being focused towards meeting the demands of the estate and making long term plans to build newer parts of the old estate. Linking in with the financial commitments was the concept discussed by some stakeholders, of the implementation of short term measures which they saw as a reactive rather than a proactive way to tackle the current Trust challenges. One placeholder pointed out that AbR was a good example where the problem has been a part of the Trust for a long time, it is not a new phenomenon the Trust was facing, it is a long term problem needing a long term solution. Although the current structure of business cases did not make room for long term planning for such long term problems.

BOX 6: Competing priorities

"And then I think the only other challenge is, sometimes because of the way things are organised or the way NHS targets work, it can mean that differently people have slightly different agendas, and sometimes they conflict with one another. And finding a way to sort of bring those together can be a challenge." (Case A003)

Within the second theme, besides financial and estate specific challenges, three thought-provoking focused codes were also identified from the interviews. The first was associated with communication across different stakeholder groups. In particular the estates, clinical teams, and the financial teams. The differing language and lack of understanding across these teams were reported to add to the challenges in the Trust. Following on from communication between these three crucial teams in the Trust was the challenge of competing priorities. Some stakeholders spoke about the issue of competing priorities as a challenge in general in the Trust due to the way the NHS targets are set up. Competing priorities was also discussed as a problem when it comes to prioritising AbR and antibiotic prescribing, or AbR related organisms for isolation rooms over other life-threatening organisms and priorities at the Trust. It should be noted that competing priorities was also discussed in terms of lack of resource availability which was fuelling the need to prioritise for example staff time or isolation rooms. The last of the focused codes under theme 2 was concerning the lack of engagement surrounding AbR related activities at the Trust. Lack of engagement was discussed as an issue amongst antibiotic prescribers on the ground. One stakeholder in particular discussed how until a clinician is part of an AbR related outbreak scenario, they would not understand the complete repercussion of not prescribing antibiotics appropriately. There also seemed to be a mismatch between how some clinical stakeholders felt about IPC and AbR, so some stakeholders were more engaged with the importance of IPC measures over measures tackling antibiotic use such as stewardship. Topic 4 discusses Trust wide engagement in detail.

The last theme ‘Impact of external issues’ was related to the challenges the Trust faces due to the immediate surrounding community and overall NHS structure and policies. The population structure and patient activity were two crucial focused codes identified which impact resource availability and further heighten the challenges of tackling AbR at the Trust. An ageing population and unplanned

patient activity during the winter period often cause black alerts[17] at the Trust. During the time period that the interviews were being conducted the Trust was just coming out of an extended period of being on black alert. During these periods the Trust was under extreme pressure to deliver additional levels of patient care with limited additional resource availability in terms of staff and space. Given the quality of the estate at the time the interviews were conducted, these periods likely created increased risk of transmission of AbR related organisms. Within Topic 1, where the risks of AbR were discussed, a number of stakeholders discussed about how unplanned patient activity required additional beds to be added to wards, increasing the patient to toilet ratios, and creating increased demand for the already limited isolation rooms available. Aside from these pressures, a number of stakeholders also discussed some of the challenges of the current policy measures that were being implemented. During the course of the interviews, the advantages and disadvantages of the national CQUIN target related to antibiotic prescribing and Gram-negative reduction was discussed to a great extent which was a useful outcome from a policy perspective. Some stakeholders perceived the CQUIN targets as a short term focus for a long term problem. Again, the concept of a reactive as opposed to a proactive approach to policy implementation was discussed. Some stakeholders mentioned that collecting the relevant data to inform the CQUIN target would require additional staff to be hired, for which they had insufficient resources. Therefore, it was felt to be worth it to forgo meeting the CQUIN target and lose the additional money the Trust would have received. Some stakeholders also seemed a bit unhappy with the concept of CQUIN, since they saw the CQUIN target money to be the Trust's in the first place.

[17] Black alerts refer to the scenario when the Trust is running at maximum capacity and new patients are being redirected to nearby hospitals.

BOX 7: Short term measures

"I don't think.. a CQUIN particularly helps for this [AMR/prescribing] sort of thing because all it does is gives you a short-term focus on a problem. And the big issue is generally, you're junior medical staff, who will only be here for usually half the life cycle of a CQUIN and then move on to another organization. So what generally happens with a CQUIN is, if we know we got a CQUIN coming up we will spend some the money on employing some more pharmacists to help the antibiotic stewardship but they don't become embedded in the system, so when the CQUIN ends you lose the pharmacists and instead of trying to tick that box for the short-term , it's almost like you should probably..[be] thinking about how you educate about the management of bacterial infection and also about the, why do you do antibiotic stewardship?.. And I think [this] is a very short-sighted approach to what is actually a big cultural problem" (Case A006)

Abbreviations: [AMR = Antimicrobial resistance; CQUIN = Commissioning For Quality And Innovation]

5.5.3.4 Topic 4 – Business case decision making

The last Topic discussed with stakeholders at the interview was related to the two business cases associated with implementing interventions to tackle AbR at the Trust. A business case template requires a background summary of what the problem is at present in the Trust using individual patient case reports of incidences. These case reports are then further backed up by what is published in the wider medical literature. Within both the individual case reports and the wider medical literature, the cost consequence of the problem features significantly and forms the basis for the argument of why the problem requires an intervention at the Trust.

Following on from the rationale of why the business case is needed, the document requires information on current arrangements in place in the Trust, the challenges associated with these arrangements and how this intervention can help overcome the challenges.

The problem the intervention is aiming to minimise is then discussed in more detail from a regulatory and Trust's strategic objective point of view. Both the financial and non-financial benefits are emphasised further. The intervention which is the proposed business plan is then provided, with a number of options, one of that includes not making any changes.

The following financial and non-financial repercussions of the intervention are then provided:

- Total cost and time horizon required to execute the intervention
- Cumulative discounted cash flow needed for the intervention
- Net present value of the intervention
- The year the intervention will start paying backing from
- Cost impact and cost benefit of the intervention per across the divisions in the Trust
- *Return on investment (payback period)
- *Strategic fit
- *Statutory/regulatory compliance
- *Operational/patient safety
- *Clinical benefit
- *Patient experience
- Financial and non-financial risk and benefits
- Stakeholders in charge of executing the intervention
- The accountability of the intervention following implementation per division within the Trust

*items with asterisks are used as a scoring tool

This description of a business case is only based on the two business cases that I was provided with by the IPC teams. However, the Trust does use a similar template for all of their business cases.

One business case related to investing in decontamination equipment (known as HPV fogging) which would help identify and eradicate CPE from a room after an outbreak or after patient has been found to be colonised by the organism. The Trust was already getting an external contractor to provide this service however, due to contracting and ease of logistics, the IPC team were trying to develop a business case to bring the services in-house.

The second business case was regarding setting up an SSI surveillance system in the Trust to help identify surgical site infections (SSI) early. The primary motivation behind the SSI system was for the Trust to provide data for the mandatory surveillance requests which need to be submitted to Public Health England. At the time the proposal was submitted, the Trust was struggling to gather resources together to collect this data on SSIs in the first place. Secondly, the SSI system would also enable areas of improvement by identifying which surgeries are associated with higher infection levels.

The key difference between the two cases was that the former was already being used in the Trust, and stakeholders across the estates, clinical team, and the finance teams were aware of the intervention and the clinical effectiveness of the intervention to the Trust due to the CPE outbreaks.

In particular for the SSI business case, the proposed interventions needed to be approved by all the divisions (affected medical specialties) who are affected by the intervention implementation as well as the following departments:

- Emergency & Critical Care
- Affected surgery specialties
- Cancer & Specialist Care

- Family & Public Health
- Finance
- Procurement
- Information community and technology
- Human resources
- Business Planning and Development
- Information
- Clinical Support Services
- Medical Physics
- Service Development team
- Estates

Based on the examples of the two business cases, two themes seemed predominant, firstly the financial viability of the intervention paying off long term across all divisions and secondly the need for the whole Trust to be engaged with the interventions for them to sign it off before it goes to the Chief Financial Officer and their team to be signed off for implementation. Therefore, the cost of the intervention and Trust wide engagement were the key factors necessary for a business case to be considered viable based on the business case template alone.

Following the interviews,the stakeholders themselves provided a hierarchy of how decisions regarding finance would usually be made. This hierarchy system was also seen within the scoring tool items within the business case.

The interviews identified a number of themes which touched upon what is needed for a strong business case to be accepted and ultimately implemented in the Trust. These were: meeting

immediate patient safety needs, followed by a strong financial evidence base, which also includes epidemiological incidence and prevalence related data. The importance of Trust-wide engagement by the division heads was felt to be more easily attainable if the reason for the business case was either to meet an immediate patient safety concerns and if there was a sound financial argument for investing funds which would end up saving money or generating income in the long run.

The order in which decisions were made was commonly provided by the stakeholders, more than one participant discussed a hierarchy of factors which they felt had helped a business case to be ultimately signed off on. Based on this result the potential hierarchy provided in Figure 57 was created. In addition, the IPC team was also consulted following the creation of this model to sense check the hierarchy.

Selected quotes per element of the hierarchy have been provided below.

1. Importance of patient safety or regulatory guidelines over other priorities including finance:

"*And then, you know, look, there are situations where these things go to the executive and we have to be honest and say to the exec ""Look, this is a circumstance because there's a real safety issue or a quality issue or the Care Quality Commission (CQC) have identified something, that we can't necessarily get this business case to stack up on its own merits, in terms of the benefits outweighing the costs, but we still think it's a good thing for the organization to be spending money on and investing in because the clinical outcomes that it will deliver or the risks that it will mitigate are worth the investment*."" (Case B006)

"*sometimes the clinical risk to patients will outweigh any kind of financial viability argument." (*Case A013)

2. Need for a strong financial argument:

"*So, all business cases have to have, at a bare minimum, a financial position*." Case B005

"*But ultimately, for something to be approved, whatever that data is, it needs to be as fully quantifiable as possible, just purely because there's such scarce finance*" Case B001

3. Trust wide engagement:

"*But I think that prioritization takes place on a Trust-wide basis, looking at the available resource and the cost pressures from all areas. There's a process at the beginning of the year ... so at the moment ... as part of the business planning, where all of the divisions and corporate areas have got to put forward their cost pressures, which is where these business cases should also be playing into. And to get a decision made about what priorities across the Trust people want to fund. Because, the problem we have is, that funding only becomes available if people make savings elsewhere to be able to fund. So, there is a prioritization process that has to be put in place. That said, I think it's done in a Trust-wide way. And the divisions have got to be absolutely included in that*." Case A002

Despite the claim that most business cases are already robust before being seen by the executive team, and a large amount of evidence being provided within them, the final decisions made at the executive team meeting are dependent on peer consultation and expert opinion. Any business case therefore needs approval across the system, hence Trust wide engagement is another key ingredient following patient safety and a strong financial position.

Discussion with the IPC team responsible for creating these two business cases confirmed that this decision making process was something of a 'black box' for them. It was therefore difficult to determine from the interviews how exactly the ultimate decision of choosing one business over another gets made, but themes identified from this qualitative study represent important influences on decisions.

Previous studies conducted to investigate innovation adoption across a large number of Trusts identified that peer '*localised*' opinion was more significant than evidence from *'centralised'* published research when it came to gaining engagement with regards to adopting innovation(210). We can draw parallels with the strong financial argument theme which talks about the level of

evidence required for an innovation to be adopted. The importance of peer consultation and expert opinion was also identified across the different stakeholders in the Kyratsis et al. study(210). Within this study (210) certain groups of stakeholders were seen to rely on expert and peer opinion to a greater extent evidence-based research. Within a different context, regarding antibiotic prescribing decision making. Charani et al. (211) also found that peers have an influence of decision making. Therefore, within the hospital setting peer influence can be a key determinant of how decisions are made, whether that be in a clinical or a non-clinical context.

In summary, it is challenging to determine with a degree of certainty, a hierarchy within the resource allocation decision making regarding tackling AbR, as stakeholders involved are not always sure how the decisions are being made.

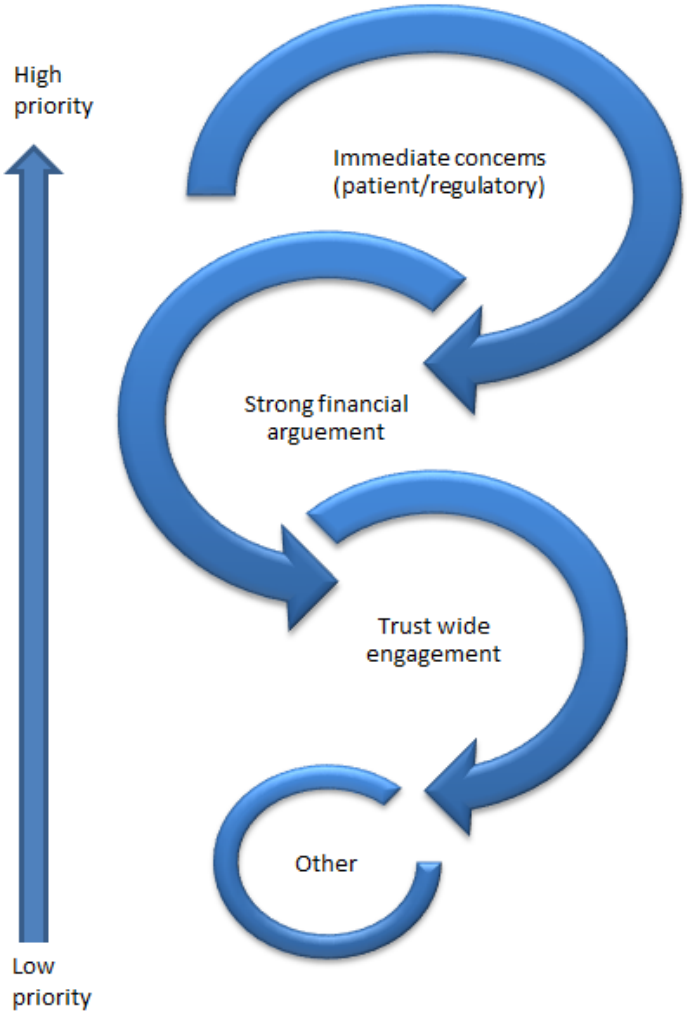


Figure 57: Visualisation of the hierarchy of the resource allocation decision making process

5.5.4 Personal reflection from the interviews

All teams across the Trust, and not just the clinical teams, were very much aware of MRSA and CPE as the key AbR issues. Improved control of MRSA means that CPE is now the key cause for concern and given the outbreaks that the Trust has experienced and the associated costs, awareness of AbR is all the more acute.

The sample included more stakeholders from the clinical teams than the other teams, so the viewpoint would be slightly biased towards the clinicians' perspectives. However, the challenges are being faced on the ground by the clinicians and it is important for the finance and estates teams to

have some idea about these issues. The size of this Trust impacts on communication and knowledge translation, therefore, the data collected from this Trust would be primarily applicable to a complex Trust of a similar size.

Since the stakeholders were aware that I was a researcher affiliated with the IPC team, it could have potentially biased the way the questions were answered. An example would be that the stakeholders who were not directly involved in patient care felt obliged to acknowledge that the clinical teams are always included in every step of the decision making process. They reiterated that patient safety comes first and would never be compromised due to finances.

5.5.5 Axial coding application

Building a foundation for a systems thinking causal loop model

As previously discussed under the data analysis methodology in Section 5.5.2.4, axial coding aims to uncover a central phenomenon that might underlie a research question. In my case, it was therefore important to use the data derived from the interviews to explore the possibility of a central phenomenon which was driving the other categories identified from the open codes. This required further analysis of the focused codes. From the interviews and the themes identified, we can make three observations.

First, based on the results of the business case Topic, 'whole system engagement' was a core theme underlying the challenge of successful uptake of new interventions to tackling AbR. Without the sign off from clinical and non-clinical team a long term large scale intervention cannot be introduced in the Trust. During the interviews, the business case related to HPV fogging[18] had already been signed off across the division and was close to implementation. However, the SSI surveillance system was still waiting to be signed off by a number of divisions. Additionally, Topic 3 also identified stakeholder engagement as a recurring challenge when it comes to tackling AbR on the ground. Engagement from

[18] Related to the decontamination business case discussed previously

junior doctors who are prescribing was discussed. Engagement in relation to effective infection control measures was also highlighted. Thus, without whole system engagement across the clinical and non-clinical teams (e.g. estates department or finance department), it is clearly a challenge to tackle AbR long term within the Trust.

Secondly, the causal conditions primarily contributing to the presence or absence of whole system engagement revolved around resource availability in the Trust, which then had an effect on competition for resources (leading to 'competing priorities') and how 'data and evidence' could be disseminated efficiently (e.g. related to timely availability of antibiotic prescribing data). For example, if there was an infinite amount of resources, the divisions in the Trust would not care about putting in some extra money towards a SSI surveillance system which would help identify further areas of improvement. However, because there are resource constraints, one division is having to prioritise certain areas that are of most concern to them over a SSI surveillance system.However, the IPC team have more of a vested interest, i.e., are 'more engaged' in developing this SSI system since they are in charge of ensuring that the SSI data is periodically sent to regulatory bodies and IPC improvement areas are identified promptly.

Thirdly, the overarching NHS structure also had an intervening role to play, the resource pressures in the Trust promoted the need to cut costs via cost improvement plans, and increased competing priorities due to performance target pressures. The population structure, in terms of the ageing population adding to the winter pressure burden every year, also has a further impact on resources. Thus, according the axial coding terminology the 'intervening conditions' outside the context of the Trust were indirectly impacting the 'central phenomenon' via the 'causal conditions'.

Next, the size of the Trust, with many services and stakeholders, and the quality of the ageing estate, were context specific factors which were continually brought up during the interviews, further adding to the causal conditions and hence the central phenomenon driving the challenges of tackling AbR.

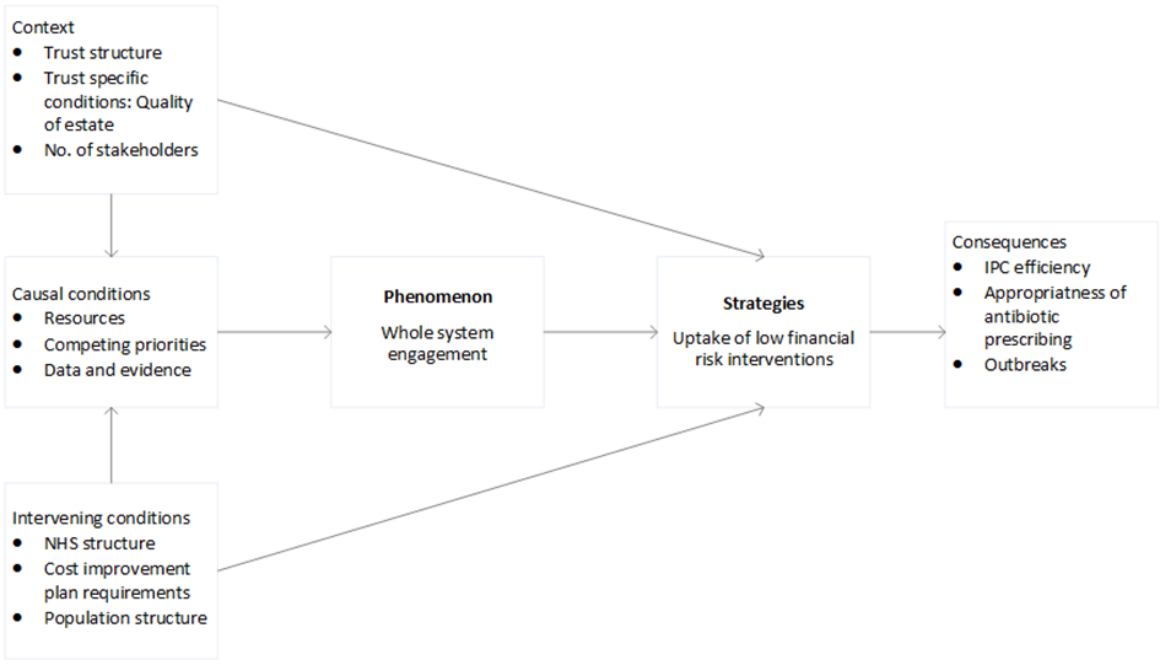
Based on the views on the business cases, and given the limited resource availability mentioned in the interviews, the strategies most often being adopted are those that involve very little financial risk. So, aside from immediate patient safety concerns, it seems unlikely that the Trust would easily gain whole system engagement for a financially risky intervention such as the SSI surveillance intervention discussed in Section 5.5.2.3.

Taking the SSI surveillance system as an example again, during the interviews the SSI business case was seen as the riskier business case compared to the HPV fogging one. The SSI business case was deemed riskier because it required a long term financial commitment with a risky payback period. Althoughthe HPV fogging business case would show immediate impact by identifying and reducing CPE organism related outbreaks. If we think about these interventions in terms of preventative and curative measures, the HPV business case is a curative measure which helps to eliminate CPE once it has already been identified and possibly spread. The focus of this curative measure is only to reduce a 'symptom' of the problem of AbR rather than a 'cause'. However, the SSI business case is a more preventive measure, which has the capability of identifying these infections and providing trends over time of where the problem areas are with infection levels at the Trust. In particular in the surgical units where antibiotics are used as prophylaxis. Therefore, such surveillance systems, although a large and financially risky investment, could nudge surgical staff to prescribe antibiotics appropriately by 'feeding back' to them their prescribing behaviour. Hence, the latter business case has the potential to impact the 'causes' of AbR not simply the 'symptoms'.

Furthermore, based on these two examples we can see that given the challenges the Trust was facing at the time of the interviews, there was a willingness to engage with interventions which could have immediate benefit in the short term as opposed to a potential long term solution. The SSI surveillance interventions has the potential to prevent a basket of challenges surrounding AbR altogether within one interventions. For example, quicker identification of infections leading to fewer infections from spreading in the future. Potential promotion of better antibiotic prescribing

behaviour amongst surgical units, which overall could even limit the risk of future outbreaks. However, given the long term investment and high financial risk surrounding this intervention, engagement surrounding its adoption was slow.

As previously shown in Figure 56 (a copy of the figure also provided below) when describing the axial coding methodology, the figure helps to visualise this axial framework explicitly. We now take the findings from the interview data and the axial coding framework further to visualise and explore the relationships within the data in more detail, using causal loop diagrams.



*Note this is a repeat figure of Figure 56

5.6 Part 3: Causal Loop Models

The axial coding framework helps to bring together the initial and focused codes identified to answer the two key research questions related to the challenges of controlling and preventing antibiotic resistance and how decisions related to business cases are being made related to antibiotic resistance. However, it is difficult to visualise and understand the potential relationships between these categories identified from the initial codes. To understand the whole system and the

underlying systems driving the 'phenomenon', 'strategies', and 'consequences' identified from the axial framework, a systems thinking approach was deemed an appropriate method to investigate the underlying feedback loops further.

5.6.1 Causal Loop Methods

Using the categories identified in Part 2 and in particular the axial coding framework, the causal loop models were developed guided by the quotes identified per category. These models were then iteratively discussed and revised with input from my research supervisors and research teams (discussed further in Section 5.6.1.1) to ensure the logic behind the systems made sense. I incorporated evidence identified from the 16 Trust studies to better understand the logic and relationships between the themes. The connections between the themes were established from analysis of the interviews. Furthermore, the underlying causes of some of the themes were often discussed in the interview. After the initial models were created, with causal loops linking various themes, these were then further discussed with representatives from the Trust for validation and also to feedback the results which were gathered from the interviews.

5.6.1.1 Validation of models

The models were presented for validation at a peer to peer research meeting, the list of stakeholders have been described below in Table 21. Following the initial validation, the individual models were discussed in detail with a systems dynamics modeller and a healthcare policy researcher. Finally, two key members of the IPC team who make decisions related to tackling AbR at an operational as well as organisational level were consulted to ensure the models reflected how the current Trust was operating and to sense check the models.

These two IPC team members had been previously interviewed. It was therefore made clear to the them that no additional themes would be added since this could bias the overall themes identified,

and the purpose of this validation meeting was to ensure that the structural logic of the causal loop diagram made sense from an operational perspective.

Issues raised by following this validation process included:

1) Labelling and definition (opinions of clinical teams versus finance teams).

2) No additional key issues currently facing the IPC and AMR teams were mentioned.

One member highlighted that issues regarding the estates management and resources identified as loops in the models were the key reason a lot of time, effort and energy are spent when this could be spent elsewhere.

Table 21: Meeting 1: Peer to Peer research meeting

Attended by	Participant background
Participant 1	Qualitative researcher and sociologist working on AMR in the community
Participant 2	AMR researcher involved in Business case development
Participant 3	AMR researcher involved in health economics research of AMR
Participant 4	Medical doctor (from Thailand) and CPE researcher
Participant 5	Medical doctor (Junior Doctor at ICHCNT) and AMR researcher
Participant 6	AMR researcher specialising in Systems Dynamics modelling
Participant 7	Clinical pharmacist at ICHCNT
Participant 8	AMR researcher – social scientist, policy, qualitative research
Participant 9	AMR researcher (Social scientist + mathematical modeller)
Participant 10	AMR researcher (Pharmacist)

Abbreviations: [AMR = Antimicrobial resistance; CPE = Carbapenemase-Producing Enterobacteriaceae; ICHCNT = Imperial College Healthcare NHS Trust]

5.6.1.2 Causal loop terminology

Causal loop models have their own terminology, and this has been provided in the Panel below to help understand the models better. The panel below displays the meaning of these terms.

Panel to understanding causal loop terminology
Positive: A positive sign indicates that there is a direct relationship between the variables. So an increase in one variable will lead to an increase in the other variable (given the direction of the connector arrow) and vice versa for a decrease in one variable.

Negative: A negative sign indicates that there is an inverse relationship between the variables. So an increase in one variable will lead to a decrease in the other variable (given the direction of the connector arrow) and vice versa for a decrease in one variable.

Reinforcing loop: The reinforcing loop denoted by (R) indicates that all else being equal overtime the behaviour of that system may increase.

Balancing loop: The balancing loop denoted by a (B) assumes that all else being equal the system will either oscillate or 'seek a goal' and balance out over time.

Lags: The double lines on the arrow connectors imply that there could be a potential delay in the variables impacting one another in the direction that the arrow is pointing.

5.6.2 Causal Loop Modelling Results

High level overview loop

Figure 58 below is the 'high level causal diagram' which has four individual causal loops embedded within it: a quality and estates loop, a competing priorities loop, a data and evidence loop, and an outbreak loop. These represent four 'stories' identified from the interviews which are able to describe the challenges to tackling AbR and interconnection between them at the time of the interviews. The individual loops are described in detail below.

The high level loop visualises the complexity and interconnectedness of the four loops. We can theorise that availability of IPC resources and how 'whole system engagement' are impacted are the core mechanisms which influence how the Trust may be able to control and prevent AbR. The other

four loops feed in and out of these two core factors. Given the results of the interview and following creation of the high level causal loop diagram, the two solutions possible within this system therefore involve either *greater whole system engagement* or more *IPC resources*. These solutions assume that the quality of estate would remain a significant investment challenge for the next 5-10 years until the buildings are completely rebuilt. As a result, for the foreseeable future, resource issues will remain embedded in the system, therefore influencing whole system engagement in tackling AbR could be a better place to start when it comes to tackling AbR at the Trust.

Secondary to whole system engagement, the mechanism via which data and evidence are being utilised in the Trust could also provide a more robust solution within this system, as it also influences the *outbreak occurrence* and the *competing priorities* loops. A low cost fix to improve the way data and evidence is being incorporated in the Trust's day to day activities could have the potential to impact IPC efficiency, Trust staff time availability, as well as clarify the importance of AbR management thus enhancing whole system engagement, especially when engaging with non-clinical stakeholders.

Even if a low cost solution is not possible, improving data and evidence accessibility and application plays a key role within this system, and to gain a long term solution to the AbR system level issue, the data and evidence loop should be prioritised as an area of intervention.

The causal loop figures were developed using a free online software called Vensim free academic PLE.[19]

[19] The terms of conditions from the software states: *MODELS AND RESULTS. The Software may be used to create simulation models and generate results. Ownership in, and responsibility for, the models and results created using the Software remains entirely with you.* https://vensim.com/license/ (accessed: 29/07/2019)

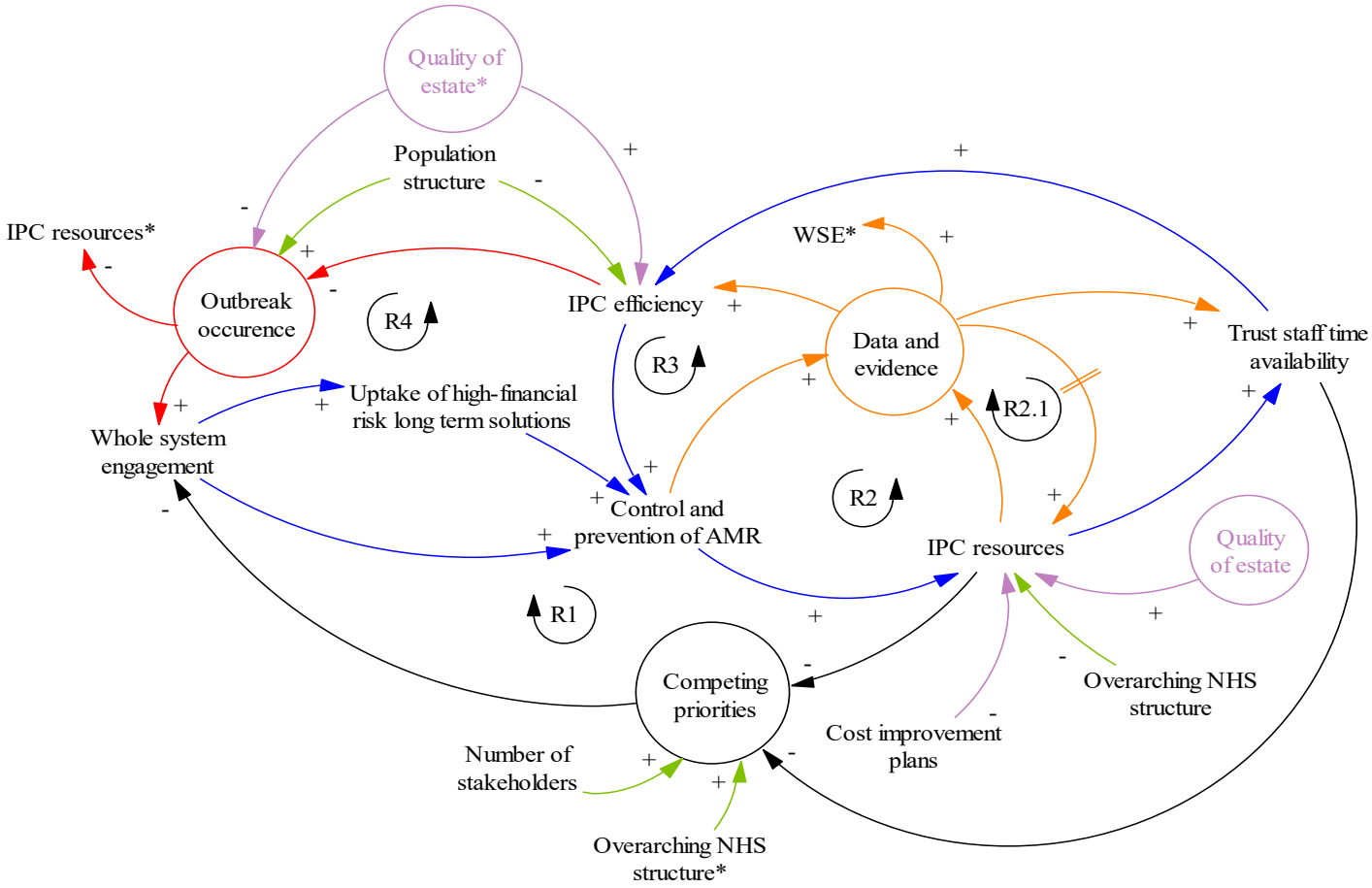


Figure 58: High level overview loop

Abbreviations: [AMR = Antimicrobial resistance; NHS = National Health Service; IPC = Infection prevention and control ; R = Reinforcing loop; WSE = Whole system engagement ; * = Repeated factor which is also appearing in a different part of the causal loop (it was not possible to create a perfect loop without cross-overs for these factors)]
Line colours: [Mauve = Quality of estate loop ; Green = External factors ; Red = Outbreak occurrence loop; Orange = Data and evidence loop; Blue = Key factors being influenced by or influencing other loops; Black = competing priorities loop]

5.6.2.1 Underlying loops

By focusing on the high level loop, the research question is only partially explored and theorised. It is therefore necessary to understand the overall key factors driving the systems level issues of tackling AbR at an organisational level. Emphasising these underlying system level issues could potentially help determine the ground level problems faced by the policy implementers. Subsequently, helping policymakers inform a bottom-up policy framework.

Similar to the high level loop, the underlying drivers loop has been split into four key loops or 'stories' which better help explain the high level loop. These loops were commonly discussed during the interviews with the stakeholders.

5.6.2.1.1. The system's boundaries – Quality of estate loop

The system's boundaries are creating a balancing loop which I labelled as the 'quality of estate balancing loop' (Figure 59). Starting with the quality of the estate, given the depreciating nature of the buildings, the internal deficit needs to be able to cover a substantial amount of the 'backlog maintenance' required to address the year on year needs of the quality of the estate. To be able to meet the internal deficit targets, the Trust needs to incorporate cost-efficiency plans, which then generate Trust income to maintain the quality of the estate. This is creating a balancing loop, at least for the next five years since the old buildings will need to be completely demolished to provide a healthcare facility fit for modern day healthcare provision.

The quote below describes the impact the estate is having overall and why it creates this system's boundary.

"working within an estate, working within buildings that are absolutely inappropriate in terms of providing safe care and a safe environment to take care of patients and to prevent the acquisition and transmission of organisms and particularly the concern about acquisition and transmission of highly resistant organisms….. I also mean the response to immediate needs and requests for repairs, refurbishment that take months, weeks, months, years to get done. So, this is continuous and it's particularly bad at the moment." **(Case A010)**

Figure 59 below demonstrates the one of the key factors currently driving the causal loops identified from the interviews.

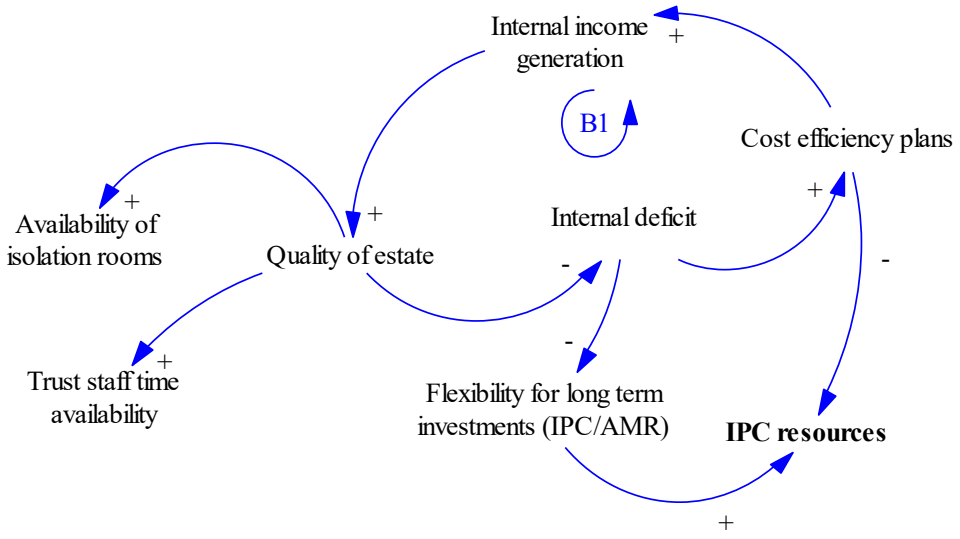


Figure 59: Quality of estate balancing loop

Table 22: Guidance to quality of estate balancing loop

B1	*↓Quality of estate (worse the quality of the estate) ↑Internal deficit (more internal deficit needs to budget at the beginning of the year) ↑Cost efficiency plans ↑Internal income generation ↑ Quality of estate (more cost efficiency plans need to be generated across the Trust to generate income to cover the improvement needed to help improved the quality of the estate)*
Other factors influenced by the balancing loop	*↑Internal deficit ↓Flexibility for long term investments (IPC/AMR) (Higher the internal deficit in a given year the less flexibility remains in uptake of long term investments to tackle IPC related issues (e.g. AMR)* *↑Flexibility for long term investments (IPC/AMR) ↑Resources*

In addition to the quality of the estate, the overarching NHS structure including the changing nature of the political pressure on the NHS and its impacts on funding, as well as the ageing population structure, all have an external impact on the resources which are available to the infection prevention control team and the overall resources available to the Trust. Within the loops below, the external factors forming the boundaries of the system are coded with green arrow connectors. It can be noted that the boundaries of this model have been defined by the 'context' and the 'intervening conditions' in the axial framework developed from the interviews.

5.6.2.1.2. Competing priorities loop

The second loop has been labelled the 'competing priorities' loop (Figure 60). Competition for resource, meeting performance targets and its 'link to Trust staff time availability to carry out tasks' were often brought up in the interviews. In addition, interviews on multiple occasions reported the

relationship between the need for engagement to tackle AbR and the lack of engagement on the ground, often due to competing priorities. Based on these results, the competing priorities loop was created.

Within this loop the overarching NHS structure is a boundary of the system which impacts the performance targets which cannot be controlled locally. Therefore, additional targets such as the 'CQUIN antibiotic prescribing' targets, despite its well-intentioned rationale for reducing antibiotic use and curbing the emergence and spread of AbR, in fact has been said by the stakeholders to increase competition for resources in an already resource constrained setting.

Table 23 provides a detailed description of how the loop works in Figure 60. The quotes below are illustrative examples of the data underlying this competing priorities loop:

"*And then I think the only other challenge is, sometimes because of the way things are organised or the way NHS targets work, it can mean that differently people have slightly different agendas, and sometimes they conflict with one another. And finding a way to sort of bring those together can be a challenge*." **(Case A003)**

"*The main one [challenge] probably is, even though in my small world it's my priority. It's got a lot of conflicting priorities in the Trust as a whole. So, if I go back to that nurse on the ward, or a consultant on a ward,… and say "This is terrible. This is a big problem. Armageddon. It's all going to go wrong in a few years, and we need to protect our future generations.[related to repercussions of AMR+prescribing]" They are dealing with 16 other people coming in with their own agendas and sores, or pressure ulcers, or failure to rescue. Whole host of things that are the priority. And it [AMR + IPC] seems sometimes very flavour of the week, and for the ward staff it's very hard for us to keep our IPC agenda up there when they're faced with lots of people like me coming in and telling them "No, no, no. This is more important than IPC. This is what you need to focus on*."" **(Case A005)**

"But the doctors in training are ... you know, they're stretched very thinly. They know the right thing to do. But actually, the safe ... Sometimes the safe thing to do is not to spend the time getting the

*samples [cultures to identify what organism it is for appropriate prescribing]. It's to give the antibiotics because they actually have to go and see somebody else in five minutes. So ... And there aren't enough of them to delegate some of those tasks to other people and say, "Could you take those samples? I need to go and see the other person."" **(Case A004)***

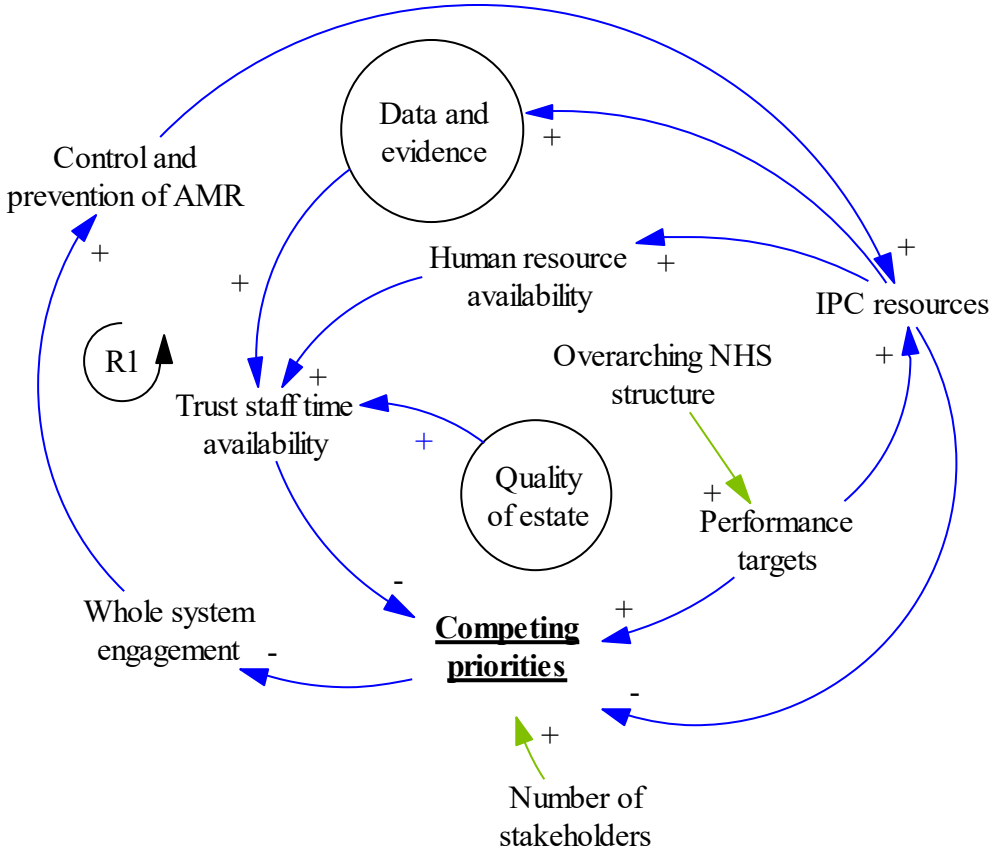


Figure 60: Competing priorities loop

Table 23: Guidance to understanding competing priorities loop

R1	↑IPC resources ↑Human resource availability + ↑data and evidence loop ↑Trust staff time availability ↓Competing priorities ↑Whole system engagement ↑Control and prevention of AMR ↑IPC resources
Other relationships	External: ↑Number of stakeholders ↑Competing priorities (The more stakeholders involved in the decision making process to control and prevent AMR and the more competing priorities is a barrier to tackling AMR in the Trust) ↑Performance targets (due to Overarching NHS structure) ↓IPC resources (more resources are needed to achieve these targets so less resources available for the IPC teams to deal to other immediate AMR related issues) ↑Performance targets (due to Overarching NHS structure) ↑Competing priorities (to meet these performance targets)

5.6.2.1.3. Data and evidence loop

The third loop is labelled 'Data and evidence' (Figure 61). As previously discussed, the data and evidence loop have the potential to impact all the other loops, apart from the 'quality of estate' loop. With regards to controlling and preventing AbR, how prescribers receive patient and antibiotic prescribing data has an impact on overall Trust staff time availability. Within the interviews, it was often discussed that if the prescriber was able to easily identify which patients are on 'broad-spectrum' antibiotics and which patients are on 'narrow-spectrum' antibiotics, it would save them

from having to go on entire ward rounds. Since broad spectrum antibiotics have been known to increase the risk of AbR so where ever possible narrow spectrum antibiotics should be prescribed to target the pathogenic bacteria effectively. Therefore, monitoring patients on broad spectrum antibiotics was deemed an importance use of staff time as opposed to reviewing all patients. The combination of better prescribing data and more staff time availability has the potential to increase IPC and AMS efficiency. Improving IPC/AMS efficiency in general would help control and prevent AbR, it would also reduce the risk of an outbreak occurrence.

Better Trust staff time allocation could also enable a reduction in competing priorities, improving whole system engagement for AbR, thus helping control for AbR. Figure 60 below demonstrates the data and evidence loop, Table 24 provides the mechanisms for each of the reinforcing loops and the other relationships which create the data and evidence loop.

The quote below provides an example of how mismatch between CCG level (i.e., the stakeholders who will pay the Trusts based on the level of patient activity) and the individual Trust level data on patient activity can impact how Trusts are getting paid:

"*if you think of patient activity, you're presenting clear data that shows, over the years activity has increased 10%. That's what auditor is telling us. We have instances, where even those kind of cases cannot be approved, because the first question that we will ask is, does the commissioner acknowledge that there's a 10% increase in activity? And have they acknowledged they pay for it?..... And nine times out of ten ... in fact, I've never come ... I've been here five years now, and I've never come across a situation where we've presented a case and the commissioner's agreed to pay for something up front, based on activity. Never*." **(Case B001)**

This next quote discusses how efficient data dissemination would improve prescribing efficiency:

"[Regarding challenges on implementing AMS] *it's identifying patients. It's okay where you've got your regular routes, but it's identifying the patients who can have an early intervention I think is quite*

challenging actually. So, I know that pharmacists had tried looking at pulling off a list of the patients on certain antibiotics. Which would be great, but they don't have the resources to do that every day. So, you need to have a really good infrastructure with the IT, to be able to use the access.

If I was able to log on in the morning to my site, and you know, pull up 5 wards or something of interest and say okay this person is on a target antibiotic, this ones on a target antibiotic. It would make life so much easier, as opposed to some of my colleagues who still having to go through a full list of patients in the ward before they get to the ward to, to see who's appropriate. So, I think there is that lack of infrastructure as well. To help us prioritize who needs discussing most." **(Case A007)**

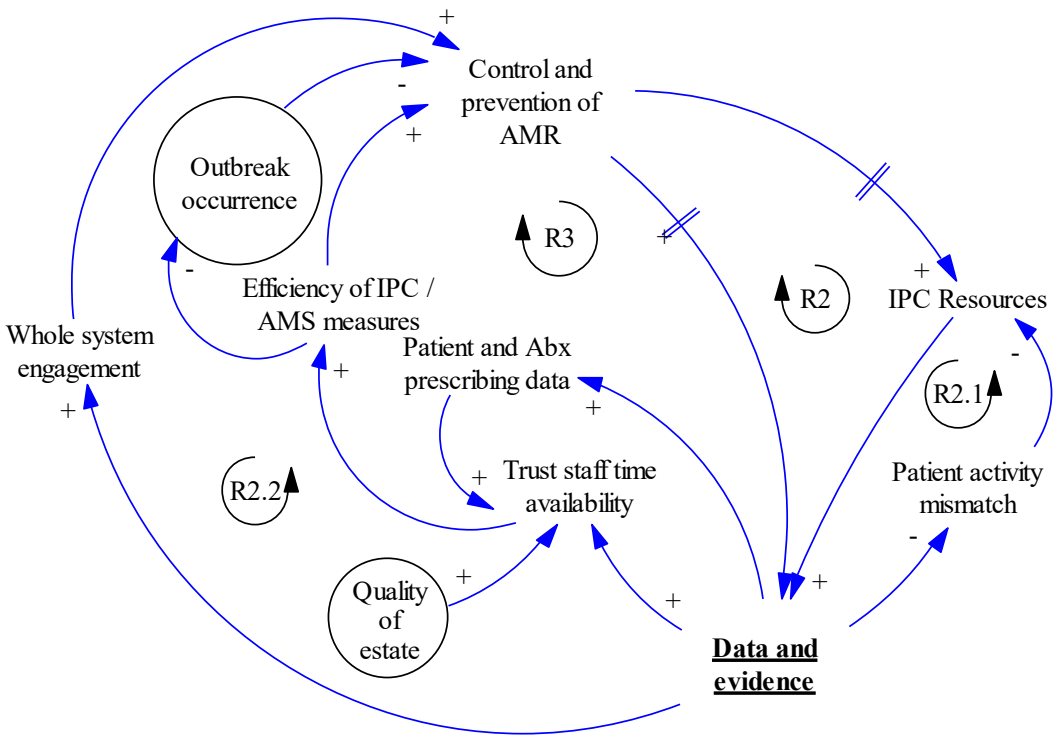


Figure 61: Data and evidence loop

Table 24: Guidance to understanding Data and evidence loop

R2 (includes R3 within it)	↑IPC resources ↑Data and evidence *(increased capability of IT systems to capture the appropriate data and evidence)* ↑Control and prevention of AMR *(improvement in controlling AMR, including via reduction in outbreak occurrence)* ↑IPC resources *(less pressure on IPC resources to be devoted to AMR or pay for outbreaks)*
R2.1	↑IPC resources ↑Data and evidence *(increased capability of IT systems to capture the appropriate data for accurate patient activity in the Trust)* ↓Patient activity mismatch *(less chance of patient activity mismatch so Commissioners would potentially pay for the patient activity the Trust needs to process annually)* ↑IPC resources *(more resource availability as Trust is being paid for the patient activity it processes)*
R2.2 (includes R3 within it)	↑Data and evidence *(the better data and evidence is being captured about AMR in the Trust)* ↑Whole system engagement *(the more all stakeholders are aware of the problem of AMR and just are engaged in tackling AMR and would be on board to invest in long term interventions with potentially high financial risk in the short term)* ↑Control and prevention of AMR ↑Data and evidence *(the better AMR is controlled in the Trust the more data and evidence surrounding how AMR can be tackled in captured)*
R3	↑Data and evidence *(increased capability of IT systems to capture the appropriate data and evidence)* ↑Patient and Abx prescribing data ↑Trust staff time availability ↑Efficiency of IPC/AMS measures ↓Outbreak occurrence ↑Control and prevention of AMR *(improvement in controlling AMR, including via reduction in outbreak occurrence)* ↑Data and evidence *(the better AMR is controlled in the Trust the more data and evidence surrounding how AMR can be tackled in captured)*

5.6.2.1.4. Outbreak occurrence loop

The fourth loop has been labelled the 'Outbreak occurrence' loop (Figure 62). The loop delves deeper into the ground-level issues surrounding availability of isolation rooms and movement of high risk patients. The quality of estate loop also plays a role in the outbreak occurrence loop along with the external factor of the population structure and how every year the 'black alert' scenario and the 'winter effect' also impacts effective control and prevention of AbR. An interesting phenomenon uncovered during the interviews was the idea of retaining 'organisational memory' of AbR. Across the finance and estates teams who are not directly acquainted with AbR, the organisation had a good memory of what 'CPE' was and repercussions of 'CPE outbreaks'. Even if non-clinical stakeholders were not aware of what AbR was, they were very much aware and engaged with how to resolve the issues of CPE. Out of the two business cases discussed in Section 5.5.3.4, the decontamination business case gained relatively easier approval as it was so closely linked to CPE outbreaks. This played a role in helping the whole Trust system (clinical and non-clinical stakeholders) get on board with investing in the business case as a long term solution.

The quote below demonstrates an example of the link between outbreaks and organisational memory of AbR:

"oddly before the outbreak there was passing interest in it [AMR]. But once people saw the consequence of it and there were wards closed for ages and there was a cost to the organization in terms of scrutiny and time and interaction with external partners and loss of revenue, I think that got attention in a way that just talking in an abstract sense, I don't think would" **(Case A004)**

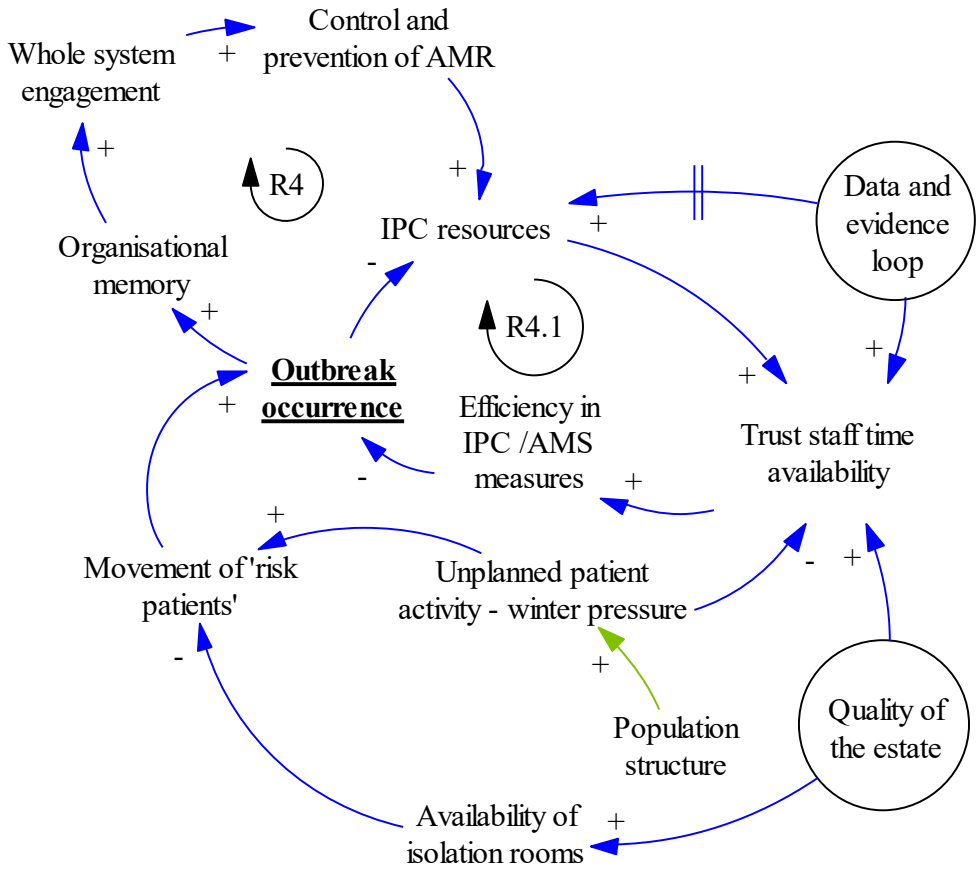


Figure 62: Outbreak loop

Table 25: Guidance to understanding the outbreak loop

R4	*↑Outbreak occurrence ↑Organisation memory (of the repercussions of an outbreak and how much it cost in terms of resources (i.e,. time, money, labour) ↑Whole system engagement ↑Control and prevention of AMR (improvement in controlling AMR, including via reduction in outbreak occurrence) ↑IPC resources (less pressure on IPC resources to pay for outbreaks)*

R4.1	*↑IPC resources ↑Human resource availability ↑Trust staff time availability (Improved in staff time availability also influenced by ↑data and evidence loop + ↑Quality of estate) ↑Efficiency in IPC/AMS measures ↓ Outbreak occurrence ↑IPC resources (more IPC resources due to less pressure on IPC resources to pay for outbreaks)*
R1	Already discussed in Table 23
Other relationships	*↑Quality of estate ↑Availability of isolation rooms (improvement of quality of estate could enable more space to availability of isolation rooms) ↓ Movement of 'high risk' patients (limited need to move high risk patients who are tested +ive for CPE or MRSA and require isolation) ↓ Outbreak occurrence (which limits the chance for an outbreak occurrence due to CPE – as is a common occurrence within this Trust)*
	↑Population structure (current ageing population structure implied more frail patients being admitted due the cold-winter season) ↑Unplanned patient activity – winter pressure (creating the winter-pressure and more frequent 'black-alert scenarios') ↑ Movement of 'high risk' patients (increasing the risk of movement of high risk patients as not enough isolation rooms would be available to accommodate this sudden increasing pressure of patient activity)

5.6.3 Conclusions

The high level loop identified the key barriers to tackling AbR in the Trust. Limited resources and the flexibility that would come about with availability of more resources will in the long run have the potential to reduce some of the problems commonly seen with tackling AbR. However, given that the resource issue is potentially going to last for at least the foreseeable future in the NHS, the areas of

potential ‘fix’ could be greater whole system engagement by raising more awareness of the root causes of AbR across all stakeholders in the Trust. This would involve making the non-clinical teams aware that antibiotic use has an important role to play, especially in a hospital setting where antibiotics are prescribed at high doses and using intravenous routes. At present infection control is seen as the main mechanism by which to tackle AbR amongst the non-clinical stakeholders. The benefits of a proactive approach to AbR rather than a reactive approach were commonly expressed in the interviews as a solution to tackling AbR. However, this concern was expressed in relation to the current NHS policy framework for tackling AbR and the role of CQUINs as being a reactive short term approach. Based on the interview analysis the following key areas for attention were identified:

Competing priorities, which primarily arise from competition for resources, means that whole system engagement related to AbR – from ground level staff all the way up to the executive teams – needs to be strengthened to simplify tackling AbR.

Although timely knowledge of the organism and the patient is essential for the prescriber to make appropriate decisions related to antibiotic prescribing, the way data and evidence is being fed back to the clinicians appears to be weak and needs to be an area of immediate priority for the executive team to consider.

The issue of the impact of resources on the whole system problem of tackling AbR should be highlighted as a matter of urgency to the commissioners. The impact of resource constraints is not highlighted in these AbR strategy documents – for example, the repercussions of cost improvement plans are not understood properly, and even though quality improvement teams are involved in overseeing that no adverse consequences result from the cost improvement plans, interviewees raised concerns with regards to the underlying consequences of these plans.

A potential separate fund for tackling AbR in the Trusts could be set up as a mechanism for Trusts to bid for more money to implement long term solutions when tackling AbR, rather than using the Trust’s existing overstretched resources.

Resources and staffing issues were also challenges identified from the 16 Trust study, especially in relation to recruitment, but this was not an issue particularly raised by ICHCNT interviewees. Problems here were more about the lack of funding available to recruit new staff members. For example, in the case of meeting the CQUIN target, there was only resource available to hire one pharmacist and the Trust would not be able to renew this contract for another year due to funding, not because a pharmacist could not be recruited.

5.6.4 Limitations

I coded the data myself and a second coder was not used to corroborate my codes. My supervisor was independently consulted following the coding process to discuss the themes being identified. An inductive and exploratory open minded approach was taken to code the data. Although, since a standard level of knowledge is required when formulating a research question in the first place, a certain degree of knowledge is required when designing the open-ended questions for the interviewing process. In order to gain the interviewee's Trust and attention during interviews, a certain degree of knowledge about the Trust, and their respective job roles is required to make the interview process as smooth and informative as possible to be able to obtain rich data. However, saying that, not being a clinician, not having a Trust background, and only being a third party researcher which the interviewees had never interacted with, did greatly help to elicit rich data from the research questions. In addition, given my prior limited experience and working knowledge of a secondary care environment may have limited any pre-conceived biases arising during the coding and category development stages of this study.

Therefore, the codes and themes are subject to some researcher bias. There was a limited time frame between which the interviews could be conducted. I believe thematic saturation of the categories in the axial framework was reached half way through the interviews, however, it was necessary to carry out all remaining interviews planned to ensure all stakeholder perspectives were incorporated.

5.7 Discussion

5.7.1 Key Findings

In summary, the 16 Trust study identified finance and capacity issues as the key challenges commonly faced across these representative Trusts. Stewardship teams have been set up across these Trusts, but there is still some variability in what interventions are being implemented. IPC efficiency and staffing were highlighted as key concerns across these Trusts, with implications for the risk of increased transmission of AbR organisms, thus immediately affecting the 'safe' domain assessed by the CQC.

The semi-structured interviews within one NHS Trust identified the complex organisational set up of the Trust. Multiple stakeholders were involved in the resource allocation decision making process which gave rise to competing priorities. These included the lack of resources and the NHS performance targets. The current quality of the estate and the resource pressures were identified as the key factors currently driving the barriers of tackling AbR at an operational level. On the ground level, cultural and behavioural differences were also uncovered as impacting prescribing practices, which was further aggravated by the way data and evidence was being made available to these stakeholders. Given the resource limitations, the decisions regarding future long term investment in the Trust were being made on an immediate patient safety priority basis, which some stakeholders viewed as a reactive short term approach to a problem which is 'deeply cultural' and requires a long term investment. A similar sentiment was shown with respect to the national level policy implementation of the CQUIN targets. Policy implementers on the ground felt that these targets were not solving the core issues with regards to the culture and behaviour surrounding AbR.

Therefore, the challenges of tackling AbR and interventions adopted are context specific. In the case of this Trust case study, the underlying issues related to the estate at the time of the interview was having an indirect effect on tackling AbR effectively. However, the overarching healthcare system – the NHS and the population demographics – were also fuelling these challenges. Therefore,

policymakers need to understand the whole system issue of AbR, given the intricate feedback and balancing loops which were identified simply by looking into one large NHS Trust.

5.7.2 Recommendations

Having analysed and spoken to the stakeholders in charge of AbR intervention adoption and implementation policy with an NHS Trust, the following recommendations can be made to guide policymakers' investment decisions supported by a bottom-up policy implementation approach.

Policy level solutions need to be more tailored with regards to AbR national efforts. For example, the CQUIN initiative for tackling Gram-negatives and antibiotic use, may not necessarily bring about long term results unless the data and evidence structure, i.e., the IT infrastructure of certain Trusts are improved as a first step. Usage of data for measuring improvement rather than purely regulation was highlighted as a current barrier to tackling AbR by one of the stakeholders. An interesting message which I think policymakers could really benefit from acting upon.

A funding mechanism should be set up in the short term by the NHS potentially with the help of non-profit and private organisations. The short term and potential long term costs to the NHS of AbR are significant, and resources are the key barrier to long term solutions to prevent AbR in these secondary care settings. The problem of AbR and NHS funding should not be treated separately, and the Department of Health and Social Care should focus their efforts to these long standing NHS funding priorities which may only get worse with the growing rates of AbR.

5.7.3 Future Direction

Following the qualitative data phase, the next step of a causal loop diagram usually involves quantification of the inter-relationships which were identified between the key factors identified. It may be proposed that given the variety of data collected by the NHS Trusts which inform the hospital and facilities dataset (ERIC), which if combined with the PHE fingertips data in a cross-sectional study could help identify measures to quantify these interrelationships. Moreover, this approach could

help explore the potential impact of interventions by building a systems dynamics model based on the causal loops by utilising resource use, cost, and infection level data. However, for the purpose of this study, we felt the qualitative causal loop diagrams were useful, especially when shared with the Trust IPC team. When the causal loop models were shown to the IPC teams, certain factors such as the impact of organisation memory on stakeholder engagement was identified as a potential way to improve engagement. Additionally, the opinions regarding the AbR CQUIN initiatives add to the growing evidence base that the cost impact of implementing CQUIN measures should also be taken into consideration. The cost burden of trying to meet these financial incentives should not outweigh the financial incentive itself. In particular, such top-down measures should be made with the stakeholders implementing the initiatives and not without them.

CHAPTER 6.

6 DISCUSSION AND CONCLUDING REMARKS

The Introduction of this thesis emphasised the growing 'one health' global concern antibiotic resistance (AbR) has become. Certain underlying barriers, which have made tackling AbR challenging from a policymaker's perspective, were also discussed within the Introduction (Chapter 1). These barriers were surrounding the identification and quantification of the risks of AbR, how to prioritise targeting of one risk over another, and the adoption and implementation issues surrounding existing interventions tackling AbR.

Four research questions were framed around addressing certain aspects of these barriers to help identify investment options tackle AbR. These research questions looked at understanding where the current quantified evidence was regarding the risks of AbR in humans, how these current quantified risks were being targeted by policy, where policymakers could focus to tackle AbR, and lastly what process-level factors were increasing the challenges of tackling AbR.

Policymakers make decisions when implementing policy in two ways, either a top-down or a bottom-up approach. Given the common challenges surrounding a top-down approach to policymaking discussed in the Introduction (Chapter 1) combined with the complex multifaceted nature of the problem of AbR, a bottom-up approach to health policy was deemed a more suitable framework to follow when answering the four aforementioned research questions.

The answers to the research questions informed the bottom up approach in four different ways. Firstly, by identifying evidence surrounding the driver of AbR from literature. Secondly by, analysing global action plans and associated policy documents in light of the key risks of AbR. Thirdly by synthesising national data as well as recent evidence sources using a mathematical modelling framework, and lastly by qualitative approaches applied to elicit evidence at a secondary care hospital and individual stakeholder level, synthesized though a systems thinking framework.

By answering the four questions targeted around the barriers to tackling AbR via the bottom-up policy frameworks created, it is hoped that healthcare policymakers will be able to make more informed investment decisions in terms of how best to allocate healthcare resources to tackle AbR in humans. In consequence, the findings from these four research questions help meet the overarching aim of this thesis, to address the barriers to tackling AbR and enabling policymakers to make more informed investment strategies to tackle antibiotic resistance in humans.

The aim of this chapter is to discuss the overall results, limitations, strengths, key contributions, and future research opportunities created from these four studies. Secondly this chapter provides concluding remarks from the overall thesis.

6.1 Summary Of Findings

6.1.1 Study 1: Systematic Review

The aim of the first study was to answer where the current quantified evidence was regarding the drivers of AbR in humans. Following the completion of the study, the majority of the evidence identified from the systematic review on drivers of AbR were risks arising from within the human reservoir impacting the emergence of AbR in humans, as opposed to risks from the animal or environmental reservoirs. Antibiotic use, followed by underlying disease, and invasive procedures were the key cited risks. When comparing this systematic review to similar systematic reviews identified from the targeted review conducted in Chapter 2, a similar list of risk factors was identified for specific drug-bug combinations (e.g. Meticillin-resistant *Staphylococcus aureus* or Carbapenem-resistant *Enterobacteriaceae*). The fact that antibiotic use is the most frequently reported risk factor for AbR emergence therefore highlights the importance of strategies to optimize antibiotic use in humans.

With regards to drivers of AbR transmission in humans, only 11 risk factors were identified from within the human reservoir. Prior antibiotic exposure, provision of type of care by healthcare

workers, and healthcare worker transmission were the key risks most frequently cited, therefore, making the secondary care setting and in particular healthcare workers and healthcare contact a key transmission route of AbR within the human reservoir. With both antibiotic use and healthcare worker related factors being reported as risk factors for transmission of AbR, the need for measures to control antibiotic use in humans as well as prevent and control infection spread, particularly in secondary care settings, is highlighted.

The bulk of the evidence on cross-reservoir drivers were in terms of food being a potential transmission route from the animal or the environment reservoir to humans, emphasising the importance of the one health aspect of tackling AbR.

One of the key results of the systematic review was the systematic mapping of the quantified evidence which showed the whole system problem of AbR with the help of the risk domains map.

Antibiotic use, healthcare contact, patient characteristics were the three risk domains with the greatest number of studies identifying them as key risks driving AbR. Community factors domain and patient demographics were the risk domains with the least amount of evidence compared to the aforementioned domains. The community factors domain in particular included a large array of risks which ranged from socioeconomic conditions to cross reservoir factors.

Gaps from the review

Apart from identification of where current quantified evidence lies regarding the drivers of AbR in humans, the main finding of the systematic review was to highlight where there currently are gaps in the evidence base.

Firstly, a disproportionate amount of good quality evidence reported antibiotic use as a risk factor when compared to the rest of the individual risk factors. Antibiotic use is already an established risk factor of AbR with a number of key meta-analysis studies, which take account of numerous drug-bug combinations in primary or hospital settings. These have proved the link between antibiotic use and

increased risk of AbR. However, studies investigating more granular underlying causal factors were not identified.

Secondly, given the interconnectedness of the community setting with the animal or environment reservoir, the data on risk factors driving AbR was limited in quantity and quality compared to antibiotic use. The granularity in the evidence regarding household level factors, country specific factors, or cross-reservoir specific factors driving AbR was lacking. There were singular studies identified which discussed household size, number and type of members in the household, or socioeconomic factors which could be driving AbR. However, the quality of these studies was low compared to the high quality evidence identified for antibiotic use. Compared to the community setting, the hospital setting provided more granular evidence related to the factors driving AbR. Although, the granularity in the evidence was biased towards patient specific factors (e.g. the type of procedure the patient underwent) rather than the hospital specific factors. The impact of staff to patient ratios in hospitals on levels of AbR or hospital specific characteristic such as size, location etc on levels of AbR were not as frequently quantified in good quality studies.

Thirdly, the evidence was skewed towards the evidence on the factors driving the emergence of AbR, with limited evidence in comparison on the factors driving transmission of AbR in humans. During the data analysis phase which aimed to categorise the risk factors driving emergence versus transmission, it was also noted that the definitions for these two stratifications was unclear, with limited reference case guidelines in literature to help define them. Therefore, currently there is a lack of information from risk factors studies which accurately define the risk that is being studied. For example, if the risk factor is related to emergence of new cases of AbR or if the risk is related to transmission of existing AbR cases.

Key research since the findings

Since the completion of this thesis and the publication of the systematic review on the drivers of AbR in Chapter 2 (212), a number of crucial research papers were published which have helped towards addressing some of the gaps identified from Chapter 2.

The first is a paper by Collignon et al. (213). Collignon and colleagues set out to understand the community factors risk domain in more depth at a global scale with the help of real world data. A multivariate analysis was performed to understand the sociodemographic factors driving AbR in humans. The paper concluded infrastructure and governance to be global factors driving AbR , rather than antibiotic use. The authors concluded that their results suggested the factors driving transmission of AbR trumped the factors driving emergence of AbR in humans. Furthermore, the paper highlighted the importance of appropriately defining emergence and transmission factors, so policymakers understand if they are tackling the factors driving emergence or transmission of AbR or both.

The systematic review in Chapter 2 highlighted the greater risk of information and confounding bias for some factors that were included in the identified studies which informed the community factors risk domain. The analysis conducted by Collignon et al. could also be subject to similar types of bias, since the databases combined to inform the multivariate analysis would have some degree of inconsistency in which data is collected across countries and settings. Given the heterogeneity in the community setting and the lack of consistency in data collection, analysing data from the community setting becomes challenging. Therefore, without consistent data collection protocols in place at a global scale which collect data routinely on antibiotic use and antibiotic resistance similar to the

Please note the aforementioned argument about global database inconsistencies was put forward within a commentary, on which I was second author, published in Lancet Planetary Health in reply to Collignon et al's paper.

Citation:

Pouwels KB, Chatterjee A, Cooper BS, Robotham JV. Antibiotic resistance, stewardship, and consumption. The Lancet Planetary Health. 2019 Feb 1;3(2):e66.

hospital setting, the underlying drivers from the community setting would be difficult to identify without bias. The Global Antimicrobial Surveillance System initiative set up by the World Health Organization (WHO) will help us get a step closer to minimise these data inconsistencies across variable databases.

Following and parallel to completion of Study 1, the next set of papers were published by the AMR modelling team at Public Health England (185,214–217). These research articles utilised the primary care datasets informed by the routinely collected data provided by General Practices (GPs) across England. The aim of these papers was to understand the current trends, patterns, and anomalies in antibiotic prescribing practices across GPs in England. The most recent paper (217) drew policymakers attention to the fact that antibiotic treatment prescribed by GPs in particular for respiratory related issues (e.g. bronchitis or upper respiratory tract infections) accounted for majority of the antibiotic prescriptions in primary care and large proportion of these treatments exceeded the recommended guidelines. Previous articles published in 2018 based on expert elicitation and primary care data also highlighted differences between actual prescribing rates for common conditions versus what clinicians would perceive as ideal prescribing rates for these indications (214). However, even though these articles were able to describe inappropriate antibiotic use within the primary care setting, apart from one study, the remaining studies did not go on to examine further if this use is indeed increasing AbR in the community or the hospital setting. One study (218) from the researchers, did conduct an investigation between antibiotic use and resistance, which identified an interesting outcome of potential co-selection for resistance. The authors were able to conclude a relationship between amoxicillin / ampicillin use and trimethoprim resistance, concluding that bacteria can acquire resistance not just to the antibiotic class it has been exposed to but also other antibiotic classes.

Based on these publications by the team at Public Health England, a number of interesting trends were identified which have been able to inform health policymakers about where policy should focus in the future. For example, one of the publications conducted a cross sectional study investigating the indication level prescribing data in the primary care setting. This cross sectional study identified that majority of antibiotic prescribing are attributable to indications related to respiratory tract infections (e.g. acute cough, bronchitis, upper respiratory tract infection). Furthermore, at least 80% of these prescriptions exceeded the recommended prescribing duration stated within current clinical guidelines. The results of this paper therefore provide policymakers evidence supporting the underlying causes of the high antibiotic use within the community in England and areas. Moreover, these causes can be targeted with policy, for example by monitoring or even incentivising guideline adherence within GP prescribing in particular related to respiratory tract indications.

Therefore, these papers are a good example of how the ground-level evidence can be used to identify the underlying factors driving the key established risks of AbR. Further emphasising the need for similar research into factors driving established risks, such as antibiotic use, as concluded from the first study of this thesis. Identifying the underlying factors driving these key established factors also informs granular policy interventions, which can often be as simple as providing feedback to GPs on their own prescribing behaviour, to nudge them into better antibiotic prescribing guideline adherence. Thus, already implemented policies such as audit and feedback can become even more effective in the future, by narrowing down on indication specific (e.g. by focusing on respiratory tract infections specifically) audit and feedback.

6.1.2 Study 2: Mapping Interventions And Drivers

The aim of the second study of this thesis was to map which drivers of AbR were being targeted by policy. Stakeholders currently tackling AbR at a policy level were identified from recently published white papers and policy documents. The five objectives set out within the WHO Global Action Plan was used as a foundation to assess where stakeholders who are tackling AbR are focusing their policy

measures. The study concluded that surveillance and research was a key policy focus for the majority of the stakeholders, closely followed by antibiotic use.

Based on the result of the mapping exercise, at present the majority of the policy focus could only be directly mapped with the antibiotic use risk domain identified from Study 1. However, it can be speculated that with better surveillance and research, underlying target risk areas would be identified to tackle AbR in the community and the hospital settings. With increased focus on surveillance and research, the other underlying factors driving the understudied risk domains as identified from Study 1 namely community factors could be quantified and consequently targeted by policy.

Some mismatches were identified when comparing the global stakeholder policy focus with the ground-level interventions that are currently being implemented. The interventions identified tackling AbR on the ground were closely aligned with the hierarchy of evidence on the drivers of AbR. Antibiotic use and healthcare contact were the two risk domains currently targeted by ground-level interventions. Clinically effective interventions were also identified which were currently able to reduce antibiotic use in both the community (primary care) and the hospital settings, as well as infection control practices which were able to reduce the incidence of AbR.

Gaps from the study

In summary, there was limited evidence to suggest that the understudied risk domains identified in the systematic review were actually being targeted by clinically effective interventions. Without better granularity in the drivers of AbR, the ground-level interventions motivated by policy are also limited in their granularity.

Following the completion of the targeted review on policy and interventions tackling AbR, a recent systematic review was published looking into the effectiveness of stewardship programmes in hospitals (217). The results of this recently published review further validated the key clinical efficacy outcomes (related to AbR interventions) which Chapter 3 identified.

These outcomes were in terms of reduced length of stay, antibiotic expenditure, or antibiotic use. As also concluded in Chapter 3, there are limited methods currently reported which are able to quantify the impact of the implemented interventions. Chapter 3 made a distinction between the *intended* targets of an interventions and the *final* target that was quantified by the clinical effectiveness data reported. Indirect intervention targets such as 'awareness' are more challenging to quantify than direct intervention targets such as change in antibiotic usage at a GP practice. However, more investment in AbR research is needed to understand these indirect effects. There is currently a gap in literature to help inform a framework to better quantify the clinical effectiveness of the interventions tackling AbR. A framework to quantify the indirect effects will enable identification of the holistic clinical and cost effectiveness of interventions tackling AbR.

6.1.3 Study 3: Dynamic Transmission Modelling

The aim of the third study of this thesis was to use the highest quality evidence identified from Study 1 and Study 2 to inform a framework whereby policymakers could see where they should be investing their resources to tackle AbR.

A published transmission model for ESBL-*E. coli* was expanded and data identified from Study 1 and Study 2 incorporated.

Given importance of underlying disease, but due to limited data, the model was developed to include comorbidities as an approximate measure for underlying disease.

Despite the model having a number of caveats in terms of limited model inputs and low granularity in the clinical effectiveness data identified from Study 2, the model predicted that the higher levels of resistant colonisations in the community will ultimately translate into infections in the hospital thus contributing to the economic burden of AbR due to increased length of stay. Therefore, based on the predictions of the model a reduction in prescribing rates in the community has the potential to be translated into savings from infections prevented in the hospitals.

Given the limitations in real world datasets using which it is challenging to link the community prescribing levels to hospital infections levels, there is a need for more hybrid decision models such as the one in this thesis which combine dynamic transmission modelling with cost consequences. These models are needed to nudge policymakers to understand the ultimate whole system problem of AbR. Furthermore, showing primary care prescribers the direct impact their prescribing practices could have on the burden of AbR. Such models also allow provision of quantitative evidence to the government and the end level policymakers demonstrating that both the community and the hospital settings require attention to tackle AbR.

Gaps from the study

Basic model parameters such as the rate at which resistance is acquired per antibiotic dose are still yet to be identified and reported. Hence, the models developed for AbR are still constraint by the current data landscape.

The key gap this study identified was the need for more granularity when it comes to reporting the clinical effectiveness of a particular intervention. Chapter 2 showed that only a handful of efficacy measures are reported. Often it is not possible to establish a causality between the intervention and the impact it may have on reducing AbR. Therefore, policymakers need to be aware of this challenge when it comes to measuring and modelling the clinical and cost effectiveness of an implemented intervention or policy. The spill over effects of a particular intervention may not always be captured in terms of currently quantified efficacy measures, i.e., reduced antibiotic use or reduced length of stay.

6.1.4 Study 4: Process-Level Barriers To Tackling AbR

The last study of the thesis focused on the process-level factors which currently impact how AbR is being tackled. An NHS Trust was used as a case study to inform policymakers about these process-level factors.

The main findings of this Study highlighted how the challenges of tackling AbR are closely connected to the immediate healthcare setting. The challenges of a specific healthcare setting combined with the multifactorial ways AbR emerges and transmits makes AbR even more difficult to tackle in a healthcare setting.

Using a systems thinking approach and causal loop diagrams as tools to show how gaining whole system engagement across a complex healthcare setting with multiple priorities was needed for AbR to be tackled. Within the case study, the non-clinical stakeholders (i.e., participants in the interview) who are often in charge of making intervention adoption decisions see AbR as a problem associated primarily with infection control rather than antibiotic use as well. Thus, awareness of the emergence and transmission mechanisms are a potential to encourage greater whole system engagement to also tackling the antibiotic use related issues and not only issues surrounding infection control within the healthcare setting. Moreover, with greater whole system engagement it may be easier to get long term solutions which may be more financially risky to be signed off. For example, as suggested by the stakeholders during the interviews, a proactive long term solution is needed to tackle the root causes of AbR rather than a reactive short term approach, which only address the symptoms of the problem. Furthermore, the comparison of the two business cases conducted as part of the Study displayed propensity towards engaging in less financially risky options to tackling spread of already identified infections compared to a long term surveillance system which would have the potential to identify earlier areas of improvement prior to infections occurring.

Another key finding was that the current NHS strategy of the AbR specific Commissioning for Quality and Innovation (CQUIN) measure can be perceived as a top-down policy measure. This particular measure was brought up in the interviews with the stakeholders, and the challenges surrounding this policy tool provide a signal that policymakers are not aware of how this policy measure is currently perceived by policy implementers.

6.2 Limitations

No study can be conducted without a certain degree of bias associated with the methods and the results. All the studies in this thesis have limitations which can give rise to bias towards certain research findings over others. Starting with the first study, the systematic review relied upon a set of search strings to identify the studies included in the results. The search strings did not include individual drug-bug combinations but aimed to identify risk factor studies related to antibiotic resistance. Therefore, the studies may be biased towards some drug-bug combinations over others. The systematic review focused on quantified evidence rather than evidence from qualitative studies because the Department of Health and Social Care's AMR systems maps already attempted to use qualitative data from expert elicitation to map the reservoirs and drivers of AbR within these reservoirs. The second study on the policy and interventions tackling AbR took a less systematic approach to identify and map the data. I was the only researcher who searched, selected, and extracted the data. This could have introduced some researcher bias towards the data selection and result dissemination process. The highest quality of evidence on the clinical effectiveness data was prioritised and sought out. Therefore, there are a large number of case control and cohort studies which were not included since the focus was on head to head randomised controlled trials. Randomised controlled trials are considered the gold standard when assessing clinical effectiveness of intervention due to the scope of limited bias being introduced, hence these were the primary focus.

The goal of the third study was to inform a framework with the evidence identified from the first two studies so policymakers could quantitatively see the impact of an intervention in the community on the whole system burden of AbR. Even though an effort was made in the thesis to identify recent and reliable inputs, the AbR data related transmission of resistant bacteria or the exact rate of acquisition per antibiotic treatment is still weak to inform the granular data required by such dynamic transmission models. Additionally, within the English healthcare setting, the NHS and individual Trusts have been adopting multiple interventions to tackle AbR at the same time. It is challenging to

quantify the intervention effectiveness of the overall mix of interventions, since this granular level of data was not identified from Study 2.

The last study looking at the process-level factors impacting how AbR is being tackled suffers from the key limitation that it was a study conducted only within one Trust which has its own very specific problems. Certain challenges faced within this NHS Trust were setting specific to the Trust and may not be generalisable, such as the quality of the estate. However, other factors such as those related to the NHS as a whole, the population structure and increasing unplanned activity were challenges which were also identified across the 16 Trusts which were studied prior to the interviews that were conducted. From a methodological point of view, the coding and the theme creation was done by one researcher, that is myself. During the code development stage, Prof James Barlow, my supervisor was consulted to discuss why certain codes were labelled in a particular way and to discuss overlap of certain codes. Furthermore, the focused codes and the themes along with the causal loop frameworks were presented to firstly the wider research teams and then the individual infection prevention control teams to gather feedback and sense checks for the models.

6.3 Strengths

The key strength of this PhD thesis was its potential to bring together large bodies of evidence and mapping them against each other to enable policymakers visualise where the current evidence lies on the risks of AbR, whether policies address them, and the effectiveness of the interventions that aim to tackle them. Concurrently, informing policymakers where more work needs to be done in terms of identifying underlying drivers of established risks of AbR. Furthermore, it was identified where future investigation is needed to assess the long term effectiveness of existing interventions targeting the established risks. The causal loop mapping process also uncovered how the current work that is being done to tackle AbR can be further improved by paying closer attention to the barriers highlighted by policy implementers on the ground.

The systematic review was one of largest pieces of research on the drivers of AbR that has been conducted to date. A large number of systematic reviews on risk factors of AbR for individual drug-bug combinations are currently available, however, the systematic review conducted as part of this thesis pools together evidence from over 500 peer reviewed articles to show policymakers the current bias that exists towards the quantified evidence on the drivers of AbR, which previously published smaller systematic reviews were unable to show.

The case study to identify process-level factors currently impacting how AbR is being tackled was able to follow different examples of interventions which were being considered for implementation within an NHS Trust. Moreover, being able to interview stakeholders about these two distinct interventions was a key strength of this study. Furthermore, being able to incorporate the finance, facilities and estates, as well as the clinical staff across different division in the Trust helped identification of system level factors from both clinical and non-clinical stakeholders. Thus different stakeholders perspectives were holistically summarised to identify ground-level challenges of tackling AbR.

Last of all, this PhD thesis was able to show that quantitative and qualitative research can go hand in hand and complement one another by bringing out an integrated perspective to tackling a multifactorial public health issues such as AbR. Objective quantification of where the risks are, how they are being tackled, quantifying the interventions' direct effects, and the monetary cost savings from interventions is indeed important for policymakers to make definitive decisions about where they should invest or not when it comes to tackling AbR.However, qualitative research is also needed since multiple stakeholders contribute to the rising burden of AbR. Moreover, multiple stakeholders are also involved in tackling AbR. Therefore, the complexity surrounding the behaviour of individual stakeholders are also powerful tools which policymakers need to be aware of to ensure that policy targets are being appropriately implemented. Additionally, following policy implementation, qualitative studies are also needed to monitor the direct and indirect effects of these interventions.

Qualitative research enables a greater understanding to justify the patterns uncovered by quantitative studies. Such studies also enable identification of policy areas which may be difficult to quantify. Study 4 was therefore able to identify competing priorities and stakeholder engagement as barriers to intervention adoption which policymakers should take into considerations. These factors may not necessarily be quantified but they may determine whether a policy measure may be adopted and effectively implemented on the ground.

6.3.1 Contribution

The contributions of this thesis can be split into theoretical and policy specific contributions.

Theoretical

From a theoretical standpoint, the risk domains framework is a large evidence based tool created to inform and assess the quantified drivers of AbR. All the studies included within this framework were systematically identified and individually quality assessed. The drivers of AbR were summarised in risk domains which were then ranked based on the quality as well as the quantity of the studies.

The second study mapped the key risk domains with the current global policy framework for tackling AbR. A potential mapping framework was created with the help of expert opinion elicitation from researchers working within the field of AbR. This framework of mapping evidence on drivers of AbR with policy and subsequently with clinical effectiveness data on currently implemented interventions has not been explicitly developed yet within the field of AbR. This framework tells you which risks are considered important based on literature, which of these are being addressed by policymakers, and what is actually happening on the ground in terms of the clinical effectiveness of the interventions. Moreover, this framework informs where risks can be tackled through new policy as well as where they would be best tackled through improved implementation.

Previously, dynamic transmission model studies have also modelled the clinical effectiveness of interventions alongside the natural history pathway of AbR in humans. Although, the model structure built by Knight et al. provided a unique opportunity to incorporate the evidence that was identified

from studies 1 and 2 and assess the impact of clinical effectiveness of an intervention in the community setting and predict the cost impact of these interventions in the hospital setting and vice versa. As far as I am aware, this is the first time the highest quality evidence from meta-analysis studies on clinical effectiveness of antimicrobial stewardship programmes have been assessed within such a transmission dynamic modelling framework combined with input of length of stay parameters estimated using appropriate methods applied to recent national data. Dynamic transmission models have been used for example to assess the cost effectiveness of other infectious disease areas such as for Human papilloma virus for the assessment of national vaccination programmes (219,220) but with regards to AbR the evidence of such analysis is currently limited.

Last of all, the final study of this thesis applied a systems thinking approach to identify and establish the setting specific process-level factors of tackling AbR within a high infection risk and high cost burden setting. An overarching causal loop framework supported by granular underlying causal loop frameworks were created to inform policymakers of the challenges of tackling AbR. The theoretical strength of these causal loop maps were that they did not only focus on the clinical aspects of AbR, non-clinical and system specific factors were also incorporated to provide a whole system theoretical perspective.

Policy

A recent policy meeting in the UK on the reservoirs of AMR (221) has cited the imbalance in the current landscape of evidence regarding the drivers of AbR in humans which was identified from the systematic review which was published (212) from Study 1. The published policy paper (221) discusses how this imbalance in the evidence can result in a bias towards where policy should be focused. The direct translation of the work conducted within this PhD can be highlighted as a key policy level contribution to the field of AbR.

The second study was able to show that given the limited granularity amongst the drivers of AbR within the community risk domain created in Study 1, the current policy focus and evidence on

clinically effective interventions in the community setting are limited. This finding gives policymakers a direct, quantified, evidence-based example of why granularity on the drivers of AbR is needed.

The third study informed policymakers, with the help of a mathematical model simulating the emergence and transmission of *E. coli* in England, that investing in the community setting has the potential to save money as a result of infections prevented from entering the hospital where the largest burden of treating resistant infection lies, as per recently published studies and a systematic review on the burden on AMR (28). The third study therefore further highlights to policymakers the importance of a granular evidence base on drivers of AbR within the community setting.

The final study showed policymakers that one of the current policies to tackling AbR in England can be considered a top-down approach to policy implementation. Prior to implementing policy, the context within which the policy will be executed needs to be given greater consideration. In particular, the impact of recent resource limitations the NHS in England was facing, was also shown as being a barrier to tackling AbR within the Trust case study. Policy implementers on the ground should be able to vocalise their concerns through more direct channels to establish better collaborations between the policymakers and policy implementers. In consequence, these open collaborations would help in narrowing the gap between what policymakers want to implement versus what is actually being implemented.

6.4 Future Research And Next Steps

Individual study specific recommendations have been provided per Chapter in Section 2.4.2, 3.6.3, 4.4.2, and 5.7.2. This section discusses some of the overarching recommendations and future steps for investing in measures to tackle AbR; largely investment in research.

The risk domains identified from the systematic review should be utilised to identify more systematic evidence per domain. A review looking into the individual factors identified in the risk domain and the possibility of causal factors underlying these risk domains can be further researched. A recently

registered systematic review protocol for example is aiming to review the evidence focusing only on the ethnicity related factors which could be driving AbR (222). Cumulative risk factors from reviews of this nature could broaden our understanding of future policy investment targets.

The last study of this thesis concluded that setting specific factors can have an impact on how well AbR can be tackled. Since the WHO Global Action Plan is being rolled out into national action plans across countries, as part of this global policy framework implementation process, the risk domains framework developed from the quantified evidence can be used to collect and understand what setting specific factors drive the risks of AbR within individual countries. It may also be the case that other risk domains could be added to the risk domains developed from Study 1. A global map of the risk domains framework with granular country specific risks could help policy influencers such as the WHO tailor these national action plans rather than limiting recommendations to high level targets that are currently seen with the five objectives of the WHO's global action plan.

As data collection improves across countries, input availability for the mathematical transmission models similar to the one presented in Chapter 4 will improve. With better data, certainty in outputs will increase, enabling models to be used for prediction over longer time horizons. Thus aiding policy decisions through estimation of the potential (cost) effectiveness of interventions in the long term.

The process-level factors could be further expanded to other NHS and Foundation Trusts around England, so a more generalisable picture can be framed to inform health policy researchers. A large scale study of this nature is needed to pool together and identify the common barriers policy implementers are facing. Furthermore, a pooled analysis of this nature can also help identify if current NHS policy implementation landscape is skewed towards a top down approach. Since policy measures tackling AbR require a bottom-up approach to policy implementation to increase the clinical efficacy of currently implemented interventions. Moreover, following a large scale study of this nature, the causal loop diagrams could be supported by quantitative evidence from national databases. The interrelationships can be supported by evidence from the NHS Estates and Hospital

facilities database (also known as the Estates returns information collection database) (223) together with the AMR Fingertips data (224) routinely collected and reported by Public Health England.

The overall aim of this thesis was to develop four frameworks to enable policymakers to tackle AbR by overcoming the barriers highlighted in Chapter 1. The motivation behind the overall aim was to help policymakers make more informed investment decisions when it comes to tackling AbR. Therefore a crucial next step of this thesis would be to assess how the policymakers perceive these frameworks as an everyday policy tool.

Following the initial development of the AbR drivers map in Chapter 2, the results were disseminated during the quarterly UK 5 year AMR strategy meeting, with the agreement that once the results were published, they would be a supplement to the systems maps developed by the Department of health and Social Care's working group. As a next step, attending the AMR 5 year UK strategy meeting to evaluate the results of Study 3 and 4 and discuss with the stakeholders whether the frameworks are useful tools for the Department of Health and Social Care would be a way to assess the applicability of both frameworks.

The process level barriers and the causal loop frameworks have previously been presented to the ICHCNT IPC team. However, from a policy perspective, the next step would be to disseminate the results by publishing Study 4 in a peer reviewed journal. Followed by the result dissemination, the Department of Health and Social Care (AMR strategy team), NHS Improvement, and NHS England could be contacted to assess if the results from the one Trust study is how these stakeholders view an AMR intervention adoption and diffusion to be carried out. Subsequently asking these stakeholders if similar studies would be of interest as a policy tool. If these stakeholders view such causal frameworks useful then the one Trust study could be further expanded to include more Trusts to help generalise the results from the ICHCNT study.

6.5 Conclusion

Since the completion of the studies in this thesis a number of global and national reports on AbR have been published. The rates of AbR around the globe are not showing signs of slowing down. Within a recent second survey on how well the national action plans are being implemented using the WHO's global action plan framework (224), the study concluded the target of ensuring all WHO member countries have a national action plan in place by 2017 was ambitious. At the time of the survey, 93 out of the 194 member countries had a national action plan in place. Therefore, policymakers still have a challenging task ahead when it comes to engaging stakeholders to effectively tackle AbR.

The evidence gaps, and process-level factors identified from this thesis will help policymakers from over focusing their investment efforts within a few areas and broaden the scope of AbR policy. Furthermore, the thesis was able to show policymakers the need for an understanding of the whole system challenges of tackling AbR thus promoting the need for more bottom-up approaches to implementing AbR policy in the future.

REFERENCES

1. WHO - regional office Europe. Antimicrobial resistance [Internet]. [cited 2018 May 29]. Available from: http://www.euro.who.int/en/health-topics/disease-prevention/antimicrobial-resistance/about-amr

2. Thompson LR, Sanders JG, McDonald D, Amir A, Ladau J, Locey KJ, et al. A communal catalogue reveals Earth's multiscale microbial diversity. Nature [Internet]. 2017 Nov 1;551:457. Available from: https://doi.org/10.1038/nature24621

3. Gilbert JA, Jansson JK, Knight R. The Earth Microbiome project: successes and aspirations. BMC Biol [Internet]. 2014 Aug 22;12:69. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25184604

4. United Nation. Political Declaration of the high-level meeting of the General Assembly on antimicrobial resistance. 2016;15751(September 2016):1–22.

5. Dr David Garner. Microbiology Nuts & Bolts : Key Concepts of Microbiology & Infection. 2nd Editio. CreateSpace; 2014.

6. Exner M, Bhattacharya S, Christiansen B, Gebel J, Goroncy-Bermes P, Hartemann P, et al. Antibiotic resistance: What is so special about multidrug-resistant Gram-negative bacteria? GMS Hyg Infect Control [Internet]. 2017 Apr 10;12:Doc05–Doc05. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28451516

7. Holmes AH, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet [Internet]. 2016 Jan [cited 2015 Nov 18];387(10014):176–87. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84947313859&partnerID=tZOtx3y1

8. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations the review on antimicrobial resistance. 2016.

9. WHO. ANTIMICROBIAL RESISTANCE Global Report on Surveillance 2014. 2014;

10. Wellcome Trust, United Nations Foundation. Sustaining global action on antimicrobial resistance. 2017;1–14.

11. United Nations. The Millennium Development Goals Report 2015. MDG Report. 2015.

12. World Health Organisation (WHO). Antimicrobial Resistance (Fact sheet) [Internet]. WHO Media centre. 2017 [cited 2017 Nov 24]. Available from: http://www.who.int/mediacentre/factsheets/fs194/en/

13. Fleming A. Penicillin, Nobel Lecture, December 11, 1945. 1945.

14. Fleming, A. On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenzae. 1929. Br J Exp Pathol. 1929;10(3):226.

15. World Health Organisation (WHO). Antibacterial agents in clinical development [Internet]. 2017 [cited 2017 Oct 6]. Available from: http://www.who.int/medicines/news/2017/IAU_AntibacterialAgentsClinicalDevelopment_webfinal_2017_09_19.pdf?ua=1.

16. European Centre for Disease Prevention and Control (ECDC). Healthcare-associated infections acquired in intensive care units - Annual Epidemiological Report 2016 [2014 data] [Internet]. 2016. Available from: https://ecdc.europa.eu/en/publications-data/infections-acquired-

intensive-care-units-annual-report-2016

17. The Center For Disease Dynamics, Economics & Policy (CDDEP). ResistanceMap [Internet]. [cited 2018 May 29]. Available from: https://resistancemap.cddep.org/About.php

18. Gelband H, Laxminarayan R. Tackling antimicrobial resistance at global and local scales. Trends Microbiol. 2015;23(9):524–6.

19. O'Neill J. Antimicrobial Resistance : Tackling a crisis for the health and wealth of nations. 2014.

20. O'Neill J. Securing New Drugs for Future Generations: The Pipeline of Antibiotics [Internet]. 2015. Available from: http://amr-review.org/sites/default/files/SECURING NEW DRUGS FOR FUTURE GENERATIONS FINAL WEB_0.pdf%5Cnhttp://amr-review.org/Publications

21. The Center for Disease Dynamics Economics & Policy. ResistanceMap [Internet]. 2018 [cited 2019 Jun 1]. Available from: https://resistancemap.cddep.org/AntibioticResistance.php

22. Otter JA, Burgess P, Davies F, Mookerjee S, Singleton J, Gilchrist M, et al. Counting the cost of an outbreak of carbapenemase-producing Enterobacteriaceae: an economic evaluation from a hospital perspective. Clin Microbiol Infect [Internet]. 2017 Mar;23(3):188–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27746394

23. Yin W, Li H, Shen Y, Liu Z, Wang S, Shen Z, et al. Novel Plasmid-Mediated Colistin Resistance Gene mcr-3 in Escherichia coli. MBio [Internet]. 2017 Jun 27;8(3). Available from: http://www.ncbi.nlm.nih.gov/pubmed/28655818

24. KPMG. The global economic impact of antimicrobial resistance. London; 2014.

25. Taylor J, Hafner M, Yerushalmi E, Smith R, Bellasio J, Vardavas R, et al. Estimating the economic costs of antimicrobial resistance: Model and Results. [Internet]. 2014. Available from: https://www.rand.org/pubs/research_reports/RR911.html.

26. Adeyi OO., Baris E, Jonas OB., Irwin A, Berthe FCJ, Le Gall FG., et al. Drug resistant infections A Threat to Our Economic Future. Washington, D.C.; 2017.

27. Centres for Disease Control and Prevention UD of H and HS. Antibiotic resistance threats in the United States. [Internet]. Atlanta; 2013. Available from: http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf

28. Naylor NR, Atun R, Zhu N, Kulasabanathan K, Silva S, Chatterjee A, et al. Estimating the burden of antimicrobial resistance: a systematic literature review. Antimicrob Resist Infect Control [Internet]. 2018 Dec 25;7(1):58. Available from: https://doi.org/10.1186/s13756-018-0336-y

29. O'Neill J. Infection prevention, control and surveillance: Limiting the development & spread of drug resistance [Internet]. 2016. Available from: http://amr-review.org/Publications

30. de Kraker MEA, Davey PG, Grundmann H, group B study. Mortality and hospital stay associated with resistant Staphylococcus aureus and Escherichia coli bacteremia: estimating the burden of antibiotic resistance in Europe. PLoS Med [Internet]. 2011 Oct 11;8(10):e1001104–e1001104. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22022233

31. Jasovský D, Littmann J, Zorzet A, Cars O. Antimicrobial resistance-a threat to the world's sustainable development. Ups J Med Sci [Internet]. 2016 Aug;121(3):159–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27416324

32. The Lancet Infectious Diseases. The endless struggle. Lancet Infect Dis [Internet].

2011;11(April). Available from: https://www.thelancet.com/action/showPdf?pii=S1473-3099%2811%2970077-9

33. World Health Organization. Global Action Plan on Antimicrobial Resistance. Geneva; 2015.

34. The World Health Organization (WHO). WHO global strategy for containment of antimicrobial resistance. Geneva; 2001.

35. Buse K, Mays N, Walt G. Making health policy. McGraw-Hill Education (UK); 2012.

36. (NICE) National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [Internet]. 2018. Available from: https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview

37. ReAct - Action on Antibiotic Resistance. AMR Stakeholder mapping. 2016.

38. Hoffman SJ, Caleo GM, Daulaire N, Elbe S, Matsoso P, Mossialos E, et al. Strategies for achieving global collective action on antimicrobial resistance. Bull World Health Organ [Internet]. 2015;93(12):867–76. Available from: http://www.who.int/entity/bulletin/volumes/93/12/15-153171.pdf

39. Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. Lancet Infect Dis [Internet]. 2013 Dec [cited 2014 Jul 10];13(12):1057–98. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84887627398&partnerID=tZOtx3y1

40. Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen J-A, Klugman K, et al. Access to effective antimicrobials: a worldwide challenge. Lancet (London, England) [Internet]. 2016 Jan 9;387(10014):168–75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26603918

41. The Center For Disease Dynamics E& P (CDDEP). Scoping Report on Antimicrobial Resistance in India, November 06, 2017 [Internet]. 2017. Available from: https://cddep.org/publications/scoping-report-antimicrobial-resistance-india/

42. Freire-Moran L, Aronsson B, Manz C, Gyssens IC, So AD, Monnet DL, et al. Critical shortage of new antibiotics in development against multidrug-resistant bacteria-Time to react is now. Drug Resist Updat [Internet]. 2011 Apr;14(2):118–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21435939

43. Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE. Trends in antimicrobial drug development: implications for the future. Clin Infect Dis [Internet]. 2004 May 1;38(9):1279–86. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15127341

44. Renwick MJ, Brogan DM, Mossialos E. A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics. J Antibiot (Tokyo) [Internet]. 2016 Feb 14;69(2):73–88. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4775540

45. Mestre-Ferrandiz J, Towse JS and A, Economics O of H. THE R&D COST OF A NEW MEDICINE. 2012.

46. Wernli D, Jørgensen PS, Morel CM, Carroll S, Harbarth S, Levrat N, et al. Mapping global policy discourse on antimicrobial resistance. BMJ Glob Heal [Internet]. 2017;2(2):e000378. Available from: http://gh.bmj.com/lookup/doi/10.1136/bmjgh-2017-000378

47. United Nations. Resolution adopted by the General Assembly on 25 September 2015. 2015;15751(September 2015):1–22.

48. United Nations. Resolution adopted by the General Assembly on 12 December 2012

[Internet]. 2012. Available from: papers3://publication/uuid/187C36A1-6342-4FD4-80C3-E7620A6AC29A

49. Cars O, Jasovsky D, Action R. Brief for GSDR 2015 Antibiotic resistance (ABR) - - - no sustainability without antibiotics. 2015.

50. Holmes AH, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet (London, England) [Internet]. 2016 Jan 9;387(10014):176–87. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26603922

51. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect Dis [Internet]. 2014;14(1):13. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3897982&tool=pmcentrez&rendertype=abstract%5Cnhttp://www.biomedcentral.com/1471-2334/14/13

52. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. Bmj. 2010;340:c2096.

53. Bryce A, Hay AD, Lane IF, Thornton H V, Wootton M, Costelloe C. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by *Escherichia coli* and association with routine use of antibiotics in primary care: systematic review and meta-analysis. BMJ [Internet]. 2016 Mar 15 [cited 2018 Feb 22];i939. Available from: http://www.bmj.com/lookup/doi/10.1136/bmj.i939

54. Bryce A, Costelloe C, Wootton M, Butler CC, Hay AD. Comparison of risk factors for, and prevalence of, antibiotic resistance in contaminating and pathogenic urinary Escherichia coli in children in primary care: prospective cohort study. J Antimicrob Chemother [Internet]. 2018;(March):1–9. Available from: https://academic.oup.com/jac/advance-article/doi/10.1093/jac/dkx525/4828185

55. Laura B Nellums, PhDa, †, Hayley Thompson, MPHa, †, Prof Alison Holmes, FMedScia, Enrique Castro-Sánchez, PhDa, Jonathan A Otter, PhDa, Marie Norredam, MDb, c, Jon S Friedland, FMedScia, Sally Hargreaves, FRCPEa. Antimicrobial resistance among migrants in Europe: a systematic review and meta-analysis. Lancet Infect Dis [Internet]. 2018; Available from: https://doi.org/10.1016/S1473-3099(18)30219-6

56. Department of Health. Antimicrobial Resistance (AMR) Systems Map Antimicrobial Resistance (AMR) Systems. 2014.

57. The World Health Organization (WHO). Antibiotic Resistance: Multi-country public awareness survey [Internet]. Geneva; 2015. Available from: https://www.who.int/drugresistance/documents/baselinesurveynov2015/en/

58. International Coordination Group on Antimicrobial Resistance. AMR mapping exercise. 2017;1–18. Available from: http://www.who.int/antimicrobial-resistance/interagency-coordination-group/ActivityMapping_Nov2017.pdf

59. Behdinan A, Hoffman SJ, Pearcey M. Some Global Policies for Antibiotic Resistance Depend on Legally Binding and Enforceable Commitments. J Law, Med Ethics [Internet]. 2015 Aug 1;43(3_suppl):68–73. Available from: https://doi.org/10.1111/jlme.12277

60. Spicknall IH, Foxman B, Marrs CF, Eisenberg JNS. A modeling framework for the evolution and spread of antibiotic resistance: Literature review and model categorization. Am J Epidemiol.

2013;178(4):508–20.

61. Walt G, Shiffman J, Schneider H, Murray SF, Brugha R, Gilson L. “Doing” health policy analysis: methodological and conceptual reflections and challenges. Health Policy Plan [Internet]. 2008/08/12. 2008 Sep;23(5):308–17. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18701552

62. Dowdy DW, Dye C, Cohen T. Data needs for evidence-based decisions: a tuberculosis modeler’s “wish list”. Int J Tuberc Lung Dis [Internet]. 2013 Jul [cited 2016 Jan 8];17(7):866–77. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84878947759&partnerID=tZOtx3y1

63. Robotham JV, Graves N, Cookson BD, Barnett AG, Wilson JA, Edgeworth JD, Batra R, Cuthbertson BH CB. Screening, isolation, and decolonisation strategies in the control of meticillin resistant Staphylococcus aureus in intensive care units: cost effectiveness evaluation. BMJ. 2011;

64. Van Kleef E, Robotham J V, Jit M, Deeny SR, Edmunds WJ. Modelling the transmission of healthcare associated infections: a systematic review. BMC Infect Dis. 2013;13:1.

65. Tonkin-Crine SK, Tan PS, van Hecke O, Wang K, Roberts NW, McCullough A, et al. Clinician-targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care: an overview of systematic reviews. Cochrane database Syst Rev [Internet]. 2017;9:CD012252. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28881002

66. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane database Syst Rev [Internet]. 2017;2:CD003543. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28178770

67. Charani E, Castro-Sanchez E, Sevdalis N, Kyratsis Y, Drumright L, Shah N, et al. Understanding the determinants of antimicrobial prescribing within hospitals: the role of “prescribing etiquette”. Clin Infect Dis [Internet]. 2013 Jul;57(2):188–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23572483

68. Pulcini C, Gyssens IC. How to educate prescribers in antimicrobial stewardship practices. Virulence [Internet]. 2013 Feb 15;4(2):192–202. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23361336

69. Tomson G, Vlad I. The need to look at antibiotic resistance from a health systems perspective. Ups J Med Sci [Internet]. 2014 May 1;119(2):117–24. Available from: https://doi.org/10.3109/03009734.2014.902879

70. Clements A, Halton K, Graves N, Pettitt A, Morton A, Looke D, et al. Overcrowding and understaffing in modern health-care systems: key determinants in meticillin-resistant Staphylococcus aureus transmission. Lancet Infect Dis [Internet]. 2008 Jul;8(7):427–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18582835

71. Atun R, De Jongh T, Secci F, Ohiri K, Adeyi O. Integration of targeted health interventions into health systems: A conceptual framework for analysis. Health Policy Plan. 2010;25(2):104–11.

72. Sternam J. Business dynamics: systems thinking and modeling for a complex world. 2000.

73. Peters DH. The application of systems thinking in health: Why use systems thinking? Heal Res Policy Syst. 2014;12:12–28.

74. Wolstenholme E, Monk D, McKelvie D, Smith G. Influencing and Interpreting Health and Social

Care Policy in the UK. Complex Decis Mak Theory Pract. 2008;155–84.

75. Vandenbroeck P, Goossens J, Clemens M. Foresight Tackling Obesities: Future Choices – Building the Obesity System Map [Internet]. 2007. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/295154/07-1179-obesity-building-system-map.pdf

76. WHO, PAHO. Monitoring and Evaluation of the Global Action Plan on Antimicrobial Resistance (AMR): Regional Expert Consultation on Monitoring and Evaluation of AMR Interventions. 2017;(January):40. Available from: file:///C:/Users/wbarrantes/Downloads/2017-cha-monit-eval-gapar-meeting-report (1).pdf

77. World Health Organization (WHO) F and AO of the UN (FAO) and WO for AH (OIE). Monitoring global progress on addressing antimicrobial resistance: analysis report of the second round of results of AMR country self-assessment survey 2018. 2018.

78. Wells V, Jenkins A, Wanford J, Piddock LJ V. Implementing Who , Eu and Uk Amr Strategies and Action Plans : Has the World Lived Up To the Challenge ? 2017;(November).

79. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci [Internet]. 2018;201717295. Available from: http://www.pnas.org/lookup/doi/10.1073/pnas.1717295115

80. Department for Environment, Food & Rural Affairs, Department of Health and Social Care, Public Health England and VMD. Antimicrobial resistance (AMR) [Internet]. 2019. Available from: https://www.gov.uk/government/collections/antimicrobial-resistance-amr-information-and-resources

81. Shallcross LJ, Howard SJ, Fowler T, Davies SC. Tackling the threat of antimicrobial resistance: from policy to sustainable action. Philos Trans R Soc Lond B Biol Sci [Internet]. 2015 Jun 5;370(1670):20140082. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25918440

82. Department of Health. UK Five Year Antimicrobial Resistance Strategy 2013 to 2018 [Internet]. London; 2013. Available from: https://www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018

83. Department of Health. Antimicrobial Resistance Empirical and Statistical Evidence-Base A report from the Department of Health Antimicrobial Resistance Strategy Analytical Working Group. 2014.

84. McCullough AR, Rathbone J, Parekh S, Hoffmann TC, Del Mar CB. Not in my backyard: a systematic review of clinicians' knowledge and beliefs about antibiotic resistance. J Antimicrob Chemother [Internet]. 2015;70(9):2465–73. Available from: http://www.jac.oxfordjournals.org/cgi/doi/10.1093/jac/dkv164

85. Marshall BM, Levy SB. Food animals and antimicrobials: Impacts on human health. Clin Microbiol Rev. 2011;24(4):718–33.

86. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ. 2010;340:c2096.

87. van Loon K, Voor In 't Holt AF, Vos MC. A Systematic Review and Meta-analyses of the Clinical Epidemiology of Carbapenem-Resistant Enterobacteriaceae. Antimicrob Agents Chemother [Internet]. 2018 Jan;62(1):1–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29038269

88. Gilbert EM, Zembower TR, Rhodes NJ, Qi C, Reiner S, Malczynski M, et al. Factors contributing to vancomycin-resistant Enterococcus spp. horizontal transmission events: exploration of the role of antibacterial consumption. Diagn Microbiol Infect Dis [Internet]. 2017;89(1):72–7. Available from: http://dx.doi.org/10.1016/j.diagmicrobio.2017.05.014

89. Kantele A, Mero S, Kirveskari J, Lääveri T. Fluoroquinolone antibiotic users select fluoroquinolone-resistant ESBL-producing Enterobacteriaceae (ESBL-PE) – Data of a prospective traveller study. Travel Med Infect Dis. 2017;16:23–30.

90. Jiang HL, Zhou Z, Wang LS, Fang Y, Li YH, Chu CI. The Risk Factors, Costs, and Survival Analysis of Invasive VRE Infections at a Medical Center in Eastern Taiwan. Int J Infect Dis [Internet]. 2017;54(701):18–24. Available from: http://dx.doi.org/10.1016/j.ijid.2016.11.005

91. Magiorakos A-P, Kleinkauf N, Struelens M, Monnet D. Updated ECDC risk assessment on the spread of New Delhi metallo-β-lactamase and its variants within Europe [Internet]. 2011. Available from: http://ecdc.europa.eu/en/publications/Publications/1111_TER_Risk-assessment-NDM.pdf

92. Mateus A, Takahashi E, Elkholly D, Crotta M, Ekiri A, Wylie C, et al. A systematic review to assess the significance of the food chain in the context of antimicrobial resistance (AMR) with particular reference to pork and poultry meat, dairy products, seafood and fresh produce on retail sale in the UK. R Vet Coll [Internet]. 2016;1–104. Available from: https://www.food.gov.uk/sites/default/files/amr-systematic-review-final-report-2016.pdf

93. Food Standards Agency (FSA). A Microbiological survey of campylobacter contamination in fresh whole UK produced chilled chickens at retail sale (2014-15): FSA Project FS241044 Antibiotic Resistance Report for FS241044 - Sept 2016. 2016.

94. Voor in ’t holt AF, Severin JA, Lesaffre EMEH, Vos MC. A Systematic Review and Meta-Analyses Show that Carbapenem Use and Medical Devices Are the Leading Risk Factors for Carbapenem-Resistant Pseudomonas aeruginosa. Antimicrob Agents Chemother [Internet]. 2014 May 1 [cited 2018 Feb 22];58(5):2626–37. Available from: http://aac.asm.org/cgi/doi/10.1128/AAC.01758-13

95. Zacharioudakis IM, Zervou FN, Ziakas PD, Mylonakis E. Meta-Analysis of Methicillin-Resistant Staphylococcus aureus Colonization and Risk of Infection in Dialysis Patients. J Am Soc Nephrol [Internet]. 2014;25:1–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24652802

96. Zervou FN, Zacharioudakis IM, Ziakas PD, Rich JD, Mylonakis E. Prevalence of and risk factors for methicillin-resistant staphylococcus aureus colonization in HIV infection: A meta-analysis. Clin Infect Dis. 2014;59(9):1302–11.

97. Tacconelli E, Cataldo MA, Paul M, Leibovici L, Kluytmans J, Schroder W, et al. STROBE-AMS: recommendations to optimise reporting of epidemiological studies on antimicrobial resistance and informing improvement in antimicrobial stewardship. BMJ Open. 2016;6(2):e010134.

98. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P SL. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1).

99. Harris a D, Karchmer TB, Carmeli Y, Samore MH. Methodological principles of case-control studies that analyzed risk factors for antibiotic resistance: a systematic review. Clin Infect Dis. 2001;32(7):1055–61.

100. Katy L. James, Nicola P. Randal NRH. A methodology for systematic mapping in environmental sciences. Environ Evid [Internet]. 2016;5(7). Available from: https://doi.org/10.1186/s13750-016-0059-6

101. Lawton R, Mceachan RRC, Giles SJ, Sirriyeh R, Watt IS, Wright J. Development of an evidence-based framework of factors contributing to patient safety incidents in hospital settings : a systematic review. 2012;(March).

102. Pathirana T, Clark J, Moynihan R. Mapping the drivers of overdiagnosis to potential Thanya Pathirana and colleagues explore strategies to tackle the problem of too much medicine. 2017;3879:1–9.

103. Bouchard P, Carra MC, Boillot A, Mora F. Risk factors in periodontology : a conceptual framework. 2017;125–31.

104. Kalra N NM. A systematic map of the research on the relationship between obesity and sedentary behaviour in young people. Technical report. 2009.

105. Vandenbroeck IP, Goossens DJ, Marshall Clemens. Foresight - Tackling Obesities: Future Choices – Obesity System Atlas [Internet]. 2007. Available from: https://www.gov.uk/government/publications/reducing-obesity-obesity-system-map

106. ECDC/EFSA/EMA. ECDC/EFSA/EMA second joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals Joint Interagency Antimicrobial Consumption and Resistanc. 2017.

107. Barkovskii AL, Bridges C. Persistence and profiles of tetracycline resistance genes in swine farms and impact of operational practices on their occurrence in farms' vicinities. Water Air Soil Pollut. 2012;223(1):49–62.

108. Köck R, Harlizius J, Bressan N, Laerberg R, Wieler LH, Witte W, et al. Prevalence and molecular characteristics of methicillin-resistant Staphylococcus aureus (MRSA) among pigs on German farms and import of livestock-related MRSA into hospitals. Eur J Clin Microbiol Infect Dis. 2009;28(11):1375–82.

109. Price LB, Graham JP, Lackey LG, Roess A, Vailes R, Silbergeld E. Elevated risk of carrying gentamicin-resistant escherichia coli among U.S. poultry workers. Environ Health Perspect. 2007;115(12):1738–42.

110. Leistner R, Meyer E, Gastmeier P, Pfeifer Y, Eller C, Dem P, et al. Risk factors associated with the community-acquired colonization of extended-spectrum beta-lactamase (ESBL) positive Escherichia Coli. an exploratory case-control study. PLoS One [Internet]. 2013;8(9):e74323. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3770595&tool=pmcentrez&rendertype=abstract

111. Coleman BL, Salvadori MI, McGeer AJ, Sibley KA, Neumann NF, Bondy SJ, et al. The role of drinking water in the transmission of antimicrobial-resistant *E. coli*. Epidemiol Infect [Internet]. 2012;140(4):633–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21733246

112. Alali WQ, Scott HM, Christian KL, Fajt VR, Harvey RB, Lawhorn DB. Relationship between level of antibiotic use and resistance among *Escherichia coli* isolates from integrated multi-site cohorts of humans and swine. Prev Vet Med. 2009;90(3–4):160–7.

113. Vandendriessche S, Vanderhaeghen W, Soares FV, Hallin M, Catry B, Hermans K, et al.

Prevalence, risk factors and genetic diversity of methicillin-resistant Staphylococcus aureus carried by humans and animals across livestock production sectors. J Antimicrob Chemother. 2013;68(7):1510–6.

114. van Hoek AHAM, Veenman C, van Overbeek WM, Lynch G, de Roda Husman AM, Blaak H. Prevalence and characterization of ESBL- and AmpC-producing Enterobacteriaceae on retail vegetables. Int J Food Microbiol [Internet]. 2015;204:1–8. Available from: http://dx.doi.org/10.1016/j.ijfoodmicro.2015.03.014

115. Sana Ilyas, Muhammad Usman Qamar, Muhammad Hidayat Rasool, Nazia Abdulhaq ZN. Multidrug-resistant pathogens isolated from ready-to-eat salads available at a local market in Pakistan. Br Food J. 2016;118(8):2068–75.

116. Lin D, Ou Q, Lin J, Peng Y, Yao Z. A meta-analysis of the rates of Staphylococcus aureus and methicillin-resistant S aureus contamination on the surfaces of environmental objects that health care workers frequently touch. Am J Infect Control [Internet]. 2017 Apr 1;45(4):421–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28010909

117. Lin J, Lin D, Xu P, Zhang T, Ou Q, Bai C, et al. Non-hospital environment contamination with Staphylococcus aureus and methicillin-resistant Staphylococcus aureus: proportion meta-analysis and features of antibiotic resistance and molecular genetics. Environ Res [Internet]. 2016 Oct [cited 2018 Feb 22];150:528–40. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0013935116302778

118. Tang KL, Caffrey NP, Nóbrega DB, Cork SC, Ronksley PE, Barkema HW, et al. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. Lancet Planet Heal [Internet]. 2017;1(8):e316–27. Available from: http://linkinghub.elsevier.com/retrieve/pii/S2542519617301419

119. Interagency Coordination Group on antimicrobial resistance. AMR Framework for Action Supported by the IACG. 2017;1–28. Available from: http://www.who.int/antimicrobial-resistance/interagency-coordination-group/20170818_AMR_FfA_v01.pdf?ua=1

120. Batura N, Cuevas C, Khan M, Wiseman V. How effective and cost-effective are behaviour change interventions in improving the prescription and use of antibiotics in low-income and middle-income countries? A protocol for a systematic review. BMJ Open. 2018;8(5):e021517.

121. Rogers Van Katwyk S, Grimshaw JM, Mendelson M, Taljaard M, Hoffman SJ. Government policy interventions to reduce human antimicrobial use: Protocol for a systematic review and meta-analysis. Syst Rev. 2017;6(1):1–10.

122. Annie Wilkinson AE and HM. Interventions to Reduce Antibiotic Prescribing in LMICs: A Scoping Review of Evidence from Human and Animal Health Systems. Antibiotics. 2019;8(1):2.

123. (NICE) National Institute for Health and Care Excellence. The guidelines manual 2009 [Internet]. 2012 [cited 2018 Oct 13]. Available from: https://www.nice.org.uk/process/pmg6/chapter/introduction

124. Ashiru-Oredope D, Budd EL, Bhattacharya A, Din N, McNulty CAM, Micallef C, et al. Implementation of antimicrobial stewardship interventions recommended by national toolkits in primary and secondary healthcare sectors in England: TARGET and Start Smart Then Focus. J Antimicrob Chemother. 2016;71(5):1408–14.

125. Hu Y, Walley J, Chou R, Tucker JD, Harwell JI, Wu X, et al. Interventions to reduce childhood antibiotic prescribing for upper respiratory infections: Systematic review and meta-analysis. J

Epidemiol Community Health. 2016;70(12):1162–70.

126. Andrews T, Thompson M, Buckley DI, Heneghan C, Deyo R, Redmond N, et al. Interventions to influence consulting and antibiotic use for acute respiratory tract infections in children: A systematic review and Meta-Analysis. PLoS One. 2012;7(1):1–11.

127. Huang Y, Chen R, Wu T, Wei X, Guo A. Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: A systematic review and meta-analysis of primary care studies. Br J Gen Pract. 2013;63(616):787–94.

128. Odermatt J, Friedli N, Kutz A, Briel M, Bucher HC, Christ-Crain M, et al. Effects of procalcitonin testing on antibiotic use and clinical outcomes in patients with upper respiratory tract infections. An individual patient data meta-analysis. Clin Chem Lab Med [Internet]. 2017;0(0):170–7. Available from: http://www.degruyter.com/view/j/cclm.ahead-of-print/cclm-2017-0252/cclm-2017-0252.xml

129. Honda H, Ohmagari N, Tokuda Y, Mattar C, Warren DK. Antimicrobial stewardship in inpatient settings in the Asia pacific region: A systematic review and meta-analysis. Clin Infect Dis. 2017;64(June):S119–26.

130. Ibrahim WH, Mushtaq K, Raza T, Kartha A, Saleh AO, Malik RA. Effects of procalcitonin-guided treatment on antibiotic use and need for mechanical ventilation in patients with acute asthma exacerbation: Meta-analysis of randomized controlled trials. Int J Infect Dis [Internet]. 2017;65:75–80. Available from: http://dx.doi.org/10.1016/j.ijid.2017.10.005

131. Karanika S, Paudel S, Grigoras C, Kalbasi A, Mylonakis E. Systematic Review and Meta-analysis of Clinical and Economic Outcomes from the Implementation of Hospital-Based Antimicrobial Stewardship Programs. Antimicrob Agents Chemother [Internet]. 2016 Aug [cited 2018 Feb 22];60(8):4840–52. Available from: http://aac.asm.org/lookup/doi/10.1128/AAC.00825-16

132. Schuetz P, Müller B, Stolz D, Tamm M, Bouadma L, Ce L, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections (Review). Cochrane Database Syst Rev. 2017;(10):Art.No.: CD007498.

133. Baysari MT, Lehnbom EC, Li L, Hargreaves A, Day RO, Westbrook JI. The effectiveness of information technology to improve antimicrobial prescribing in hospitals: A systematic review and meta-analysis. Int J Med Inform [Internet]. 2016;92:15–34. Available from: http://dx.doi.org/10.1016/j.ijmedinf.2016.04.008

134. Kopterides P, Siempos II, Tsangaris I, Tsantes A, Armaganidis A. Procalcitonin-guided algorithms of antibiotic therapy in the intensive care unit: A systematic review and meta-analysis of randomized controlled trials. Crit Care Med. 2010;38(11):2229–41.

135. De Angelis G, Cataldo MA, De Waure C, Venturiello S, La Torre G, Cauda R, et al. Infection control and prevention measures to reduce the spread of vancomycin-resistant enterococci in hospitalized patients: a systematic review and meta-analysis. J Antimicrob Chemother [Internet]. 2014;69(5):1185–92. Available from: https://academic.oup.com/jac/article-lookup/doi/10.1093/jac/dkt525

136. Daneman N, Sarwar S, Fowler RA, Cuthbertson BH. Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. Lancet Infect Dis. 2013 Apr;13(4):328–41.

137. Teerawattanapong N, Kengkla K, Dilokthornsakul P, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Prevention and control of multidrug-resistant Gram-negative bacteria in adult intensive care units: A systematic review and network meta-analysis. Clin Infect Dis.

2017;64(June):S51–60.

138. Tang KL, Caffrey NP, Nóbrega DB, Cork SC, Ronksley PE, Barkema HW, et al. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. Lancet Planet Heal. 2017;1(8):e316–27.

139. Baur D, Gladstone BP, Burkert F, Carrara E, Foschi F, Döbele S, et al. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection : a systematic review and meta-analysis. 2017;17(September).

140. Zhao D, Wu Y, Song J, Gao F, Gao X, Lu Y, et al. Selective oropharyngeal decontamination versus selective digestive decontamination in critically ill patients: a meta-analysis of randomized controlled trials. Drug Des Devel Ther [Internet]. 2015 Jul [cited 2018 Feb 22];3617. Available from: http://www.dovepress.com/selective-oropharyngeal-decontamination-versus-selective-digestive-dec-peer-reviewed-article-DDDT

141. Schuts EC, Hulscher MEJL, Mouton JW, Verduin CM, Stuart JWTC, Overdiek HWPM, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis [Internet]. 2016 [cited 2017 Apr 17];16(7):847–56. Available from: http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S1473309916000657

142. Baur D, Gladstone BP, Burkert F, Carrara E, Foschi F, Döbele S, et al. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis. Lancet Infect Dis [Internet]. 2017 Sep;17(9):990–1001. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28629876

143. Tang KL, Caffrey NP, Nóbrega DB, Cork SC, Ronksley PE, Barkema HW, et al. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. Lancet Planet Heal [Internet]. 2017 Nov;1(8):e316–27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29387833

144. Emonet S, Charles PG, Harbarth S, Stewardson AJ, Renzi G, Uckay I, et al. Rapid molecular determination of methicillin resistance in staphylococcal bacteraemia improves early targeted antibiotic prescribing: a randomized clinical trial. Clin Microbiol Infect [Internet]. 2016;22(11):946.e9-946.e15. Available from: http://dx.doi.org/10.1016/j.cmi.2016.07.022

145. Hallsworth M, Chadborn T, Sallis A, Sanders M, Berry D, Greaves F, et al. Provision of social norm feedback to high prescribers of antibiotics in general practice: A pragmatic national randomised controlled trial. Lancet [Internet]. 2016;387(10029):1743–52. Available from: http://dx.doi.org/10.1016/S0140-6736(16)00215-4

146. McNulty C, Hawking M, Lecky D, Jones L, Owens R, Charlett A, et al. Effects of primary care antimicrobial stewardship outreach on antibiotic use by general practice staff: Pragmatic randomized controlled trial of the TARGET antibiotics workshop. J Antimicrob Chemother. 2018;73(5):1423–32.

147. Butler CC, Simpson SA, Dunstan F, Rollnick S, Cohen D, Gillespie D, et al. Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: Practice based randomised controlled trial. BMJ. 2012;344(7843):1–13.

148. Roque F, Teixeira-Rodrigues A, Breitenfeld L, Piñeiro-Lamas M, Figueiras A, Herdeiro MT.

Decreasing antibiotic use through a joint intervention targeting physicians and pharmacists. Future Microbiol. 2016;11(7):877–86.

149. Dekker ARJ, Verheij TJM, Broekhuizen BDL, Butler CC, Cals JWL, Francis NA, et al. Effectiveness of general practitioner online training and an information booklet for parents on antibiotic prescribing for children with respiratory tract infection in primary care: a cluster randomized controlled trial. J Antimicrob Chemother [Internet]. 2018;(February):1416–22. Available from: https://academic.oup.com/jac/advance-article/doi/10.1093/jac/dkx542/4846902

150. van der Velden AW, Kuyvenhoven MM, Verheij TJM. Improving antibiotic prescribing quality by an intervention embedded in the primary care practice accreditation: The ARTI4 randomized trial. J Antimicrob Chemother. 2016;71(1):257–63.

151. Lee MHM, Pan DST, Huang JH, Chen MIC, Chong JWC, Goh EH, et al. Results from a patient-based health education intervention in reducing antibiotic use for acute upper respiratory tract infections in the private sector primary care setting in Singapore. Antimicrob Agents Chemother. 2017;61(5):1–11.

152. Lesprit P, de Pontfarcy A, Esposito-Farese M, Ferrand H, Mainardi JL, Lafaurie M, et al. Postprescription review improves in-hospital antibiotic use: A multicenter randomized controlled trial. Clin Microbiol Infect [Internet]. 2015;21(2):180.e1-180.e7. Available from: http://dx.doi.org/10.1016/j.cmi.2014.08.015

153. X. Z, C. L, L. W. Public reporting improves antibiotic prescribing for upper respiratory tract infections in primary care: a matched-pair cluster-randomized trial in China. Health Res Policy Syst [Internet]. 2014;12:61. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=25304996

154. Linder JA, Schnipper JL, Tsurikova R, Yu DT, Volk LA, Melnikas AJ, et al. Electronic Health Record Feedback to Improve Antibiotic Prescribing for Acute Respiratory Infections. Am J Manag Care. 2010;16:E311–9.

155. Little P, Hobbs FDR, Moore M, Mant D, Williamson I, McNulty C, et al. Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management). BMJ [Internet]. 2013 Oct 10;347:f5806. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24114306

156. Brown DP, Charani E, Fenelon E, Im G, Holmes A, Cr R, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients (Review). Available from: http://www.thecochranelibrary.com

157. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane database Syst Rev. 2013 Apr;(4):CD003543.

158. Skg T, Ps T, O VH, Wang K, Nw R, Mccullough A, et al. Clinician-targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care : an overview of systematic reviews (Review). 2017;(9).

159. Box, George EP and NRD. Empirical model-building and response surfaces. John Wiley & Sons; 1987.

160. Ramsay DE, Invik J, Checkley SL, Gow SP, Osgood ND, Waldner CL. Application of dynamic modelling techniques to the problem of antibacterial use and resistance: a scoping review. Epidemiol Infect [Internet]. 2018 Dec 31 [cited 2019 Mar 10];146(16):2014–27. Available

from:
https://www.cambridge.org/core/product/identifier/S0950268818002091/type/journal_article

161. Arepeva M, Kolbin A, Kurylev A, Balykina J, Sidorenko S. What should be considered if you decide to build your own mathematical model for predicting the development of bacterial resistance? Recommendations based on a systematic review of the literature. Front Microbiol [Internet]. 2015;6:352. Available from: https://www.frontiersin.org/article/10.3389/fmicb.2015.00352

162. Bonten MJ, Weinstein RA. The role of colonization in the pathogenesis of nosocomial infections. Infect Control Hosp Epidemiol. 1996 Mar;17(3):193–200.

163. Shallcross L, Beckley N, Rait G, Hayward A, Petersen I. Antibiotic prescribing frequency amongst patients in primary care: a cohort study using electronic health records. J Antimicrob Chemother [Internet]. 2017 Jun;72(6):1818–24. Available from: https://academic.oup.com/jac/article-lookup/doi/10.1093/jac/dkx048

164. Public Health England (PHE). National Statistics MRSA, MSSA and Gram-negative bacteraemia and CDI: annual report [Internet]. 2017 [cited 2019 Jun 1]. Available from: https://www.gov.uk/government/statistics/mrsa-mssa-and-e-coli-bacteraemia-and-c-difficile-infection-annual-epidemiological-commentary

165. Public Health England (PHE). Escherichia coli (E. coli): guidance, data and analysis. 2017.

166. Abernethy J, Guy R, Sheridan EA, Hopkins S, Kiernan M, Wilcox MH, et al. Epidemiology of Escherichia coli bacteraemia in England: results of an enhanced sentinel surveillance programme. J Hosp Infect. 2017;95(4):365–75.

167. Bou-Antoun S, Davies J, Guy R, Johnson AP, Sheridan EA, Hope RJ. Descriptive epidemiology of Escherichia coli bacteraemia in England , April 2012 to March 2014. 2016;(March 2014):1–9.

168. NR Naylor, KB Pouwels, R Hope, N Green, KL Henderson, GM Knight, R Atun, JV Robotham SD. A National Estimate of the Health and Cost Burden of Escherichia coli Bacteraemia in the Hospital Setting: The Importance of Antibiotic Resistance. bioRxiv. 2017;153775.

169. Office of National Statistics (ONS). National life tables, UK: 2015 to 2017 [Internet]. 2017 [cited 2019 Jun 1]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2015to2017

170. Public Health England: ESPAUR team. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR). Public Heal Engl [Internet]. 2017;1–143. Available from: www.gov.uk/phe%5Cnwww.facebook.com/PublicHealthEngland

171. Public Health England and NHS Improvement. Preventing healthcare associated Gram - negative bloodstream infections : an improvement resource. 2017;(May).

172. Bhattacharya A, Nsonwu O, Johnson AP, Hope R. Estimating the incidence and 30-day all-cause mortality rate of Escherichia coli bacteraemia in England by 2020 / 21. J Hosp Infect [Internet]. 2020;98(3):228–31. Available from: https://doi.org/10.1016/j.jhin.2017.09.021

173. Gurieva T, Dautzenberg MJD, Gniadkowski M, Derde LPG, Bonten MJM, Bootsma MCJ. The Transmissibility of Antibiotic-Resistant Enterobacteriaceae in Intensive Care Units. Clin Infect Dis [Internet]. 2018 Feb 1;66(4):489–93. Available from: https://academic.oup.com/cid/article/66/4/489/4158824

174. Haverkate MR, Platteel TN, Fluit AC, Cohen Stuart JW, Leverstein-van Hall MA, Thijsen SFT, et al. Quantifying within-household transmission of extended-spectrum β-lactamase-producing bacteria. Clin Microbiol Infect [Internet]. 2017 Jan;23(1):46.e1-46.e7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1198743X16303603

175. Karanika S, Paudel S, Grigoras C, Kalbasi A, Mylonakis E. Systematic Review and Meta-analysis of Clinical and Economic Outcomes from the Implementation of Hospital-Based Antimicrobial Stewardship Programs. Antimicrob Agents Chemother [Internet]. 2016 Aug;60(8):4840–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27246783

176. NHS England. Bed Availability and Occupancy Data – Overnight [Internet]. 2017 [cited 2019 Jun 1]. Available from: https://www.england.nhs.uk/statistics/statistical-work-areas/bedavailability-and-occupancy/bed-data-overnight/

177. NHS Digital. Hospital Admitted Patient Care Activity, 2016-17 [Internet]. 2017 [cited 2019 Jun 1]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2016-17

178. NHS Digital. Hospital Admitted Patient Care Activity, 2015-16 [Internet]. 2016 [cited 2019 Jun 1]. Available from: https://digital.nhs.uk/news-and-events/news-archive/2016-news-archive/hospital-admissions-hit-record-high-as-population-ages

179. Knight GM, Costelloe C, Deeny SR, Moore LSP, Hopkins S, Johnson AP, et al. Quantifying where human acquisition of antibiotic resistance occurs: a mathematical modelling study. BMC Med [Internet]. 2018 Aug 23;16(1):137. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30134939

180. Hurford A, Morris AM, Fisman DN, Wu J. Linking antimicrobial prescribing to antimicrobial resistance in the ICU: Before and after an antimicrobial stewardship program. Epidemics [Internet]. 2012 Dec;4(4):203–10. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1755436512000540

181. Teunis PFM, Evers EG, Hengeveld PD, Dierikx CM, Wielders CCCH, van Duijkeren E. Time to acquire and lose carriership of ESBL/pAmpC producing E. coli in humans in the Netherlands. Vadivelu J, editor. PLoS One [Internet]. 2018 Mar 21;13(3):e0193834. Available from: http://dx.plos.org/10.1371/journal.pone.0193834

182. Melnyk AH, Wong A, Kassen R. The fitness costs of antibiotic resistance mutations. Evol Appl [Internet]. 2015 Mar;8(3):273–83. Available from: http://doi.wiley.com/10.1111/eva.12196

183. Department of Health and Social Care. NHS reference costs 2016 to 2017 [Internet]. 2017 [cited 2019 Jun 1]. Available from: https://improvement.nhs.uk/resources/reference-costs/

184. Bou-Antoun, S Holmes A, Costelloe C, Honeyford K, Aylin P, Bou-Antoun S, Johnson AP, et al. Age-related decline in antibiotic prescribing for uncomplicated respiratory tract infections in primary care in England following the introduction of a national financial incentive (the Quality Premium) for health commissioners to reduce use of antibiotic. J Antimicrob Chemother [Internet]. 2018;73(10):2883–92. Available from: https://dx.doi.org/10.1093/jac/dky237

185. Pouwels KB, Dolk FCK, Smith DRM, Smieszek T, Robotham J V. Explaining variation in antibiotic prescribing between general practices in the UK. 2018;(March).

186. Stewardson AJ, Allignol A, Beyersmann J, Graves N, Schumacher M, Meyer R, et al. The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible Enterobacteriaceae and Staphylococcus aureus in European hospitals, 2010 and

2011: a multicentre retrospective cohort study. Euro Surveill [Internet]. 2016 Aug 18;21(33). Available from: http://www.ncbi.nlm.nih.gov/pubmed/27562950

187. Department of Health. UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. London; 2013.

188. Dattée B, Barlow J. Multilevel Organizational Adaptation: Scale Invariance in the Scottish Healthcare System. Organ Sci [Internet]. 2017;28(2):301–19. Available from: http://pubsonline.informs.org/doi/10.1287/orsc.2017.1113

189. Charmaz K. Constructing Grounded Theory, A Practical Guide through Qualitative Analysis. SAGE Publications Ltd; 2006.

190. Crossan MM, Apaydin M. A Multi-Dimensional Framework of Organizational Innovation : A Systematic Review of the Literature Mary M . Crossan and Marina Apaydin. 2010;(September).

191. Glaser, Barney G & Strauss, Anselm L. The Discovery of Grounded Theory: Strategies for Qualitative Research. Chicago: Aldine Publishing Company; 1967.

192. Sbaraini A, Carter SM, Evans RW, Blinkhorn A. How to do a grounded theory study : a worked example of a study of dental practices. BMC Med Res Methodol [Internet]. 2011;11(1):128. Available from: http://www.biomedcentral.com/1471-2288/11/128

193. Charani E, Castro-Sanchez E, Sevdalis N, Kyratsis Y, Drumright L, Shah N, et al. Understanding the determinants of antimicrobial prescribing within hospitals: the role of “prescribing etiquette”. Clin Infect Dis. 2013 Jul;57(2):188–96.

194. Perozziello A, Routelous C, Charani E, Truel A, Birgand G, Yazdanpanah Y, et al. The experiences and perspectives of implementing antimicrobial stewardship in five French hospitals: a qualitative study. Int J Antimicrob Agents [Internet]. 2018; Available from: https://doi.org/10.1016/j.ijantimicag.2018.01.002

195. World Health Organisation (WHO). WHO Guidelines on Hand Hygiene in Health Care: First Global Patient Safety Challenge Clean Care Is Safer Care. 18, Behavioural considerations. [Internet]. Geneva; 2009. Available from: https://www.ncbi.nlm.nih.gov/books/NBK144052/

196. Zingg W, Holmes A, Dettenkofer M, Goetting T, Secci F, Clack L, et al. Review Hospital organisation, management, and structure for prevention of health-care-associated infection: a systematic review and expert consensus. Lancet Infect Dis. 2015;15:212–24.

197. Rawson TM, Charani E, Moore LSP, Hernandez B, Castro-Sánchez E, Herrero P, et al. Mapping the decision pathways of acute infection management in secondary care among UK medical physicians: A qualitative study. BMC Med [Internet]. 2016;14(1):1–10. Available from: http://dx.doi.org/10.1186/s12916-016-0751-y

198. Charani E, Castro-Sánchez E, Holmes A. The Role of Behavior Change in Antimicrobial Stewardship. Infect Dis Clin [Internet]. 2014 Jun 1;28(2):169–75. Available from: https://doi.org/10.1016/j.idc.2014.01.004

199. Charani E, Smith I, Skodvin B, Perozziello A, Lucet J-C, Lescure F-X, et al. Investigating the cultural and contextual determinants of antimicrobial stewardship programmes across low-, middle- and high-income countries—A qualitative study. PLoS One [Internet]. 2019 Jan 16;14(1):e0209847. Available from: https://doi.org/10.1371/journal.pone.0209847

200. Sterman JD. Learning from evidence in a complex world. Am J Public Health [Internet]. 2006 Mar;96(3):505–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16449579

201. Arnold RD, Wade JP. A Definition of Systems Thinking : A Systems Approach. Procedia - Procedia Comput Sci [Internet]. 2015;44:669–78. Available from: http://dx.doi.org/10.1016/j.procs.2015.03.050

202. Sterman, J.D. Business dynamics: systems thinking and modeling for a complex world. No. HD30. 2000.

203. Azoulay, Peirre, Nelson P. Repenning EWZ. Nasty , Brutish , and Short : Embeddedness Failure in the Pharmaceutical Industry. Adm Sci Q. 2010;55(3):472–507.

204. Eker S, Zimmermann N. Using Textual Data in System Dynamics Model Conceptualization. Systems [Internet]. 2016;4(3):28. Available from: http://www.mdpi.com/2079-8954/4/3/28

205. Bowen GA. Document Analysis as a Qualitative Research Method. Qual Res J [Internet]. 2009 Aug 3;9(2):27–40. Available from: http://www.emeraldinsight.com/doi/10.3316/QRJ0902027

206. O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. Acad Med [Internet]. 2014 Sep;89(9):1245–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24979285

207. Schmidtke KA, Poots AJ, Carpio J, Vlaev I, Kandala NB, Lilford RJ. Considering chance in quality and safety performance measures: An analysis of performance reports by boards in English NHS trusts. BMJ Qual Saf. 2017;26(1):61–9.

208. Jones L, Pomeroy L, Robert G, Burnett S, Anderson JE, Fulop NJ. How do hospital boards govern for quality improvement? A mixed methods study of 15 organisations in England. BMJ Qual Saf [Internet]. 2017;(July):bmjqs-2016-006433. Available from: http://qualitysafety.bmj.com/lookup/doi/10.1136/bmjqs-2016-006433

209. Endacott R, Sheaff R, Jones R, Woodward V. Clinical focus and public accountability in English NHS trust board meetings. J Heal Serv Res Policy. 2013;18(1):13–20.

210. Kyratsis Y, Ahmad R, Holmes A. Technology adoption and implementation in organisations : comparative case studies of 12 English NHS Trusts. 2012;1–9.

211. Charani E, Castro-Sanchéz E, Bradley S, Nathwani D, Holmes AH, Davey P. Implementation of antibiotic stewardship in different settings - results of an international survey. Antimicrob Resist Infect Control [Internet]. 2019 Feb;8(1):34. Available from: https://doi.org/10.1186/s13756-019-0493-7

212. Chatterjee A, Modarai M, Naylor NR, Boyd SE, Atun R, Barlow J, et al. Quantifying drivers of antibiotic resistance in humans: a systematic review. Lancet Infect Dis [Internet]. 2018 Dec;18(12):e368–78. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1473309918302962

213. Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. Lancet Planet Heal [Internet]. 2018 Sep 1;2(9):e398–405. Available from: https://doi.org/10.1016/S2542-5196(18)30186-4

214. Smith DRM, Dolk FCK, Pouwels KB, Christie M, Robotham J V, Smieszek T. Defining the appropriateness and inappropriateness of antibiotic prescribing in primary care. J Antimicrob Chemother. 2018 Feb;73(suppl_2):ii11–8.

215. Dolk FCK, Pouwels KB, Smith DRM, Robotham J V, Smieszek T. Antibiotics in primary care in England: which antibiotics are prescribed and for which conditions? J Antimicrob Chemother. 2018 Feb;73(suppl_2):ii2–10.

216. Pouwels KB, Dolk FCK, Smith DRM, Robotham J V, Smieszek T. Actual versus ‘ ideal ’ antibiotic prescribing for common conditions in English primary care. 2018;(March):19–26.

217. Pouwels KB, Hopkins S, Llewelyn MJ, Walker AS, McNulty CAM, Robotham J V. Duration of antibiotic treatment for common infections in English primary care: cross sectional analysis and comparison with guidelines. BMJ [Internet]. 2019;364. Available from: https://www.bmj.com/content/364/bmj.l440

218. Pouwels KB, Freeman R, Muller-Pebody B, Rooney G, Henderson KL, Robotham J V, et al. Association between use of different antibiotics and trimethoprim resistance: going beyond the obvious crude association. J Antimicrob Chemother. 2018 Jun;73(6):1700–7.

219. Brisson M, Laprise J-F, Chesson HW, Drolet M, Malagón T, Boily M-C, et al. Health and Economic Impact of Switching from a 4-Valent to a 9-Valent HPV Vaccination Program in the United States. J Natl Cancer Inst [Internet]. 2016 Jan 4;108(1):djv282. Available from: https://academic.oup.com/jnci/article-lookup/doi/10.1093/jnci/djv282

220. Jit M, Choi YH, Edmunds WJ. Economic evaluation of human papillomavirus vaccination in the United Kingdom. BMJ [Internet]. 2008 Jul 17;337(jul17 2):a769–a769. Available from: http://www.bmj.com/cgi/doi/10.1136/bmj.a769

221. The Parliamentary Office of Science and Technology. Reservoirs of Antimicrobial Resistance [Internet]. London; 2019. Available from: https://researchbriefings.parliament.uk/ResearchBriefing/Summary/POST-PN-0595#fullreport

222. Lishman H, Aylin P, Alividza V, Castro-Sanchez E, Chatterjee A, Mariano V, et al. Investigating the burden of antibiotic resistance in ethnic minority groups in high-income countries: Protocol for a systematic review and meta-analysis. Syst Rev. 2017;6(1).

223. NHS Digital. Estates Returns Information Collection [Internet]. 2018 [cited 2019 Jun 1]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/estates-returns-information-collection

224. Public Health England (PHE). AMR local indicators [Internet]. 2019 [cited 2019 Jun 1]. Available from: https://fingertips.phe.org.uk/profile/amr-local-indicators

225. Abdel-Hady H, Hawas S, El-Daker M, El-Kady R. Extended-spectrum beta-lactamase producing *Klebsiella pneumoniae* in neonatal intensive care unit. J Perinatol. 2008;28(10):685–90.

226. Abebe W, Endris M, Tiruneh M, Moges F. Prevalence of vancomycin resistant *Enterococci* and associated risk factors among clients with and without HIV in Northwest Ethiopia: a cross-sectional study. BMC Public Health [Internet]. 2014;14:185. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3943508&tool=pmcentrez&rendertype=abstract

227. Achermann Y, Eigenmann K, Ledergerber B, Derksen L, Rafeiner P, Clauss M, et al. Factors associated with rifampin resistance in *staphylococcal* periprosthetic joint infections (PJI): A matched case-control study. Infection. 2013;41(2):431–7.

228. Agudo S, Pérez-Pérez G, Alarcón T, López-Brea M. High prevalence of clarithromycin-resistant *Helicobacter pylori* strains and risk factors associated with resistance in Madrid, Spain. J Clin Microbiol. 2010;48(10):3703–7.

229. Ahn JY, Song JE, Kim MH, Choi H, Kim JK, Ann HW, et al. Risk factors for the acquisition of carbapenem-resistant *Escherichia coli* at a tertiary care center in South Korea: A matched case-control study. Am J Infect Control [Internet]. 2014;42(6):621–5. Available from: http://dx.doi.org/10.1016/j.ajic.2014.02.024

230. Akinci E, Çolpan A, Bodur H, Balaban N, Erbay A. Risk factors for ICU-acquired imipenem-resistant Gram-negative bacterial infections. J Hosp Infect. 2005;59(4):317–23.

231. Akinyemi KO, Iwalokun BA, Foli F, Oshodi K, Coker AO. Prevalence of multiple drug resistance and screening of enterotoxin (*stn*) gene in *Salmonella enterica* serovars from water sources in Lagos, Nigeria. Public Health [Internet]. 2011;125(2):65–71. Available from: http://dx.doi.org/10.1016/j.puhe.2010.11.010

232. Alali WQ, Scott HM, Norby B. Assessing the similarity of antimicrobial resistance phenotypes among fecal *Escherichia coli* isolates from two aggregated occupational cohorts of humans versus swine using cluster analysis and multivariate statistics. Prev Vet Med [Internet]. 2010;94(1–2):77–83. Available from: http://dx.doi.org/10.1016/j.prevetmed.2009.11.014

233. Al-Assil B, Mahfoud M, Hamzeh AR. Resistance trends and risk factors of extended spectrum β-lactamases in *Escherichia coli* infections in Aleppo, Syria. Am J Infect Control [Internet]. 2013;41(7):597–600. Available from: http://dx.doi.org/10.1016/j.ajic.2012.09.016

234. Albright JB, Pidala MJ, Cali JR, Snyder MJ, Voloyiannis T, Bailey HR. MRSA-related perianal abscesses: An underrecognized disease entity. Dis Colon Rectum. 2007;50(7):996–1003.

235. Aldeyab MA, Harbarth S, Vernaz N, Kearney MP, Scott MG, Darwish Elhajji FW, et al. The impact of antibiotic use on the incidence and resistance pattern of extended-spectrum beta-lactamase-producing bacteria in primary and secondary healthcare settings. Br J Clin Pharmacol. 2012;74(1):171–9.

236. Almeida N, Romãozinho JM, Donato MM, Luxo C, Cardoso O, Cipriano MA, et al. *Helicobacter pylori* antimicrobial resistance rates in the central region of Portugal. Clin Microbiol Infect. 2014;20(11):1127–33.

237. Almeida ST, Nunes S, Paulo ACS, Faria NA, de Lencastre H, Sa-Leao R. Prevalence, risk factors, and epidemiology of methicillin-resistant *Staphylococcus aureus* carried by adults over 60 years of age. Eur J Clin Microbiol Infect Dis. 2015;34(3):593–600.

238. Al-Nammari SS, Bobak P, Venkatesh R. Methicillin resistant *Staphylococcus aureus* versus methicillin sensitive *Staphylococcus aureus* adult haematogenous septic arthritis. Arch Orthop Trauma Surg. 2007;127(7):537–42.

239. Alsan M, Schoemaker L, Eggleston K, Kammili N, Kolli P, Bhattacharya J. Out-of-pocket health expenditures and antimicrobial resistance in low-income and middle-income countries: An economic analysis. Lancet Infect Dis. 2015;15(10):1203–10.

240. Altoparlak U, Koca O, Ozkurt Z, Akcay MN. Incidence and risk factors of vancomycin-resistant *Enterococcus* colonization in burn unit patients. Burns. 2011;37(1):49–53.

241. Amin PB, Magnotti LJ, Fischer PE, Fabian TC, Croce MA. Prophylactic antibiotic days as a predictor of sensitivity patterns in *Acinetobacter pneumonia*. Surg Infect (Larchmt) [Internet]. 2011;12(1):33–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21186957

242. Anderson MEC, Lefebvre SL, Weese JS. Evaluation of prevalence and risk factors for methicillin-resistant *Staphylococcus aureus* colonization in veterinary personnel attending an international equine veterinary conference. Vet Microbiol [Internet]. 2008 Jun 22;129(3–4):410–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18187274

243. Andersson H, Lindholm C, Iversen A, Giske CG, Örtqvist Å, Kalin M, et al. Prevalence of antibiotic-resistant bacteria in residents of nursing homes in a Swedish municipality: Healthcare staff knowledge of and adherence to principles of basic infection prevention. Scand J Infect Dis. 2012;44(9):641–9.

244. Andriatahina T, Randrianirina F, Hariniana ER, Talarmin A, Raobijaona H, Buisson Y, et al. High prevalence of fecal carriage of extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in a pediatric unit in Madagascar. BMC Infect Dis [Internet]. 2010;10:204. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20624313%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2912907

245. Apisarnthanarak A, Kiratisin P, Saifon P, Kitphati R, Dejsirilert S, Mundy LM. Clinical and molecular epidemiology of community-onset, extended-spectrum β-lactamase-producing *Escherichia coli* infections in Thailand: A case-case-control study. Am J Infect Control. 2007;35(9):606–12.

246. Argudín MA, Mendoza MC, González-Hevia MA, Bances M, Guerra B, Rodicio MR. Genotypes, exotoxin gene content, and antimicrobial resistance of *Staphylococcus aureus* strains recovered from foods and food handlers. Appl Environ Microbiol. 2012;78(8):2930–5.

247. Arnan M, Gudiol C, Calatayud L, Liñares J, Dominguez MÁ, Batlle M, et al. Risk factors for, and clinical relevance of, faecal extended-spectrum β-lactamase producing *Escherichia coli* (ESBL-EC) carriage in neutropenic patients with haematological malignancies. Eur J Clin Microbiol Infect Dis. 2011;30(3):355–60.

248. Arslan H, Azap OK, Ergonul O, Timurkaynak F. Risk factors for ciprofloxacin resistance among *Escherichia coli* strains isolated from community-acquired urinary tract infections in Turkey. J Antimicrob Chemother. 2005;56(5):914–8.

249. Arvaniti K, Lathyris D, Ruimy R, Haidich A, Koulourida V, Nikolaidis P, et al. The importance of colonization pressure in multiresistant *Acinetobacter baumannii* acquisition in a Greek intensive care unit. Crit Care [Internet]. 2012;16(3):R102. Available from: http://ccforum.com/content/16/3/R102%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3580657&tool=pmcentrez&rendertype=abstract

250. Askarian M, Afkhamzadeh R, Monabbati A, Daxboeck F, Assadian O. Risk factors for rectal colonization with vancomycin-resistant *enterococci* in Shiraz, Iran. Int J Infect Dis. 2008;12(2):171–5.

251. Askarian M, Zeinalzadeh A, Japoni A, Alborzi A, Memish ZA. Prevalence of nasal carriage of methicillin-resistant *Staphylococcus aureus* and its antibiotic susceptibility pattern in healthcare workers at Namazi Hospital, Shiraz, Iran. Int J Infect Dis [Internet]. 2009 Sep;13(5):e241-7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19269873

252. Aspa J, Rajas O, Rodr?guez de Castro F, Torres A, Blanquer J, Zalacain R, et al. Risk Factors for Multidrug-Resistant Pneumococcal Pneumonia. Infect Dis Clin Pract [Internet]. 2008 Nov;16(6):368–75. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00019048-200811000-00006

253. Assadian O, Askarian M, Stadler M, Shaghaghian S. Prevalence of vancomycin-resistant *enterococci* colonization and its risk factors in chronic hemodialysis patients in Shiraz, Iran. BMC Infect Dis [Internet]. 2007;7:52. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1894971&tool=pmcentrez&rendertype=abstract

254. Bakunas-Kenneley I, Madigan EA. Infection prevention and control in home health care: The nurse's bag. Am J Infect Control [Internet]. 2009;37(8):687–8. Available from: http://dx.doi.org/10.1016/j.ajic.2009.03.004

255. Baran G, Erbay A, Bodur H, Öngürü P, Akinci E, Balaban N, et al. Risk factors for nosocomial imipenem-resistant *Acinetobacter baumannii* infections. Int J Infect Dis. 2008;12(1):16–21.

256. Batard E, Ollivier F, Boutoille D, Hardouin J-B, Montassier E, Caillon J, et al. Relationship between hospital antibiotic use and quinolone resistance in *Escherichia coli*. Int J Infect Dis [Internet]. 2013;17(4):e254-8. Available from: http://www.sciencedirect.com/science/article/pii/S1201971212012763

257. Benenson S, Yinnon AM, Schlesinger Y, Rudensky B, Raveh D. Optimization of empirical antibiotic selection for suspected Gram-negative bacteraemia in the emergency department. Int J Antimicrob Agents. 2005;25(5):398–403.

258. Bhat S, Fujitani S, Potoski BA, Capitano B, Linden PK, Shutt K, et al. *Pseudomonas aeruginosa* infections in the Intensive Care Unit: can the adequacy of empirical β-lactam antibiotic therapy be improved? Int J Antimicrob Agents. 2007;30(5):458–62.

259. Bilavsky E, Temkin E, Lerman Y, Rabinovich A, Salomon J, Lawrence C, et al. Risk factors for colonization with extended-spectrum beta-lactamase-producing *enterobacteriaceae* on admission to rehabilitation centres. Clin Microbiol Infect [Internet]. 2014;20(11):O804–10. Available from: http://dx.doi.org/10.1111/1469-0691.12633

260. Bitsori M, Maraki S, Kalmanti M, Galanakis E. Resistance against broad-spectrum β-lactams among uropathogens in children. Pediatr Nephrol. 2009;24(12):2381–6.

261. Blaettler L, Mertz D, Frei R, Elzi L, Widmer AF, Battegay M, et al. Secular trend and risk factors for antimicrobial resistance in *Escherichia coli* isolates in Switzerland 1997-2007. Infection. 2009;37(6):534–9.

262. Bleumin D, Cohen MJ, Moranne O, Esnault VLM, Benenson S, Paltiel O, et al. Carbapenem-resistant *Klebsiella pneumoniae* is associated with poor outcome in hemodialysis patients. J Infect [Internet]. 2012;65(4):318–25. Available from: http://dx.doi.org/10.1016/j.jinf.2012.06.005

263. Bocher S, Gervelmeyer A, Monnet DL, Molbak K, Skov RL. Methicillin-resistant *Staphylococcus aureus*: risk factors associated with community-onset infections in Denmark. Clin Microbiol Infect. 2008;14(10):942–8.

264. Bodro M, Sabe N, Tubau F, Llado L, Baliellas C, Gonzalez-Costello J, et al. Extensively drug-resistant *Pseudomonas aeruginosa* bacteremia in solid organ transplant recipients. Transplantation. 2015;99(3):616–22.

265. Borer A, Saidel-Odes L, Eskira S, Nativ R, Riesenberg K, Livshiz-Riven I, et al. Risk factors for developing clinical infection with carbapenem-resistant *Klebsiella pneumoniae* in hospital patients initially only colonized with carbapenem-resistant *K pneumoniae*. Am J Infect Control [Internet]. 2012;40(5):421–5. Available from: http://dx.doi.org/10.1016/j.ajic.2011.05.022

266. Brugnaro P, Fedeli U, Pellizzer G, Buonfrate D, Rassu M, Boldrin C, et al. Clustering and risk factors of methicillin-resistant *Staphylococcus aureus* carriage in two italian long-term care facilities. Infection. 2009;37(3):216–21.

267. Bucheli E, Kralidis G, Boggian K, Cusini A, Garzoni C, Manuel O, et al. Impact of enterococcal colonization and infection in solid organ transplantation recipients from the Swiss Transplant Cohort Study. Transpl Infect Dis. 2014;16(1):26–36.

268. Caffrey AR, Quilliam BJ, LaPlante KL. Risk factors associated with mupirocin resistance in meticillin-resistant *Staphylococcus aureus*. J Hosp Infect [Internet]. 2010;76(3):206–10. Available from: http://dx.doi.org/10.1016/j.jhin.2010.06.023

269. Cai T, Verze P, Brugnolli A, Tiscione D, Luciani LG, Eccher C, et al. Adherence to European Association of Urology Guidelines on Prophylactic Antibiotics: An Important Step in Antimicrobial Stewardship. Eur Urol. 2016;69(2):276–83.

270. Campos PA, Batistão DWF, Gontijo-Filho PP, Ribas RM, Campos PA, Batist WF. Scandinavian Journal of Infectious Diseases A sustained endemic outbreak of vancomycin- resistant Enterococcus faecium: A 30-month surveillance study A sustained endemic outbreak of vancomycin-resistant Enterococcus faecium: A 30-month surveillance study. Scand J Infect Dis [Internet]. 2014;46(September 2016):547–54. Available from: http://www.tandfonline.com/action/journalInformation?journalCode=infd19%5Cnhttp://dx.doi.org/10.3109/00365548.2014.912348

271. Canizalez-Roman A, Gonzalez-Nuñez E, Vidal JE, Flores-Villaseñor H, León-Sicairos N. Prevalence and antibiotic resistance profiles of diarrheagenic *Escherichia coli* strains isolated from food items in northwestern Mexico. Int J Food Microbiol [Internet]. 2013;164(1):36–45. Available from: http://dx.doi.org/10.1016/j.ijfoodmicro.2013.03.020

272. Carnicer-Pont D, Bailey KA, Mason BW, Walker AM, Evans MR, Salmon RL. Risk factors for hospital-acquired methicillin-resistant *Staphylococcus aureus* bacteraemia: a case-control study. Epidemiol Infect [Internet]. 2006 Dec 20;134(6):1167–73. Available from: http://www.journals.cambridge.org/abstract_S0950268806006327

273. Cassier P, Lallechère S, Aho S, Astruc K, Neuwirth C, Piroth L, et al. Cephalosporin and fluoroquinolone combinations are highly associated with CTX-M β-lactamase-producing *Escherichia coli*: A case-control study in a French teaching hospital. Clin Microbiol Infect. 2011;17(11):1746–51.

274. Castelo Branco Fortaleza CM, Moreira De Freitas F, Da Paz Lauterbach G. Colonization pressure and risk factors for acquisition of imipenem-resistant *Acinetobacter baumannii* in a medical surgical intensive care unit in Brazil. Am J Infect Control [Internet]. 2013;41(3):263–5. Available from: http://dx.doi.org/10.1016/j.ajic.2012.03.016

275. Cattaneo C, Quaresmini G, Casari S, Capucci MA, Micheletti M, Borlenghi E, et al. Recent changes in bacterial epidemiology and the emergence of fluoroquinolone-resistant *Escherichia coli* among patients with haematological malignancies: Results of a prospective study on 823 patients at a single institution. J Antimicrob Chemother. 2008;61(3):721–8.

276. Cavalcante R de S, Canet P, Fortaleza CMCB. Risk factors for the acquisition of imipenem-resistant Acinetobacter baumannii in a burn unit: an appraisal of the effect of colonization pressure. Scand J Infect Dis. 2014;46(September 2016):593–8.

277. Cenizal MJ, Hardy RD, Anderson M, Katz K, Skiest DJ. Prevalence of and risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) nasal colonization in HIV-infected ambulatory patients. J Acquir Immune Defic Syndr [Internet]. 2008 Aug 15;48(5):567–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18645516

278. Cezário RC, Duarte De Morais L, Ferreira JC, Costa-Pinto RM, da Costa Darini AL, Gontijo-Filho PP. Nosocomial outbreak by imipenem-resistant metallo-beta-lactamase-producing *Pseudomonas aeruginosa* in an adult intensive care unit in a Brazilian teaching hospital. Enferm Infecc Microbiol Clin [Internet]. 2009 May;27(5):269–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19386392

279. Chen CC, Pass SE. Risk factors for and impact of methicillin-resistant *Staphylococcus aureus* nasal colonization in patients in a medical intensive care unit. Am J Infect Control [Internet]. 2013;41(11):1100–1. Available from: http://dx.doi.org/10.1016/j.ajic.2013.01.035

280. Chen CJ, Hsu KH, Lin TY, Hwang KP, Chen PY, Huang YC. Factors associated with nasal colonization of methicillin-resistant *Staphylococcus aureus* among healthy children in Taiwan. J Clin Microbiol. 2011;49(1):131–7.

281. Chen S-Y, Wu GH-M, Chang S-C, Hsueh P-R, Chiang W-C, Lee C-C, et al. Bacteremia in Previously Hospitalized Patients: Prolonged Effect From Previous Hospitalization and Risk Factors for Antimicrobial-Resistant Bacterial Infections. Ann Emerg Med. 2008;51(5):639–46.

282. Chen SY, Wang JL, Chen THH, Chiang WC, Wang JT, Chen SC, et al. Differences between methicillin-resistant *Staphylococcus aureus* bacteremic isolates harboring type IV and type v staphylococcal cassette chromosome *mec* genes based on prior patient healthcare exposure. Eur J Clin Microbiol Infect Dis. 2010;29(12):1539–46.

283. Chen SY, Chiang WC, Ma MHM, Hsueh PR, Chang SC, Fang CC, et al. Predicting methicillin resistance among community-onset *Staphylococcus aureus* bacteremia patients with prior healthcare-associated exposure. Eur J Clin Microbiol Infect Dis. 2012;31(10):2727–36.

284. Cheng VCC, Chen JHK, Poon RWS, Lee WM, So SYC, Wong SCY, et al. Control of hospital endemicity of multiple-drug-resistant *Acinetobacter baumannii* ST457 with directly observed hand hygiene. Eur J Clin Microbiol Infect Dis. 2015;34(4):713–8.

285. Cheng VCC, Chen JHK, So SYC, Wong SCY, Yan MK, Chau PH, et al. Use of fluoroquinolones is the single most important risk factor for the high bacterial load in patients with nasal and gastrointestinal colonization by multidrug-resistant *Acinetobacter baumannii*. Eur J Clin Microbiol Infect Dis. 2015;34(12):2359–66.

286. Cho DT, Cha HY, Chang HH, Kim SW, Chung JM, Kim J, et al. Risk factors for specific methicillin-resistant *Staphylococcus aureus* clones in a Korean hospital. J Antimicrob Chemother. 2006;57(6):1122–7.

287. Chopra T, Marchaim D, Awali RA, Krishna A, Johnson P, Tansek R, et al. Epidemiology of bloodstream infections caused by *Acinetobacter baumannii* and impact of drug resistance to both carbapenems and ampicillin-sulbactam on clinical outcomes. Antimicrob Agents Chemother. 2013;57(12):6270–5.

288. Chusri S, Silpapojakul K, McNeil E, Singkhamanan K, Chongsuvivatwong V. Impact of antibiotic exposure on occurrence of nosocomial carbapenem-resistant *Acinetobacter baumannii* infection: A case control study. J Infect Chemother [Internet]. 2015;21(2):90–5. Available from: http://dx.doi.org/10.1016/j.jiac.2014.10.002

289. Cisneros JM, Rodríguez-Baño J, Fernández-Cuenca F, Ribera A, Vila J, Pascual A, et al. Risk-factors for the acquisition of imipenem-resistant *Acinetobacter baumannii* in Spain: A nationwide study. Clin Microbiol Infect. 2005;11(11):874–9.

290. Cobos-Trigueros N, Solé M, Castro P, Torres JL, Hernández C, Rinaudo M, et al. Acquisition of *Pseudomonas aeruginosa* and its resistance phenotypes in critically ill medical patients: role of colonization pressure and antibiotic exposure. Crit Care [Internet]. 2015;19:218. Available from: /pmc/articles/PMC4432505/?report=abstract

291. Cohen R, Levy C, de La Rocque F, Gelbert N, Wollner A, Fritzell B, et al. Impact of pneumococcal conjugate vaccine and of reduction of antibiotic use on nasopharyngeal carriage of nonsusceptible pneumococci in children with acute otitis media. Pediatr Infect Dis J [Internet]. 2006;25(11):1001–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17072121

292. Cohen-Nahum K, Saidel-Odes L, Riesenberg K, Schlaeffer F, Borer A. Urinary Tract Infections

Caused by Multi-Drug Resistant *Proteus mirabilis*: Risk Factors and Clinical Outcomes. Infection. 2010;38(1):41–6.

293. Coleman BL, Louie M, Salvadori MI, McEwen SA, Neumann N, Sibley K, et al. Contamination of Canadian private drinking water sources with antimicrobial resistant *Escherichia coli*. Water Res [Internet]. 2013;47(9):3026–36. Available from: http://dx.doi.org/10.1016/j.watres.2013.03.008

294. Conceição T, Coelho C, Silva IS, de Lencastre H, Aires-de-Sousa M. *Staphylococcus aureus* in former Portuguese colonies from Africa and the Far East: missing data to help fill the world map. Clin Microbiol Infect [Internet]. 2015 Sep;21(9):842.e1-842.e10. Available from: http://dx.doi.org/10.1016/j.cmi.2015.05.010

295. Cook PP, Gooch M, Rizzo S. Reduction in fluoroquinolone use following introduction of ertapenem into a hospital formulary is associated with improvement in susceptibility of *Pseudomonas aeruginosa* to group 2 carbapenems: a 10-year study. Antimicrob Agents Chemother [Internet]. 2011 Dec;55(12):5597–601. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21968357

296. Cordery RJ, Roberts CH, Cooper SJ, Bellinghan G, Shetty N. Evaluation of risk factors for the acquisition of bloodstream infections with extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella* species in the intensive care unit; antibiotic management and clinical outcome. J Hosp Infect. 2008;68(2):108–15.

297. Coronado F, Nicholas JA, Wallace BJ, Kohlerschmidt DJ, Musser K, Schoonmaker-Bopp DJ, et al. Community-associated methicillin-resistant *Staphylococcus aureus* skin infections in a religious community. Epidemiol Infect [Internet]. 2007 Apr;135(3):492–501. Available from: c:%5CKarsten%5CPDFs%5CStaphylokokken-PDFs%5CStaph-2006%5CCoronado et al.-Community-associated methicillin-resistant Staphylococcus aureus skin infections in a religious community.pdf

298. Correa L, Martino MDV, Siqueira I, Pasternak J, Gales AC, Silva CV, et al. A hospital-based matched case-control study to identify clinical outcome and risk factors associated with carbapenem-resistant *Klebsiella pneumoniae* infection. BMC Infect Dis [Internet]. 2013 Feb 11;13(1):80. Available from: http://www.biomedcentral.com/1471-2334/13/80

299. Crowther-Gibson P, Cohen C, Klugman KP, De Gouveia L, Von Gottberg A. Risk factors for multidrug-resistant invasive pneumococcal disease in South Africa, a setting with high HIV prevalence, in the prevaccine era from 2003 to 2008. Antimicrob Agents Chemother. 2012;56(10):5088–95.

300. Crum-Cianflone NF, Burgi A a, Hale BR. Increasing rates of community-acquired methicillin-resistant *Staphylococcus aureus* infections among HIV-infected persons. Int J STD AIDS [Internet]. 2007;18(8):521–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17686212

301. Cunningham JB, Kernohan WG, Sowney R. Bed occupancy and turnover interval as determinant factors in MRSA infections in acute settings in Northern Ireland: 1 April 2001 to 31 March 2003. J Hosp Infect. 2005;61(3):189–93.

302. Czekalski N, Sigdel R, Birtel J, Matthews B, Bürgmann H. Does human activity impact the natural antibiotic resistance background? Abundance of antibiotic resistance genes in 21 Swiss lakes. Environ Int [Internet]. 2015;81:45–55. Available from: http://dx.doi.org/10.1016/j.envint.2015.04.005

303. da Silva NS, Muniz VD, Estofolete CF, Furtado GHC, Rubio FG. Identification of temporal

clusters and risk factors of bacteremia by nosocomial vancomycin-resistant enterococci. Am J Infect Control [Internet]. 2014 Apr;42(4):389–92. Available from: http://dx.doi.org/10.1016/j.ajic.2013.11.010

304. da Silva Winter J, Dos Santos RP, de Azambuja AZ, Cechinel AB, Goldani LZ. Microbiologic isolates and risk factors associated with antimicrobial resistance in patients admitted to the intensive care unit in a tertiary care hospital. Am J Infect Control [Internet]. 2013 Sep;41(9):846–8. Available from: http://dx.doi.org/10.1016/j.ajic.2012.11.010

305. Daikos GL, Kosmidis C, Tassios PT, Petrikkos G, Vasilakopoulou A, Psychogiou M, et al. *Enterobacteriaceae* bloodstream infections: presence of integrons, risk factors, and outcome. Antimicrob Agents Chemother [Internet]. 2007 Jul;51(7):2366–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17452479

306. Daikos GL, Vryonis E, Psichogiou M, Tzouvelekis LS, Liatis S, Petrikkos P, et al. Risk factors for bloodstream infection with *Klebsiella pneumoniae* producing VIM-1 metallo-β-lactamase. J Antimicrob Chemother. 2010;65(4):784–8.

307. Dambrosio A, Lorusso V, Quaglia NC, Parisi A, La Salandra G, Virgilio S, et al. *Escherichia coli* O26 in minced beef: Prevalence, characterization and antimicrobial resistance pattern. Int J Food Microbiol. 2007;118(2):218–22.

308. Dayan N, Dabbah H, Weissman I, Aga I, Even L, Glikman D. Urinary tract infections caused by community-acquired extended-spectrum β-lactamase-producing and nonproducing bacteria: A comparative study. J Pediatr [Internet]. 2013;163(5):1417–21. Available from: http://dx.doi.org/10.1016/j.jpeds.2013.06.078

309. De Lastours V, Chau F, Tubach F, Pasquet B, Ruppé E, Fantin B. Independent behavior of commensal flora for carriage of fluoroquinolone-resistant bacteria in patients at admission. Antimicrob Agents Chemother. 2010;54(12):5193–200.

310. De Regt MJA, Willems RJL, Hené RJ, Siersema PD, Verhaar HJJ, Hopmans TEM, et al. Effects of probiotics on acquisition and spread of multiresistant enterococci. Antimicrob Agents Chemother. 2010;54(7):2801–5.

311. del Mar Tomas M, Cartelle M, Pertega S, Beceiro A, Llinares P, Canle D, et al. Hospital outbreak caused by a carbapenem-resistant strain of *Acinetobacter baumannii*: patient prognosis and risk-factors for colonisation and infection. Clin Microbiol Infect [Internet]. 2005 Jul;11(7):540–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15966971

312. DeLorenzo ME, Thompson B, Cooper E, Moore J, Fulton MH. A long-term monitoring study of chlorophyll, microbial contaminants, and pesticides in a coastal residential stormwater pond and its adjacent tidal creek. Environ Monit Assess [Internet]. 2012 Jan 16;184(1):343–59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21409361

313. Dent LL, Marshall DR, Pratap S, Hulette RB. Multidrug resistant *Acinetobacter baumannii*: a descriptive study in a city hospital. BMC Infect Dis [Internet]. 2010;10:196. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2909240&tool=pmcentrez&rendertype=abstract

314. Depuydt PO, Vandijck DM, Bekaert MA, Decruyenaere JM, Blot SI, Vogelaers DP, et al. Determinants and impact of multidrug antibiotic resistance in pathogens causing ventilator-associated-pneumonia. Crit Care [Internet]. 2008;12(6):R142. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2646301&tool=pmcentrez&rendertype=abstract

315. Didier C, Streicher MP, Chognot D, Campagni R, Schnebelen A, Messer J, et al. Late-onset neonatal infections: Incidences and pathogens in the era of antenatal antibiotics. Eur J Pediatr. 2012;171(4):681–7.

316. Dixon JJ, Steele M, Makanjuola AD. Anti-microbial locks increase the prevalence of *Staphylococcus aureus* and antibiotic-resistant *Enterobacter*: Observational retrospective cohort study. Nephrol Dial Transplant. 2012;27(9):3575–81.

317. Dizbay M, Tunccan OG, Sezer BE, Hizel K. Nosocomial imipenem-resistant Acinetobacter baumannii infections: epidemiology and risk factors. Scand J Infect Dis. 2010;42(10):741–6.

318. Drapeau CMJ, Angeletti C, Festa A, Petrosillo N. Role of previous hospitalization in clinically-significant MRSA infection among HIV-infected inpatients: results of a case-control study. BMC Infect Dis [Internet]. 2007;7:36. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1868735&tool=pmcentrez&rendertype=abstract

319. Dromigny JA, Nabeth P, Juergens-Behr A, Perrier-Gros-Claude JD. Risk factors for antibiotic-resistant *Escherichia coli* isolated from community-acquired urinary tract infections in Dakar, Senegal. J Antimicrob Chemother. 2005;56(1):236–9.

320. Dueger EL, Asturias EJ, Matheu J, Gordillo R, Torres O, Halsey N. Increasing penicillin and trimethoprim-sulfamethoxazole resistance in nasopharyngeal *Streptococcus pneumoniae* isolates from Guatemalan children, 2001-2006. Int J Infect Dis. 2008;12(3):289–97.

321. Duerink OD, Lestari ES, Hadi U, Nagelkerke NJD, Severin JA, Verbrugh HA, et al. Determinants of carriage of resistant *Escherichia coli* in the Indonesian population inside and outside hospitals. J Antimicrob Chemother. 2007;60(2):377–84.

322. Duman M, Abacioglu H, Karaman M, Duman N, Ozkan H. Beta-lactam antibiotic resistance in aerobic commensal fecal flora of newborns. Pediatr Int [Internet]. 2005 Jun;47(3):267–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15910449

323. Duran N, Ocak S, Eskiocak AF. *Staphylococcus aureus* nasal carriage among the diabetic and non-diabetic haemodialysis patients. Int J Clin Pract [Internet]. 2006 Oct;60(10):1204–9. Available from: c:%5CKarsten%5CPDFs%5CStaphylokokken-PDFs%5CStaph-2006%5CDuran et al.-Staphylococcus aureus nasal carriage among the diabetic and non-diabetic haemodialysis patients.pdf

324. Dyar OJ, Hoa NQ, Trung N V, Phuc HD, Larsson M, Chuc NTK, et al. High prevalence of antibiotic resistance in commensal *Escherichia coli* among children in rural Vietnam. BMC Infect Dis [Internet]. 2012;12(1):92. Available from: http://www.biomedcentral.com/1471-2334/12/92

325. European Centre for Disease Prevention and Control, European Food Safety Authority, European Medicines Agency. ECDC / EFSA / EMA first joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals 1 Joint Interagency Antimicrobial Consumption and Resi. EFSA J. 2015;13(January):1–114.

326. Ecker KL, Donohue PK, Kim KS, Shepard JA, Aucott SW. The impact of group B Streptococcus prophylaxis on early onset neonatal infections. J Neonatal Perinatal Med [Internet]. 2013;6(1):37–44. Available from: http://dx.doi.org/10.1038/jp.2012.76

327. Efe Iris N, Sayıner H, Yıldırmak T, Simsek F, Arat ME. Vancomycin-resistant Enterococcus carrier status in the reanimation units and related risk factors. Am J Infect Control [Internet].

2013 Mar [cited 2017 Jan 28];41(3):261–2. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0196655312008139

328. Etienne M, Van Elslande H, Choplin-Renard J, Pestel-Caron M, Caron F. Antibiotic resistance in adult female patients hospitalized for acute pyelonephritis: Rates and predicting factors. Med Mal Infect [Internet]. 2014;44(5):217–22. Available from: http://dx.doi.org/10.1016/j.medmal.2014.03.003

329. Eun SH, Lee YS, Cha JO, Yoo JI, Lee JG, Lee HJ, et al. The point prevalence and associated factors of nasal methicillin-resistant Staphylococcus aureus colonisation in eight geriatric hospitals in Korea. Clin Microbiol Infect. 2006;12(1):81–3.

330. Eveillard M, Lancien E, Hidri N, Barnaud G, Gaba S, Benlolo JA, et al. Estimation of methicillin-resistant Staphylococcus aureus transmission by considering colonization pressure at the time of hospital admission. J Hosp Infect. 2005;60(1):27–31.

331. Eveillard M, Mortier E, Lancien E, Lescure FX, Schmit JL, Barnaud G, et al. Consideration of age at admission for selective screening to identify methicillin-resistant Staphylococcus aureus carriers to control dissemination in a medical ward. Am J Infect Control. 2006;34(3):108–13.

332. Fernández A, Pereira MJ, Suárez JM, Poza M, Treviño M, Villalón P, et al. Emergence in Spain of a multidrug-resistant Enterobacter cloacae clinical isolate producing SFO-1 extended-spectrum beta-lactamase. J Clin Microbiol [Internet]. 2011 Mar;49(3):822–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21227991

333. Fernández-Cuenca F, Gómez-Sánchez M, Rodríguez-Baño J, Martínez-Martínez L, Vila J, Bou G, et al. Epidemiological and clinical features associated with colonisation/ infection by Acinetobacter baumannii with phenotypic heterogeneous resistance to carbapenems. Int J Antimicrob Agents. 2012;40(3):235–8.

334. Fihman V, Messika J, Hajage D, Tournier V, Gaudry S, Magdoud F, et al. Five-year trends for ventilator-associated pneumonia: Correlation between microbiological findings and antimicrobial drug consumption. Int J Antimicrob Agents [Internet]. 2015;46(5):518–25. Available from: http://dx.doi.org/10.1016/j.ijantimicag.2015.07.010

335. Filozov A, Visintainer P, Carbonaro C, Aguero-Rosenfeld M, Wormser GP, Montecalvo MA. Epidemiology of an outbreak of antibiotic-resistant Klebsiella pneumoniae at a tertiary care medical center. Am J Infect Control [Internet]. 2009;37(9):723–8. Available from: http://dx.doi.org/10.1016/j.ajic.2009.02.006

336. Freeman JT, McBride SJ, Nisbet MS, Gamble GD, Williamson DA, Taylor SL, et al. Bloodstream infection with extended-spectrum beta-lactamase-producing Enterobacteriaceae at a tertiary care hospital in New Zealand: Risk factors and outcomes. Int J Infect Dis [Internet]. 2012;16(5):e371–4. Available from: http://dx.doi.org/10.1016/j.ijid.2012.01.008

337. Freire MP, Van Der Heijden IM, do Prado GVB, Cavalcante LS, Boszczowski I, Bonazzi PR, et al. Polymyxin use as a risk factor for colonization or infection with polymyxin-resistant Acinetobacter baumannii after liver transplantation. Transpl Infect Dis. 2014;16(3):369–78.

338. Freitas MCS, Pacheco-Silva A, Barbosa D, Silbert S, Sader H, Sesso R, et al. Prevalence of vancomycin-resistant Enterococcus fecal colonization among kidney transplant patients. BMC Infect Dis [Internet]. 2006;6(1):133. Available from: http://www.biomedcentral.com/1471-2334/6/133

339. Fritz SA, Garbutt J, Elward A, Shannon W, Storch GA. Prevalence of and Risk Factors for Community-Acquired Methicillin-Resistant and Methicillin-Sensitive Staphylococcus aureus

Colonization in Children Seen in a Practice-Based Research Network. Pediatrics [Internet]. 2008;121(6):1090–8. Available from: http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.2007-2104

340. Frye JG, Fedorka-Cray PJ. Prevalence, distribution and characterisation of ceftiofur resistance in Salmonella enterica isolated from animals in the USA from 1999 to 2003. Int J Antimicrob Agents. 2007;30(2):134–42.

341. Fujitani S, George WL, Morgan MA, Nichols S, Murthy AR. Implications for vancomycin-resistant Enterococcus colonization associated with Clostridium difficile infections. Am J Infect Control [Internet]. 2011;39(3):188–93. Available from: http://dx.doi.org/10.1016/j.ajic.2010.10.024

342. Fukuta Y, Muder RR, Agha ME, Clarke LG, Wagener MM, Hensler AM, et al. Risk factors for acquisition of multidrug-resistant Acinetobacter baumannii among cancer patients. Am J Infect Control [Internet]. 2013;41(12):1249–52. Available from: http://dx.doi.org/10.1016/j.ajic.2013.04.003

343. Furuno JP, McGregor JC, Harris AD, Johnson J a, Johnson JK, Langenberg P, et al. Identifying groups at high risk for carriage of antibiotic-resistant bacteria. Arch Intern Med. 2006;166:580–5.

344. Gadepalli R, Dhawan B, Kapil A, Sreenivas V, Jais M, Gaind R, et al. Clinical and molecular characteristics of nosocomial meticillin-resistant Staphylococcus aureus skin and soft tissue isolates from three Indian hospitals. J Hosp Infect. 2009;73(3):253–63.

345. Gandolfi-Decristophoris P, De Benedetti A, Petignat C, Attinger M, Guillaume J, Fiebig L, et al. Evaluation of pet contact as a risk factor for carriage of multidrug-resistant staphylococci in nursing home residents. Am J Infect Control. 2012;40(2):128–33.

346. Garcia CP, Rosa JF, Cursino MA, Lobo RD, Mollaco CH, Gobara S, et al. Non-multidrug-resistant, methicillin-resistant Staphylococcus aureus in a neonatal unit. Pediatr Infect Dis J [Internet]. 2014;33(10):e252-9. Available from: http://genomemedicine.com/content/3/8/53%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/24892848

347. Garlantézeca R, Bourigault C, Boles JM, Prat G, Baron R, Tonnelier JM, et al. Investigation and management of an imipenem-resistant oxa-23 Acinetobacter baumannii outbreak in an intensive care unit. Med Mal Infect. 2011;41(8):430–6.

348. Gbaguidi-Haore H, Dumartin C, L'Hériteau F, Péfau M, Hocquet D, Rogues AM, et al. Antibiotics involved in the occurrence of antibiotic-resistant bacteria: A nationwide multilevel study suggests differences within antibiotic classes. J Antimicrob Chemother. 2013;68(2):461–70.

349. Gearhart M, Martin JE, Rudich S, Thomas M, Wetzel D, Solomkin J, et al. Consequences of vancomycin-resistant Enterococcus in liver transplant recipients: A matched control study. Clin Transplant. 2005;19(6):711–6.

350. Gedik H. Does antimicrobial use increase the rate of antimicrobial resistance? A one year experience. Indian J Med Microbiol [Internet]. 2012;(30):198–202. Available from: http://www.ijmm.org/text.asp?2012/30/2/198/96692

351. Gilbert M, MacDonald J, Gregson D, Siushansian J, Zhang K, Elsayed S, et al. Outbreak in Alberta of community-acquired (USA300) methicillin-resistant Staphylococcus aureus in people with a history of drug use, homelessness or incarceration. Cmaj. 2006;175(2):149–54.

352. Giuffrè M, Amodio E, Bonura C, Geraci DM, Saporito L, Ortolano R, et al. Methicillin-resistant Staphylococcus aureus nasal colonization in a level III neonatal intensive care unit: Incidence and risk factors. Am J Infect Control [Internet]. 2015;43(5):476–81. Available from: http://dx.doi.org/10.1016/j.ajic.2014.12.027

353. Goel N, Wattal C, Oberoi JK, Raveendran R, Datta S, Prasad KJ. Trend analysis of antimicrobial consumption and development of resistance in non-fermenters in a tertiary care hospital in Delhi, India. J Antimicrob Chemother. 2011;66(7):1625–30.

354. Gómez-Zorrilla S, Camoez M, Tubau F, Periche E, Cañizares R, Dominguez MA, et al. Antibiotic pressure is a major risk factor for rectal colonization by multidrug-resistant Pseudomonas aeruginosa in critically ill patients. Antimicrob Agents Chemother. 2014;58(10):5863–70.

355. Gopal Rao G, Michalczyk P, Nayeem N, Walker G, Wigmore L. Prevalence and risk factors for meticillin-resistant Staphylococcus aureus in adult emergency admissions - a case for screening all patients? J Hosp Infect. 2007;66(1):15–21.

356. Gross AE, Van Schooneveld TC, Olsen KM, Rupp ME, Bui TH, Forsung E, et al. Epidemiology and predictors of multidrug-resistant community-acquired and health care-associated pneumonia. Antimicrob Agents Chemother. 2014;58(9):5262–8.

357. Gruber I, Heudorf U, Werner G, Pfeifer Y, Imirzalioglu C, Ackermann H, et al. Multidrug-resistant bacteria in geriatric clinics, nursing homes, and ambulant care - Prevalence and risk factors. Int J Med Microbiol [Internet]. 2013;303(8):405–9. Available from: http://dx.doi.org/10.1016/j.ijmm.2013.05.002

358. Gudiol C, Tubau F, Calatayud L, Garcia-Vidal C, Cisnal M, Sánchez-Ortega I, et al. Bacteraemia due to multidrug-resistant gram-negative bacilli in cancer patients: Risk factors, antibiotic therapy and outcomes. J Antimicrob Chemother. 2011;66(3):657–63.

359. Ha YE, Kang C-I, Joo E-J, Park SY, Kang SJ, Wi YM, et al. Clinical implications of healthcare-associated infection in patients with community-onset acute pyelonephritis. Scand J Infect Dis [Internet]. 2011;43(8):587–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21453206

360. Hadley AC, Karchmer TB, Russell GB, McBride DG, Freedman BI. The prevalence of resistant bacterial colonization in chronic hemodialysis patients. Am J Nephrol. 2007;27(4):352–9.

361. Haeusler GM, Mechinaud F, Daley AJ, Starr M, Shann F, Connell TG, et al. Antibiotic-resistant Gram-negative bacteremia in pediatric oncology patients--risk factors and outcomes. Pediatr Infect Dis J [Internet]. 2013;32(7):723–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23838774

362. Haley CC, Mittal D, LaViolette A, Jannapureddy S, Parvez N, Haley RW. Methicillin-resistant Staphylococcus aureus infection or colonization present at hospital admission: Multivariable risk factor screening to increase efficiency of surveillance culturing. J Clin Microbiol. 2007;45(9):3031–8.

363. Hamel M, Zoutman D, O'Callaghan C. Exposure to hospital roommates as a risk factor for health care-associated infection. Am J Infect Control [Internet]. 2010;38(3):173–81. Available from: http://dx.doi.org/10.1016/j.ajic.2009.08.016

364. Han JH, Kasahara K, Edelstein PH, Bilker WB, Lautenbach E. Risk factors for infection or colonization with CTX-M extended-spectrum- β-lactamase-positive escherichia coli. Antimicrob Agents Chemother. 2012;56(11):5575–80.

365. Harbarth S, Sax H, Fankhauser-Rodriguez C, Schrenzel J, Agostinho A, Pittet D. Evaluating the

probability of previously unknown carriage of MRSA at hospital admission. Am J Med. 2006;119(3):15–23.

366. Harbarth S, Sax H, Uckay I. A Predictive Model for Identifying Surgical Patients at Risk of Methicillin-Resistant Staphylococcus Aureus Carriage on Admission. J Vasc Surg. 2009;49(3).

367. Hare KM, Leach AJ, Morris PS, Smith-Vaughan H, Torzillo P, Bauert P, et al. Impact of recent antibiotics on nasopharyngeal carriage and lower airway infection in Indigenous Australian children with non-cystic fibrosis bronchiectasis. Int J Antimicrob Agents [Internet]. 2012;40(4):365–9. Available from: http://dx.doi.org/10.1016/j.ijantimicag.2012.05.018

368. Hasanin A, Eladawy A, Mohamed H, Salah Y, Lotfy A, Mostafa H, et al. Prevalence of extensively drug-resistant gram negative bacilli in surgical intensive care in Egypt. Pan Afr Med J. 2014;19:1–7.

369. Hashimoto M, Sugawara Y, Tamura S, Kaneko J, Matsui Y, Moriya K, et al. Impact of New Methicillin-Resistant Staphylococcus aureus Carriage Postoperatively After Living Donor Liver Transplantation. Transplant Proc. 2007;39(10):3271–5.

370. Hashimoto M, Sugawara Y, Tamura S, Kaneko J, Matsui Y, Togashi J, et al. Acquisition of methicillin-resistant Staphylococcus aureus after living donor liver transplantation: a retrospective cohort study. BMC Infect Dis [Internet]. 2008;8:155. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2625350&tool=pmcentrez&rendertype=abstract

371. Hashimoto M, Sugawara Y, Tamura S, Kaneko J, Matsui Y, Moriya K, et al. Methicillin-resistant Staphylococcus aureus infection after living-donor liver transplantation in adults. Transpl Infect Dis. 2008;10(2):110–6.

372. Hauser E, Tietze E, Helmuth R, Junker E, Blank K, Prager R, et al. Pork contaminated with Salmonella enterica serovar 4,[5],12:i:-, an emerging health risk for humans. Appl Environ Microbiol. 2010;76(14):4601–10.

373. Hayakawa K, Gattu S, Marchaim D, Bhargava A, Palla M, Alshabani K, et al. Epidemiology and risk factors for isolation of escherichia coli producing ctx-m-type extended-spectrum-lactamase in a large U.S. Medical Center. Antimicrob Agents Chemother. 2013;57(8):4010–8.

374. Hayakawa K, Marchaim D, Bathina P, Martin ET, Pogue JM, Sunkara B, et al. Independent risk factors for the co-colonization of vancomycin-resistant Enterococcus faecalis and methicillin-resistant Staphylococcus aureus in the region most endemic for vancomycin-resistant Staphylococcus aureus isolation. Eur J Clin Microbiol Infect Dis. 2013;32(6):815–20.

375. Hayakawa K, Marchaim D, Palla M, Gudur UM, Pulluru H, Bathina P, et al. Epidemiology of vancomycin-resistant enterococcus faecalis: A case-case-control study. Antimicrob Agents Chemother. 2013;57(1):49–55.

376. Hendrik TC, Voor In 't Holt AF, Vos MC. Clinical and Molecular Epidemiology of Extended-Spectrum Beta-Lactamase-Producing Klebsiella spp.: A Systematic Review and Meta-Analyses. PLoS One [Internet]. 2015;10(10):e0140754. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4617432&tool=pmcentrez&rendertype=abstract

377. Heng YK, Tan KT, Sen P, Chow A, Leo YS, Lye DC, et al. *Staphylococcus aureus* and topical fusidic acid use : results of a clinical audit on antimicrobial resistance. Int J Dermatol. 2013;

378. Ho PL, Ho AY, Chow KH, Lai EL, Ching P, Seto WH. Epidemiology and clonality of multidrug-resistant Acinetobacter baumannii from a healthcare region in Hong Kong. J Hosp Infect

[Internet]. 2010;74(4):358–64. Available from: http://dx.doi.org/10.1016/j.jhin.2009.10.015

379. Hoban D, Baquero F, Reed V, Felmingham D. Demographic analysis of antimicrobial resistance among Streptococcus pneumoniae: Worldwide results from PROTEKT 1999-2000. Int J Infect Dis. 2005;9(5):262–73.

380. Horasan ES, Ersoz G, Horoz M, Göksu M, Karacorlu S, Kaya A. Risk factors for infections caused by multidrug-resistant bacteria in patients with solid tumours. Scand J Infect Dis. 2011;43(2):107–11.

381. Hoshuyama T, Moriguchi H, Muratani T, Matsumoto T. Vancomycin-resistant enterococci (VRE) outbreak at a university hospital in Kitakyushu, Japan: Case-control studies. J Infect Chemother. 2008;14(5):354–60.

382. Bala Hota, MD, MPH; Charlotte Ellenbogen, MD; Mary K. Hayden, MD; Alla Aroutcheva, MD P, Thomas W. Rice, PhD; Robert A. Weinstein M. Community-Associated Methicillin-Resistant *Staphylococcus aureus* Skin and Soft Tissue Infections at a Public Hospital Do Public Housing and Incarceration Amplify Transmission? 2007;167.

383. Hota BN, Pur S, Phillips L, Weinstein RA, Segreti J. Impact of a fluoroquinolone formulary change on acquisition of quinolone-resistant gram-negative bacilli. Eur J Clin Microbiol Infect Dis. 2005;24(6):405–10.

384. Hsu DI, Okamoto MP, Murthy R, Wong-Beringer A. Fluoroquinolone-resistant Pseudomonas aeruginosa: Risk factors for acquisition and impact on outcomes. J Antimicrob Chemother. 2005;55(4):535–41.

385. Hsu HY, Lind JT, Miller D, Tseng L. Assessment of risk factors for oxacillin-resistant ocular flora in eyes having cataract surgery. J Cataract Refract Surg. 2015;41(2):387–92.

386. Huang H, Cohen SH, King JH, Monchaud C, Nguyen H, Flynn NM. Injecting drug use and community-associated methicillin-resistant Staphylococcus aureus infection. Diagn Microbiol Infect Dis. 2008;60(4):347–50.

387. Huang SS, Datta R, Platt R. Risk of Acquiring Antibiotic-Resistant Bacteria From Prior Room Occupants. Arch Intern Med. 2006;166(18):1945–51.

388. Hufnagel M, Liese C, Loescher C, Kunze M, Proempeler H, Berner R, et al. Enterococcal colonization of infants in a neonatal intensive care unit: associated predictors, risk factors and seasonal patterns. BMC Infect Dis. 2007;7:107.

389. Huh K, Kang CI, Kim J, Cho SY, Ha YE, Joo EJ, et al. Risk factors and treatment outcomes of bloodstream infection caused by extended-spectrum cephalosporin-resistant Enterobacter species in adults with cancer. Diagn Microbiol Infect Dis [Internet]. 2014;78(2):172–7. Available from: http://dx.doi.org/10.1016/j.diagmicrobio.2013.11.002

390. Hui C, Lin MC, Jao MS, Liu TC, Wu RG. Previous antibiotic exposure and evolution of antibiotic resistance in mechanically ventilated patients with nosocomial infections. J Crit Care [Internet]. 2013;28(5):728–34. Available from: http://dx.doi.org/10.1016/j.jcrc.2013.04.008

391. Huijbers PMC, van Hoek AHAM, Graat EAM, Haenen APJ, Florijn A, Hengeveld PD, et al. Methicillin-resistant Staphylococcus aureus and extended-spectrum and AmpC β-lactamase-producing Escherichia coli in broilers and in people living and/or working on organic broiler farms. Vet Microbiol [Internet]. 2015;176(1–2):120–5. Available from: http://dx.doi.org/10.1016/j.vetmic.2014.12.010

392. Hussein K, Raz-Pasteur A, Finkelstein R, Neuberger A, Shachor-Meyouhas Y, Oren I, et al.

Impact of carbapenem resistance on the outcome of patients' hospital-acquired bacteraemia caused by Klebsiella pneumoniae. J Hosp Infect [Internet]. 2013;83(4):307–13. Available from: http://dx.doi.org/10.1016/j.jhin.2012.10.012

393. Ikram R, Psutka R, Carter A, Priest P. An outbreak of multi-drug resistant Escherichia coli urinary tract infection in an elderly population: a case-control study of risk factors. BMC Infect Dis [Internet]. 2015;15:224. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26054866%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4459452

394. Inchai J, Liwsrisakun C, Theerakittikul T, Chaiwarith R, Khositsakulchai W, Pothirat C. Risk factors of multidrug-resistant, extensively drug-resistant and pandrug-resistant Acinetobacter baumannii ventilator-associated pneumonia in a Medical Intensive Care Unit of University Hospital in Thailand. J Infect Chemother [Internet]. 2015;21(8):570–4. Available from: http://dx.doi.org/10.1016/j.jiac.2015.04.010

395. Isea-Pena MC, Sanz-Moreno JC, Esteban J, Fernandez-Roblas R, Fernandez-Guerrero ML. Risk factors and clinical significance of invasive infections caused by levofloxacin-resistant Streptococcus pneumoniae. Infection. 2013;41(5):935–9.

396. Jenkins TC, Sakai J, Knepper BC, Swartwood CJ, Haukoos JS, Long JA, et al. Risk factors for drug-resistant Streptococcus pneumoniae and antibiotic prescribing practices in outpatient community-acquired pneumonia. Acad Emerg Med. 2012;19(6):703–6.

397. Jeon M-H, Choi S-H, Kwak YG, Chung J-W, Lee S-O, Jeong J-Y, et al. Risk factors for the acquisition of carbapenem-resistant Escherichia coli among hospitalized patients. Diagn Microbiol Infect Dis. 2008;62(4):402–6.

398. Jeong BH, Koh WJ, Yoo H, Park HY, Suh GY, Chung MP, et al. Risk factors for acquiring potentially drug-resistant pathogens in immunocompetent patients with pneumonia developed out of hospital. Respiration. 2014;88(3):190–8.

399. Jiang X, Yu T, Wu N, Meng H, Shi L. Detection of qnr, aac(6')-Ib-cr and qepA genes in Escherichia coli isolated from cooked meat products in Henan, China. Int J Food Microbiol [Internet]. 2014;187:22–5. Available from: http://dx.doi.org/10.1016/j.ijfoodmicro.2014.06.026

400. Johnson L, Sabel A, Burman WJ, Everhart RM, Rome M, MacKenzie TD, et al. Emergence of Fluoroquinolone Resistance in Outpatient Urinary Escherichia coli Isolates. Am J Med. 2008;121(10):876–84.

401. Jung JY, Park MS, Kim SE, Park BH, Son JY, Kim EY, et al. Risk factors for multi-drug resistant Acinetobacter baumannii bacteremia in patients with colonization in the intensive care unit. BMC Infect Dis [Internet]. 2010;10:228. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2921386&tool=pmcentrez&rendertype=abstract

402. Kaminski C, Timsit J-F, Dubois Y, Zahar J-R, Garrouste-Orgeas M, Vesin A, et al. Impact of ureido/carboxypenicillin resistance on the prognosis of ventilator-associated pneumonia due to Pseudomonas aeruginosa. Crit Care [Internet]. 2011;15(2):R112. Available from: http://ccforum.com/content/15/2/R112

403. Kang C-I, Chung DR, Ko KS, Peck KR, Song J-H. Risk factors for infection and treatment outcome of extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae bacteremia in patients with hematologic malignancy. Ann Hematol. 2012;91(1):115–21.

404. Kang CI, Song JH, Kim SH, Chung DR, Peck KR, So TM, et al. Risk factors for levofloxacin-nonsusceptible Streptococcus pneumoniae in community-acquired pneumococcal pneumonia: A nested case-control study. Eur J Clin Microbiol Infect Dis. 2014;33(1):55–9.

405. Kang Y, Vicente M, Parsad S, Brielmeier B, Pisano J, Landon E, et al. Evaluation of risk factors for vancomycin-resistant Enterococcus bacteremia among previously colonized hematopoietic stem cell transplant patients. Transpl Infect Dis. 2013;15(5):466–73.

406. Kantele A, Lääveri T, Mero S, Vilkman K, Pakkanen SH, Ollgren J, et al. Antimicrobials increase travelers' risk of colonization by extended-spectrum betalactamase-producing enterobacteriaceae. Clin Infect Dis. 2015;60(6):837–46.

407. Karaaslan A, Soysal A, Altinkanat Gelmez G, Kepenekli Kadayifci E, S??yletir G, Bakir M. Molecular characterization and risk factors for carbapenem-resistant Gram-negative bacilli colonization in children: Emergence of NDM-producing Acinetobacter baumannii in a newborn intensive care unit in Turkey. J Hosp Infect. 2016;92(1):67–72.

408. Karanika S, Zervou FN, Zacharioudakis IM, Paudel S, Mylonakis E. Risk factors for meticillin-resistant Staphylococcus aureus colonization in dialysis patients: a meta-analysis. J Hosp Infect [Internet]. 2015 [cited 2017 Apr 17];91(3):257–63. Available from: http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0195670115003229

409. Karki S, Land G, Aitchison S, Kennon J, Johnson PDR, Ballard SA, et al. Long-term carriage of vancomycin-resistant enterococci in patients discharged from hospitals: A 12-year retrospective cohort study. J Clin Microbiol. 2013;51(10):3374–9.

410. Katsaragakis S, Markogiannakis H, Toutouzas KG, Drimousis P, Larentzakis A, Theodoraki EM, et al. Acinetobacter baumannii infections in a surgical intensive care unit: Predictors of multi-drug resistance. World J Surg. 2008;32(6):1194–202.

411. Kazakova S, Hageman J, Matava M. A Clone of Methicillin-Resistant. N Engl J Med. 2005;352:468–75.

412. Kennedy K, Collignon P. Colonisation with Escherichia coli resistant to "critically important" antibiotics: A high risk for international travellers. Eur J Clin Microbiol Infect Dis. 2010;29(12):1501–6.

413. Khawcharoenporn T, Vasoo S, Ward E, Singh K. High rates of quinolone resistance among urinary tract infections in the ED. Am J Emerg Med [Internet]. 2012;30(1):68–74. Available from: http://dx.doi.org/10.1016/j.ajem.2010.09.030

414. Khudaier BY, Tewari R, Shafiani S, Sharma M, Emmanuel R, Sharma M, et al. Epidemiology and molecular characterization of vancomycin resistant Enterococci isolates in India. Scand J Infect Dis [Internet]. 2007;39(8):662–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17654341

415. Kim J, Kang CI, Joo EJ, Ha YE, Cho SY, Gwak GY, et al. Risk factor of community-onset spontaneous bacterial peritonitis caused by fluoroquinolone-resistant Escherichia coli in patients with cirrhosis. Liver Int. 2014;34(5):695–9.

416. Kim SB, Min YH, Cheong J-W, Kim JS, Kim SJ, Ku NS, et al. Incidence and risk factors for carbapenem- and multidrug-resistant Acinetobacter baumannii bacteremia in hematopoietic stem cell transplantation recipients. Scand J Infect Dis [Internet]. 2014 Feb 11;46(2):81–8. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014049557

417. Yeon AK, Jun Yong C, Chang Ki K, Chang Oh K, Myung Soo K, Suk Hoon C, et al. Risk factors and outcomes of bloodstream infections with metallo-β-lactamase-producing Acinetobacter. Scand J Infect Dis [Internet]. 2008;40(3):234–40. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=29435177&site=ehost-live%5Cnhttp://informahealthcare.com/doi/pdfplus/10.1080/00365540701633004

418. Kim YJ, Kim S Il, Kim YR, Lee JY, Park YJ, Kang MW. Risk factors for vancomycin-resistant enterococci infection and mortality in colonized patients on intensive care unit admission. Am J Infect Control [Internet]. 2012;40(10):1018–9. Available from: http://dx.doi.org/10.1016/j.ajic.2012.01.009

419. Kini AR, Shetty V, Kumar AM, Shetty SM, Shetty A. Community-associated, methicillin-susceptible, and methicillin-resistant Staphylococcus aureus bone and joint infections in children: experience from India. J Pediatr Orthop B. 2013;22(2):158–66.

420. Ko YJ, Moon HW, Hur M, Yun YM. Risk factors of fecal carriage with extended-spectrum ??-lactamase- producing Enterobacteriaceae in hospitalized patients. Am J Infect Control [Internet]. 2013;41(12):1241–3. Available from: http://dx.doi.org/10.1016/j.ajic.2013.05.018

421. Kofteridis DP, Valachis A, Dimopoulou D, Maraki S, Christidou A, Mantadakis E, et al. Risk factors for carbapenem-resistant Klebsiella pneumoniae infection/colonization: a case-case-control study. J Infect Chemother [Internet]. 2014 May [cited 2016 Jan 8];20(5):293–7. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84903723112&partnerID=tZOtx3y1

422. Kohlenberg A, Brümmer S, Higgins PG, Sohr D, Piening BC, De Grahl C, et al. Outbreak of carbapenem-resistant Acinetobacter baumannii carrying the carbapenemase OXA-23 in a German university medical centre. J Med Microbiol. 2009;58(11):1499–507.

423. Kohlenberg A, Weitzel-Kage D, van der Linden P, Sohr D, Vögeler S, Kola A, et al. Outbreak of carbapenem-resistant Pseudomonas aeruginosa infection in a surgical intensive care unit. J Hosp Infect. 2010;74(4):350–7.

424. Kollef MH, Chastre J, Fagon J-Y, François B, Niederman MS, Rello J, et al. Global Prospective Epidemiologic and Surveillance Study of Ventilator-Associated Pneumonia due to Pseudomonas aeruginosa*. Crit Care Med. 2014;42(10):2178–87.

425. Kontopidou F, Plachouras D, Papadomichelakis E, Koukos G, Galani I, Poulakou G, et al. Colonization and infection by colistin-resistant Gram-negative bacteria in a cohort of critically ill patients. Clin Microbiol Infect. 2011;17(11):16–8.

426. Korona-Glowniak I, Niedzielski A, Malm A. Upper respiratory colonization by Streptococcus pneumoniae in healthy pre-school children in south-east Poland. Int J Pediatr Otorhinolaryngol [Internet]. 2011;75(12):1529–34. Available from: http://dx.doi.org/10.1016/j.ijporl.2011.08.021

427. Koupetori M, Retsas T, Antonakos N, Vlachogiannis G, Perdios I, Nathanail C, et al. Bloodstream infections and sepsis in Greece: over-time change of epidemiology and impact of de-escalation on final outcome. BMC Infect Dis [Internet]. 2014;14(1):272. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4035827&tool=pmcentrez&rendertype=abstract

428. Kuenzli E, Jaeger VK, Frei R, Neumayr A, Decrom S, Haller S, et al. High colonization rates of extended-spectrum β-lactamase (ESBL)-producing Escherichia coli in Swiss Travellers to South Asia– a prospective observational multicentre cohort study looking at epidemiology, microbiology and risk factors. BMC Infect Dis [Internet]. 2014;14(1):528–37. Available from:

http://www.biomedcentral.com/1471-2334/14/528

429. Kuint J, Barzilai A, Regev-Yochay G, Rubinstein E, Keller N, Maayan-Metzger A. Comparison of community-acquired methicillin-resistant Staphylococcus aureus bacteremia to other staphylococcal species in a neonatal intensive care unit. Eur J Pediatr. 2007;166(4):319–25.

430. Kurd MF, Ghanem E, Steinbrecher J, Parvizi J. Two-stage Exchange Knee Arthroplasty: Does Resistance of the Infecting Organism Influence the Outcome? Clin Orthop Relat Res [Internet]. 2010;468(8):2060–6. Available from: http://dx.doi.org/10.1007/s11999-010-1296-6

431. Kurtaran B, Tasova Y, Kibar F, Candevir A, Seydaoğlu G, Akyildiz O, et al. Colonization and Resistance Patterns of Gram-Positive and Gram-Negative Bacteria in Patients Had No Recent History of Hospitalization. Infect Dis Clin Pract [Internet]. 2011 Mar;19(2):105–10. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=2011170223

432. Kuster SP, Hasse B, Huebner V, Bansal V, Zbinden R, Ruef C, et al. Risks factors for infections with extended-spectrum beta-lactamase- producing escherichia coli and klebsiella pneumoniae at a tertiary care university hospital in Switzerland. Infection. 2010;38(1):33–40.

433. Lamaro-Cardoso J, De Lencastre H, Kipnis A, Pimenta FC, Oliveira LSC, Oliveira RM, et al. Molecular epidemiology and risk factors for nasal carriage of Staphylococcus aureus and methicillin-resistant S. aureus in infants attending day care centers in Brazil. J Clin Microbiol. 2009;47(12):3991–7.

434. Laupland KB, Church DL, Vidakovich J, Mucenski M, Pitout JDD. Community-onset extended-spectrum ??-lactamase (ESBL) producing Escherichia coli: Importance of international travel. J Infect [Internet]. 2008;57(6):441–8. Available from: http://dx.doi.org/10.1016/j.jinf.2008.09.034

435. Le Hello S, Falcot V, Lacassin F, Mikulski M, Baumann F. Risk factors for carbapenem-resistant Acinetobacter baumannii infections at a tertiary care hospital in New Caledonia, South Pacific. Scand J Infect Dis [Internet]. 2010;42(11/12):821–6. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=55171627&site=ehost-live%5Cnhttp://informahealthcare.com/doi/pdfplus/10.3109/00365548.2010.496087

436. Lee DS, Ryu JA, Chung CR, Yang JH, Jeon K, Suh GY, et al. Risk factors for acquisition of multidrug-resistant bacteria in patients with anastomotic leakage after colorectal cancer surgery. Int J Colorectal Dis. 2015;30(4):497–504.

437. Lee H-S, Lee SK, Park DH, Lee SS, Seo D-W, Kim M-H, et al. Emergence of multidrug resistant infection in patients with severe acute pancreatitis. Pancreatology. 2014;14(6):450–3.

438. Lee HY, Chen CL, Wang SB, Su LH, Chen SH, Liu SY, et al. Imipenem heteroresistance induced by imipenem in multidrug-resistant Acinetobacter baumannii: Mechanism and clinical implications. Int J Antimicrob Agents [Internet]. 2011;37(4):302–8. Available from: http://dx.doi.org/10.1016/j.ijantimicag.2010.12.015

439. Lee HY, Chang RC, Su LH, Liu SY, Wu SR, Chuang CH, et al. Wide spread of Tn2006 in an AbaR4-type resistance island among carbapenem-resistant Acinetobacter baumannii clinical isolates in Taiwan. Int J Antimicrob Agents [Internet]. 2012;40(2):163–7. Available from: http://dx.doi.org/10.1016/j.ijantimicag.2012.04.018

440. Lee JW, Kim N, Kim JM, Nam RH, Chang H, Kim JY, et al. Prevalence of primary and secondary antimicrobial resistance of helicobacter pylori in Korea from 2003 through 2012. Helicobacter.

2013;18(3):206–14.

441. Lee NY, Wu JJ, Lin SH, Ko WC, Tsai LH, Yan JJ. Characterization of carbapenem-nonsusceptible Klebsiella pneumoniae bloodstream isolates at a Taiwanese hospital: Clinical impacts of lowered breakpoints for carbapenems. Eur J Clin Microbiol Infect Dis. 2012;31(8):1941–50.

442. Lee SC, Lee CW, Shih HJ, Chiou MJ, See LC, Siu LK. Clinical features and risk factors of mortality for bacteremia due to community-onset healthcare-associated methicillin-resistant S. aureus. Diagn Microbiol Infect Dis [Internet]. 2013;76(1):86–92. Available from: http://dx.doi.org/10.1016/j.diagmicrobio.2013.01.017

443. Lepelletier D, Caroff N, Riochet D, Bizouarn P, Bourdeau A, Le Gallou F, et al. Risk-factors for gastrointestinal colonisation with resistant Enterobacteriaceae among hospitalised patients: A prospective study. Clin Microbiol Infect. 2006;12(10):974–9.

444. Leroy O, D'Escrivan T, Devos P, Dubreuil L, Kipnis E, Georges H. Hospital-acquired pneumonia in critically III patients: Factors associated with episodes due to imipenem-resistant organisms. Infection. 2005;33(3):129–35.

445. Lestari ES, Duerink DO, Hadi U, Severin JA, Nagelkerke NJD, Kuntaman K, et al. Determinants of carriage of resistant Staphylococcus aureus among S. aureus carriers in the Indonesian population inside and outside hospitals. Trop Med Int Heal. 2010;15(10):1235–43.

446. Levin PD, Simor AE, Moses AE, Sprung CL. End-of-life treatment and bacterial antibiotic resistance: A potential association. Chest. 2010;138(3):588–94.

447. Li H, Liu DH, Chen LL, Zhao Q, Yu YZ, Ding JJ, et al. Meta-Analysis of the adverse effects of long-term azithromycin use in patients with chronic lung diseases. Antimicrob Agents Chemother. 2014;58(1):511–7.

448. Li J, Wang T, Shao B, Shen J, Wang S, Wu Y. Plasmid-Mediated Quinolone Resistance Genes and Antibiotic Residues in Wastewater and Soil Adjacent to Swine Feedlots: Potential Transfer to Agricultural Lands. Environ Health Perspect [Internet]. 2012 May 8;120(8):1144–9. Available from: http://ehp.niehs.nih.gov/1104776

449. Liao CH, Hsueh PR, Jacoby GA, Hooper DC. Risk factors and clinical characteristics of patients with qnr-positive klebsiella pneumoniae bacteraemia. J Antimicrob Chemother. 2013;68(12):2907–14.

450. Libert M, Elkholti M, Massaut J, Karmali R, Mascart G, Cherifi S. Risk factors for meticillin resistance and outcome of Staphylococcus aureus bloodstream infection in a Belgian university hospital. J Hosp Infect. 2008;68(1):17–24.

451. Lietzau S, Raum E, von Baum H, Marre R, Brenner H. Clustering of antibiotic resistance of E. coli in couples: suggestion for a major role of conjugal transmission. BMC Infect Dis [Internet]. 2006;6(1):119. Available from: http://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-6-119

452. Lietzau S, Raum E, von Baum H, Marre R, Brenner H. Household contacts were key factor for children's colonization with resistant Escherichia coli in community setting. J Clin Epidemiol. 2007;60(11):1149–55.

453. Lim CJ, Cheng AC, Kong DC, Peleg AY. Community-onset bloodstream infection with multidrug-resistant organisms: a matched case-control study. BMC Infect Dis [Internet]. 2014 Dec 4;14(1):126. Available from: http://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-14-126

454. Lim CJ, Cheng AC, Kennon J, Spelman D, Hale D, Melican G, et al. Prevalence of multidrug-resistant organisms and risk factors for carriage in long-term care facilities: A nested case-control study. J Antimicrob Chemother. 2014;69(7):1972–80.

455. Lin MF, Yang CM, Lin CH, Huang ML, Tu CC, Liou ML. Clinical features and molecular epidemiology of multidrug-resistant Acinetobacter calcoaceticus-A baumannii complex in a regional teaching hospital in Taiwan. Am J Infect Control [Internet]. 2009;37(9):e1–3. Available from: http://dx.doi.org/10.1016/j.ajic.2009.03.008

456. Liss BJ, Vehreschild JJ, Cornely OA, Hallek M, Fätkenheuer G, Wisplinghoff H, et al. Intestinal colonisation and blood stream infections due to vancomycin-resistant enterococci (VRE) and extendedspectrum beta-lactamase- producing Enterobacteriaceae (ESBLE) in patients with haematological and oncological malignancies. Infection. 2012;40(6):613–9.

457. Lo W-U, Ho P-L, Chow K-H, Lai EL, Yeung F, Chiu SS. Fecal carriage of CTXM type extended-spectrum beta-lactamase-producing organisms by children and their household contacts. J Infect. 2010;60(4):286–92.

458. Lodise TP, Miller CD, Graves J, Furuno JP, McGregor JC, Lomaestro B, et al. Clinical prediction tool to identify patients with Pseudomonas aeruginosa respiratory tract infections at greatest risk for multidrug resistance. Antimicrob Agents Chemother. 2007;51(2):417–22.

459. Lu P, Chin L, Peng C, Chiang Y, Chen T, Ma L, et al. Risk Factors and Molecular Analysis of Community Methicillin-Resistant Staphylococcus aureus Carriage. Society. 2005;43(1):132–9.

460. Lucena A, Dalla Costa LM, Nogueira KS, Matos AP, Gales AC, Paganini MC, et al. Nosocomial infections with metallo-beta-lactamase-producing Pseudomonas aeruginosa: Molecular epidemiology, risk factors, clinical features and outcomes. J Hosp Infect [Internet]. 2014;87(4):234–40. Available from: http://dx.doi.org/10.1016/j.jhin.2014.05.007

461. Luna RA, Millecker LA, Webb CR, Mason SK, Whaley EM, Starke JR, et al. Molecular epidemiological surveillance of multidrug-resistant pseudomonas aeruginosa isolates in a pediatric population of patients with cystic fibrosis and determination of risk factors for infection with the houston-1 strain. J Clin Microbiol. 2013;51(4):1237–40.

462. Lupei MI, Mann HJ, Beilman GJ, Oancea C, Chipman JG. Inadequate Antibiotic Therapy in Solid Organ Transplant Recipients is Associated with a Higher Mortality Rate. Surg Infect. 2009;11(1).

463. Luvsansharav U-O, Hirai I, Nakata A, Imura K, Yamauchi K, Niki M, et al. Prevalence of and risk factors associated with faecal carriage of CTX-M β-lactamase-producing Enterobacteriaceae in rural Thai communities. J Antimicrob Chemother [Internet]. 2012 Jul;67(7):1769–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22514260

464. Lye DC, Earnest A, Ling ML, Lee TE, Yong HC, Fisher DA, et al. The impact of multidrug resistance in healthcare-associated and nosocomial Gram-negative bacteraemia on mortality and length of stay: Cohort study. Clin Microbiol Infect. 2012;18(5):502–8.

465. Ma HM, Ip M, Woo J, Hui DSC, Lui GCY, Lee NLS, et al. Risk factors for drug-resistant bacterial pneumonia in older patients hospitalized with pneumonia in a Chinese population. Qjm. 2013;106(9):823–9.

466. Ma HM, Ip M, Woo J, Hui DSC. Development and validation of a clinical risk score for predicting drug-resistant bacterial pneumonia in older Chinese patients. Respirology [Internet]. 2014;19(4):549–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24661357

467. Machado A, Bordalo AA. Prevalence of antibiotic resistance in bacteria isolated from drinking well water available in Guinea-Bissau (West Africa). Ecotoxicol Environ Saf [Internet]. 2014;106:188–94. Available from: http://dx.doi.org/10.1016/j.ecoenv.2014.04.037

468. Machida H, Seki M, Yoshioka N, Yabuno K, Miyawaki K, Yoshida H, et al. Correlation between outbreaks of multidrug-resistant Pseudomonas aeruginosa infection and use of bronchoscopes suggested by epidemiological analysis. Biol Pharm Bull [Internet]. 2014;37(1):26–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24389477

469. Maclayton DO, Suda KJ, Coval KA, York CB, Garey KW. Case-control study of the relationship between MRSA bacteremia with a vancomycin MIC of 2 ??g/mL and risk factors, costs, and outcomes in inpatients undergoing hemodialysis. Clin Ther. 2006;28(8):1208–16.

470. Macnow T, O'Toole D, DeLaMora P, Murray M, Rivera K, Whittier S, et al. Utility of surveillance cultures for antimicrobial resistant organisms in infants transferred to the neonatal intensive care unit. Pediatr Infect Dis J [Internet]. 2013;32(12):e443-50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23811747

471. Mammina C, Di Carlo P, Cipolla D, Giuffrè M, Casuccio A, Di Gaetano V, et al. Surveillance of multidrug-resistant gram-negative bacilli in a neonatal intensive care unit: prominent role of cross transmission. Am J Infect Control. 2007;35(4):222–30.

472. Mammina C, Bonura C, Vivoli AR, Di Bernardo F, Sodano C, Saporito MA, et al. Co-colonization with carbapenem-resistant Klebsiella pneumoniae and Acinetobacter baumannii in intensive care unit patients. Scand J Infect Dis [Internet]. 2013 Aug 8;45(8):629–34. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=2013447392

473. Manageiro V, Ferreira E, Jones-Dias D, Louro D, Pinto M, Diogo J, et al. Emergence and risk factors of β-lactamase–mediated resistance to oxyimino-β-lactams in Enterobacteriaceae isolates. Diagn Microbiol Infect Dis [Internet]. 2012 Mar;72(3):272–7. Available from: http://dx.doi.org/10.1016/j.diagmicrobio.2011.11.009

474. Mansouri M, Ramazanzadeh R, Norabadi P. Cefepime resistance and associated risk factors among Escherichia coli strains isolated from clinical specimens. Chemotherapy. 2011;57:134–7.

475. Manzur A, Vidal M, Pujol M, Cisnal M, Hornero A, Masuet C, et al. Predictive factors of meticillin resistance among patients with Staphylococcus aureus bloodstream infections at hospital admission. J Hosp Infect. 2007;66(2):135–41.

476. Manzur A, Gavalda L, Ruiz De Gopegui E, Mariscal D, Dominguez MA, Perez JL, et al. Prevalence of methicillin-resistant Staphylococcus aureus and factors associated with colonization among residents in community long-term-care facilities in Spain. Clin Microbiol Infect. 2008;14(9):867–72.

477. March A, Aschbacher R, Dhanji H, Livermore DM, Böttcher A, Sleghel F, et al. Colonization of residents and staff of a long-term-care facility and adjacent acute-care hospital geriatric unit by multiresistant bacteria. Clin Microbiol Infect. 2010;16(7):934–44.

478. Marchenay P, Blasco G, Navellou J-C, Leroy J, Cholley P, Talon D, et al. Acquisition of carbapenem-resistant Gram-negative bacilli in intensive care unit: Predictors and molecular epidemiology. Médecine Mal Infect [Internet]. 2015 Jan [cited 2016 Jan 8];45(1–2):34–40. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84926178208&partnerID=tZOtx3y1

479. Maseda E, Maggi G, Gomez-Gil R, Ruiz G, Madero R, Garcia-Perea A, et al. Prevalence of and risk factors for biliary carriage of bacteria showing worrisome and unexpected resistance traits. J Clin Microbiol. 2013;51(2):518–21.

480. Mathews WC, Caperna JC, Barber RE, Torriani FJ, Miller LG, May S, et al. Incidence of and risk factors for clinically significant methicillin-resistant Staphylococcus aureus infection in a cohort of HIV-infected adults. J Acquir Immune Defic Syndr [Internet]. 2005;40(2):155–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16186732

481. McCarthy NL, Sullivan PS, Gaynes R, Rimland D. Health care-associated and community-associated methicillin-resistant Staphylococcus aureus infections: A comparison of definitions. Am J Infect Control [Internet]. 2010;38(8):600–6. Available from: http://dx.doi.org/10.1016/j.ajic.2010.01.006

482. McGregor JC, Perencevich EN, Furuno JP, Langenberg P, Flannery K, Zhu J, et al. Comorbidity risk-adjustment measures were developed and validated for studies of antibiotic-resistant infections. J Clin Epidemiol. 2006;59(12):1266–73.

483. McKinnell JA, Miller LG, Eells SJ, Cui E, Huang SS. A systematic literature review and meta-analysis of factors associated with methicillin-resistant Staphylococcus aureus colonization at time of hospital or intensive care unit admission. Infect Control Hosp Epidemiol [Internet]. 2013;34(10):1077–86. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3883507&tool=pmcentrez&rendertype=abstract

484. McLaughlin M, Advincula MR, Malczynski M, Qi C, Bolon M, Scheetz MH. Correlations of antibiotic use and carbapenem resistance in enterobacteriaceae. Antimicrob Agents Chemother. 2013;57(10):5131–3.

485. McNulty CAM, Lasseter G, Shaw I, Nichols T, D'Arcy S, Lawson AJ, et al. Is Helicobacter pylori antibiotic resistance surveillance needed and how can it be delivered? Aliment Pharmacol Ther. 2012;35(10):1221–30.

486. Memish ZA, Assiri A, Almasri M, Alhakeem RF, Turkestani A, Al Rabeeah AA, et al. Impact of the hajj on pneumococcal transmission. Clin Microbiol Infect [Internet]. 2015;21(1):77.e11-77.e18. Available from: http://dx.doi.org/10.1016/j.cmi.2014.07.005

487. Mendelson G, Hait V, Ben-Israel J, Gronich D, Granot E, Raz R. Prevalence and risk factors of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in an Israeli long-term care facility. Eur J Clin Microbiol Infect Dis. 2005;24(1):17–22.

488. Merlo CA, Boyle MP, Diener-West M, Marshall BC, Goss CH, Lechtzin N. Incidence and risk factors for multiple antibiotic-resistant Pseudomonas aeruginosa in cystic fibrosis. Chest [Internet]. 2007;132(2):562–8. Available from: http://dx.doi.org/10.1378/chest.06-2888

489. Messi P, Guerrieri E, De Niederhäusern S, Sabia C, Bondi M. Vancomycin-resistant enterococci (VRE) in meat and environmental samples. Int J Food Microbiol. 2006;107(2):218–22.

490. Meyer E, Gastmeier P, Kola A, Schwab F. Pet animals and foreign travel are risk factors for colonisation with extended-spectrum b-lactamase-producing Escherichia coli. Infection. 2012;40(6):685–7.

491. Michalopoulos A, Falagas ME, Karatza DC, Alexandropoulou P, Papadakis E, Gregorakos L, et al. Epidemiologic, clinical characteristics, and risk factors for adverse outcome in multiresistant gram-negative primary bacteremia of critically ill patients. Am J Infect Control [Internet]. 2011;39(5):396–400. Available from: http://dx.doi.org/10.1016/j.ajic.2010.06.017

492. Miliani K, L'Hériteau F, Lacavé L, Carbonne A, Astagneau P. Imipenem and ciprofloxacin consumption as factors associated with high incidence rates of resistant Pseudomonas aeruginosa in hospitals in northern France. J Hosp Infect. 2011;77(4):343–7.

493. Millar M, Philpott A, Wilks M, Whiley A, Warwick S, Hennessy E, et al. Colonization and persistence of antibiotic-resistant *Enterobacteriaceae* strains in infants nursed in two neonatal intensive care units in East London, United Kingdom. J Clin Microbiol. 2008;46(2):560–7.

494. Min L, Galecki A, Mody L. Functional disability and nursing resource use are predictive of antimicrobial resistance in nursing homes. J Am Geriatr Soc. 2015;63(4):659–66.

495. Minhas P, Perl TM, Carroll KC, Shepard JW, Shangraw KA, Fellerman D, et al. Risk factors for positive admission surveillance cultures for methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci in a neurocritical care unit. Crit Care Med [Internet]. 2011;39(10):2322–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21705905

496. Mitchell BG, Dancer SJ, Anderson M, Dehn E. Risk of organism acquisition from prior room occupants: a systematic review and meta-analysis. J Hosp Infect [Internet]. 2015 [cited 2017 Apr 27];91(3):211–7. Available from: http://www.sciencedirect.com/science/article/pii/S0195670115003126

497. Miyake M, Ohbayashi Y, Iwasaki A, Ogawa T, Nagahata S. Risk Factors for Methicillin-Resistant Staphylococcus aureus (MRSA) and Use of a Nasal Mupirocin Ointment in Oral Cancer Inpatients. J Oral Maxillofac Surg. 2007;65(11):2159–63.

498. Mody L, Maheshwari S, Galecki A, Kauffman CA, Bradley SF. Indwelling device use and antibiotic resistance in nursing homes: Identifying a high-risk group. J Am Geriatr Soc. 2007;55(12):1921–6.

499. Montero M, Sala M, Riu M, Belvis F, Salvado M, Grau S, et al. Risk factors for multidrug-resistant Pseudomonas aeruginosa acquisition. Impact of antibiotic use in a double case-control study. Eur J Clin Microbiol Infect Dis. 2010;29(3):335–9.

500. Montravers P, Dufour G, Guglielminotti J, Desmard M, Muller C, Houissa H, et al. Dynamic changes of microbial flora and therapeutic consequences in persistent peritonitis. Crit Care [Internet]. 2015;19(1):70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25887649%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4354758

501. Morange-Saussier V, Giraudeau B, van der Mee N, Lermusiaux P, Quentin R. Nasal Carriage of Methicillin-Resistant Staphylococcus aureus in Vascular Surgery. Ann Vasc Surg [Internet]. 2006;20(6):767–72. Available from: http://dx.doi.org/10.1007/s10016-006-9088-x

502. Morgan DJ, Rogawski E, Thom KA, Johnson JK, Perencevich EN, Shardell M, et al. Transfer of multidrug-resistant bacteria to healthcare workers' gloves and gowns after patient contact increases with environmental contamination. Crit Care Med [Internet]. 2012;40(4):1045–51. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3534819&tool=pmcentrez&rendertype=abstract

503. Morris SR, Knapp JS, Moore DF, Trees DL, Wang SA, Bolan G, et al. Using strain typing to characterise a fluoroquinolone-resistant Neisseria gonorrhoeae transmission network in southern California. Sex Transm Infect. 2008;84(4):290–1.

504. Mosqueda-Gómez JL, Montaño-Loza A, Rolón AL, Cervantes C, Bobadilla-del-Valle JM, Silva-Sánchez J, et al. Molecular epidemiology and risk factors of bloodstream infections caused by

extended-spectrum ??-lactamase-producing Klebsiella pneumoniae. A case-control study. Int J Infect Dis. 2008;12(6):653–9.

505. Mossong J, Gelhausen E, Decruyenaere F, Devaux a, Perrin M, Even J, et al. Prevalence, risk factors and molecular epidemiology of methicillin-resistant Staphylococcus aureus (MRSA) colonization in residents of long-term care facilities in Luxembourg, 2010. Epidemiol Infect [Internet]. 2013;141(6):1199–206. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22953727

506. Mózes J, Ebrahimi F, Gorácz O, Miszti C, Kardos G. Effect of carbapenem consumption patterns on the molecular epidemiology and carbapenem resistance of Acinetobacter baumannii. J Med Microbiol. 2014;63:1654–62.

507. Nadesalingam K, Conway SP, Denton M. Risk factors for acquisition of methicillin-resistant Staphylococcus aureus (MRSA) by patients with cystic fibrosis. J Cyst Fibros. 2005;4(1):49–52.

508. Nagy B, Szmolka A, Smole Možina S, Kovač J, Strauss A, Schlager S, et al. Virulence and antimicrobial resistance determinants of verotoxigenic Escherichia coli (VTEC) and of multidrug-resistant E. coli from foods of animal origin illegally imported to the EU by flight passengers. Int J Food Microbiol. 2015;209:52–9.

509. Nasa P, Juneja D, Singh O, Dang R, Singh A. An observational study on bloodstream extended-spectrum beta-lactamase infection in critical care unit: Incidence, risk factors and its impact on outcome. Eur J Intern Med [Internet]. 2012;23(2):192–5. Available from: http://dx.doi.org/10.1016/j.ejim.2011.06.016

510. Neulier C, Birgand G, Ruppé É, Armand-Lefèvre L, Lolom I, Yazdanpanah Y, et al. Enterobacteriaceae bacteremia: Risk factors for ESBLPE. Med Mal Infect [Internet]. 2014;44(1):32–8. Available from: http://dx.doi.org/10.1016/j.medmal.2013.11.003

511. Nixon M. Methicillin-resistant Staphylococcus aureus on orthopaedic wards: INCIDENCE, SPREAD, MORTALITY, COST AND CONTROL. J Bone Jt Surg - Br Vol [Internet]. 2006;88-B(6):812–7. Available from: http://www.bjj.boneandjoint.org.uk/cgi/doi/10.1302/0301-620X.88B6.17544

512. Nogueira K da S, Paganini MC, Conte A, Cogo LL, Taborda de Messias Reason I, da Silva MJ, et al. Emergence of extended-spectrum β-lactamase producing Enterobacter spp. in patients with bacteremia in a tertiary hospital in southern Brazil. Enferm Infecc Microbiol Clin. 2014;32(2):87–92.

513. Normanno G, La Salandra G, Dambrosio A, Quaglia NC, Corrente M, Parisi A, et al. Occurrence, characterization and antimicrobial resistance of enterotoxigenic Staphylococcus aureus isolated from meat and dairy products. Int J Food Microbiol. 2007;115(3):290–6.

514. Norström M, Hofshagen M, Stavnes T, Schau J, Lassen J, Kruse H. Antimicrobial resistance in Campylobacter jejuni from humans and broilers in Norway. Epidemiol Infect [Internet]. 2006;134(1):127–30. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2870368&tool=pmcentrez&rendertype=abstract

515. Noteboom Y, Ong DSY, Oostdijk EA, Schultz MJ, de Jonge E, Purmer I, et al. Antibiotic-Induced Within-Host Resistance Development of Gram-Negative Bacteria in Patients Receiving Selective Decontamination or Standard Care. Crit Care Med [Internet]. 2015;43(1):1–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26448616

516. Nseir S, Di Pompeo C, Cavestri B, Jozefowicz E, Nyunga M, Soubrier S, et al. Multiple-drug-

resistant bacteria in patients with severe acute exacerbation of chronic obstructive pulmonary disease: Prevalence, risk factors, and outcome. Crit Care Med [Internet]. 2006;34(12):2959–66. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17012911

517. Nseir S, Grailles G, Soury-Lavergne A, Minacori F, Alves I, Durocher A. Accuracy of American Thoracic Society/Infectious Diseases Society of America criteria in predicting infection or colonization with multidrug-resistant bacteria at intensive-care unit admission. Clin Microbiol Infect [Internet]. 2010;16(7):902–8. Available from: http://dx.doi.org/10.1111/j.1469-0691.2009.03027.x

518. Nseir S, Blazejewski C, Lubret R, Wallet F, Courcol R, Durocher A. Risk of acquiring multidrug-resistant Gram-negative bacilli from prior room occupants in the intensive care unit. Clin Microbiol Infect [Internet]. 2011 Aug;17(8):1201–8. Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1469-0691.2010.03420.x/pdf

519. Nurjadi D, Friedrich-Jänicke B, Schäfer J, Van Genderen PJJ, Goorhuis A, Perignon A, et al. Skin and soft tissue infections in intercontinental travellers and the import of multi-resistant Staphylococcus aureus to Europe. Clin Microbiol Infect [Internet]. 2015;21(6):567.e1-567.e10. Available from: http://dx.doi.org/10.1016/j.cmi.2015.01.016

520. O'Fallon E, Kandel R, Schreiber R, D'Agata EM. Acquisition of multidrug-resistant gram-negative bacteria: incidence and risk factors within a long-term care population. Infect Control Hosp Epidemiol [Internet]. 2010;31(11):1148–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20923286

521. Olalekan AO, Schaumburg F, Nurjadi D, Dike AE, Ojurongbe O, Kolawole DO, et al. Clonal expansion accounts for an excess of antimicrobial resistance in Staphylococcus aureus colonising HIV-positive individuals in Lagos, Nigeria. Int J Antimicrob Agents. 2012;40(3):268–72.

522. Oliveira a L, de Souza M, Carvalho-Dias VMH, Ruiz M a, Silla L, Tanaka PY, et al. Epidemiology of bacteremia and factors associated with multi-drug-resistant gram-negative bacteremia in hematopoietic stem cell transplant recipients. Bone Marrow Transplant. 2007;39(12):775–81.

523. Orsi GB, García-Fernández A, Giordano A, Venditti C, Bencardino A, Gianfreda R, et al. Risk factors and clinical significance of ertapenem-resistant Klebsiella pneumoniae in hospitalised patients. J Hosp Infect [Internet]. 2011;78(1):54–8. Available from: http://dx.doi.org/10.1016/j.jhin.2011.01.014

524. Orsi GB, Bencardino A, Vena A, Carattoli A, Venditti C, Falcone M, et al. Patient risk factors for outer membrane permeability and KPC-producing carbapenem-resistant Klebsiella pneumoniae isolation: results of a double case-control study. Infection [Internet]. 2013 Feb [cited 2016 Jan 8];41(1):61–7. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84873738352&partnerID=tZOtx3y1

525. Ortega M, Marco F, Soriano A, Almela M, Martínez JA, Muñoz A, et al. Analysis of 4758 Escherichia coli bacteraemia episodes: predictive factors for isolation of an antibiotic-resistant strain and their impact on the outcome. J Antimicrob Chemother [Internet]. 2009;63(3):568. Available from: +

526. Ota K V., Jamieson F, Fisman DN, Jones KE, Tamari IE, Ng LK, et al. Prevalence of and risk factors for quinolone-resistant Neisseria gonorrhoeae infection in Ontario. Cmaj. 2009;180(3):287–90.

527. Otsuka T, Ono T, Okazaki M. Resistance of nasopharyngeal pathogens and antimicrobial prescription rates for children in an area under controlled antimicrobial use. Pediatr Infect Dis

J. 2009;28(2):128–30.

528. Özgür ES, Horasan ES, Karaca K, Ersöz G, Nayci Atiş S, Kaya A. Ventilator-associated pneumonia due to extensive drug-resistant Acinetobacter baumannii: Risk factors, clinical features, and outcomes. Am J Infect Control. 2014;42(2):206–8.

529. Ozkurt Z, Ertek M, Erol S, Altoparlak U, Akcay MN. The risk factors for acquisition of imipenem-resistant Pseudomonas aeruginosa in the burn unit. Burns. 2005;31(7):870–3.

530. Oztoprak N, Cevik MA, Akinci E, Korkmaz M, Erbay A, Eren SS, et al. Risk factors for ICU-acquired methicillin-resistant Staphylococcus aureus infections. Am J Infect Control. 2006;34(1):1–5.

531. Papadimitriou-Olivgeris M, Christofidou M, Fligou F, Bartzavali C, Vrettos T, Filos KS, et al. The role of colonization pressure in the dissemination of colistin or tigecycline resistant KPC-producing Klebsiella pneumoniae in critically ill patients. Infection. 2014;42(5):883–90.

532. Papadimitriou-Olivgeris M, Spiliopoulou I, Christofidou M, Logothetis D, Manolopoulou P, Dodou V, et al. Co-colonization by multidrug-resistant bacteria in two Greek intensive care units. Eur J Clin Microbiol Infect Dis. 2015;34(10):1947–55.

533. Park SC, Kang YA, Park BH, Kim EY, Park MS, Kim YS, et al. Poor prediction of potentially drug-resistant pathogens using current criteria of health care-associated pneumonia. Respir Med [Internet]. 2012;106(9):1311–9. Available from: http://dx.doi.org/10.1016/j.rmed.2012.04.003

534. Park SH, Choi SM, Lee DG, Cho SY, Lee HJ, Choi JK, et al. Impact of extended-spectrum ??-lactamase production on treatment outcomes of acute pyelonephritis caused by escherichia coli in patients without health care-associated risk factors. Antimicrob Agents Chemother. 2015;59(4):1962–8.

535. Park YS, Lee H, Chin BS, Han SH, Hong SG, Hong SK, et al. Acquisition of extensive drug-resistant Pseudomonas aeruginosa among hospitalized patients: Risk factors and resistance mechanisms to carbapenems. J Hosp Infect. 2011;79(1):54–8.

536. Park YS, Lee H, Lee KS, Hwang SS, Cho YK, Kim HY, et al. Extensively drug-resistant Acinetobacter baumannii: Risk factors for acquisition and prevalent OXA-type carbapenemases-a multicentre study. Int J Antimicrob Agents [Internet]. 2010;36(5):430–5. Available from: http://dx.doi.org/10.1016/j.ijantimicag.2010.06.049

537. Parker CM, Kutsogiannis J, Muscedere J, Cook D, Dodek P, Day AG, et al. Ventilator-associated pneumonia caused by multidrug-resistant organisms or Pseudomonas aeruginosa: Prevalence, incidence, risk factors, and outcomes. J Crit Care. 2008;23(1):18–26.

538. Pascual V, Ortiz G, Simó M, Alonso N, Garcia MC, Xercavins M, et al. Epidemiology and risk factors for infections due to AmpC B-lactamase-producing Escherichia Coli. J Antimicrob Chemother. 2015;70(3):899–904.

539. Pasquale TR, Jabrocki B, Salstrom SJ, Wiemken TL, Peyrani P, Haque NZ, et al. Emergence of methicillin-resistant Staphylococcus aureus USA300 genotype as a major cause of late-onset nosocomial pneumonia in intensive care patients in the USA. Int J Infect Dis [Internet]. 2013;17(6):e398–403. Available from: http://dx.doi.org/10.1016/j.ijid.2012.12.013

540. Patel SJ, Oliveira AP, Zhou JJ, Alba L, Furuya EY, Weisenberg SA, et al. Risk factors and outcomes of infections caused by extremely drug-resistant gram-negative bacilli in patients hospitalized in intensive care units. Am J Infect Control [Internet]. 2014;42(6):626–31. Available from: http://dx.doi.org/10.1016/j.ajic.2014.01.027

541. Peña C, Gudiol C, Tubau F, Saballs M, Pujol M, Dominguez M a, et al. Risk-factors for acquisition of extended-spectrum beta-lactamase-producing Escherichia coli among hospitalised patients. Clin Microbiol Infect. 2006;12:279–84.

542. Peña C, Suarez C, Tubau F, Dominguez A, Sora M, Pujol M, et al. Carbapenem-resistant Pseudomonas aeruginosa: Factors influencing multidrug-resistant acquisition in non-critically ill patients. Eur J Clin Microbiol Infect Dis. 2009;28(5):519–22.

543. Peña C, Gómez-Zorrilla S, Suarez C, Dominguez M a, Tubau F, Arch O, et al. Extensively drug-resistant Pseudomonas aeruginosa: risk of bloodstream infection in hospitalized patients. Eur J Clin Microbiol Infect Dis [Internet]. 2012;31(10):2791–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22552893

544. Peng Y, Bi J, Shi J, Li Y, Ye X, Chen X, et al. Multidrug-resistant Pseudomonas aeruginosa infections pose growing threat to health care-associated infection control in the hospitals of Southern China: A case-control surveillance study. Am J Infect Control [Internet]. 2014;42(12):1308–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25444305

545. Perez F, Hujer AM, Hulten E a, Fishbain J, Hujer KM, Aron D, et al. Antibiotic resistance determinants in Acinetobacter spp and clinical outcomes in patients from a major military treatment facility. Am J Infect Control [Internet]. 2010;38(1):63–5. Available from: http://dx.doi.org/10.1016/j.ajic.2009.05.007

546. Peters PJ, Brooks JT, Limbago B, Lowery HK, McALLISTER SK, Mindley R, et al. Methicillin-resistant Staphylococcus aureus colonization in HIV-infected outpatients is common and detection is enhanced by groin culture. Epidemiol Infect. 2011;139(07):998–1008.

547. Playford EG, Craig JC, Iredell JR. Carbapenem-resistant Acinetobacter baumannii in intensive care unit patients: risk factors for acquisition, infection and their consequences. J Hosp Infect. 2007;65(3):204–11.

548. Pollett S, Rocha C, Zerpa R, Patiño L, Valencia A, Camiña M, et al. Campylobacterantimicrobial resistance in Peru: a ten-year observational study. BMC Infect Dis [Internet]. 2012;12(1):193. Available from: http://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-12-193

549. Pop-Vicas A, Mitchell SL, Kandel R, Schreiber R, D'Agata EMC. Multidrug-resistant gram-negative bacteria in a long-term care facility: Prevalence and risk factors. J Am Geriatr Soc. 2008;56(7):1276–80.

550. Pop-Vicas AE, D'Agata EM. The rising influx of multidrug-resistant gram-negative bacilli into a tertiary care hospital. Clin Infect Dis [Internet]. 2005;40(12):1792–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15909268%5Cnhttp://cid.oxfordjournals.org/content/40/12/1792.full.pdf

551. Presi P, Stärk KDC, Stephan R, Breidenbach E, Frey J, Regula G. Risk scoring for setting priorities in a monitoring of antimicrobial resistance in meat and meat products. Int J Food Microbiol [Internet]. 2009;130(2):94–100. Available from: http://dx.doi.org/10.1016/j.ijfoodmicro.2008.12.022

552. Quintero B, Araque M, Van Der Gaast-De Jongh C, Escalona F, Correa M, Morillo-Puente S, et al. Epidemiology of Streptococcus pneumoniae and Staphylococcus aureus colonization in healthy Venezuelan children. Eur J Clin Microbiol Infect Dis. 2011;30(1):7–19.

553. Rattanaumpawan P, Tolomeo P, Bilker WB, Fishman NO, Lautenbach E. Risk factors for fluoroquinolone resistance in Gram-negative bacilli causing healthcare-acquired urinary tract infections. J Hosp Infect. 2010;76(4):324–7.

554. Rattanaumpawan P, Tolomeo P, Bilker WB, Fishman NO, Lautenbach E. Risk factors for fluoroquinolone resistance in Enterococcus urinary tract infections in hospitalized patients. Epidemiol Infect [Internet]. 2011 Jun 9;139(6):955–61. Available from: https://www.cambridge.org/core/article/div-class-title-risk-factors-for-fluoroquinolone-resistance-in-span-class-italic-enterococcus-span-urinary-tract-infections-in-hospitalized-patients-div/308607F22F1E56F982A4657698D601AC

555. Rettedal S, Löhr IH, Natås O, Sundsfjord A, Øymar K. Risk factors for acquisition of CTX-M-15 extended-spectrum beta-lactamase-producing Klebsiella pneumoniae during an outbreak in a neonatal intensive care unit in Norway. Scand J Infect Dis [Internet]. 2013;45(1):54–8. Available from: http://www.tandfonline.com/doi/full/10.3109/00365548.2012.713116

556. Reyes K, Malik R, Moore C, Donabedian S, Perri M, Johnson L, et al. Evaluation of risk factors for coinfection or cocolonization with vancomycin-resistant enterococcus and methicillin-resistant Staphylococcus aureus. J Clin Microbiol. 2010;48(2):628–30.

557. Roberts MJ, Williamson DA, Hadway P, Doi SAR, Gardiner RA, Paterson DL. Baseline prevalence of antimicrobial resistance and subsequent infection following prostate biopsy using empirical or altered prophylaxis: A bias-adjusted meta-analysis. Int J Antimicrob Agents [Internet]. 2014;43(4):301–9. Available from: http://dx.doi.org/10.1016/j.ijantimicag.2014.01.008

558. Rodríguez-Baño J. c e, Navarro MD., Romero L., Muniain MA. c, Perea EJ. d, Pérez-Cano R. c, et al. Clinical and molecular epidemiology of extended-spectrum β-lactamase - Producing Escherichia coli as a cause of nosocomial infection or colonization: Implications for control. Clin Infect Dis [Internet]. 2006;42(1):37–45. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-29244436120&partnerID=40&md5=403ab9f1d0926c09daf39d2cfbc5724f

559. Rodríguez Baño J, Picón E, Gijón P, Hernández JR, Ruíz M, Peña C, et al. Community-Onset Bacteremia Due to Extended- Spectrum β-Lactamase–Producing Escherichia coli: Risk Factors and Prognosis. Clin Infect Dis [Internet]. 2010;50(1):40–8. Available from: http://cid.oxfordjournals.org/lookup/doi/10.1086/649537

560. Rogers BA, Sidjabat HE, Paterson DL, Kennedy K, Collignon P, Jones M. Prolonged carriage of resistant E. coli by returned travellers: Clonality, risk factors and bacterial characteristics. Eur J Clin Microbiol Infect Dis. 2012;31(9):2413–20.

561. Rogers BA, Ingram PR, Runnegar N, Pitman MC, Freeman JT, Athan E, et al. Community-onset Escherichia coli infection resistant to expanded-spectrum cephalosporins in low-prevalence countries. Antimicrob Agents Chemother. 2014;58(4):2126–34.

562. Rogers MAM, Mody L, Chenoweth C, Kaufman SR, Saint S. Incidence of antibiotic-resistant infection in long-term residents of skilled nursing facilities. Am J Infect Control. 2008;36(7):472–5.

563. Rogers SN, Proczek K, Sen RA, Hughes J, Banks P, Lowe D. Which patients are most at risk of methicillin resistant Staphylococcus aureus: a review of admissions to a regional maxillofacial ward between 2001 and 2005. Br J Oral Maxillofac Surg. 2008;46(6):439–44.

564. Roghmann MC, Wallin MT, Gorman PH, Johnson JA. Prevalence and Natural History of Colonization With Fluoroquinolone-Resistant Gram-Negative Bacilli in Community-Dwelling People With Spinal Cord Dysfunction. Arch Phys Med Rehabil. 2006;87(10):1305–9.

565. Romaniszyn D, Pobiega M, Wójkowska-Mach J, Chmielarczyk A, Gryglewska B, Adamski P, et al. The general status of patients and limited physical activity as risk factors of Methicillin-

resistant Staphylococcus aureus occurrence in long-term care facilities residents in Krakow, Poland. BMC Infect Dis [Internet]. 2014;14:271. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4038375/?tool=pmcentrez

566. Rooney PJ, O'Leary MC, Loughrey AC, McCalmont M, Smyth B, Donaghy P, et al. Nursing homes as a reservoir of extended-spectrum beta-lactamase (ESBL)-producing ciprofloxacin-resistant Escherichia coli. J Antimicrob Chemother [Internet]. 2009 Sep 1;64(3):635–41. Available from: https://academic.oup.com/jac/article-lookup/doi/10.1093/jac/dkp220

567. Rosengren Å, Fabricius A, Guss B, Sylvén S, Lindqvist R. Occurrence of foodborne pathogens and characterization of Staphylococcus aureus in cheese produced on farm-dairies. Int J Food Microbiol [Internet]. 2010;144(2):263–9. Available from: http://dx.doi.org/10.1016/j.ijfoodmicro.2010.10.004

568. Routh JC, Alt AL, Ashley RA, Kramer SA, Boyce TG. Increasing Prevalence and Associated Risk Factors for Methicillin Resistant Staphylococcus Aureus Bacteriuria. J Urol. 2009;181(4):1694–8.

569. Routsi C, Pratikaki M, Platsouka E, Sotiropoulou C, Nanas S, Markaki V, et al. Carbapenem-resistant versus carbapenem-susceptible Acinetobacter baumannii bacteremia in a Greek intensive care unit: Risk factors, clinical features and outcomes. Infection. 2010;38(3):173–80.

570. Ruppé E, Pitsch A, Tubach F, De Lastours V, Chau F, Pasquet B, et al. Clinical predictive values of extended-spectrum beta-lactamase carriage in patients admitted to medical wards. Eur J Clin Microbiol Infect Dis. 2012;31(3):319–25.

571. Russo A, Campanile F, Falcone M, Tascini C, Bassetti M, Goldoni P, et al. Linezolid-resistant staphylococcal bacteraemia: A multicentre case-case-control study in Italy. Int J Antimicrob Agents [Internet]. 2015;45(3):255–61. Available from: http://dx.doi.org/10.1016/j.ijantimicag.2014.12.008

572. Sadowy E, Luczkiewicz A. Drug-resistant and hospital-associated Enterococcus faecium from wastewater, riverine estuary and anthropogenically impacted marine catchment basin. BMC Microbiol [Internet]. 2014;14:66. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24629030%5Cnhttp://www.ncbi.nlm.nih.gov/pmc/articles/PMC4004213/pdf/1471-2180-14-66.pdf

573. Sánchez-Romero I, Asensio A, Oteo J, Muñoz-Algarra M, Isidoro B, Vindel A, et al. Nosocomial outbreak of VIM-1-producing Klebsiella pneumoniae isolates of multilocus sequence type 15: molecular basis, clinical risk factors, and outcome. Antimicrob Agents Chemother [Internet]. 2012;56(1):420–7. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3256054&tool=pmcentrez&rendertype=abstract

574. Satlin MJ, Soave R, Racanelli AC, Shore TB, van Besien K, Jenkins SG, et al. The emergence of vancomycin-resistant enterococcal bacteremia in hematopoietic stem cell transplant recipients. Leuk Lymphoma [Internet]. 2014;55(12):2858–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24559288%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4316723

575. Sax H, Harbarth S, Gavazzi G, Henry N, Schrenzel J, Rohner P, et al. Prevalence and prediction of previously unknown MRSA carriage on admission to a geriatric hospital. Age Ageing. 2005;34(5):456–62.

576. Schaumburg F, Alabi A, Kokou C, Grobusch MP, Köck R, Kaba H, et al. High burden of extended-spectrum β-lactamase-producing enterobacteriaceae in Gabon. J Antimicrob

Chemother. 2013;68(9):2140–3.

577. Schelenz S, Nwaka D, Hunter PR. Longitudinal surveillance of bacteraemia in haematology and oncology patients at a uk cancer centre and the impact of ciprofloxacin use on antimicrobial resistance. J Antimicrob Chemother. 2013;68(6):1431–8.

578. Schlackow I, Stoesser N, Walker AS, Crook DW, Peto TEA, Wyllie DH, et al. Increasing incidence of Escherichia coli bacteraemia is driven by an increase in antibiotic-resistant isolates: Electronic database study in Oxfordshire 1999-2011. J Antimicrob Chemother. 2012;67(6):1514–24.

579. Schoevaerdts D, Verroken A, Huang TD, Frennet M, Berhin C, Jamart J, et al. Multidrug-resistant bacteria colonization amongst patients newly admitted to a geriatric unit: A prospective cohort study. J Infect [Internet]. 2012;65(2):109–18. Available from: http://dx.doi.org/10.1016/j.jinf.2012.02.004

580. Schreiber MP, Chan CM, Shorr AF. Resistant pathogens in nonnosocomial pneumonia and respiratory failure: Is it time to refine the definition of health-care-associated pneumonia? Chest. 2010;137(6):1283–8.

581. Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant Klebsiella pneumoniae acquisition anions hospitalized adults and effect of acquisition on mortality. Antimicrob Agents Chemother. 2008;52(3):1028–33.

582. Schweickert B, Geffers C, Farragher T, Gastmeier P, Behnke M, Eckmanns T, et al. The MRSA-import in ICUs is an important predictor for the occurrence of nosocomial MRSA cases. Clin Microbiol Infect. 2011;17(6):901–6.

583. Seguin P, Laviolle B, Chanavaz C, Donnio PY, Gautier-Lerestif AL, Campion JP, et al. Factors associated with multidrug-resistant bacteria in secondary peritonitis: Impact on antibiotic therapy. Clin Microbiol Infect. 2006;12(10):980–5.

584. Seidman JC, Anitha K P, Kanungo R, Bourgeois AL, Coles CL. Risk factors for antibiotic-resistant E. coli in children in a rural area. Epidemiol Infect [Internet]. 2009;137(6):879–88. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2841309&tool=pmcentrez&rendertype=abstract

585. Sheng W-H, Liao C-H, Lauderdale T-L, Ko W-C, Chen Y-S, Liu J-W, et al. A multicenter study of risk factors and outcome of hospitalized patients with infections due to carbapenem-resistant Acinetobacter baumannii. Int J Infect Dis [Internet]. 2010;14(9):e764-9. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1201971210023581%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/20646946

586. Shi SH, Kong HS, Xu J, Zhang WJ, Jia CK, Wang WL, et al. Multidrug resistant gram-negative bacilli as predominant bacteremic pathogens in liver transplant recipients. Transpl Infect Dis. 2009;11(5):405–12.

587. Shi SH, Kong HS, Jia CK, Zhang WJ, Xu J, Wang WL, et al. Risk factors for pneumonia caused by multidrug-resistant Gram-negative bacilli among liver recipients. Clin Transplant. 2010;24(6):758–65.

588. Shigehara K, Uchibayashi T, Maeda E, Namiki M. Detection of drug-resistant Escherichia coli in patients with complicated cystitis: Analysis of risk factors: Original Article. Int J Urol. 2009;16(10):808–12.

589. Shilo S, Assous M V., Lachish T, Kopuit P, Bdolah-Abram T, Yinnon AM, et al. Risk factors for

bacteriuria with carbapenem-resistant Klebsiella pneumoniae and its impact on mortality: A case-control study. Infection. 2013;41(2):503–9.

590. Shindo Y, Ito R, Kobayashi D, Ando M, Ichikawa M, Shiraki A, et al. Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2013;188(8):985–95.

591. Shoai Tehrani M, Hajage D, Fihman V, Tankovic J, Cau S, Day N, et al. Gram-negative bacteremia: Which empirical antibiotic therapy? Med Mal Infect [Internet]. 2014;44(4):159–66. Available from: http://dx.doi.org/10.1016/j.medmal.2014.01.013

592. Shorr AF, Zilberberg MD, Micek ST, Kollef MH. Prediction of infection due to antibiotic resistant bacteria by select risk factors for health care-associated pneumonia. Arch Intern Med [Internet]. 2008;168(20):2205–10. Available from: http://dx.doi.org/10.1001/archinte.168.20.2205

593. Skiest DJ, Brown K, Cooper TW, Hoffman-Roberts H, Mussa HR, Elliott AC. Prospective comparison of methicillin-susceptible and methicillin-resistant community-associated Staphylococcus aureus infections in hospitalized patients. J Infect. 2007;54(5):427–34.

594. Skippen I, Shemko M, Turton J, Kaufmann ME, Palmer C, Shetty N. Epidemiology of infections caused by extended-spectrum ??-lactamase-producing Escherichia coli and Klebsiella spp.: a nested case-control study from a tertiary hospital in London. J Hosp Infect. 2006;64(2):115–23.

595. Slama K Ben, Jouini A, Sallem R Ben, Somalo S, Sáenz Y, Estepa V, et al. Prevalence of broad-spectrum cephalosporin-resistant Escherichia coli isolates in food samples in Tunisia, and characterization of integrons and antimicrobial resistance mechanisms implicated. Int J Food Microbiol [Internet]. 2010;137(2–3):281–6. Available from: http://dx.doi.org/10.1016/j.ijfoodmicro.2009.12.003

596. Smith JM, Avdic E, Tamma PD, Zhang L, Carroll KC, Cosgrove SE. Risk Factors for Resistance to beta-Lactam/beta-Lactamase Inhibitors and Ertapenem in Bacteroides Bacteremia. Antimicrob Agents Chemother [Internet]. 2015;59(8):5049–51. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=26033720

597. Smithson A, Chico C, Ramos J, Netto C, Sanchez M, Ruiz J, et al. Prevalence and risk factors for quinolone resistance among Escherichia coli strains isolated from males with community febrile urinary tract infection. Eur J Clin Microbiol Infect Dis. 2012;31(4):423–30.

598. Snyder GM, O'Fallon E, D'Agata EMC. Co-colonization with multiple different species of multidrug-resistant gram-negative bacteria. Am J Infect Control [Internet]. 2011;39(6):506–10. Available from: http://dx.doi.org/10.1016/j.ajic.2010.09.012

599. Sohn KM, Peck KR, Joo EJ, Ha YE, Kang CI, Chung DR, et al. Duration of colonization and risk factors for prolonged carriage of vancomycin-resistant enterococci after discharge from the hospital. Int J Infect Dis [Internet]. 2013;17(4):e240–6. Available from: http://dx.doi.org/10.1016/j.ijid.2012.09.019

600. Song JY, Cheong HJ, Jo YM, Choi WS, Noh JY, Heo JY, et al. Vancomycin-resistant Enterococcus colonization before admission to the intensive care unit: A clinico-epidemiologic analysis. Am J Infect Control. 2009;37(9):734–40.

601. Souli M, Sakka V, Galani I, Antoniadou A, Galani L, Siafakas N, et al. Colonisation with vancomycin- and linezolid-resistant Enterococcus faecium in a university hospital: molecular

epidemiology and risk factor analysis. Int J Antimicrob Agents. 2009;33(2):137–42.

602. Srinivasan S, Sheela D, Shashikala, Mathew R, Bazroy J, Kanungo R. Risk factors and associated problems in the management of infections with methicillin resistant Staphylococcus aureus. Indian J Med Microbiol [Internet]. 2006 Jul;24(3):182–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16912437

603. Sritippayawan S, Sri-Singh K, Prapphal N, Samransamruajkit R, Deerojanawong J. Multidrug-resistant hospital-associated infections in a pediatric intensive care unit: a cross-sectional survey in a Thai university hospital. Int J Infect Dis. 2009;13(4):506–12.

604. Steensels D., Slabbaert K., De Wever L., Vermeersch P., Van Poppel H., Verhaegen J. Fluoroquinolone-resistant E. coli in intestinal flora of patients\nundergoing transrectal ultrasound-guided prostate biopsy—should we\nreassess our practices for antibiotic prophylaxis? Clin Microbiol Infect [Internet]. 2012;18(6):575–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21958149

605. Sun JD, Huang SF, Yang SS, Pu SL, Zhang CM, Zhang LP. Impact of carbapenem heteroresistance among clinical isolates of invasive Escherichia coli in Chongqing, southwestern China. Clin Microbiol Infect. 2015;21(5):1–10.

606. Sung YK, Lee JK, Lee KH, Lee KT, Kang C-I. The clinical epidemiology and outcomes of bacteremic biliary tract infections caused by antimicrobial-resistant pathogens. Am J Gastroenterol [Internet]. 2012;107(3):473–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22334249

607. Tacconelli E, Cataldo MA, De Pascale G, Manno D, Spanu T, Cambieri A, et al. Prediction models to identify hospitalized patients at risk of being colonized or infected with multidrug-resistant Acinetobacter baumannii calcoaceticus complex. J Antimicrob Chemother. 2008;62(5):1130–7.

608. Tacconelli E, De Angelis G, Cataldo MA, Mantengoli E, Spanu T, Pan A, et al. Antibiotic usage and risk of colonization and infection with antibiotic-resistant bacteria: A hospital population-based study. Antimicrob Agents Chemother. 2009;53(10):4264–9.

609. Tam VH, Chang KT, LaRocco MT, Schilling AN, McCauley SK, Poole K, et al. Prevalence, mechanisms, and risk factors of carbapenem resistance in bloodstream isolates of Pseudomonas aeruginosa. Diagn Microbiol Infect Dis. 2007;58(3):309–14.

610. Tam VH, Rogers CA, Chang KT, Weston JS, Caeiro JP, Garey KW. Impact of multidrug-resistant Pseudomonas aeruginosa bacteremia on patient outcomes. Antimicrob Agents Chemother. 2010;54(9):3717–22.

611. Tan MW, Lye DC, Ng T-M, Nikolaou M, Tam VH. Mathematical model to quantify the effects of risk factors on carbapenem-resistant Acinetobacter baumannii. Antimicrob Agents Chemother [Internet]. 2014;58(9):5239–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24957824

612. Tängdén T, Cars O, Melhus Å, Löwdin E. Foreign travel is a major risk factor for colonization with Escherichia coli producing CTX-M-type extended-spectrum β-lactamases: A prospective study with Swedish volunteers. Antimicrob Agents Chemother. 2010;54(9):3564–8.

613. Taylor S, Margolick J, Abughosh Z, Goldenberg SL, Lange D, Bowie WR, et al. Ciprofloxacin resistance in the faecal carriage of patients undergoing transrectal ultrasound guided prostate biopsy. BJU Int. 2013;111(6):946–53.

614. Tedja R, Nowacki A, Fraser T, Fatica C, Griffiths L, Gordon S, et al. The impact of multidrug

resistance on outcomes in ventilator-associated pneumonia. Am J Infect Control. 2014;42(5):542–5.

615. Tekin R, Dal T, Bozkurt F, Deveci O, Palanci Y, Arslan E, et al. Risk Factors for Nosocomial Burn Wound Infection Caused by Multidrug Resistant Acinetobacter baumannii. J Burn Care Res. 2013;73–80.

616. Ternes YM, Lamaro-Cardoso J, André MCP, Pessoa VP, Vieira MADS, Minamisava R, et al. Molecular epidemiology of coagulase-negative Staphylococcus carriage in neonates admitted to an intensive care unit in Brazil. BMC Infect Dis [Internet]. 2013;13:572. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24308773

617. Thiébaut ACM, Arlet G, Andremont A, Papy E, Sollet JP, Berne'de-Bauduin C, et al. Variability of intestinal colonization with third-generation cephalosporin-resistant Enterobacteriaceae and antibiotic use in intensive care units. J Antimicrob Chemother. 2012;67(6):1525–36.

618. Thomas S, Karas JA, Emery M, Clark G. Meticillin-resistant Staphylococcus aureus carriage among district nurse patients and medical admissions in a UK district. J Hosp Infect. 2007;66(4):369–73.

619. Toltzis P, Dul M, O'Riordan MA, Jacobs MR, Blumer J. Serogroup 19 pneumococci containing both mef and erm macrolide resistance determinants in an American city. Pediatr Infect Dis J. 2006;25(1):19–24.

620. Tsai M-H, Wu T-L, Su L-H, Lo W-L, Chen C-L, Liang Y-H, et al. Carbapenem-resistant-only Pseudomonas aeruginosa infection in patients formerly infected by carbapenem-susceptible strains. Int J Antimicrob Agents [Internet]. 2014;44(6):541–5. Available from: http://dx.doi.org/10.1016/j.ijantimicag.2014.07.022

621. Tsai M-H, Chu S-M, Hsu J-F, Lien R, Huang H-R, Chiang M-C, et al. Risk factors and outcomes for multidrug-resistant Gram-negative bacteremia in the NICU. Pediatrics [Internet]. 2014;133(2):e322-9. Available from: http://pediatrics.aappublications.org/content/133/2/e322.abstract

622. Tsao FY, Kou HW, Huang YC. Dissemination of methicillin-resistant Staphylococcus aureus sequence type 45 among nursing home residents and staff in Taiwan. Clin Microbiol Infect [Internet]. 2015;21(5):451–8. Available from: http://dx.doi.org/10.1016/j.cmi.2014.12.019

623. Tsu JHL, Ma WK, Chan WKW, Lam BHS, To KC, To WK, et al. Prevalence and predictive factors of harboring fluoroquinolone-resistant and extended-spectrum ??-lactamase-producing rectal flora in Hong Kong Chinese men undergoing transrectal ultrasound-guided prostate biopsy. Urology [Internet]. 2015;85(1):15–21. Available from: http://dx.doi.org/10.1016/j.urology.2014.07.078

624. Tukenmez Tigen E, Tandogdu Z, Ergonul O, Altinkanat G, Gunaydin B, Ozgen M, et al. Outcomes of fecal carriage of extended-spectrum β-lactamase after transrectal ultrasound-guided biopsy of the prostate. Urology. 2014;84(5):1008–15.

625. Tumbarello M, Repetto E, Trecarichi EM, Bernardini C, De Pascale G, Parisini a., et al. Multidrug-resistant Pseudomonas aeruginosa bloodstream infections: risk factors and mortality. Epidemiol Infect. 2011;139(11):1740–9.

626. Tumbarello M, Trecarichi EM, Fiori B, Losito AR, D'Inzeo T, Campana L, et al. Multidrug-resistant Proteus mirabilis bloodstream infections: Risk factors and outcomes. Antimicrob Agents Chemother. 2012;56(6):3224–31.

627. Unger HW, Aho C, Ome-Kaius M, Wangnapi RA, Umbers AJ, Jack W, et al. Impact of

intermittent preventive treatment in pregnancy with azithromycin-containing regimens on maternal nasopharyngeal carriage and antibiotic sensitivity of Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus: A cross-sectional. J Clin Microbiol. 2015;53(4):1317–23.

628. Vallés J, Alvarez-Lerma F, Palomar M, Blanco A, Escoresca A, Armestar F, et al. Health-care-Associated Bloodstream Infections at Admission to the ICU. Chest [Internet]. 2011 Apr;139(4):810–5. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0012369211601815

629. Van Aken S, Lund N, Ahl J, Odenholt I, Tham J. Risk factors, outcome and impact of empirical antimicrobial treatment in extended-spectrum β-lactamase-producing Escherichia coli bacteraemia. Scand J Infect Dis [Internet]. 2014;46(11):753–62. Available from: http://informahealthcare.com/doi/abs/10.3109/00365548.2014.937454%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/25195648

630. van Cleef BA, Monnet DL, Voss A, Krziwanek K, Allerberger F, Struelens M et al. Livestock-associated Methicillin-Resistant Staphylococcus aureus in Humans, Europe. Emerg Infect Dis. 2011;17(3):502–5.

631. Van't Veen A, Van Der Zee A, Nelson J, Speelberg B, Kluytmans JAJW, Buiting AGM. Outbreak of infection with a multiresistant Klebsiella pneumoniae strain associated with contaminated roll boards in operating rooms. J Clin Microbiol. 2005;43(10):4961–7.

632. Vasudevan A, Mukhopadhyay A, Li J, Yuen EGY, Tambyah PA. A prediction tool for nosocomial multi-drug Resistant Gram-Negative Bacilli infections in critically ill patients - prospective observational study. BMC Infect Dis [Internet]. 2014;14:615. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4252002&tool=pmcentrez&rendertype=abstract

633. Veličković - Radovanović R, Stefanović N, Damnjanović I, Kocić B, Antić S, Dinić M, et al. Monitoring of antibiotic consumption and development of resistance by enterobacteria in a tertiary care hospital. J Clin Pharm Ther [Internet]. 2015 Aug;40(4):426–30. Available from: http://doi.wiley.com/10.1111/jcpt.12283

634. Vergara-López S, Domínguez MC, Conejo MC, Pascual Á, Rodríguez-Baño J. Lessons from an outbreak of metallo-β-lactamase-producing Klebsiella oxytoca in an intensive care unit: the importance of time at risk and combination therapy. J Hosp Infect [Internet]. 2015 Feb [cited 2015 Dec 14];89(2):123–31. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84921544058&partnerID=tZOtx3y1

635. Vernaz N, Huttner B, Muscionico D, Salomon JL, Bonnabry P, López-Lozano JM, et al. Modelling the impact of antibiotic use on antibiotic-resistant Escherichia coli using population-based data from a large hospital and its surrounding community. J Antimicrob Chemother. 2011;66(4):928–35.

636. Vibet MA, Roux J, Montassier E, Corvec S, Juvin ME, Ngohou C, et al. Systematic analysis of the relationship between antibiotic use and extended-spectrum beta-lactamase resistance in Enterobacteriaceae in a French hospital: a time series analysis. Eur J Clin Microbiol Infect Dis. 2015;34(10):1957–63.

637. Vigil KJ, Adachi JA, Aboufaycal H, Hachem RY, Reitzel RA, Jiang Y, et al. Multidrug-resistant Escherichia coli bacteremia in cancer patients. Am J Infect Control [Internet]. 2009;37(9):741–5. Available from: http://dx.doi.org/10.1016/j.ajic.2009.02.002

638. Volonakis K, Souli M, Kapaskelis A, Baziaka F, Grammelis V, Ziakas PD, et al. Evolution of

resistance patterns and identification of risk factors for Streptococcus pneumoniae colonisation in daycare centre attendees in Athens, Greece. Int J Antimicrob Agents. 2006;28(4):297–301.

639. Von Baum H, Ober JF, Wendt C, Wenzel RP, Edmond MB. Antibiotic-resistant bloodstream infections in hospitalized patients: Specific risk factors in a high-risk population? Infection. 2005;33(5–6):320–6.

640. von Gottberg A, Klugman KP, Cohen C, Wolter N, de Gouveia L, du Plessis M, et al. Emergence of levofloxacin-non-susceptible Streptococcus pneumoniae and treatment for multidrug-resistant tuberculosis in children in South Africa: a cohort observational surveillance study. Lancet. 2008;371(9618):1108–13.

641. Voor AF, Severin JA, Lesaffre EMEH, Vos MC. A systematic review and meta-Analyses show that carbapenem use and medical devices are the leading risk factors for carbapenem-resistant pseudomonas aeruginosa. Antimicrob Agents Chemother. 2014;58(5):2626–37.

642. Walsh C, Duffy G, O'Mahony R, Fanning S, Blair IS, McDowell DA. Antimicrobial resistance in Irish isolates of verocytotoxigenic Escherichia coli (E. coli)-VTEC. Int J Food Microbiol. 2006;109(3):173–8.

643. Wang F-D, Chen Y-Y, Chen T-L, Liu C-Y. Risk factors and mortality in patients with nosocomial Staphylococcus aureus bacteremia. Am J Infect Control. 2008;36(2):118–22.

644. Waturangi DE, Wennars M, Suhartono MX, Wijaya YF. Edible ice in Jakarta, Indonesia, is contaminated with multidrug-resistant Vibrio cholerae with virulence potential. J Med Microbiol. 2013;62(PART3):352–9.

645. Webster DP, Young BC, Morton R, Collyer D, Batchelor B, Turton JF, et al. Impact of a clonal outbreak of extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* in the development and evolution of bloodstream infections by K. pneumoniae and Escherichia coli: An 11 year experience in Oxfordshire, Uk. J Antimicrob Chemother. 2011;66(9):2126–35.

646. Wendt C, Lin D, Von Baum H. Risk factors for colonization with third-generation cephalosporin-resistant enterobacteriaceae. Infection. 2005;33(5–6):327–32.

647. Wener KM, Schechner V, Gold HS, Wright SB, Carmeli Y. Treatment with Fluoroquinolones or with -Lactam- -Lactamase Inhibitor Combinations Is a Risk Factor for Isolation of Extended-Spectrum- -Lactamase-Producing Klebsiella Species in Hospitalized Patients. Antimicrob Agents Chemother [Internet]. 2010 May 1;54(5):2010–6. Available from: http://aac.asm.org/cgi/doi/10.1128/AAC.01131-09

648. Wibbenmeyer L, Appelgate D, Williams I, Light T, Latenser B, Lewis R, et al. Effectiveness of universal screening for vancomycin-resistant enterococcus and methicillin-resistant Staphylococcus aureus on admission to a burn-trauma step-down unit. J Burn care Res Off Publ Am Burn Assoc [Internet]. 2009;30(4):648–56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19506499

649. Wibbenmeyer L, Williams I, Ward M, Xiao X, Light T, Latenser B, et al. Risk factors for acquiring vancomycin-resistant Enterococcus and methicillin-resistant Staphylococcus aureus on a burn surgery step-down unit. J Burn Care Res [Internet]. 2010;31(2):269–79. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20182380

650. Wigglesworth N, Wilcox MH. Prospective evaluation of hospital isolation room capacity. J Hosp Infect. 2006;63(2):156–61.

651. Willmann M, Klimek AM, Vogel W, Liese J, Marschal M, Autenrieth IB, et al. Clinical and

treatment-related risk factors for nosocomial colonisation with extensively drug-resistant Pseudomonas aeruginosa in a haematological patient population: a matched case control study. BMC Infect Dis [Internet]. 2014;14(1):1–8. Available from: http://dx.doi.org/10.1186/s12879-014-0650-9

652. Worth LJ, Thursky KA, Seymour JF, Slavin MA. Vancomycin-resistant Enterococcus faecium infection in patients with hematologic malignancy: Patients with acute myeloid leukemia are at high-risk. Eur J Haematol. 2007;79(3):226–33.

653. Wroe PC, Lee GM, Finkelstein JA, Pelton SI, Hanage WP, Lipsitch M, et al. Pneumococcal carriage and antibiotic resistance in young children before 13-valent conjugate vaccine. Pediatr Infect Dis J [Internet]. 2012;31(3):249–54. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3288953&tool=pmcentrez&rendertype=abstract

654. Wu D, Cai J, Liu J. Risk factors for the acquisition of nosocomial infection with carbapenem-resistant Klebsiella pneumoniae. South Med J. 2011;104(2):106–10.

655. Wueppenhorst N, Stueger HP, Kist M, Glocker EO. High secondary resistance to quinolones in German Helicobacter pylori clinical isolates. J Antimicrob Chemother. 2013;68(7):1562–6.

656. Wyllie DH, Peto TE, Crook D. MRSA bacteraemia in patients on arrival in hospital: a cohort study in Oxfordshire 1997-2003. Bmj [Internet]. 2005;331(7523):992. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16155048%5Cnhttp://www.bmj.com/content/331/7523/992.full.pdf

657. Wyllie DH, Walker AS, Peto TEA, Crook DW. Hospital exposure in a UK population, and its association with bacteraemia. J Hosp Infect. 2007;67(4):301–7.

658. Xia Y, Lu C, Zhao J, Han G, Chen Y, Wang F, et al. A bronchofiberoscopy-associated outbreak of multidrug-resistant Acinetobacter baumannii in an intensive care unit in Beijing, China. BMC Infect Dis [Internet]. 2012;12(1):335. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3562511&tool=pmcentrez&rendertype=abstract

659. Yoon YK, Lee SE, Lee J, Kim HJ, Kim JY, Park DW, et al. Risk factors for prolonged carriage of vancomycin-resistant enterococcus faecium among patients in intensive care units: A case-control study. J Antimicrob Chemother. 2011;66(8):1831–8.

660. Yoon YK, Lee J, Ryu SY, Chang H-H, Choi WS, Yoon JH, et al. Clinical significance of multidrug-resistant Acinetobacter baumannii isolated from central venous catheter tip cultures in patients without concomitant bacteremia. Scand J Infect Dis [Internet]. 2013;45(12):900–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24047226

661. Young BE, Lye DC, Krishnan P, Chan S, Leo Y. A prospective observational study of the prevalence and risk factors for colonization by antibiotic resistant bacteria in patients at admission to hospital in Singapore. BMC Infect Dis [Internet]. 2014 [cited 2016 Jan 8];14(1):298. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84902370013&partnerID=tZOtx3y1

662. Zacharioudakis IM, Zervou FN, Ziakas PD, Rice LB, Mylonakis E. Vancomycin-Resistant Enterococci Colonization Among Dialysis Patients: A Meta-analysis of Prevalence, Risk Factors, and Significance. Am J Kidney Dis [Internet]. 2015 [cited 2017 Apr 17];65(1):88–97. Available from: http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S027263861400907X

663. Zaoutis TE, Goyal M, Chu JH, Coffin SE, Bell LM, Nachamkin I, et al. Risk factors for and outcomes of bloodstream infection caused by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella species in children. Pediatrics. 2005;115(4):942–9.

664. Zaoutis TE, Toltzis P, Chu J, Abrams T, Dul M, Kim J, et al. Clinical and molecular epidemiology of community-acquired methicillin-resistant Staphylococcus aureus infections among children with risk factors for health care-associated infection: 2001-2003. Pediatr Infect Dis J [Internet]. 2006;25(4):343–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16567987

665. Zarrilli R, Di Popolo A, Bagattini M, Giannouli M, Martino D, Barchitta M, et al. Clonal spread and patient risk factors for acquisition of extensively drug-resistant Acinetobacter baumannii in a neonatal intensive care unit in Italy. J Hosp Infect [Internet]. 2012;82(4):260–5. Available from: http://dx.doi.org/10.1016/j.jhin.2012.08.018

666. Zavascki AP, Cruz RP, Goldani LZ. Risk factors for imipenem-resistant Pseudomonas aeruginosa: A comparative analysis of two case-control studies in hospitalized patients. J Hosp Infect. 2005;59(2):96–101.

667. Zervou FN, Zacharioudakis IM, Ziakas PD, Mylonakis E. MRSA colonization and risk of infection in the neonatal and pediatric ICU: a meta-analysis. Pediatrics. 2014;133(4):e1015-23.

668. Zhao S-Y, Zhang J, Zhang Y-L, Wang Y-C, Xiao S-Z, Gu F-F, et al. Epidemiology and risk factors for faecal extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) carriage derived from residents of seven nursing homes in western Shanghai, China. Epidemiol Infect [Internet]. 2016;144(197):695–702. Available from: http://www.journals.cambridge.org/abstract_S0950268815001879

669. Zhao ZC, Xu XH, Liu MB, Wu J, Lin J, Li B. Fecal carriage of carbapenem-resistant Enterobacteriaceae in a Chinese university hospital. Am J Infect Control [Internet]. 2014;42(5):e61–4. Available from: http://dx.doi.org/10.1016/j.ajic.2014.01.024

670. Zheng YL, Wan YF, Zhou LY, Ye ML, Liu S, Xu CQ, et al. Risk factors and mortality of patients with nosocomial carbapenem-resistant Acinetobacter baumannii pneumonia. Am J Infect Control [Internet]. 2013;41(7):e59–63. Available from: http://dx.doi.org/10.1016/j.ajic.2013.01.006

671. Zhong L, Men TY, Li H, Peng ZH, Gu Y, Ding X, et al. Multidrug-resistant gram-negative bacterial infections after liver transplantation - Spectrum and risk factors. J Infect [Internet]. 2012;64(3):299–310. Available from: http://dx.doi.org/10.1016/j.jinf.2011.12.005

672. Zillich AJ, Sutherland JM, Wilson SJ, Diekema DJ, Ernst EJ, Vaughn TE, et al. Antimicrobial use control measures to prevent and control antimicrobial resistance in US hospitals. Infect Control Hosp Epidemiol [Internet]. 2006;27(10):1088–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17006817

673. Ahn JH, Lee KH, Chung JH, Shin K-C, Lee CK, Kim HJ, et al. Clinical characteristics and prognostic risk factors of healthcare-associated pneumonia in a Korean tertiary teaching hospital. Medicine (Baltimore). 2017;96(42):e8243.

674. Alevizakos M, Gaitanidis A, Nasioudis D, Tori K, Flokas ME, Mylonakis E. Colonization with vancomycin-resistant enterococci and risk for bloodstream infection among patients with malignancy: A systematic review and meta-analysis. Open Forum Infect Dis. 2017;4(1):1–10.

675. Banach DB, Peaper DR, Fortune BE, Emre S, Dembry LM. The clinical and molecular epidemiology of pre-transplant vancomycin-resistant enterococci colonization among liver

transplant recipients. Clin Transplant. 2016;30(3):306–11.

676. Bencardino D, Vitali LA, Petrelli D. High prevalence of clonally diverse spa type t026 staphylococcus aureus contaminating rural eggshells. J Med Microbiol. 2017;66(8):1196–201.

677. Blanco N, Pineles L, Lydecker AD, Johnson JK, Sorkin JD, Morgan DJ, et al. Transmission of resistant Gram-negative bacteria to Healthcare Worker Gowns and Gloves during Care of Nursing Home Residents in VA Community Living Centers. Antimicrob Agents Chemother [Internet]. 2017;61(10):AAC.00790-17. Available from: http://aac.asm.org/lookup/doi/10.1128/AAC.00790-17

678. Bosch-Nicolau P, Falcó V, Viñado B, Andreu A, Len O, Almirante B, et al. Risk factors that influence the empirical treatment of patients with acute pyelonephritis: a cohort study. Antimicrob Agents Chemother [Internet]. 2017;61(12):AAC.01317-17. Available from: http://aac.asm.org/lookup/doi/10.1128/AAC.01317-17

679. Bryce A, Costelloe C, Hawcroft C, Wootton M, Hay AD. Faecal carriage of antibiotic resistant Escherichia coli in asymptomatic children and associations with primary care antibiotic prescribing: A systematic review and meta-analysis. BMC Infect Dis. 2016;16(1):1–12.

680. Campbell WR, Li P, Whitman TJ, Blyth DM, Schnaubelt ER, Mende K, et al. Multi-Drug–Resistant Gram-Negative Infections in Deployment-Related Trauma Patients. Surg Infect (Larchmt) [Internet]. 2017;18(3):357–67. Available from: http://online.liebertpub.com/doi/10.1089/sur.2017.002

681. Carmeli, Yehuda, Matthew H. Samore and WCH. The association between antecedent vancomycin treatment and hospital-acquired vancomycin-resistant enterococci: a meta-analysis. Arch Intern Med. 1999;159(20):2461–8.

682. Carrara E, Pfeffer I, Zusman O, Leibovici L, Paul M. Determinants of inappropriate empirical antibiotic treatment: systematic review and meta-analysis. Int J Antimicrob Agents [Internet]. 2017;8–13. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0924857917304478

683. Chabah M, Chemsi M, Zerouali K, Alloula O, Lehlimi M, Habzi A, et al. Healthcare-associated infections due to carbapenemase-producing Enterobacteriaceae: Bacteriological profile and risk factors. Med Mal Infect [Internet]. 2016;46(3):157–62. Available from: http://dx.doi.org/10.1016/j.medmal.2015.12.015

684. Chaves L, Tomich LM, Salomão M, Leite GC, Ramos J, Martins RR, et al. High mortality of bloodstream infection outbreak caused by carbapenem-resistant P. aeruginosa producing SPM-1 in a bone marrow transplant unit. J Med Microbiol. 2017;66(12):1722–9.

685. Chen C-H, Lin L-C, Chang Y-J, Chang C-Y. Clinical and microbiological characteristics of vancomycin-resistant Enterococcus faecium bloodstream infection in Central Taiwan. Medicine (Baltimore) [Internet]. 2017;96(49):e9000. Available from: http://insights.ovid.com/crossref?an=00005792-201712080-00065

686. Chervet D, Lortholary O, Zahar JR, Dufougeray A, Pilmis B, Partouche H. Antimicrobial resistance in community-acquired urinary tract infections in Paris in 2015. Med Mal Infect [Internet]. 2017;5–9. Available from: http://dx.doi.org/10.1016/j.medmal.2017.09.013

687. Chia L, Crum-Cianflone NF. Emergence of multi-drug resistant organisms (MDROs) causing Fournier's gangrene. J Infect [Internet]. 2018;76(1):38–43. Available from: https://doi.org/10.1016/j.jinf.2017.09.015

688. Chiotos K, Tamma PD, Flett KB, Naumann M. crossm Multicenter Study of the Risk Factors for Colonization or Infection with. 2017;61(12):1–9.

689. Cillóniz C, Gabarrús A, Ferrer M, Puig de la Bellacasa J, Rinaudo M, Mensa J, et al. Community-Acquired Pneumonia Due to Multidrug- and Non–Multidrug-Resistant Pseudomonas aeruginosa. Chest [Internet]. 2016;150(2):415–25. Available from: http://dx.doi.org/10.1016/j.chest.2016.03.042

690. DiPippo AJ, Tverdek FP, Tarrand JJ, Munita JM, Tran TT, Arias CA, et al. Daptomycin non-susceptible Enterococcus faecium in leukemia patients: Role of prior daptomycin exposure. J Infect [Internet]. 2017;74(3):243–7. Available from: http://dx.doi.org/10.1016/j.jinf.2016.11.004

691. Dulon M, Peters C, Schablon A, Nienhaus A. MRSA carriage among healthcare workers in non-outbreak settings in Europe and the United States: a systematic review. BMC Infect Dis [Internet]. 2014 Dec 3 [cited 2018 Feb 22];14(1):363. Available from: http://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-14-363

692. European Centre for Disease Prevention and Control (ECDC). The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2016. 2018.

693. Egervärn M, Englund S, Ljunge M, Wiberg C, Finn M, Lindblad M, et al. Unexpected common occurrence of transferable extended spectrum cephalosporinase-producing Escherichia coli in Swedish surface waters used for drinking water supply. Sci Total Environ [Internet]. 2017;587–588:466–72. Available from: http://dx.doi.org/10.1016/j.scitotenv.2017.02.157

694. Fasugba O, Gardner A, Mitchell BG, Mnatzaganian G. Ciprofloxacin resistance in community- and hospital-acquired Escherichia coli urinary tract infections: A systematic review and meta-analysis of observational studies. BMC Infect Dis. 2015;15(1).

695. Fernández-Barat L, Ferrer M, De Rosa F, Gabarrús A, Esperatti M, Terraneo S, et al. Intensive care unit-acquired pneumonia due to Pseudomonas aeruginosa with and without multidrug resistance. J Infect. 2017;74(2):142–52.

696. Flokas ME, Alevizakos M, Shehadeh F, Andreatos N, Mylonakis E. Extended-spectrum β-lactamase-producing Enterobacteriaceae colonisation in long-term care facilities: a systematic review and meta-analysis. Int J Antimicrob Agents [Internet]. 2017;50(5):649–56. Available from: https://doi.org/10.1016/j.ijantimicag.2017.08.003

697. Flokas ME, Karageorgos SA, Detsis M, Alevizakos M, Mylonakis E. Vancomycin-resistant enterococci colonisation, risk factors and risk for infection among hospitalised paediatric patients: a systematic review and meta-analysis. Int J Antimicrob Agents [Internet]. 2017 May [cited 2018 Feb 22];49(5):565–72. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0924857917300869

698. Fox A, Pichon B, Wilkinson H, Doumith M, Hill RLR, McLauchlin J, et al. Detection and molecular characterization of Livestock-Associated MRSA in raw meat on retail sale in North West England. Lett Appl Microbiol. 2017;64(3):239–45.

699. Freire MP, Oshiro ICVS, Pierrotti LC, Bonazzi PR, De Oliveira LM, Song ATW, et al. Carbapenem-Resistant Enterobacteriaceae Acquired before Liver Transplantation: Impact on Recipient Outcomes. Transplantation. 2017;101(4):811–20.

700. Giacobbe DR, Del Bono V, Bruzzi P, Corcione S, Giannella M, Marchese A, et al. Previous bloodstream infections due to other pathogens as predictors of carbapenem-resistant Klebsiella pneumoniae bacteraemia in colonized patients: results from a retrospective multicentre study. Eur J Clin Microbiol Infect Dis. 2017;36(4):663–9.

701. Giuffrè M, Geraci DM, Bonura C, Saporito L, Graziano G, Insinga V, et al. The Increasing Challenge of Multidrug-Resistant Gram-Negative Bacilli. Medicine (Baltimore) [Internet]. 2016;95(10):e3016. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00005792-201603080-00054

702. Giufrè M, Ricchizzi E, Accogli M, Barbanti F, Monaco M, Pimentel de Araujo F, et al. Colonization by multidrug-resistant organisms in long-term care facilities in Italy: a point-prevalence study. Clin Microbiol Infect. 2017;23(12):961–7.

703. Godič Torkar K, Dražetić M. The microbial contamination and the presence of β-lactamase producing Gram-negative bacteria in the water and on the surfaces of public recreation water facilities. Int J Environ Health Res [Internet]. 2017;27(4):293–305. Available from: https://doi.org/10.1080/09603123.2017.1342227

704. Harries M, Dreesman J, Rettenbacher-Riefler S, Mertens E. Faecal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae and Shiga toxin-producing Escherichia coli in asymptomatic nursery children in Lower Saxony (Germany), 2014. Epidemiol Infect. 2016;144(16):3540–8.

705. Hefazi M, Damlaj M, Alkhateeb HB, Partain DK, Patel R, Razonable RR, et al. Vancomycin-resistant *Enterococcus* colonization and bloodstream infection: prevalence, risk factors, and the impact on early outcomes after allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia. Transpl Infect Dis [Internet]. 2016;18(6):913–20. Available from: http://doi.wiley.com/10.1111/tid.12612

706. Igbinosa EO. Detection and Antimicrobial Resistance of *Vibrio* Isolates in Aquaculture Environments: Implications for Public Health. Microb Drug Resist [Internet]. 2016;22(3):238–45. Available from: http://online.liebertpub.com/doi/10.1089/mdr.2015.0169

707. Ishida T, Ito A, Washio Y, Yamazaki A, Noyama M, Tokioka F, et al. Risk factors for drug-resistant pathogens in immunocompetent patients with pneumonia: Evaluation of PES pathogens. J Infect Chemother [Internet]. 2017;23(1):23–8. Available from: http://dx.doi.org/10.1016/j.jiac.2016.09.002

708. Jacmel L, Timsit S, Ferroni A, Auregan C, Angoulvant F, Chéron G. Extended-spectrum β-lactamase-producing bacteria caused less than 5% of urinary tract infections in a paediatric emergency centre. Acta Paediatr Int J Paediatr. 2017;106(1):142–7.

709. Jang HM, Kim YB, Choi S, Lee Y, Shin SG, Unno T, et al. Prevalence of antibiotic resistance genes from effluent of coastal aquaculture, South Korea. Environ Pollut [Internet]. 2018;233:1049–57. Available from: https://doi.org/10.1016/j.envpol.2017.10.006

710. Kanayama A, Kawahara R, Yamagishi T, Goto K, Kobaru Y, Takano M, et al. Successful control of an outbreak of GES-5 extended-spectrum β-lactamase-producing Pseudomonas aeruginosa in a long-term care facility in Japan. J Hosp Infect [Internet]. 2016;93(1):35–41. Available from: http://dx.doi.org/10.1016/j.jhin.2015.12.017

711. Karaaslan A, Soysal A, Altinkanat Gelmez G, Kepenekli Kadayifci E, Söyletir G, Bakir M. Molecular characterization and risk factors for carbapenem-resistant Gram-negative bacilli colonization in children: Emergence of NDM-producing Acinetobacter baumannii in a newborn intensive care unit in Turkey. J Hosp Infect. 2016;92(1):67–72.

712. Kashoma IP, Kassem II, John J, Kessy BM, Gebreyes W, Kazwala RR, et al. Prevalence and Antimicrobial Resistance of *Campylobacter* Isolated from Dressed Beef Carcasses and Raw Milk in Tanzania. Microb Drug Resist [Internet]. 2016;22(1):40–52. Available from:

http://online.liebertpub.com/doi/10.1089/mdr.2015.0079

713. Khawaja T, Kirveskari J, Johansson S, Väisänen J, Djupsjöbacka A, Nevalainen A, et al. Patients hospitalized abroad as importers of multiresistant bacteria—a cross-sectional study. Clin Microbiol Infect. 2017;23(9):673.e1-673.e8.

714. Kim MW, Greenfield BK, Snyder RE, Steinmaus CM, Riley LW. The association between community-associated Staphylococcus aureus colonization and disease: a meta-analysis. BMC Infect Dis [Internet]. 2018;18(1):86. Available from: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-018-2990-3

715. Kim S, Russell D, Mohamadnejad M, Makker J, Sedarat A, Watson RR, et al. Risk factors associated with the transmission of carbapenem-resistant Enterobacteriaceae via contaminated duodenoscopes. Gastrointest Endosc. 2016;83(6):1121–9.

716. Lee CH, Chu FY, Hsieh CC, Hong MY, Chi CH, Ko WC, et al. A simple scoring algorithm predicting extendedspectrum b-lactamase producers in adults with community-onset monomicrobial Enterobacteriaceae bacteremia. Med (United States). 2017;96(16).

717. Li L, Chen Z, Guo D, Li S, Huang J, Wang X, et al. Nasal carriage of methicillin-resistant coagulase-negative staphylococci in healthy humans is associated with occupational pig contact in a dose-response manner. Vet Microbiol [Internet]. 2017;208(August):231–8. Available from: http://dx.doi.org/10.1016/j.vetmic.2017.08.012

718. Li Z, Wu X, Yu J, Wu X, Du Z, Sun Y, et al. Empirical Combination Antibiotic Therapy Improves the Outcome of Nosocomial Meningitis or Ventriculitis in Neuro-Critical Care Unit Patients. Surg Infect (Larchmt) [Internet]. 2016;17(4):465–72. Available from: http://online.liebertpub.com/doi/10.1089/sur.2015.060

719. Lin D, Ou Q, Lin J, Peng Y, Yao Z. A meta-analysis of the rates of Staphylococcus aureus and methicillin-resistant S aureus contamination on the surfaces of environmental objects that health care workers frequently touch. Am J Infect Control [Internet]. 2017;45(4):421–9. Available from: http://dx.doi.org/10.1016/j.ajic.2016.11.004

720. Liu P, Li X, Luo M, Xu X, Su K, Chen S, et al. Risk Factors for Carbapenem-Resistant Klebsiella pneumoniae Infection: A Meta-Analysis. Microb Drug Resist [Internet]. 2017 Jul 27; Available from: http://www.ncbi.nlm.nih.gov/pubmed/28749714

721. Masse J, Elkalioubie A, Blazejewski C, Ledoux G, Wallet F, Poissy J, et al. Colonization pressure as a risk factor of ICU-acquired multidrug resistant bacteria: a prospective observational study. Eur J Clin Microbiol Infect Dis. 2017;36(5):797–805.

722. McKinnell JA, Kunz DF, Moser SA, Vangala S, Tseng CH, Shapiro M, et al. Patient-level analysis of incident vancomycin-resistant enterococci colonization and antibiotic days of therapy. Epidemiol Infect. 2016;144(8):1748–55.

723. Metersky ML, Frei CR, Mortensen EM. Predictors of Pseudomonas and methicillin-resistant Staphylococcus aureus in hospitalized patients with healthcare-associated pneumonia. Respirology. 2016;21(1):157–63.

724. Moghnieh R, Siblani L, Ghadban D, El Mchad H, Zeineddine R, Abdallah D, et al. Extensively drug-resistant Acinetobacter baumannii in a Lebanese intensive care unit: Risk factors for acquisition and determination of a colonization score. J Hosp Infect [Internet]. 2016;92(1):47–53. Available from: http://dx.doi.org/10.1016/j.jhin.2015.10.007

725. Munier AL, Biard L, Rousseau C, Legrand M, Lafaurie M, Lomont A, et al. Incidence, risk factors, and outcome of multidrug-resistant Acinetobacter baumannii acquisition during an

outbreak in a burns unit. J Hosp Infect [Internet]. 2017;97(3):226–33. Available from: https://doi.org/10.1016/j.jhin.2017.07.020

726. (NARMS) NARMS. NARMS integrated report [Internet]. 2015. Available from: https://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/ucm059103.htm

727. Nour I, Eldegla HE, Nasef N, Shouman B, Abdel-Hady H, Shabaan AE. Risk factors and clinical outcomes for carbapenem-resistant Gram-negative late-onset sepsis in a neonatal intensive care unit. J Hosp Infect [Internet]. 2017;97(1):52–8. Available from: http://dx.doi.org/10.1016/j.jhin.2017.05.025

728. Osimani A, Cardinali F, Aquilanti L, Garofalo C, Roncolini A, Milanović V, et al. Occurrence of transferable antibiotic resistances in commercialized ready-to-eat mealworms (Tenebrio molitor L.). Int J Food Microbiol. 2017;263(September):38–46.

729. Osińska A, Korzeniewska E, Harnisz M, Niestępski S. The prevalence and characterization of antibiotic-resistant and virulent Escherichia coli strains in the municipal wastewater system and their environmental fate. Sci Total Environ. 2017;577:367–75.

730. Ou Q, Peng Y, Lin D, Bai C, Zhang T, Lin J, et al. A Meta-Analysis of the Global Prevalence Rates of Staphylococcus aureus and Methicillin-Resistant S. aureus Contamination of Different Raw Meat Products. J Food Prot [Internet]. 2017 Mar 30;763–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28358261

731. Ou Q, Zhou J, Lin D, Bai C, Zhang T, Lin J, et al. A large meta-analysis of the global prevalence rates of S. aureus and MRSA contamination of milk. Crit Rev Food Sci Nutr [Internet]. 2017 Jul 7;1–16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28686461

732. Ozsurekci Y, Aykac K, Cengiz AB, Basaranoglu ST, Sancak B, Karahan S, et al. Bloodstream infections in children caused by carbapenem-resistant versus carbapenem-susceptible gram-negative microorganisms: Risk factors and outcome. Diagn Microbiol Infect Dis. 2017;87(4):359–64.

733. Papadimitriou-Olivgeris M, Fligou F, Spiliopoulou A, Koutsileou K, Kolonitsiou F, Spyropoulou A, et al. Risk factors and predictors of carbapenem-resistant pseudomonas aeruginosa and acinetobacter baumannii mortality in critically ill bacteraemic patients over a 6-year period (2010–15): Antibiotics do matter. J Med Microbiol. 2017;66(8):1092–101.

734. Park GE, Kang CI, Cha MK, Cho SY, Seok H, Lee JH, et al. Bloodstream infections caused by Acinetobacter species with reduced susceptibility to tigecycline: clinical features and risk factors. Int J Infect Dis [Internet]. 2017;62:26–31. Available from: http://dx.doi.org/10.1016/j.ijid.2017.06.023

735. Patchanee P, Tansiricharoenkul K, Buawiratlert T, Wiratsudakul A, Angchokchatchawal K, Yamsakul P, et al. Salmonella in pork retail outlets and dissemination of its pulsotypes through pig production chain in Chiang Mai and surrounding areas, Thailand. Prev Vet Med [Internet]. 2016;130:99–105. Available from: http://dx.doi.org/10.1016/j.prevetmed.2016.06.013

736. Patriarca F, Cigana C, Massimo D, Lazzarotto D, Geromin A, Isola M, et al. Risk Factors and Outcomes of Infections by Multidrug-Resistant Gram-Negative Bacteria in Patients Undergoing Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant [Internet]. 2017;23(2):333–9. Available from: http://dx.doi.org/10.1016/j.bbmt.2016.11.005

737. Pérez Heras I, Sanchez-Gomez JC, Beneyto-Martin P, Ruano-de-Pablo L, Losada-Pinedo B. Community-onset extended-spectrum β-lactamase producing Escherichia coli in urinary tract

infections in children from 2015 to 2016. Medicine (Baltimore) [Internet]. 2017;96(50):e8571. Available from: http://insights.ovid.com/crossref?an=00005792-201712150-00007

738. Pfeffer I, Zemel M, Kariv Y, Mishali H, Adler A, Braun T, et al. Prevalence and risk factors for carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae among patients prior to bowel surgery. Diagn Microbiol Infect Dis [Internet]. 2016;85(3):377–80. Available from: http://dx.doi.org/10.1016/j.diagmicrobio.2016.04.002

739. Pierri MD, Crescenzi G, Capestro F, Recanatini C, Manso E, D'Errico MM, et al. Risk Factors and Impact on Clinical Outcome of Multidrug-Resistant Acinetobacter Baumannii Acquisition in Cardiac Surgery Patients. J Cardiothorac Vasc Anesth [Internet]. 2016;30(3):680–6. Available from: http://dx.doi.org/10.1053/j.jvca.2015.08.024

740. Poole K, George R, Decraene V, Shankar K, Cawthorne J, Savage N, et al. Active case finding for carbapenemase-producing Enterobacteriaceae in a teaching hospital: prevalence and risk factors for colonization. J Hosp Infect [Internet]. 2016;94(2):125–9. Available from: http://dx.doi.org/10.1016/j.jhin.2016.06.019

741. Proia L, Von Schiller D, Sànchez-Melsió A, Sabater S, Borrego CM, Rodríguez-Mozaz S, et al. Occurrence and persistence of antibiotic resistance genes in river biofilms after wastewater inputs in small rivers. Environ Pollut. 2016;210:121–8.

742. Righi E, Peri AM, Harris PNA, Wailan AM, Liborio M, Lane SW, et al. Global prevalence of carbapenem resistance in neutropenic patients and association with mortality and carbapenem use: systematic review and meta-analysis. J Antimicrob Chemother [Internet]. 2016;(March):dkw459. Available from: https://academic.oup.com/jac/article-lookup/doi/10.1093/jac/dkw459

743. Salgado CD, Farr BM, Calfee DP. Community-acquired methicillin-resistant Staphylococcus aureus: a meta-analysis of prevalence and risk factors. Clin Infect Dis. 2003;36(2):131–9.

744. Salomão MC, Guimarães T, Duailibi DF, Perondi MBM, Letaif LSH, Montal AC, et al. Carbapenem-resistant Enterobacteriaceae in patients admitted to the emergency department: prevalence, risk factors, and acquisition rate. J Hosp Infect. 2017;97(3):241–6.

745. Satlin MJ, Cohen N, Ma KC, Chen L, Kreiswirth BN, Walsh TJ, et al. Bacteremia due to carbapenem-resistant Enterobacteriaceae in neutropenic patients with hematologic malignancies. J Infect. 2016;73(4):336–45.

746. Satwani P, Freedman JL, Chaudhury S, Jin Z, Levinson A, Foca MD, et al. A Multicenter Study of Bacterial Blood Stream Infections in Pediatric Allogeneic Hematopoietic Cell Transplantation Recipients: The Role of Acute Gastrointestinal Graft-versus-Host Disease. Biol Blood Marrow Transplant [Internet]. 2017;23(4):642–7. Available from: http://dx.doi.org/10.1016/j.bbmt.2017.01.073

747. Schill F, Abdulmawjood A, Klein G, Reich F. Prevalence and characterization of extended-spectrum β-lactamase (ESBL) and AmpC β-lactamase producing Enterobacteriaceae in fresh pork meat at processing level in Germany. Int J Food Microbiol [Internet]. 2017;257(January):58–66. Available from: http://dx.doi.org/10.1016/j.ijfoodmicro.2017.06.010

748. Singh G, Vajpayee P, Rani N, Amoah ID, Stenström TA, Shanker R. Exploring the potential reservoirs of non specific TEM beta lactamase (blaTEM) gene in the Indo-Gangetic region: A risk assessment approach to predict health hazards. J Hazard Mater [Internet]. 2016;314:121–8. Available from: http://dx.doi.org/10.1016/j.jhazmat.2016.04.036

749. Strysko JP, Mony V, Cleveland J, Siddiqui H, Homel P, Gagliardo C. International travel is a risk factor for extended-spectrum β-lactamase-producing Enterobacteriaceae acquisition in children: A case-case-control study in an urban U.S. hospital. Travel Med Infect Dis [Internet]. 2016;14(6):568–71. Available from: http://dx.doi.org/10.1016/j.tmaid.2016.11.012

750. Tacconelli E, De angelis G, Cataldo MA, Pozzi E, Cauda R. Does antibiotic exposure increase the risk of methicillin-resistant Staphylococcus aureus (MRSA) isolation? A systematic review and meta-analysis. J Antimicrob Chemother. 2008;61(1):26–38.

751. Tadesse G. A meta-analysis of the proportion of animal Salmonella isolates resistant to drugs used against human salmonellosis in Ethiopia. BMC Infect Dis [Internet]. 2015 Dec 21 [cited 2018 Feb 22];15(1):84. Available from: http://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-015-0835-x

752. Tebano G, Geneve C, Tanaka S, Grall N, Atchade E, Augustin P, et al. Epidemiology and risk factors of multidrug-resistant bacteria in respiratory samples after lung transplantation. Transpl Infect Dis. 2016;18(1):22–30.

753. Thatrimontrichai A, Techato C, Dissaneevate S, Janjindamai W, Maneenil G, Kritsaneepaiboon S, et al. Risk factors and outcomes of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia in the neonate: A case-case-control study. J Infect Chemother [Internet]. 2016;22(7):444–9. Available from: http://dx.doi.org/10.1016/j.jiac.2016.03.013

754. Trinh TD, Zasowski EJ, Claeys KC, Lagnf AM, Kidambi S, Davis SL, et al. Multidrug-resistant Pseudomonas aeruginosa lower respiratory tract infections in the intensive care unit: Prevalence and risk factors. Diagn Microbiol Infect Dis [Internet]. 2017;89(1):61–6. Available from: http://dx.doi.org/10.1016/j.diagmicrobio.2017.06.009

755. Wang Q, Zhang Y, Yao X, Xian H, Liu Y, Li H, et al. Risk factors and clinical outcomes for carbapenem-resistant Enterobacteriaceae nosocomial infections. Eur J Clin Microbiol Infect Dis. 2016;35(10):1679–89.

756. Washam M, Woltmann J, Haberman B, Haslam D, Staat MA. Risk factors for methicillin-resistant Staphylococcus aureus colonization in the neonatal intensive care unit: A systematic review and meta-analysis. Am J Infect Control [Internet]. 2017 Dec [cited 2018 Feb 22];45(12):1388–93. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0196655317308398

757. Wielders CCH, van Hoek AHAM, Hengeveld PD, Veenman C, Dierikx CM, Zomer TP, et al. Extended-spectrum β-lactamase- and pAmpC-producing Enterobacteriaceae among the general population in a livestock-dense area. Clin Microbiol Infect [Internet]. 2017;23(2):120.e1-120.e8. Available from: http://dx.doi.org/10.1016/j.cmi.2016.10.013

758. Williamson DA, Lane CR, Easton M, Valcanis M, Strachan J, Veitch MG, et al. Increasing antimicrobial resistance in nontyphoidal salmonella isolates in Australia from 1979 to 2015. Antimicrob Agents Chemother. 2018;62(2):1–9.

759. Wilmore SMS, Kranzer K, Williams A, Makamure B, Nhidza AF, Mayini J, et al. Carriage of extended-spectrum beta-lactamase-producing enterobacteriaceae in HIV-infected children in Zimbabwe. J Med Microbiol. 2017;66(5):609–15.

760. Xu L, Ouyang W, Qian Y, Su C, Su J, Chen H. High-throughput profiling of antibiotic resistance genes in drinking water treatment plants and distribution systems. Environ Pollut [Internet]. 2016;213:119–26. Available from: http://dx.doi.org/10.1016/j.envpol.2016.02.013

761. Zhang Q, Zhang W, Li Z, Bai C, Li D, Zheng S, et al. Bacteraemia due to AmpC β-lactamase-producing Escherichia coli in hospitalized cancer patients: risk factors, antibiotic therapy, and outcomes. Diagn Microbiol Infect Dis [Internet]. 2017;88(3):247–51. Available from: http://dx.doi.org/10.1016/j.diagmicrobio.2017.04.006

762. Zhao SY, Zhang J, Zhang YL, Wang YC, Xiao SZ, Gu FF, et al. Epidemiology and risk factors for faecal extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) carriage derived from residents of seven nursing homes in western Shanghai, China. Epidemiol Infect. 2016;144(4):695–702.

763. Ziakas PD, Thapa R, Rice LB, Mylonakis E. Trends and significance of VRE colonization in the ICU: a meta-analysis of published studies. PLoS One. 2013;8(9):e75658.

764. Ziakas PD, Anagnostou T, Mylonakis E. The prevalence and significance of methicillin-resistant staphylococcus aureus colonization at admission in the general ICU setting: A meta-analysis of published studies. Crit Care Med. 2014;42(2):433–44.

765. Ziakas PD, Pliakos EE, Zervou FN, Knoll BM, Rice LB, Mylonakis E. MRSA and VRE colonization in solid organ transplantation: a meta-analysis of published studies. Am J Transplant. 2014 Aug;14(8):1887–94.

766. Elouafkaoui P, Young L, Newlands R, Duncan EM, Elders A, Clarkson JE, et al. An Audit and Feedback Intervention for Reducing Antibiotic Prescribing in General Dental Practice: The RAPiD Cluster Randomised Controlled Trial. PLoS Med. 2016;13(8):1–19.

767. Tang YQ, Liu CX, Zhang XP. Performance associated effect variations of public reporting in promoting antibiotic prescribing practice: a cluster randomized-controlled trial in primary healthcare settings. Prim Heal Care Res Dev. 2017;18(May 2017):482–91.

768. Spoorenberg V, Hulscher MEJL, Geskus RB, de Reijke TM, Opmeer BC, Prins JM, et al. A Cluster-Randomized Trial of Two Strategies to Improve Antibiotic Use for Patients with a Complicated Urinary Tract Infection. PLoS One [Internet]. 2015;10(12):e0142672. Available from: http://dx.plos.org/10.1371/journal.pone.0142672

769. Naughton C, Feely J, Bennett K. A RCT evaluating the effectiveness and cost-effectiveness of academic detailing versus postal prescribing feedback in changing GP antibiotic prescribing. J Eval Clin Pract. 2009;15(5):807–12.

770. Moore M, Little P, Rumsby K, Kelly J, Watson L, Warner G, et al. Effect of antibiotic prescribing strategies and an information leaflet on longer-term reconsultation for acute lower respiratory tract infection. Br J Gen Pract. 2009;59(567):728–34.

771. Worrall GJ, Kettle A, Graham W, Hutchinson J. Postdated versus usual delayed antibiotic prescriptions in primary care: Reduction in antibiotic use for acute respiratory infections? Can Fam Physician. 2010;56(10):1032–6.

772. Gulliford MC, van ST, Dregan A, McDermott L, McCann G, Ashworth M, et al. Electronic health records for intervention research: a cluster randomized trial to reduce antibiotic prescribing in primary care (eCRT study). Ann Fam Med [Internet]. 2014;12(4):344–51. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=25024243

773. Gonzales R, Anderer T, Mcculloch CE, Maselli JH, Jr FJB, Graf TR, et al. A Cluster-Randomized Trial of Decision Support Strategies for Reducing Antibiotic Use for Acute Bronchitis. 2013;173(4):267–73.

774. Bourgeois FC, Linder J, Johnson SA, Co JPT, Fiskio J, Ferris TG. Impact of a computerized

template on antibiotic prescribing for acute respiratory infections in children and adolescents. Clin Pediatr (Phila). 2010;49(10):976–83.

775. Meeker D, Knight TK, Friedberg MW, Linder JA, Goldstein NJ, Fox CR, et al. Nudging guideline-concordant antibiotic prescribing: a randomized clinical trial. JAMA Intern Med [Internet]. 2014 Mar;174(3):425–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24474434

776. Le Corvoisier P, Renard V, Roudot-Thoraval F, Cazalens T, Veerabudun K, Canoui-Poitrine F, et al. Long-term effects of an educational seminar on antibiotic prescribing by GPs: A randomised controlled trial. Br J Gen Pract. 2013;63(612):455–64.

777. Yip W, Powell-Jackson T, Chen W, Hu M, Fe E, Hu M, et al. Capitation Combined With Pay-For-Performance Improves Antibiotic Prescribing Practices In Rural China. Https://DoiOrg/101377/Hlthaff20130702 [Internet]. 2014; Available from: https://www.healthaffairs.org/doi/10.1377/hlthaff.2013.0702

778. van Daalen F V., Prins JM, Opmeer BC, Boermeester MA, Visser CE, van Hest RM, et al. Effect of an antibiotic checklist on length of hospital stay and appropriate antibiotic use in adult patients treated with intravenous antibiotics: a stepped wedge cluster randomized trial. Clin Microbiol Infect [Internet]. 2017;23(7):485.e1-485.e8. Available from: http://dx.doi.org/10.1016/j.cmi.2017.01.019

779. Drozdov D, Schwarz S, Kutz A, Grolimund E, Rast AC, Steiner D, et al. Procalcitonin and pyuria-based algorithm reduces antibiotic use in urinary tract infections: A randomized controlled trial. BMC Med [Internet]. 2015;13(1):1–13. Available from: ???

780. Lemiengre MB, Verbakel JY, Colman R, Burghgraeve T De, Buntinx F. Reducing inappropriate antibiotic prescribing for children in primary care : a cluster randomised controlled trial of two interventions. 2018;(March):1–7.

781. Cairns KA, Doyle JS, Trevillyan JM, Horne K, Stuart RL, Bushett N, et al. The impact of a multidisciplinary antimicrobial stewardship team on the timeliness of antimicrobial therapy in patients with positive blood cultures: A randomized controlled trial. J Antimicrob Chemother. 2016;71(11):3276–83.

782. Hemkens LG, Saccilotto R, Reyes SL, Glinz D, Zumbrunn T, Grolimund O, et al. Personalized prescription feedback using routinely collected data to reduce antibiotic use in primary care a randomized clinical trial. JAMA Intern Med. 2017;177(2):176–83.

783. Wei X, Zhang Z, Walley JD, Hicks JP, Zeng J, Deng S, et al. Effect of a training and educational intervention for physicians and caregivers on antibiotic prescribing for upper respiratory tract infections in children at primary care facilities in rural China: a cluster-randomised controlled trial. Lancet Glob Heal [Internet]. 2017;5(12):e1258–67. Available from: http://dx.doi.org/10.1016/S2214-109X(17)30383-2

784. Shen X, Lu M, Feng R, Cheng J, Chai J, Xie M, et al. Web-Based Just-in-Time Information and Feedback on Antibiotic Use for Village Doctors in Rural Anhui, China: Randomized Controlled Trial. J Med Internet Res [Internet]. 2018 Feb 14;20(2):e53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29444768

785. Høye S, Gjelstad S, Lindbæk M. Effects on antibiotic dispensing rates of interventions to promote delayed prescribing for respiratory tract infections in primary care. Br J Gen Pract [Internet]. 2013 Nov;63(616):e777-86. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24267861

786. Nuffield Trust. Mean length of stay in UK hospitals [Internet]. 2014 [cited 2019 Jun 1].

Available from: https://www.nuffieldtrust.org.uk/chart/mean-length-of-stay-in-uk-hospitals

787. Eurostat. Hospital discharges and length of stay statistics [Internet]. 2016 [cited 2019 Jun 1]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php/Hospital_discharges_and_length_of_stay_statistics

788. Raum E, Lietzau S, von Baum H, Marre R, Brenner H. Changes in Escherichia coli resistance patterns during and after antibiotic therapy: a longitudinal study among outpatients in Germany. Clin Microbiol Infect [Internet]. 2008 Jan;14(1):41–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18005177

789. Juan C, Gutiérrez O, Oliver A, Ayestarán JI, Borrell N, Pérez JL. Contribution of clonal dissemination and selection of mutants during therapy to Pseudomonas aeruginosa antimicrobial resistance in an intensive care unit setting. Clin Microbiol Infect [Internet]. 2005 Nov;11(11):887–92. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1198743X14626033

790. Jørgensen SB, Søraas A, Sundsfjord A, Liestøl K, Leegaard TM, Jenum PA. Fecal carriage of extended spectrum β-lactamase producing Escherichia coli and Klebsiella pneumoniae after urinary tract infection – A three year prospective cohort study. Chalumeau M, editor. PLoS One [Internet]. 2017 Mar 7;12(3):e0173510. Available from: https://dx.plos.org/10.1371/journal.pone.0173510

791. Boldt A-C, Schwab F, Rohde AM, Kola A, Bui MT, Märtin N, et al. Admission prevalence of colonization with third-generation cephalosporin-resistant Enterobacteriaceae and subsequent infection rates in a German university hospital. Chaturvedi V, editor. PLoS One [Internet]. 2018 Aug 1;13(8):e0201548. Available from: https://dx.plos.org/10.1371/journal.pone.0201548

792. Abernethy JK, Johnson AP, Guy R, Hinton N, Sheridan EA, Hope RJ. Thirty day all-cause mortality in patients with Escherichia coli bacteraemia in England. Clin Microbiol Infect [Internet]. 2015 Mar;21(3):251.e1-251.e8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1198743X15001731

APPENDICES

List of tables in the appendices

Appendix I. Appendix for Chapter 2

Appendix Table 1: PRISMA Statement

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Publication Stated within Section 2.1.1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Publication Stated within Section 2.1.1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Section 1.2.2.2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Appendix Table 2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Yes, PROSPERO (CRD42016038450).
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Appendix Table 3 and 2.1.2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Section 2.2.3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix I
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Section 2.2.4

Section/topic	#	Checklist item	Reported on page #
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Section 2.2.4, 2.2.6, and Appendix Table 3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendix Table 2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Section 2.2.5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Section 2.2.6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Section 2.2.6

Source: http://www.prisma-statement.org/ (accessed: 01/06/2019)

Appendix Table 2: PICOS Criteria*

PICOS	INCLUSION CRITERIA	EXCLUSION CRITERIA
Population	Human/Animal/Environment Colonised by/ infected by/treated for: • Resistant Gram negative/Gram positive pathogen • Pathogens resistant/non-susceptible to antibiotics • Health care associated infections (HCAI) resistant to any line of antibiotic treatment (e.g. first/2nd up to 3rd line) • Multi-drug resistant bacteria/Bacterium containing resistant gene causing infections Antimicrobial resistance in bacteria sampled from any body-site ((86) inclusion criteria)	Health care associated infections (HCAI) susceptible to antibiotics Drug resistance related to mycobacteria or related infections (e.g. TB, MDR-RB) Fungal infections or resistant fungal infections Viral infections or resistant viral infections Pathogens not resistant to antibiotics
Intervention	N/A	N/A
Comparator	N/A	N/A
Outcomes	1. Studies reporting or investigating quantifying data related to: • Transmission of resistant bacteria/resistant infections from animal to human, human to human or environment to human • Emergence of antibiotic resistant infection or antibiotic resistant bacteria colonisation in humans from human/animal/environmental sources • Transmission/emergence rates • Risk factors associated with colonization/carriage/transmission/emergence of resistant pathogens/resistant bacteria from other reservoirs into human reservoir 2. Studies reporting primary data Prevalence of resistant bacteria/bacterial infections in cooked meat/food/drinking water directly being consumed by humans 3. Results from health economic models	1. Studies do not measure / quantify either: • Transmission of resistant gene/bacteria from animal to human or human to human or environment to human NOR • Emergence of antibiotic resistant gene or antibiotic resistant bacteria colonization in humans from human/animal/environmental sources • Risk factors not associated with resistant pathogens/resistant bacteria • Risk factors not quantified 2. Studies measuring fitness cost of individual genes/mutated genes 3. Secondary data from previously published articles 4. Studies quantifying change in emergence/transmission rates of resistant genes/pathogens other than in humans 5. Prevalence of resistant bacteria/bacterial infections in animal farms/food or water not directly being consumed by humans. 6. Prevalence in companion animals without assessing the correlation of transmission/emergence in humans 7. Studies reporting on specific genetic determinants of resistant bacteria/infection

	4. Studies quantifying change (increase/decrease) and associated risk factors for the change in emergence/transmission rates of resistant genes/pathogens in humans only	transmission/acquisition without also reporting reasons due to human actions which is accelerating the process 8.Studies reporting only p-values/significance levels without actual estimates or studies reporting estimates without a measure or test of statistical significance
Study design	Observational studies: Cross sectional / Longitudinal / Case-controlled / Cohort Experimental studies Epidemiological studies Meta-analyses	Qualitative studies without quantifiable primary data Critical Appraisals without primary data Expert opinions without primary data Systematic Reviews/Reviews Health economic models
Publication type	Full text (peer reviewed) English Language ECDC/CDC reports with country level data	Abstracts / Conference abstracts Comments Notes Correspondence Letter Editorial Book Book Chapters Not English
Limitation	2005 onwards Antibiotic use quantified as risk factor in humans 2010 onwards	Published prior to 2005 Papers relating to antibiotic use in humans published before 2010 ((51) review)

* Study authors were not contacted for further information and no articles were translated from a different language.

I. SEARCH STRINGS OVID (FIRST CONDUCTED 01/03/2016)* (UPDATED ON 14/02/2018)

1. Microbial-drug-resistan$.tw.

2. ((microb$ or antimicrob$ or anti-microb$ or anti microb$) adj2 resist$).tw.

3. ((antibiot$ or anti-biot$ or anti biot$) adj2 resist$).tw.

4. Multidrug resistan$.tw. or multidrug-resistant bacteria.ti,ab.

5. exp Drug Resistance, Microbial/

6. (superbug$ or super-bug$ or super bug$).tw. or Superinfection/ or (resistant adj2 infection$).ti,ab.

7. 1 or 2 or 3 or 4 or 5 or 6

8. (emergence or spread or outbreak* or prevalence or incidence or acquisition).tw.

9. exp cross infection/

10. exp infectious disease transmission, patient-to-professional/

11. exp infection control/

12. (patient-to-patient adj2 transmission).tw.

13. exp infectious disease transmission, professional-to-patient/

14. exp disease transmission, infectious/

15. infectious disease transmission.tw.

16. disease transmission.tw. or ((transfer or transmission) adj2 resist$).ti,ab.

17. contamination.tw.

18. ((bacterial pathogen* and coloni$) or Coloni?ation).tw.

19. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. ((cause or drive or driving or driver or predictor or determinant or determinants or mechanism) adj4 resist$).ti,ab. or exp risk factor/ or risk factor.ti,ab. or risk score.tw. or infection reduction.tw. or infection risk.tw. or risk assessment.tw. or risk benefit analysis.tw. or (antibiotic adj2 (use$ or usage or consum$ or prescri$)).tw. or (food chain or (water and (supply or quality)) or animal husbandry or food producing animal or food-producing animal).tw. or (poor adj2 hygiene).tw. or (poor and (infection control or infection-control)).tw.

21. (resist$ adj2 develop$).tw.

22. 19 or 21

23. 7 and 22

24. 23 and 20

25. (risk ratio or relative risk or odds ratio or hazard ratio or statistical correlation or correlation coefficient or statistical analysis or multivariable analysis or regression).tw. or epidemiology studies.ti,ab. or exp odds ratio/ or exp epidemiologic studies/ or exp Statistics as Topic/ or exp Epidemiologic Study Characteristics as Topic/ or estimat$.tw. or quantif$.tw.

26. 24 and 25

27. limit 26 to english language

28. limit 27 to yr="2005 -Current"

29. limit 28 to full text

30. limit 29 to (book or book series or chapter or conference abstract or editorial or erratum or letter or note)

31. 29 not 30

32. remove duplicates from 31

33. (letter or comment or book or note or editorial).pt.

34. 32 not 33

*A Medical librarian was consulted to guide with the search terms

II. SEARCH STRINGS FOR META-ANALYSIS SEARCH IN PUBMED

Using the drug-bug combinations from the WHO priority pathogens list for R&D of new antibiotics to guide the search terms

Priority 1: CRITICAL

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae, carbapenem-resistant, ESBL-producing

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin-intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter spp., fluoroquinolone-resistant

Salmonellae, fluoroquinolone-resistant

Neisseria gonorrhoeae, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

Shigella spp., fluoroquinolone-resistant

Search strings:

((((((((((((Acinetobacter[Title/Abstract]) AND resistan*[Title/Abstract]) AND risk[Title/Abstract]) AND meta[Title/Abstract]))

OR

((((Pseudomonas[Title/Abstract]) AND resistan*[Title/Abstract]) AND risk[Title/Abstract]) AND meta[Title/Abstract])) OR

((((((Enterobacteriaceae[Title/Abstract] OR ESBL[Title/Abstract] OR extended spectrum[Title/Abstract] OR lactum[Title/Abstract] OR carbapenem[Title/Abstract])) AND resistan*[Title/Abstract]) AND risk[Title/Abstract]) AND meta[Title/Abstract])))

OR

(((((Enterococcus[Title/Abstract] OR faecium[Title/Abstract] OR vancomycin[Title/Abstract])) AND resistan*[Title/Abstract]) AND risk[Title/Abstract]) AND meta[Title/Abstract]))

OR

(((((Staphylococcus[Title/Abstract] OR methicillin[Title/Abstract] OR methicilin[Title/Abstract])) AND resistan*[Title/Abstract]) AND risk[Title/Abstract]) AND meta[Title/Abstract])) OR

(((((Helicobacter[Title/Abstract] OR clarithromycin[Title/Abstract])) AND resistan*[Title/Abstract]) AND risk[Title/Abstract]) AND meta[Title/Abstract]))

OR

(((((Campylobacter[Title/Abstract] OR fluoroquinolone[Title/Abstract])) AND resistan*[Title/Abstract]) AND risk[Title/Abstract]) AND meta[Title/Abstract]))

OR

((((Salmonel*[Title/Abstract]) AND resistan*[Title/Abstract]) AND risk[Title/Abstract]) AND meta[Title/Abstract]))

OR

(((((((Neisseria[Title/Abstract] OR gonorrh*[Title/Abstract] OR cephalosporin[Title/Abstract])) AND resistan*[Title/Abstract]) AND risk[Title/Abstract]) AND meta[Title/Abstract])))) OR

(((((((Streptoc*[Title/Abstract] OR penicillin[Title/Abstract])) AND resistan*[Title/Abstract]) AND risk*[Title/Abstract]) AND meta[Title/Abstract])))) OR

(((((Haemophilus[Title/Abstract] OR influenzae[Title/Abstract] OR ampicillin[Title/Abstract])) AND resistan*[Title/Abstract]) AND risk[Title/Abstract]) AND meta[Title/Abstract])

OR

((((prevalence[Title/Abstract]) AND antibiotic[Title/Abstract]) AND resistan*[Title/Abstract]) AND (meta-analysis[Title/Abstract] OR meta-analyses[Title/Abstract] OR meta analyses[Title/Abstract] OR meta analysis[Title/Abstract]))

OR

((((Escherichia coli[Title/Abstract] OR E.coli[Title/Abstract] OR E.Coli[Title/Abstract])) AND resistan*[Title/Abstract]) AND (risk[Title/Abstract] OR prevalence[Title/Abstract])) AND (meta-analysis[Title/Abstract] OR meta-analyses[Title/Abstract] OR meta analysis[Title/Abstract] OR meta-analyses[Title/Abstract])

OR

((((klebsiella[Title/Abstract]) AND resistan*[Title/Abstract]) AND (risk[Title/Abstract] OR prevalence[Title/Abstract])) AND (meta-analysis[Title/Abstract] OR meta-analyses[Title/Abstract] OR meta analysis[Title/Abstract] OR meta analyses[Title/Abstract]))

Appendix Table 3: Extracted studies

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 1965	Costelloe C. / 2010(86)	International	Mixed	Emergence	• UTI (5 studies: 14 348 participants) • RTI (7 studies: 2605 participants)	M	OR	R-B	3	Hospital / Community (Primary care focus)	Human	0.93
SC0038	Bell B.G. / 2014(51)	International	Mixed	Emergence	• NR	M	OR	R-B	3	Community	Human	0.85
OVID 2067	Abdel-Hady H. / 2008(225)	Egypt	Children	Infection	• All KP isolates • (n = 27) • ESBL-KP isolates • (n = 18) • No ESBL- KP (n=362)	C	OR	ESBL-KP	3,13,24,36,48,51	Hospital	Human	0.67
OVID 0197	Abebe W / 2014(226)	Ethiopia	Adult	Colonisation	• All (n = 226) • Negative (n = 113) • Positive (n = 113)	C (CS)	OR	VR-ENTO	3	Hospital / Community	Human	0.67
OVID 1733	Achermann Y. / 2013(227)	Switzerland	Adult	Emergence	• Cases (n = 48) • Controls (n = 48)	CC	OR	RI-R-SA	3,12,39,42	Hospital	Human	0.71
OVID 0807	Agudo S. / 2010(228)	Spain	Mixed	Colonisation (Isolation)	• Total (n = 117) • CL-S (n = 75)	C	PC	CL-R-HP	11,43,50	Hospital	Human	0.33

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• CL-R (n = 34) • Discrepant (n = 8)							
OVID 1641	Ahn J.Y. / 2014(229)	South Korea	Adult	Acquisition	• CR group (n = 57) • Control group (n = 114)	CC	OR	CR-EC	3	Hospital / Community	Human	0.86
OVID 1525	Akinci E. / 2005(230)	Turkey	Adult	Acquisition (ICU)	• IR (n = 42) • IS (n = 86)	CC	OR	IR-GN	3,12,34	Hospital	Human	0.86
OVID 0680	Akinyemi K.O. / 2011(231)	Nigeria	NA	Transmission	200 samples (60 well water, 60 pipe-borne water and 80 different brands of sachet water)	C	P	R-Sal	6	Community	Human/Environment	0.50
OVID 0888	Alali W.Q. / 2009(112)	United States	Adult	Transmission	• 39,000 male individuals across 19 unit locations. • 26,000 to 28,000 pigs across 12 units. • Total sample: (n = 7,477) (4,048 human and 3,429 swine) commensal *E. coli* isolates from wastewater and faecal matter samples	C	OR	R-EC	8	Community	Human/Animal	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 0762	Alali W.Q. / 2010(232)	United States	NA	Acquisition	EC isolates (human and swine samples) (n = 6,541)	C	PC	R-EC ; MDR-EC	8	Community	Human/Animal	0.83
OVID 0419	Al-Assil B. / 2013(233)	Syria	Mixed	Infection	UTI patients (n = 104)	C (CS)	OR	ESBL-EC	1,3,13	Hospital / Community	Human	0.67
OVID 2191	Albright J.B. / 2007(234)	United States	Adult	Infection	• MRSA-Positive (n = 24) • MRSA-Negative (n = 45)	CC	PC	MRSA	43,96	Hospital	Human	0.57
OVID 0524	Aldeyab M.A. / 2012(235)	Northern Ireland	NR	Emergence (incidence)	• ESBL-B cases (Hospital) • (n = 244) • ESBL-B community cases were (Trust) • (n = 965)	C (T)	CRC	ESBL-B	2,3,61	Hospital / Community	Human	0.67
OVID 0079	Almeida N. / 2014(236)	Portugal	Adult	Acquisition	• 180 patients (group I+II); • CL-R (n = 90); CL=S (n = 90) • MT-R (n = 62); MT-S (n = 118) • LR (n = 61); LS • (n = 119)	C	OR	CL-R-HP/MT-R-HP/LR-HP	CL-R-HP: 3,54 ; MT-R-HP: 54; LR-HP: 7,26,31	Hospital	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 0067	Almeida S.T. / 2015(237)	Portugal	Adult	Carriage	• Total screened (n = 3,361) • MRSA (n = 62)	C (CS)	OR	MRSA	1,9	Hospital / Community	Human	0.50
OVID 2185	Al-Nammari S.S. / 2007(238)	United Kingdom	Adult	Infection	• MRSA (n = 15) • MSSA septic arthritis (n = 43)	CC	PC	MRSA	2,11,33.1,75	Hospital	Human	0.29
OVID 0064	Alsan M. / 2015(239)	Worldwide: 47 countries (23 in Africa, eight in the Americas, three in Europe, eight in the Middle East, three in southeast Asia, and two in thewestern Pacific).	Mixed	Emergence	NA/47 countries	C	OR	R-B	64	Hospital / Community	Human	0.17
OVID 1914	Altoparlak U. / 2011(240)	Turkey	Adult	Colonisation	• VR-ENTO (n = 28) • VS-ENTO (n = 70)	CC	OR	VR-ENTO	91	Hospital	Human	0.86
OVID 0671	Amin P.B. / 2011(241)	United States	Adult	Acquisition	• Sensitive (n = 62) • MDR-AB (n = 34)	C	OR	MDR-AB	3	Hospital	Human	0.50
OVID 2105	Anderson M.E. / 2008(242)	Countries of practice which were represented were the United States of America (USA)	Adult	Colonisation	MRSA (n = 26/257 (10.1%))	C (CS)	OR	MRSA	31	Community	Human/Animal	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
		(189, 73.5%), Canada (46, 17.9%), Ireland (5, 1.9%), Australia, New Zealand, United Kingdom (2 each, 0.8% each), Austria, Belgium, Germany, Sweden, the United Arab Emirates (1 each, 0.4% each), and not indicated (6, 2.3%).										
OVID 0486	Andersson H. / 2012(243)	Sweden	Adult	Emergence	• ESBL- ENT cultured • (n = 495) • ESBL- ENT positive • (n = 15)	C	PC	ESBL-ENT	3	Hospital / Community	Human	0.33
OVID 0900	Andriatahina T. / 2009(244)	Madagascar	Children	Carriage	• Patient full cohort (n = 244) • Rectal swabs • (n = 154) (on discharge)	C	OR	ESBL-ENT	1,3,11	Hospital	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 2158	Apisarnthanarak A. / 2007(245)	Thailand	Adult	Infection	• CO-ESBL-EC infections (n = 46) • CO-non-ESBL-EC infections (n = 46) • Controls (without infection) (n = 138)	CC	OR	ESBL-EC	3,30,31	Hospital / Community	Human	0.71
OVID 1821	Argudin M.A. / 2012(246)	Spain	NA	Indirect transmission	• Total isolates • (n = 64) • Food handlers (14 isolates) ; manually handled foods (50 isolates)	C	P	R-SA	4	Community	Human/Animal	0.33
OVID 0686	Arnan M. / 2011(247)	Spain	Adult	Carriage	• Total episodes • (n = 217) • ESBL-EC Carriage (n = 63) • ESBL-EC Non-carriage (n = 154)	C	OR	ESBL-EC	3	Hospital	Human	0.50
OVID 1442	Arslan H. / 2005(248)	Turkey	Adult	Colonisation (Isolation)	• Total cohort (n = 514) • CP-R (n = 135)	C	OR	CP-R-EC	3,11,45	Community	Human	0.83
OVID 1765	Arvaniti K. / 2012(249)	Greece	Adult	Carriage	At ICU admission: • AB carriers • (n = 16)	C	OR	MDR-AB	3,24,33,36	Hospital	Human	0.83

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• Non-carriers • (n = 268)							
OVID 1093	Askarian M. / 2008(250)	Iran	Mixed	Colonisation (rectal)	• 700 randomly selected hospitalised patients • VR-ENTO(f): (n = 99) • VS-ENTO(f): (n = 59)	CC	OR	VR-ENTO(f)	2,3	Hospital	Human	0.86
OVID 0992	Askarian M. / 2009(251)	Iran	Adult	Carriage	• HCWs screened for SA: 600/1220 (• SA carriers: 186 (31%) • MSSA carriers: 154 (82.8%) • MRSA carriers: 32 (17.2%) (25.7% and 5.3% of all HCWs, respectively).	C (CS)	OR	MRSA	46	Hospital	Human	0.67
OVID 1017	Aspa J. / 2008(252)	Spain	Adult	Infection	• 35 Spanish hospitals • 682 patients	C	OR	MDR-STR(p) / MDR-AB	1,2,9	Hospital	Human	0.83
OVID 1220	Assadian O. / 2007(253)	Iran	Adult	Colonisation	• Consenting haemodialysis patients (n = 146)	C (CS)	PC	VR-ENTO	1,3	Hospital	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 0981	Bakunas-Kenneley I. / 2009(254)	United States	Adult	Transmission	• Nurses from 4 separate home health care agencies • (n = 126) submitted personal nurses' bags routinely used in patient care	C	RR	MDR-B	46	Hospital / Community	Human	0.00
OVID 2140	Baran G. / 2008(255)	Turkey	Adult	Infection	• IS-AB (n = 57) • IR-AB (n = 66)	CC	OR	IR-AB	3,24,33	Hospital	Human	0.86
OVID 0564	Barkovskii A.L. / 2012(107)	United States	NA	Emergence	3 farms	C	CRC	Tet	6	Community	Human/Animal	0.50
OVID 0454	Batard E. / 2013(256)	France	NR	Emergence (incidence)	• The median number of isolates per hospital was 285 (IQR 139–570). • The median percentage of QR-EC = 15.3% (IQR 11.1–17.9%) • The median incidence density of QR-EC was 0.66 isolates/1000	C (CS)	I	QR-EC	3	Hospital	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					patient-days (IQR 0.38 - 0.97).							
OVID 1506	Benenson S. / 2005(257)	Israel	Mixed	NS	• Total (n = 131), Risk factor analysis: • GR (n = 32) • CP-R (n = 37)	C	OR	GR/CP-R - ENT	GR-ENT: 9,42,*(2.1) ; CIR-ENT: 1,9,13,42,(2.1)	Hospital	Human	0.83
OVID 2167	Bhat S. / 2007(258)	United States	NR	Infection	• 140 patients (13 patients = 2 episodes, 1 patient = 3 episodes and 1 patient = 4 episodes) ; • PT-R-PA: 25 (37%) • CF-R-PA: 16 (31%)	C	PC	R-PA	3,31	Hospital	Human	0.33
OVID 1604	Bilavsky E. / 2014(259)	Israel/ Spain/Italy/France	Adult	Colonisation	• ESBL-ENT colonisation • (n = 748) • ESBL-ENT non-colonisation • (n = 2125)	C	OR	ESBL-ENT	3,12,24,30,31,55	Hospital / Community	Human	0.83
OVID 0976	Bitsori M. / 2009(260)	Greece	Children	Infection	• Total: 523 ENT pathogens from 473 children; • BSBL- R UTI (n = 27)	C	OR	BSBL-ENT	2,3,24,33.1,42,45	Hospital	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• BSBL- S UTI • (n = 363)							
OVID 0972	Blaettler L. / 2009(261)	Switzerland	Adult	Colonisation/acquisition	• Total: 1100 • EC: (n = 106) • Among the 335 ciprofloxacin-resistant (CIR) strains analyzed, 171 (51%) were co-resistant against Trimethoprim/sulfamethoxazole	C	OR	CIR-EC	11,42	Hospital	Human	0.50
OVID 1789	Bleumin D. / 2012(262)	Israel	Adult	Acquisition	• CR-KP positive • (n = 43) • CR-KP negative • (n = 150)	CC	OR	CR-KP	11,59	Hospital	Human	1.00
OVID 1045	Bocher S. / 2008(263)	Denmark	Mixed	Infection	• Total: 121 patients • Cases: (n = 34) • Controls: (n = 87)	CC	OR	MRSA	43	Community	Human	0.43
OVID 1583	Bodro M. / 2015(264)	Spain	Adult	Emergence (associated with resistant organism)	• XDR-PA (n=31) • Other etiologies (n=287)	C	OR	XDR-PA	2,12,33.1	Hospital	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 1809	Borer A. / 2012(265)	Israel	Adult	Infection	• Total: 464 patients with CR-KP colonisation • 42 (9%) developed CR-KP infection	CC	OR	CR-KP	2,3,9,13,15	Hospital	Human	0.71
OVID 0995	Brugnaro P. / 2009(266)	Italy	Adult	Carriage	• Total: Nasal swabs taken from: 551 subjects; • 43 MRSA carriers were detected (7.8%; CI = 5.7–10.4%).	C (CS)	OR	MRSA	1,2,3	Hospital / Community	Human	0.67
OVID 0309	Bucheli E. / 2014(267)	Switzerland	Adult	Colonisation	• All patients (n = 1234) • ENTO: (n = 255) • APN-R-ENTO susceptibility testing (n = 277)	C	OR	PN-R-ENTO	2,3,34	Hospital	Human	0.50
OVID 0858	Caffrey A.R. / 2010(268)	United States	Adult	Emergence (predictor of resistance)	• Cases (n = 40) • Controls (n = 270)	CC	OR	MU-R-SA / MDR-AB	3,50	Hospital	Human	0.71
OVID 0020	Cai T. / 2016(269)	Italy	Adult	Emergence	• Before protocol implementation: (n = 2698) • After protocol implementation: (n = 3584)	C	CRC	R-ENT (ENT=KP/EC)	3,61	Hospital	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 0262	Campos P.A. / 2014(270)	Brazil	NR	Infection	• VR-ENTO(f) infection • (n = 22) • Controls: (n = 45)	CC	OR	VR-ENTO(f)	3	Hospital	Human	0.71
OVID 0444	Canizalez-Roman A. / 2013(271)	Mexico	NA	Indirect transmission (food)	• Total: 5162 food items and beverages consumed; • EC: 409 (7.92%) • Diarrheogenic EC: 56 (1.08%)	C	P	R-EC	4	Community	All	0.50
OVID 2254	Carnicer-Pont D. / 2006(272)	United Kingdom	Adult	Infection	• Cases exposed (n=42) • Controls exposed (n=90)	CC	OR	MRSA	13,31	Hospital	Human	0.43
OVID 0645	Cassier P. / 2011(273)	France	Adult	Colonisation/Infection	• Cases (n = 98) • Controls (n = 98)	CC	OR	CTX-M-EC	3,13,50	Hospital	Human	0.71
OVID 0453	Castelo Branco Fortaleza C.M / 2013(274)	Brazil	NR	Acquisition	Patients admitted to a medical-surgical intensive care unit: (n = 582) IR-AB (n = 69)	C	OR	IR-AB	3,12,13	Hospital	Human	0.50
OVID 1087	Cattaneo C. / 2008(275)	Italy	Adult	Emergence	• FR-GN/GP: (n = 64 (56.1%))	C	OR	MRSA/FR-B	MRSA: 2,3,13;	Hospital	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• MRSA: (n = 16 (59.3%))							
OVID 0261	Cavalcante R.D.S. / 2014(276)	Brazil	Mixed	Acquisition	• Cases (n = 29) • Non-cases (n = 179)	C	OR	IR-AB	3,16	Hospital	Human	0.83
OVID 2084	Cenizal M.J. / 2008(277)	United States	Adult	Colonisation	• MRSA colonised (n = 15) • MRSA not colonised • (n = 131)	C	OR	MRSA	2,31,50,*(3.2)	Hospital / Community	Human	0.67
OVID 2025	Cezario R.C. / 2009(278)	Brazil	Adult	Infection	• Cases: (n = 47) • Controls: (n = 122)	CC	OR	IR-PA	3,11,13,36	Hospital	Human	0.86
OVID 0369	Chen C.C. / 2013(279)	United States	Adult	Colonisation	• MRSA positive (n = 90) • MRSA negative (n = 90)	C	OR	MRSA	2,30	Hospital	Human	0.67
OVID 0674	Chen C.-J. / 2011(280)	Taiwan	Children	Colonisation	• MRSA carrier (n = 473) • MSSA carrier (n = 931) • Non-carrier (n = 4,653)	C (CS)	OR	MRSA	11,40,74,100	Hospital / Community	Human	0.67
OVID 1124	Chen S.-Y. / 2008(281)	Taiwan	Mixed	Emergence	789 non-duplicated bacteraemia episodes	C	OR	R-B	31,34	Hospital / Community	Human	0.83

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					from community adult patients were enrolled in a 1-year study period.							
OVID 1919	Chen S.Y. / 2010(282)	Taiwan	Mixed	Emergence (associated with resistant organism)	• CA-MRSA (n=34) • HCA-MRSA (n=81)	C	PC	MRSA	2,3,11,13,16, 42,54,71,75,8 3	Hospital / Community	Human	0.67
OVID 1786	Chen S.Y. / 2012(283)	Taiwan	Adult	Emergence (predictor of resistance)	• Derivation cohort: (n=457) • MRSA: (n = 193 (42.2%)) • Validation cohort (n=229) • MRSA: (n = 88 (38.4%))	C	OR	MRSA	2,3,9,16,24	Hospital	Human	0.83
OVID 0032	Cheng V.C.C. / 2015(284)	Hong Kong	Adult	Gastrointestinal Colonisation by CRAB	• CR-AB (n=244) • without gastrointestinal colonisation by CR-AB (n=488)	C	OR	CR-AB	3,9,11,16,42	Hospital	Human	0.67
OVID 0118	Cheng V.C.C./2015 (2) (285)	Hong Kong	Adult	Acquisition	• MDR-AB (n = 18) • CS-AB (n = 86)	C	OR	MDR-AB	3,9	Hospital / Community	Human	0.50
OVID 2293	Cho D.T. / 2006(286)	Korea	Adult	Infection	MRSA clones (ST) • ST239: (n = 75) (56%).	C	OR	MRSA	12	Hospital	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• ST5: (n = 39) (29%) • ST72 (n = 9) • ST344 (n = 6) • ST1 (n = 3) • ST221 (n = 1) • undetermined ST (n = 1), accounted for 15% (n = 20).							
OVID 0363	Chopra T. / 2013(287)	United States	Adult	Infection	• CAS-R-AB: (n = 68) • Non-CAS-R-AB: (n = 206)	C	OR	MDR-AB	2,3	Hospital	Human	0.83
OVID 1593	Chusri S. / 2015(288)	Thailand	Adult	Infection	• CR-AB (n = 139) • CS-AB (n = 58) • Control (n = 197)	CC	RR	CR-AB	3	Hospital	Human	0.57
OVID 1449	Cisneros J.M. / 2005(289)	Spain	Adult	Acquisition	• Resistant cases: (n = 43) • Susceptible cases: (n = 66 susceptible) (approximated based on % and numbers provided in Table 2 of article)	C (CS)	OR	IR-AB	3,12,13,44	Hospital	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 0129	Cobos-Trigueros N. / 2015(290)	Spain	Adult	Acquisition	• Susceptible to all antipseudomonal antibiotics (n = 56 patients (53%)) • MDR (n = 4 (4%)) • R-B (1 or 2 groups of antipseudomonal antibiotics) (n = 27 (26%)) • Upon acquisition, resistance to carbapenems (n = 39 (37%)) • piperacillin-tazobactam (n = 19 (18%)), ceftazidime (n = 30 (29%)), • fluoroquinolones (n = 29 (28%)) • amikacin (n = 1 (1%))	C	OR	CR-PA/PTR-PA/CTZ-R-PA/QR-PA/MDR-PA	CR-PA:2,3,12,13,42; PTR-PA/QR-PA/MDR-PA: 3,12,13,42; CTZ-R-PA: 12,13,25,42	Hospital	Human	0.83
OVID 1304	Cohen R. / 2006(291)	France	Children	Carriage	• Year 1, (n = 668) • Year 2, (n = 578 • Year 3, (n = 660)	C	OR	PN-R-STR(p)	3,11	Hospital / Community	Human	0.83

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• Vaccinated(-) & Antibiotics(-) (n = 307) • Vaccinated(+) & Antibiotics (+) (n = 266)							
OVID 1980	Cohen-Nahum K. / 2010(292)	Israel	Adult	Infection	• Cases (n = 56) • Controls (n = 56)	CC	OR	MDR-PM	3	Hospital / Community	Human	0.86
OVID 0549	Coleman B.L. / 2012(111)	Canada	Mixed	Colonisation / transmission	Susceptibility testing was completed on 958 swabs; 878 participants from 595 households included	CC + C (CS)	P	R-EC	4,5,6,42,103	Community	Human/Environment	0.71
OVID 0440	Coleman B.L. / 2013(293)	Canada	NA	Indirect transmission (contamination)	• Total: 353,388 water samples were tested • EC contamination (one or more colony forming units): 15,806 (4.5%) • 7063 isolates (one per sample) were screened for antimicrobial susceptibility. • EC (resistant to 1 or more	C (CS)	OR	R-EC / MDR-EC	4,6,8	Community	Human/Environment	0.33

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					antibiotics): 743 (10.5%) • EC (resistant to 3 or more antibiotic classes): 258 (3.7%)							
OVID 0087	Conceicao T. / 2015(294)	Portuguese colonies from Africa and the Far East (Angola (ANG), São Tomé and Príncipe (STP), Cape Verde (CV) and East Timor (ET))	Mixed	Nasal carriage	• Total: (n = 2065) • Total: Patients: (n = 1267) • HCWs (n = 798) • MRSA: (n = 148 (34.9%)) • MRSA patients: (n = 108 (73.0%)) • MRSA HCW: (n = 40 (27.0%))	C	OR	MRSA	10,11,12,24	Hospital	Human	0.83
OVID 1853	Cook PP. / 2011(295)	United States	NR	Emergence	NR;10 year study	C	CRC	CR-PA	3	Hospital	Human	0.67
OVID 1139	Cordery R.J. / 2008(296)	United Kingdom	Adult	Infection	• Total: (n = 55) • Cases: (n = 16) • Controls (n = 39)	CC	OR	ESBL-ENT (ENT: KP/EC)	39, 101.1	Hospital	Human	0.71
OVID 1256	Coronado F. / 2007(297)	United States	Mixed	Infection	• 175 community members • 24 MRSA cases (17 confirmed and 7	C	OR	MRSA	3,87	Community	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					probable case-patients)							
OVID 1748	Correa L. / 2013(298)	Brazil	Adult	Infection	• Case patients (n = 20) • Control patients (n = 40)	CC	OR	CR-KP	13	Hospital	Human	0.86
OVID 0738	Crowther-Gibson P. / 2012(299)	South Africa	Mixed	Infection	• 2003: MDR isolates: (n = 195 (16.1%)) • 2004: MDR isolates: (n = 264 (16.4%)) • 2005: MDR isolates: (n = 291 (18.4%)) • 2006: MDR isolates: (n = 276 (18.1%)) • 2007: MDR isolates: (n = 301 (21.2%)) • 2008: MDR isolates: (n = 244 (21.7%))	C	OR	MDR-STR(p)	1,2,3,11,38,71	Hospital / Community	Human	0.33
OVID 2182	Crum-Cianflone N.F. / 2007(300)	United States	Adult	Infection	• Total: (n = 435);	C	OR	MRSA / INT-EC	2	Hospital / Community	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• Developed MRSA infection: (n = 31 (7.1%)) • CA-MRSA: 29 (93.5%)							
OVID 2344	Cunningham J.B. /2005(301)	Northern Ireland	NR	Infection	NA	C	CRC	MRSA	23	Hospital	Human	0.33
OVID 0013	Czekalski N. / 2015(302)	Switzerland	NA	Indirect transmission	21 Lakes	C	P	SUL-R-Genes	6	Community	Human/Environment	0.17
OVID 1650	Da Silva NS. / 2014(303)	Brazil	Adult	Acquisition	• Total: (n = 304) (VR-ENTO or VS-ENTO) • VR-ENTO: (n = 30)	C	OR	VR-ENTO	34	Hospital	Human	0.67
OVID 0397	Da Silva Winter J. / 2013(304)	Brazil	Adult	Emergence	685 microbiologic samples from 394 patients	C	OR	MR-B	2,3,24	Hospital	Human	0.83
OVID 2183	Daikos G.L. / 2007(305)	Greece	Adult	Infection	• Integron-positive BSIs • (n = 81) • Integron-negative BSIs • (n =169)	C	OR	INT-EC / MRSA	3,33.1	Hospital	Human	0.83
OVID 0813	Daikos G.L. / 2010(306)	Greece	Adult	Infection	• VP positive (n=67) • VP negative (n=111)	C	OR	VP-KP	3,34	Hospital	Human	0.83

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 1192	Dambrosio A. / 2007(307)	Italy	NA	Indirect transmission	(n = 250) samples we analysed EC-O26: (n =3 (1.2%)) of	C	P	R-EC (EC O26)	4	Community	Human/Animal	0.33
OVID 1684	Dayan N. / 2013(308)	Israel	Children	Infection	• ESBL positive • (n = 25) • ESBL negative • (n = 125)	CC	OR	ESBL-ENT	1,3,45	Community	Human	0.86
OVID 0801	De Lastours V. / 2010(309)	France	Mixed	Carriage	• FS- CON-SA: • (n = 333) • FR- CON-SA: • (n = 168) • FS-STR(h): • (n = 386) • FR-STR(h): • (n = 151) • FS-SA: (n = 74) • FR-SA: (n = 22) • FS-EC: (n = 318) • FR-EC: (n = 42)	C	OR	FR-CON-SA / FR-EC / FR-STR(h)	FR-CNS: 3,9,11; CIR-EC: 31; FR-STR(h): 3	Hospital	Human	0.83

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 0820	De Regt M.J.A. / 2010 (310)	Netherlands	NR	Acquisition	Patients (n = 436)	C	HR	APR-ENTO(f)	3	Hospital	Human	0.50
OVID 2367	del Mar Tomas M. / 2005(311)	Spain	Adult	Colonisation /infection	• Cases: (n = 30) • Controls: (n = 31)	CC	OR	MDR-AB / R-B	3,13	Hospital	Human	0.71
OVID 0576	Delorenzo M.E. / 2012(312)	United States	NA	Indirect transmission	540 EC isolates / 2 storm water ponds were selected	C	PC	R-EC	6	Community	Human/Environment	0.50
OVID 0863	Dent L.L. / 2010(313)	United States	NR	Colonisation/acquisition	General population: • MDR-AB (n = 122) • Control (n = 42); Surgical patients: • MDR-AB (n = 51) • Control (n = 24)	C	OR	MDR-AB / CR-AB	2,3,36,101	Hospital	Human	0.67
OVID 2052	Depuydt P.O. / 2008(314)	Belgium	Adult	Infection	MDR (n = 52) Non-MDR (n = 140)	CC	OR	MDR-B	2,3	Hospital	Human	0.86
OVID 1823	Didier C. / 2012(315)	France	Children	Infection	139 infants were included in the study population	C	RR	AR-EC	90	Hospital	Human	0.67
OVID 0743	Dixon J.J. / 2012(316)	United Kingdom	Adult	Emergence	No AML (n = 265) ; AML (n = 662)	C	RR	R-GN / CR-PA	3	Hospital	Human	0.50
OVID 0810	Dizbay M. / 2010(317)	Turkey	Adult	Infection	• Total: (n = 925 (100%)) • IR: (n = 524 (56.6%)) • IS: (n = 401 (43.3%))	C	OR	IR-AB/VP-KP/ESBL-KP	2,36	Hospital	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 2202	Drapeau C.M. / 2007(318)	Italy	Adult	Infection	(n = 27 CS-MRSA infections, i.e., 0.9 CS-MRSA infections per 100 HIV-infected individuals cared for in our Institute. Cases n = 27 Controls n = 54	CC	OR	MRSA	12,24	Hospital	Human	0.86
OVID 1462	Dromigny J.A. / 2005(319)	Senegal	Adult	Colonisation (Isolation)	398 non-duplicate, consecutive, biologically significant *E. coli* were isolated	C	OR	APR-EC/AMC-R-EC/NAL-R-EC/SXT-R-EC/R-EC	3,11,42,45	Hospital / Community	Human	0.67
OVID 1073	Dueger E.L. / 2008(320)	Guatemela	Children	Colonisation	(n = 751) children 2001/2 study: (n = 200) children 2005/6 study PN-non-susceptible STR(p): 149 vs 405 (susceptible) ; TRS-Non-susceptible vs susceptible: STR(p): 207 vs 347	C	OR	TRS-R - STR(p)/PR-STR(p)	3,74	Hospital / Community	Human	0.67
OVID 1199	Duerink O.D. / 2007(321)	Indonesia	Mixed	Carriage	• Community • (n = 2494) • Hospital (n = 781)	C	OR	R-EC	1,3,47	Hospital / Community	Human	0.50
OVID 1495	Duman M. / 2005(322)	Turkey	Children	Colonisation	• NICU group (n = 38)	C	RR	ESBL-ENT	2,3,42,51,52	Hospital	Human	0.67

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					• Neonatal ward group: • (n = 36) • Control group (n = 44)							
OVID 1319	Duran N. / 2006(323)	Turkey	Adult	Colonisation / acquisition	(n = 67 (25.7%)) T2DM (n = 194 (74.3%)) were with diverse aetiology for end-stage renal disease, forming the non-diabetic cohort. The control group consisted of (n = 80 healthy individuals) and (n = 80 diabetic patients).	CC	PC	MRSA	2	Hospital	Human	0.57
OVID 0533	Dyar O.J. / 2012(324)	Vietnam	Children	Emergence (development)	Participating children (n = 818)	C	OR	R-EC	3	Community	Human	0.33
AD004 - ECDC	ECDC/EFSA/EMA / 2015(325)	28 EU Member States	Mixed	Infection	Member states (variable per estimate): 507 416 607 humans (EU-28 countries, year 2014); 1 898 767 540 food producing animals (variable species) (EU-28 countries, year 2013)	C	OR	R-EC/R-KP/R-CJ/ R-Sal	3,4	Community + Hospital	Human/Animal	0.33
OVID 1742	Ecker K.L. / 2013(326)	United States	Children	Emergence	APR/PN- in late-onset infections over epochs:	C	OR	R-EC	3	Hospital	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• 1990–1995 (n=219) • 1996–2002 (n = 239) • 2003–2007 (n = 157)							
OVID 1741	Efe Iris N. / 2013(327)	Turkey	Adult	Carriage	• VR-ENTO negative patients (n = 43) • VR-ENTO-positive patients (n = 21)	C	PC	VR-ENTO	3,13,34	Hospital	Human	0.33
OVID 1636	Etienne M. / 2014(328)	France	Adult	NS	• R-EC (n = 129)	C	PC	R-EC	2,9	Hospital	Human	0.50
OVID 2323	Eun S.H. / 2006(329)	South Korea	Adult	Colonisation	• Colonised patients • (n = 228) • Non-colonised patients • (n = 404)	C	PC	MRSA	3,22	Hospital	Human	0.67
OVID 2376	Eveillard M. / 2005(330)	France	NR	Transmission (resulting in infection/colonisation)	• Total admitted patients: • (n = 14 202) • Screened for MRSA:1128 (7.9%)	C	RR	MRSA	98	Hospital	Human	0.50
OVID 2303	Eveillard M. / 2006(331)	France	Adult	Carriage	• Total screened: (n = 403)	C	OR	MRSA	11	Hospital	Human	0.50

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					• MRSA carriers: (n = 22)							
OVID 0666	Fernandez A. / 2011(332)	Spain	Adult	Acquisition	• Cases: (n = 24) • Controls: (n = 80)	CC	OR	MDR-ENTO	1,2,3,13	Hospital	Human	0.86
OVID 0485	Fernandez-Cuenca F. / 2012(333)	Spain	Adult	Colonisation/ acquisition	• IPM-PHR: (n = 42) • Non-IPM-PHR: • (n = 99); • IPM-FR: (n = 70) • MER-PHR: (n = 53) • Non-MER-PHR: • (n = 88) • MER-FR: (n = 70)	C	OR	CR-AB	3,11	Hospital	Human	0.67
OVID 1540	Fihman V. / 2015(334)	France	Mixed	Infection	• VAP episodes (252) • Total patients (n = 184) • Causal bacteria isolation episodes from 252 (364)	C	CRC	3GC-EC/MDR-B	3	Hospital	Human	0.50
OVID 0983	Filozov A. / 2009(335)	United States	Mixed	Acquisition	• Cases: (n = 34) • Controls: (n = 65)	CC	OR	MDR-KP	3,22,24	Hospital	Human	0.71
OVID 0541	Freeman J.T. / 2012(336)	New Zealand	Adult	Infection	• All ESBL-ENT: (n = 44)	CC	OR	ESBL-ENT	2,3,24,28	Hospital	Human	0.86

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					• Community-onset: (n = 21) • Hospital-onset: (n = 23)							
OVID 0274	Freire M.P. / 2014(337)	Brazil	NR	Emergence (development)	• Total evaluated: (n = 65) • Total LTs: (n = 75) • PR-AB positive: • (n = 7) • PR-AB infection: • (n = 4)	C	OR	PR-AB	3	Hospital	Human	0.83
OVID 1321	Freitas M.C.S. / 2006(338)	Brazil	Adult	Colonisation	• Total: (n = 280) • Group 1 (less than 30 days after transplantation) 102 (36.4%) • Group 2 (1 to 6 months after transplantation) 73 (26%) • Group 3 (> 6 months after transplantation) 105 (37.5%)	C	CRC	VR-ENTO	2,3	Hospital	Human	0.67
OVID 2098	Fritz S.A. / 2008(339)	United States	Children	Colonisation	• MRSA: (n = 32)	C (CS)	PC	MRSA	43,50	Hospital / Community	Human	0.50

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					• MSSA: (n = 331) • Not Colonised: • (n = 937)							
OVID 1226	Frye J.G. / 2007(340)	United States	NA	Indirect transmission	• Sal isolates: (n = 34,411) Diagnostic sources: (n = 11,822), • On-farm studies: • (n = 4059) • Sampling at federally inspected slaughter facilities: (n = 17,539) • Other sources: • (n = 991).	C	I	R/MDR-Sal	4,8	Community	Human/Animal	0.33
OVID 1899	Fujitani S. / 2011(341)	United States	Adult	Colonisation	• VR-ENTO positive: • (n = 88) • VR-ENTO negative: (n = 70)	C	OR	VR-ENTO	1,2,9	Hospital	Human	0.33
OVID 0353	Fukuta Y. / 2013(342)	United States	Adult	Acquisition	• Cases: (n = 31) • Controls: (n = 62)	CC	OR	MDR-AB	2,34	Hospital	Human	0.57
OVID 2311	Furuno J.P. / 2006(343)	United States	Adult	Colonisation	Final Sample: (n = 699)	C	PC	MRSA / VR-ENTO	1	Hospital	Human	0.67

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OVID 1997	Gadepalli R. / 2009(344)	India	Mixed	Infection	• MRSA: (n = 221) • MSSA: (n = 488)	C	OR	MRSA	2,3,9,24	Hospital	Human	0.67
OVID 0557	Gandolfi-Decristophoris P. / 2012(345)	Switzerland	Adult	Carriage	• With pets: (n = 229) • Without pets: (n = 216) • With Cats: (n = 53) • With Dogs: (n = 45)	C	OR	MDR-SA	3	Hospital / Community	Human	0.50
OVID 0215	Garcia C.P. / 2014(346)	Brazil	Children	Carriage	• All the new-borns: • (n= 403) • New-borns Remained in the Neonatal Unit ≥ 72 Hours (n = 80) • MRSA-colonized New born (59) • New born Not Colonized by MRSA (344)	C	OR	MRSA	26	Hospital	Human	0.83
OVID 1870	Garlantézeca R.B. / 2011(347)	France	Mixed	Acquisition	• Cases: (n = 5) • Controls: (n = 28)	CC	OR	IR-AB / ESBL-EC	2104	Hospital	Human	0.57
OVID 0472	Gbaguidi-Haore H. / 2013(348)	France	NR	Emergence (incidence)	• 3GC-R-EC (n=656/27833)	C	I	R-EC /R-ENT	3	Hospital	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• CIP-R-EC: (n=645/74135) • CTX-R-ECO: (n=375/16059) Seven hundred and one HCFs (and up to 1339 HCF-years) were included in this study between 2007 and 2009							
OVID 2336	Gearhart M. / 2005(349)	United States	Adult	NS	• Cases: (n = 19) • Controls: (n = 38)	CC	PC	VR-ENTO	1,2,3,12	Hospital	Human	0.57
OVID 0518	Gedik H. / 2012(350)	Turkey	Mixed	Infection	• 174 patients 189 isolates; • ESBL-GN: (n = 36) • non-ESBL-GN: • (n = 112) • GP: (n = 41)	CC	OR	ESBL-B	ESBL-B: 1,2,3; MRSA: 1	Hospital	Human	0.14
OVID 2279	Gilbert M. / 2006(351)	Canada	Mixed	Infection	• Total cases: (n = 40) • High risk: (n = 28) • Low risk (n = 12)	C	RR	MRSA	75	Community	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 0131	Giuffre M. / 2015(352)	Italy	Children	Acquisition	• First nasal swab: MRSA negative: (n = 832 (87.67)) • MRSA positive: (n = 117 (12.33)) • Patients who tested negative for MRSA in first swab: Infants who acquired MRSA: (n = 100 (12.02%)) • Infants who did not acquire MRSA (n = 732 (87.98%))	C	OR	MRSA	24,44	Hospital	Human	0.83
OVID 0617	Goel N. / 2011(353)	India	NR	Emergence (development)	Total blood cultures: (n = 69010)	C (T)	CRC	R-AB ;	3	Hospital	Human	0.67
OVID 0239	Gomez-Zorrilla S. / 2014(354)	Spain	Adult	Acquisition (ICU)	• PA intestinal colonization (n = 112); • No PA intestinal colonization (n = 302); • PA episodes (n = 215) • non-MDR (n = 132) • MDR (n = 83) (MDR-non-XDR (n	C	OR	MDR-PA	2,3	Hospital	Human	0.83

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					= 37) and XDR (n = 46) episodes)							
OVID 2204	Gopal Rao G. / 2007(355)	United Kingdom	Mixed	Colonisation	Adult emergency admissions : 7801 (56.4%) by 6469 patients screened for MRSA. Colonised by MRSA (n = 433) (6.7%)	C	PC	MRSA	1,9,11,31	Hospital	Human	0.33
OVID 0243	Gross A.E. / 2014(356)	United States	Adult	Colonisation/infection	(n = 521 patients) (50.5% Community Associated Pneumonia and 49.5% Health care Associated Pneumonia) • Patients with MDR-B pneumonia (n = 20) • Patients with pneumonia • but no MDR-B isolated • (n = 501)	C	OR	MDR-B	3,9,24,28	Hospital / Community	Human	0.83
OVID 0328	Gruber I. / 2013(357)	Germany	NR	Acquisition	• Colonised with MDR-B: (n = 58 patients) (20.1%) (n = 4 staff members) (6.2%) • MRSA (n = 29)	C	OR	ESBL-ENT/MDR-B/MRSA/VR-ENTO	ESBL-ENT: 1,13,15; MDR-B: 1,13,15,16; MRSA: 12,16,28,30; VR-ENTO: 15,16	Hospital / Community	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• VR-ENTO (n = 12) • ESBL-ENT (n = 27)							
OVID 0670	Gudiol C. / 2011(358)	Spain	Mixed	Acquisition	• MDR-GN (n = 51) • Non-MDR-GN • (n = 312)	C	OR	MDR-GN	3,13	Hospital	Human	0.50
OVID 1875	Ha Y.E. / 2011(359)	South Korea	Adult	Infection	• non-ESBL (n = 215) • ESBL (n = 21) • QS (n = 173) • QR (n = 63)	C	OR	ESBL-EC/QR-EC	ESBL-EC: 3,33.1; QR-EC: 33.1,66	Community	Human	0.83
OVID 1205	Hadley A.C. / 2007(360)	United States	Adult	Colonisation	• MRSA nasal colonization (n = 11) (5.6%) • VR-ENTO perirectal colonization (n = 6) (3.1%)	C (CS)	OR	VR-ENTO	VR-ENTO: 1	Hospital	Human	0.50
OVID 0395	Haeusler G.M. / 2013(361)	Australia	Mixed	Colonisation (isolation)	• R-GN (n = 42) • S-GN (n = 238)	C	OR	R-ENT	25,28,33.1	Hospital	Human	0.83
OVID 2176	Haley C.C. / 2007(362)	United States	Adult	Infection	• MRSA positive (n = 41) • MRSA negative (n = 360)	C	RR	MRSA / VR-ENTO(f)	9,31,75	Hospital	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 1974	Hamel M. / 2010(363)	Canada	Adult	Transmission (resulting in infection/colonisation)	MRSA/VR-ENTO (n = 26,242)	C	HR	MRSA	44	Hospital	Human	0.67
OVID 0717	Han J.H. / 2012(364)	United States	Adult	Colonisation/Infection	• With CTX-M (n = 83) • Without CTX-M (n = 63)	CC	OR	CTX-M-EC	3	Hospital	Human	0.71
OVID 2319	Harbarth S. / 2006(365)	Switzerland	Adult	Carriage	• Patients With MRSA (n = 355) • Patients Without MRSA (n = 1372) • The final data set comprised 204 new MRSA	CC	OR	MRSA	1,3,11,13,25, 42	Hospital	Human	0.71
OVID 2060	Harbarth S. / 2008(366)	Switzerland	Adult	Carriage	• The derivation cohort MRSA patients (n = 57) • Controls (n = 348) without MRSA carriage	C	OR	MRSA	1,3,11	Hospital	Human	0.83
OVID 0742	Hare K.M. / 2012(367)	Australia	Children	Carriage	Total cohort (n = 104)	C	OR	AZ-R-STR(p) / APR-STR(p) /R-GP	3	Community	Human	0.33
SC0004	Hasanin A. / 2014(368)	Egypt	Mixed	Acquisition	• XDR group (n = 152)	C	PC	XDR-GN	12	Hospital	Human	0.67

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					• Non XDR group (n = 82)							
OVID 2144	Hashimoto M. / 2007(369)	Tokyo	Adult	Infection	Total LDLT patients (n = 242)	C	OR	MRSA	12,31	Hospital	Human	0.50
OVID 2053	Hashimoto M. / 2008(370)	Tokyo	Adult	Acquisition	Total LDLT patients (n = 242)	C	OR	MRSA	11,12	Hospital	Human	0.50
OVID 2121	Hashimoto M. / 2008(371)	Tokyo	Adult	Infection	• Total LDLT patients • (n = 158) • MRSA no infection (n = 217) • MRSA infection (n = 25)	C	OR	MRSA	3,12,13,31	Hospital	Human	0.83
OVID 1954	Hauser E. / 2010(372)	Germany	NA	Indirect transmission (contamination)	Distribution of different resistance profiles by isolate source (n): Primary production (52); Pork (30); Human (66); Total (148)	C	P	R-Sal	4	Community	Human/Animal	0.67
OVID 1712	Hayakawa K. / 2013 (2)(373)	United States	Adult	Colonisation (Isolation)	• Total (n = 575) • Isolates from Detroit Medical Center (n = 377) (65.6%)	CC	OR	CXT-M-EC	2,3,9,13,22,42,45,55,56	Hospital / Community	Human	0.86

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					• Isolates from ambulatory clinic (n = 198) (34.4%) • CTX-M-EC (n = 319) Non-CTX-M-EC (n = 58) • Uninfected controls (n = 319)							
OVID 1723	Hayakawa K. / 2013 (3)(374)	United States	Adult	Colonisation	• VR-ENT(f2) co-colonized with MRSA (n=85) • Non-co-colonized VR-ENT(f2) (n=461)	CC	OR	VR-ENT(f2) + MRSA	13,16,34,42,55	Hospital	Human	0.86
OVID 0476	Hayakawa K. / 2013(375)	United States	Adult	Colonisation (Isolation)	• VR-ENT(f2) cases (n = 532) • VS-ENT(f2) cases (n = 532) • Uninfected controls • (n = 532)	CC	HR	VR-ENT(f2)	2,3,9,11,12,13,16,30	Hospital / Community	Human	1.00
AS0001	Hendrik / 2015(376)	International	Mixed	Presence or acquisition	10 - 292 cases (total patient cases not reported)	M	OR	ESBL-ENT	2,3,13,24,104	Hospital	Human	0.96
OVID 0329	Heng Y.K. / 2013(377)	Singapore	Adult	Emergence (development)	• FA-R-SA (n = 37) • FA-S-SA (n = 148)	C	OR	FA-R-SA	3	Hospital	Human	0.83

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OVID 1976	Ho P.L. / 2010(378)	Hong Kong	Adult	Colonisation (Isolation)	• Cases (n =45) • Controls (n = 135)	CC	OR	MDR-AB	16	Hospital	Human	0.57
OVID 1475	Hoban D. / 2005(379)	Global study: 15 centers in North America, 13 in Latin America, 29 in Europe, nine in the Far East, and three in Australasia	Mixed	Emergence (predictor of resistance)	Each center was requested to collect 60 isolates of STR(p). from clinical samples	C	OR	PN-R-STR(p)/ERT-R-STR(p)	11,83	Hospital / Community	Human	0.67
OVID 1911	Horasan E.S. / 2011(380)	Turkey	Adult	Infection	145 HCAI	C	OR	MDR-B	3,12,24	Hospital	Human	0.67
OVID 2061	Hoshuyama T. / 2008(381)	Japan	Adult	Colonisation/infection	• Study 1: Cases (n = 8) Controls (n = 26) • Study 2: Cases (n = 14) Controls (n = 45)	CC	OR	VR-ENTO	15,82	Hospital	Human	0.71
OVID 2199	Hota B. / 2007(382)	United States	Adult	Infection	• CA-MRSA (n = 518) • CA-MSSA (n = 704)	CC	OR	MRSA	16,32,43	Hospital / Community	Human	0.71
OVID 1488	Hota B.N. / 2005(383)	United States	Adult	Acquisition	• Time period 1 (8/1996–3/1997) • Ciprofloxacin - unexposed (n = 90) • Ciprofloxacin - exposed (n = 51)	C	I	QR-GN	3,9,13	Hospital	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• • Time period 2 (5/2000–12/2000): Levofloxacin-unexposed (n = 114) Levofloxacin-exposed (n = 61) QR-GN bacilli: • Time period 1 (8/96–3/97) (n = 25 patients) • Time period 2 (5/00–12/00) • (n=17)							
OVID 2381	Hsu D.I. / 2005(384)	United States	Adult	Acquisition	• Cases (FQ-R) (n = 91) • Controls (FQ-S) (n = 86)	CC	OR	FQ-PA	3,30,33.1	Hospital	Human	0.86
OVID 0155	Hsu H.Y. / 2015(385)	United States	Adult	Colonisation (presence)	172 eyes from 183 ; 6/24 were able to provide information on prior antibiotic use	CC	OR	R-SA	3	Community	Human	0.86
OVID 2124	Huang H. / 2008(386)	United States	Adult	Infection	• CA-MRSA (n = 127) • Control group 1 (n = 127)	CC	OR	MRSA	75	Hospital / Community	Human	0.71

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					• Control group 2 (n = 381)							
OVID 1308	Huang S.S. / 2006(387)	United States	Adult	Acquisition	A total of 8203 patients had 11,528 ICU room stays.	C	OR	MRSA/VR-ENTO	MRSA:11,34,44 ; VR-ENTO: 2,11,34,44	Hospital	Human	0.67
OVID 1168	Hufnagel M. / 2007(388)	Germany	Children	Colonisation	274 infant-mother pairs enrolled	C	OR	MDR-ENTO	86	Hospital	Human	0.83
OVID 0315	Huh K. / 2014(389)	South Korea	Adult	Infection	• Susceptible group (n = 139) • Resistant group (n = 53)	C	OR	ESC-R-ENT	2,3,11,12,33.1	Hospital	Human	0.83
OVID 1697	Hui C. / 2013(390)	Taiwan	Adult	Infection	• Resistant (n = 104) • Not resistant (n = 63)	C	OR	R-B	3	Hospital	Human	0.83
OVID 1585	Huijbers P M.C / 2015(391)	Netherlands	Mixed	Carriage	9 certified organic broiler farms were present. On 8 of these farms, 60 throat swabs and 20 cloacal swabs were taken per farm; Faecal swabs and questionnaires were returned by 27 out of 36 humans	C	P	ESBL/AmpC-EC	8	Community	Human/Animal	0.33
OVID 0451	Hussein K. / 2013(392)	Israel	Adult	Acquisition	• CR-KP (N = 103) • CS-KP (N = 214)	CC	OR	CR-KP	3	Hospital	Human	0.86

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OVID 1561	Ikram R. / 2015(393)	New Zealand	Adult	Infection (outbreak)	• Cases (n = 76) • Controls (n = 156)	CC	OR	MDR-EC	3,15,54	Hospital	Human	0.86
OVID 0104	Inchai J. / 2015(394)	Thailand	Adult	Infection	• Susceptible (n = 33) • MDR (n = 72) • XDR (n = 220 • PDR (n = 12)	C	OR	MDR-AB/XDR-AB/PDR-AB	MDR-AB: 3; XDR-AB: 3,22; PDR-AB:3,22	Hospital	Human	0.83
OVID 0373	Isea-Pena M.C. / 2013(395)	Spain	Adult	Infection	• LR (n = 20) • LS (n = 102)	C	OR	LR-STR(p)	1,2,10,32	Hospital	Human	0.83
OVID 0520	Jenkins T.C. / 2012(396)	United States	Adult	Infection	175 cases included in the analysis	C	PC	R-STR(p)	10,11,50,56,75	Hospital / Community	Human	0.33
OVID 1105	Jeon M.-H. / 2008(397)	Korea	Adult	Emergence	• Cases (n = 46) • Controls (n = 138)	CC	OR	CR-EC	1,3,13	Hospital	Human	0.71
OVID 1619	Jeong B.H / 2014(398)	South Korea	Adult	Acquisition	A total of 315 patients were included in the analysis.	C	OR	R-B	1,2,3,9,22	Hospital / Community	Human	0.83
OVID 0265	Jiang X. / 2014(399)	China	NA	Indirect transmission	75 EC (12.1%) were recovered from 620 cooked meat samples tested (23 from 199 roasted meats, 38 from 230 pot stewed meats, five from 102 sausages	C	P	R-EC	4	Community	Human/Animal	0.33

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					and nine from89 smoked meats).							
OVID 1042	Johnson L. / 2008(400)	United States	Adult	Infection	LR (n = 41) LS (n = 82)	CC	OR	LR-EC	1,3	Hospital	Human	0.71
OVID 1942	Jung J.Y. / 2010(401)	South Korea	Adult	Colonisation	• Non-Bacteremic (n = 92) • Bacteremic (n = 108)	C	OR	MDR-AB	2,3,13,33,36, 50,93	Hospital / Community	Human	0.83
OVID 0646	Kaminski C. / 2011(402)	France	Adult	Colonisation (ICU admission)	• PS-PA-VAP (n = 153) • PR-PA-VAP (n = 70)	CC	PC	R-PA	2,3,12	Hospital	Human	0.43
OVID 1836	Kang C.I. / 2012(403)	South Korea	Adult	Infection	• Resistant group (n=37) • Susceptible group (n=119)	C	OR	ESBL-ENT	3,33,33.1	Hospital	Human	0.50
OVID 0313	Kang C.I. / 2014(404)	ANSORP: Asian surveillance study - All cases were from Korea, Taiwan, and Hong Kong	Adult	Infection	• Levofloxacin non-susceptible (n=39); • Levofloxacin-susceptible (n=490)	CC	OR	LR-STR(p)	2,3,33.1	Community	Human	0.57
OVID 1691	Kang Y. / 2013(405)	United States	Adult	Infection	• Total HSCT patients (n = 152) • No VR-ENTO bacteremia (n = 133)	C	OR	VR-ENTO	2,3	Hospital	Human	0.67

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					• VR-ENTO bacteremia • (n = 19)							
OVID 0108	Kantele A./2015(406)	Scandinavia	Mixed	Colonisation	• Total (n = 430) • ESBL-ENT (n = 90)	C	OR	ESBL-ENT	3,47	Community	Human	0.83
OVID 0017	Karaaslan A. / 2016(407)	Turkey	Children	Colonisation	• CR-GNB-colonized (n = 176) • Controls (n = 222) (ratio of 1:1.2)	CC	OR	CR-GN/NDM-AB	CR-GN: 2,3,11,12,13 ; NDM-AB: 13	Hospital	Human	0.71
AS0004	Karanika / 2015 (408)	International	Adult	Colonisation	Total sample: 1173 - 1368	M	OR	MRSA	1,2,13,28	Hospital / Community	Human	0.93
OVID 1694	Karki S. / 2013(409)	Australia	Adult	Carriage	• VR-ENTO Positive • (n = 13) • VR-ENTO Negative • (n = 90)	C	OR	VR-ENTO	1,3,57	Hospital	Human	0.50
OVID 1120	Katsaragakis S. / 2008(410)	Greece	Adult	Emergence (predictor of resistance)	• AB group (n = 52) • MDR-AB (n = 23) • Non-MDR-AB (n = 29)	C	OR	MDR-AB	2,12	Hospital	Human	0.83
OVID 2393	Kazakova S.V. / 2005(411)	United States	Adult	Infection	• MRSA infecton (n = 5) • no MRSA infection	C	PC	MRSA	63,99	Community	Human	0.50

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					• (n = 48)							
OVID 0771	Kennedy K. / 2010(412)	Australia	Mixed	Colonisation	• 106 enrolled pre-travel • 4 did not return post-travel swabs	C	PC	ESBL-EC / R-EC / MRSA	5	Community	Human	0.33
OVID 0577	Khawcharoenporn T. / 2012(413)	United States	Adult	Emergence (high rates)	• All patients (n = 337) • CA-UTI (n = 248) • HCA-UTI (n = 89)	C	OR	LR-B	2,3,45	Hospital / Community	Human	0.83
OVID 1200	Khudaier B.Y. / 2007(414)	India	Mixed	Colonisation/acquisition	• Cases (n = 28) • Control (n = 84)	CC	OR	VR-ENTO	3,24	Hospital	Human	0.57
OVID 0180	Kim J. / 2014(415)	South Korea	Adult	Colonisation (isolation)	• FR-EC (n = 26) • FS-EC (n = 56) • Culture-negative (n = 57)	CC	OR	FR-EC	2,3	Hospital / Community	Human	0.71
OVID 1667	Kim S.B. / 2014(416)	South Korea	Adult	Emergence (development)	• With MDR-AB • (n = 19) • Without any infection • (n = 38)	CC	OR	MDR-AB	2,34	Hospital	Human	0.57
OVID 1092	Kim Y.-A. / 2008(417)	Korea	Adult	Emergence	• Case 1 (n = 27) • Case 2 (n = 7)	CC	OR	IR-AB/MBL-AB	2,3	Hospital	Human	0.71

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					• Control (n = 41)							
OVID 0707	Kim Y.J. / 2012(418)	South Korea	NR	Infection	• Perianal swab culture 1,048/1,128 (92.9%) patients • VR-ENTO colonisation at the time of ICU admission (n = 184) (17.6%). • VR-ENTO infection during hospitalisation out of colonised 28 (11.9%)	C	OR	VR-ENTO	2,3,13	Hospital	Human	0.33
OVID 0464	Kini A.R. / 2013(419)	India	Children	Emergence (predictor of resistance)	• MRSA (n = 41) • MSSA (n = 33)	C	PC	MRSA	69	Hospital / Community	Human	0.83
OVID 0352	Ko Y.J. / 2013(420)	South Korea	Mixed	Carriage	• ESBL carrier (n = 37) • Non carrier (n = 60)	C	OR	ESBL-ENT	24,31,34	Hospital	Human	0.83
OVID 0975	Kock R. / 2009(108)	Germany	Mixed	Colonisation	• Cases (n = 100) • Controls (n = 100)	CC	OR	MRSA / MDR-B	8,11	Hospital / Community	Human/Animal	0.57
OVID 0171	Kofteridis D.P. / 2014(421)	Greece	Adult	Emergence (development)	• CR-KP (n = 83)	CC	OR	CR-KP	2,12,33	Hospital	Human	0.86

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					• Control group (n = 161) • CS-KP (n = 78)							
OVID 1998	Kohlenberg A. / 2009(422)	Germany	Children	Acquisition	• Cases (n = 13) • Controls (n = 24)	CC	OR	MDR-AB	22	Hospital	Human	0.71
OVID 0763	Kohlenberg A. / 2010(423)	Germany	NR	Acquisition	• Cases (n = 15) • Controls (n = 18)	CC	OR	CR-PA / CTX-M-ENT (ENT=KP/EC)	3,13	Hospital	Human	0.86
OVID 1620	Kollef M.H / 2014(424)	United States/Europe/Latin America/Asia-Pacific/Global (11 countries (four global regions): Continental United States (the United States); Belgium, France, Germany, and Spain (Europe); Chile, Colombia, and Mexico (Latin America); and Australia, Singapore, and South	Adult	Infection	• United States (n = 502) • Europe (n = 495) • Latin America (n = 500) • Asia Pacific (n = 376) • Global (n = 1,873)	C	OR	MDR-B	44	Hospital / Community	Human	0.33

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		Korea (Asia Pacific).)										
OVID 0621	Kontopidou F. / 2011(425)	Greece	Mixed	Colonisation/Infection	• Total (n = 150) • COR-KP (n = 30)	C	OR	COR-GN	3	Hospital	Human	0.67
OVID 0623	Korona-Glowniak I. / 2011(426)	Poland	Children	Colonisation	• All (n = 311) • Day Care Centre group • (n = 241) • Home group (n = 70)	C	OR	MDR-STR(p) / PR-STR(p)	MDR-B: 10,50,74 ; PR-STR(p): 59,74	Community	Human	0.67
OVID 0275	Koupetori M. / 2014(427)	Greece	Adult	Infection	Total BSI patients (n = 754)	C	OR	MDR-B	2,3,9	Hospital	Human	0.83
OVID 0230	Kuenzli E. / 2014(428)	Swiss Travellers to South Asia	Adult	Colonisation	• Total (n = 170) • Colonized with ESBL-ENT (immediately after trip) (n = 118) (69.4%); • Colonised after the trip to South Asia: (n = 52) (30.6%)	C	RR	ESBL-ENT	4,5	Community	Human	0.83
OVID 2228	Kuint J. / 2007(429)	Israel	Children	Acquisition	• CA-MRSA (n = 11)	C	PC	MRSA / MDR-MRSA / MDR-PA	3,33,36,97	Hospital / Community	Human	0.50

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					• MDR-MRSA (n = 20) • MSSA (n =12)							
OVID 0778	Kurd M.F. / 2010(430)	United States	Adult	Infection	• MRSA Positive (n = 30) • MRSA Negative (n = 72)	C	OR	MRSA	2,11,63	Hospital	Human	0.50
OVID 0664	Kurtaran B. / 2011(431)	Turkey	Mixed	Colonisation	Total number of yielding organism (n = 653)	C (CS)	OR	MRSA / R-B	1	Hospital	Human	0.67
OVID 1979	Kuster S.P. / 2010(432)	Switzerland	Adult	Infection	• ESBL (n = 58 (100)) • Non-ESBL (n = 116 (100))	CC	OR	ESBL-ENT	3,5,36	Hospital	Human	0.86
OVID 0919	Lamaro-Cardoso J. / 2009(433)	Brazil	Children	Carriage	1,192 children attending 62 public day care centres	C (CS)	PC	MRSA	40	Community	Human	0.17
OVID 1106	Laupland K.B. / 2008(434)	Canada	Adult	Acquisition	247 incident CO-ESBL-EC	C	RR	ESBL-EC	2,5,30,32,54	Hospital / Community	Human	0.50
OVID 0804	Le Hello S. / 2010(435)	New caledonia - south pacific	Adult	Infection	• CR-AB (n = 50) • Other MDR bacteria (n = 152)	C	OR	CR-AB/CLR-HP	1,3	Hospital	Human	0.67
OVID 0003	Lee D.-S. / 2015(436)	South Korea	Adult	Acquisition	• Total enrolled (n = 143) • MDR (n = 46) • Non-MDR (n = 97)	C	OR	MDR-B (B=ENT/ENTE/S)	3,30	Hospital	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 0211	Lee H.-S. / 2014(437)	South Korea	Adult	Infection	• MDR (n=29) • Non-MDR (n=17)	C	OR	ESBL-ENT	34	Hospital / Community	Human	0.67
OVID 1902	Lee H.Y. / 2011(438)	Taiwan	Adult	Emergence (loss of susceptibility)	• Cases (n = 14) • Controls (n = 10)	CC	PC	IR-AB	3	Hospital	Human	0.71
OVID 0499	Lee H.-Y. / 2012(439)	Taiwan	Adult	Acquisition	• IR-AB (n = 42) • IS-AB (n = 20)	C	OR	IR-AB	3	Hospital	Human	0.50
OVID 0432	Lee J.W. / 2013(440)	South Korea	Adult	Emergence	• 2003–2005 (n = 64) • 2006–2008 (n = 169) • 2009–2012 (n = 114	C	OR	R-HP	7,31,32	Hospital	Human	0.67
OVID 0735	Lee N.Y. / 2012(441)	Taiwan	Adult	Infection	• ER-S group (n=62) • Revised ER-NS group (n=41)	C	PC	ER-KP	2	Hospital	Human	0.50
OVID 0435	Lee S.-C. / 2013(442)	Taiwan	Adult	Acquisition	• CO-HCA-MRSA (n = 48) • CA-MRSA (n = 13)	C	OR	MRSA	2	Hospital / Community	Human	0.67
SC0011	Leistner R. / 2013(110)	Germany	Adult	Colonisation	• Cases (n = 85) • Controls (n = 173)	CC	OR	ESBL-EC	4,43	Community	Human/Animal	0.86
OVID 1324	Lepelletier D. / 2006(443)	France	NR	Colonisation (gastrointestinal colonisation)	• Total swabs (n = 3713)	C	OR	CTZ-R-ENT/OF-R-ENT	1,3	Hospital	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• Total patients (n = 933) • R-ENT (n = 585) • CTZ-R-ENT resistance: • On admission: (n = 20 (3.4%)); • Acquired: (n = 35 (5.6%)) • OF-R-RNT resistance: • On admission: (n = 14 (2.4%)); Acquired: (n = 14 (2.4%))							
OVID 1490	Leroy O. / 2005(444)	France	Adult	Infection	• Cases patients (n = 42) • Control patients (n = 126)	CC	OR	IR-B	3,13,82	Hospital	Human	0.57
OVID 0811	Lestari E.S. / 2010(445)	Indonesia	Mixed	Carriage	• Community (n = 263) • Hospital (n = 98)	C	OR	R-SA / MDR-SA	1,3,40,41	Hospital / Community	Human	0.50
OVID 0753	Levin P.D. / 2010(446)	Toronto, ON, Canada, and	Adult	Acquisition	• Resistant organism • (n = 82)	C	OR	R-B	84	Hospital	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
		Jerusalem, Israel			• No Resistant Organism • (n = 341)							
OVID 0300	Li H. / 2014(447)	NA - Systematic review results	Mixed	Emergence (development)	6 trials	M	RR	R-B	3	Hospital	Human	0.89
OVID 0492	Li J. / 2012(448)	China	NA	Indirect transmission	Absolute concentrations of all PMQR genes combined ranged from 1.66 × 107 to 4.06 × 108 copies/mL	C	RR	AZ-R-B	6	Community	Human/Environment	0.33
OVID 0360	Liao C.-H. / 2013(449)	Taiwan	Adult	Colonisation (patients isolated with)	Cohort of (n=227) ; Positive for *qnr* (n=9), Negative for *qnr* (n=87),	C	PC	QR-KP	1,3,12,15,33, 33.1	Hospital	Human	0.67
OVID 2137	Libert M. / 2008(450)	Belgium	Adult	Infection	• MRSA BSI (n = 66) • MSSA BSI (n = 88)	CC	OR	MRSA	3,9,30,50	Hospital	Human	0.71
OVID 1336	Lietzau S. / 2006(451)	Germany	Adult	Colonisation	206 couples were included in the analysis.	C	OR	R-EC	7	Community	Human	0.50
OVID 2164	Lietzau S. / 2007(452)	Germany	Children	Colonisation	• Total study population • (n = 884) • Children with stool samples at baseline • (n = 786) • Children with EC colonization at	C	OR	APR-EC/DXR-EC	1,7	Hospital / Community	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					baseline (n = 492)							
OVID 0206	Lim C.J. / 2014(453)	Australia	Adult	Infection	• Cases (n = 180) • Controls (n = 180)	CC	OR	MDR-B/ MDR-GN/MRSA	MDR-B: 2,3,9,12,16,25; MRSA: 1,2,9,16	Hospital / Community	Human	0.86
OVID 0271	Lim C.J. / 2014(454)	Australia	Adult	Colonisation	• Total (n=24) • Colonization with MDR (n=41) • Colonization without MDR colonization (n=74) • Colonization with MRSA, (n=18) • Colonization with MDR GNB (n=23)	CC	OR	MDR-GN / MDR-B / MRSA	MDR-B: 3,13,16; MRSA: 2,3	Hospital / Community	Human	0.86
OVID 0980	Lin M.-F. / 2009(455)	Taiwan	Adult	Acquisition	• AB isolates (614) • 120 isolates from 53 patients were MDR-AB	CC	PC	MDR-AB	24	Hospital	Human	0.71
OVID 1779	Liss B.J. / 2012(456)	Germany	Adult	Infection	• ESBL-ENT (n = 90) • VR-ENTO (n = 51)	C	OR	ESBL-ENT	2	Hospital	Human	0.67
OVID 0764	Lo W.-U. / 2010(457)	China	Mixed	Carriage (Faecal)	• Admission children • (n = 53)	C	PC	CTX-M-ENT (ENT=KP/EC) ; R-EC	7,40	Hospital / Community	Human	0.33

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• Household children • (n = 29) • Household members • (n = 143)							
OVID 2230	Lodise T.P. / 2007(458)	United States	Adult	Infection	• Overall (n = 351); • MDR-PA (n = 122); • Non-MDR PA (n = 229)	CC	PC	MDR-PA /MRSA	2,3,11,16,24, 30,33,34,36	Hospital	Human	0.86
OVID 2394	Lu P.L. / 2005(459)	Taiwan	Mixed	Colonisation	• 2,231 subjects, including 1,838 community residents • 393 subjects from health care facility-related settings, were recruited for the study. • Health care worker (n = 139) • MRSA: Community (n = 64); • Healthcare facility (n = 27) •	C	OR	MRSA	1,47	Hospital / Community	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 0254	Lucena A. / 2014(460)	Brazil	Mixed	Infection	• MBL-PA (n = 58) • Non-MBL-PA (n = 26)	CC	OR	MBL-PA	34,45	Hospital	Human	0.71
OVID 0446	Luna R.A. / 2013(461)	United States	NR	Infection	Isolates from 32 patients (45%) were found to be members of the Houston-1 group, and the remaining 39 patients (55%) yielded isolates that were classified as a strain other than Houston-1.	C	OR	MDR-PA	1	Hospital / Community	Human	0.33
OVID 1982	Lupei M.I. / 2010(462)	United States	Adult	Infection	(n = 114)	C	OR	R-B	33	Hospital	Human	0.50
OVID 0513	Luvsansharav U. / 2012(463)	Thailand	Adult	Carriage (Faecal)	• Thong Pha Phum, (n=232) ; • Tha Maka, (n=185) • 289 of 417 (69.3%) samples contained ESBL-producing bacteria; • CTX-M gene (n = 274)	C (CS)	OR	CTX-M-ENT	1,3,26	Community	Human	0.67
OVID 1815	Lye D.C / 2012(464)	Singapore	Adult	Colonisation/acquisition	• Non-MDR bacteraemia (n = 374) • MDR bacteraemia (n = 301)	C	PC	MDR-GN	22,24,31,34,42	Hospital	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 1698	Ma H.M. / 2013(465)	China	Adult	Infection	• Study population • (n = 1176) • With pathogen • (n = 472) • Without pathogen • (n = 704)	C	RR	R-B	1,2,58	Hospital	Human	0.83
OVID 1645	Ma H.M. / 2014(466)	China	Adult	Infection	• Derivation cohort • (n = 354) • Validation cohort • (n = 96) • Derivation cohort : PDR pathogen • (n = 48) • No PDR pathogen • (n = 306) • Validation cohort: PDR pathogen • (n = 21) • No PDR pathogen • (n = 75)	C	PC	R-B	1,3	Hospital	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 0237	Machado A. / 2014(467)	West Africa (Guinea-Bissau)	NA	Indirect transmission	Four major wells that supply population with water for domestic use were visited during the dry (DS) and wet (WS) season of 2010	C	P	R-B	6	Community	Human/Environment	0.50
OVID 1670	Machida H. / 2014(468)	Japan	Adult	Infection	• Case (n = 11) • Non cases (n = 17)	CC	RR	MDR-PA	13	Hospital	Human	0.57
OVID 2264	Maclayton D.O. / 2006(469)	United States	Adult	Infection	• High-MIC Group • (n = 17) • Low-MIC Group • (n = 33) • Control (n = 100)	CC	OR	MRSA	2,54,63	Hospital	Human	0.86
OVID 0349	Macnow T. / 2013(470)	United States	Children	Colonisation	• NICU 1 (n = 1182) • NICU 2 (n = 569) • Antibiotic Resistant Organism Colonization • (n = 91) • No Antibiotic Resistant Organism Colonization • (n = 1660)	C	OR	R-B (MRSA/VR-ENTO/R-GN)	11	Hospital	Human	0.83

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 1243	Mammina C. / 2007(471)	Italy	Children	Colonisation	• Colonized with MDR-GN (n = 116) • Colonized with susceptible GN (n = 39) • Not colonized (n = 55)	C	PC	MDR-GN	3,13,24,34,51,86	Hospital	Human	0.50
OVID 0411	Mammina C. / 2013(472)	Italy	Adult	Colonisation	• Co-colonized (n = 30) • Not co-colonized (n = 45)	C	PC	CR-KP+AB	2,11,24,35	Hospital	Human	0.50
OVID 0566	Manageiro V. / 2012(473)	Portugal	Mixed	Emergence	• Non-ESBL (n = 24) • Total ESBL (n = 167)	C	OR	R-ENT	1,11,12,33.11,66,83	Hospital / Community	Human	0.17
OVID 0648	Mansouri M. / 2011(474)	Iran	NR	Acquisition	• Cases (n = 73) • Control (n = 182)	CC	OR	CFR-EC	3,13,31,33,33.1,34,35,36	Hospital	Human	0.43
OVID 1235	Manzur A. / 2007(475)	Spain	Adult	Infection	• MRSA-BSI (n = 50) • MSSA-BSI (n = 98)	CC	OR	MRSA	9,31	Hospital	Human	0.86
OVID 2064	Manzur A. / 2008(476)	Spain	Adult	Carriage	• MRSA carriers (n = 231) • Non-MRSA carriers (n = 1146)	C (CS)	OR	MRSA	1,2,3,11,13,16,48	Hospital / Community	Human	0.67
OVID 1928	March A. / 2009(477)	Italy	Adult	Colonisation	• LTCF (residents) (n = 111)	C	OR	MRSA/ESBL-B/R-B	MRSA: 2 ; ESBL-B:	Hospital / Community	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• LTCF (staff) (n = 69) • Geriatrics unit (patients) (n = 45)				3,11,22; R-B:2,11,13,22			
OVID 0146	Marchenay P. / 2015(478)	France	Adult	Acquisition	• Patient carrying CR-GNB (n = 23) • Patients not carrying CR-GNB (n = 324)	C	OR	CR-GN	3,22,33	Hospital	Human	0.83
OVID 1753	Maseda E. / 2013(479)	Spain	Adult	Carriage (bile samples)	(n = 198)	C	OR	R-B	13	Hospital / Community	Human	0.83
OVID 1464	Mathews Wm.C. / 2005(480)	United States	Adult	Infection	• Clinically Significant-MRSA (n = 94) • Controls (n = 3361)	C	HR	MRSA	2,3,85	Hospital / Community	Human	0.67
OVID 1933	McCarthy N.L. / 2010(481)	United States	NR	Infection	352 infections with unique positive MRSA cultures during the 1-year study period from 321 patients.	C	OR	MRSA	1,3,13,60	Hospital / Community	Human	0.67
OVID 2251	McGregor J.C. / 2006(482)	United States	Adult	Infection	• The MRSA cohort contained 56,125 inpatient admissions • The VR-ENTO cohort contained 57,785 inpatient admissions	C	OR	VR-ENTO / MRSA	MRSA: 2,3,9,24,33; VR-ENTO: 2,3,24,33	Hospital	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
AS0003	McKinnell / 2013(483)	International	Adult	Colonisation	• Hospital admission • (n = 31429) • ICU admission • (n = 5568)	M	OR	MRSA	1,2,3,9,13,16, 28,30,31,45,5 0	Hospital	Human	0.89
OVID 0388	McLaughlin M. / 2013(484)	United States	NR	Emergence (correlation)	A total of 27,818 isolates were identified as ENT	C	CRC	CR-ENT	3	Hospital	Human	0.50
OVID 1816	McNulty C.A. / 2012(485)	United Kingdom	NR	Emergence (prevalence)	• Total sample (n = 7791) • Resistant specimens (n = 2063)	C	RR	LR-HP	3	Hospital / Community	Human	0.50
OVID 1590	Memish Z.A. / 2015(486)	18 countries: Africa to Asia (Country* Algeria Chad Comoros Egypt Ethiopia Guinea India Indonesia Libya Mauritania Nigeria Sudan Alg.+India+Indo nes.	Adult	Carriage	3203 subjects (1590 at beginning of Hajj and 1613 at end of Hajj, all unique individuals)	C (CS)	CRC	R-STR(p)	5	Community	Human	0.33

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
		Africa Asia)										
OVID 1533	Mendelson G. / 2005(487)	Israel	Adult	Emergence (appearance of resistant organism)	• ESBL-positive group (n=105) • ESBL-negative group (n=104)	CC	OR	ESBL-ENT	2,3,13	Hospital / Community	Human	0.86
OVID 1197	Merlo C.A. / 2007(488)	United States	Children	Acquisition	• MDR-PA positive (n = 341 • MDR-PA (negative) (n = 3,952)	C	HR	MDR-PA	3,30,44	Hospital	Human	0.83
OVID 1399	Messi P. / 2006(489)	Italy	NA	Indirect transmission	Total isolates 616: 120 meat samples: (35 bovine,7 equine, 42 poultry, 25 swine, 11 other samples); 123 environmental samples: (88 superficial waters, 15 solid waste, 20 air)	C	P	R-ENTO	4	Community	All	0.33
OVID 1778	Meyer E. / 2012(490)	Germany	Adult	Colonisation	• ESBL-positive (n = 8) • ESBL-negative (n = 223)	C	OR	ESBL-EC	5,8	Community	Human	0.33
OVID 1881	Michalopoulos A. / 2011(491)	Greece	Adult	Emergence (development)	• Study group (n=42) • Control group (n=42)	CC	PC	MDR-GN	30	Hospital	Human	0.57
OVID 0679	Miliani K. / 2011(492)	France	NR	Emergence (incidence)	A total of 13,993 PA. isolates tested for	C	OR	R-PA	3	Hospital	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					antimicrobial susceptibility							
OVID 1095	Millar M. / 2008(493)	United Kingdom	Children	Colonisation	• MDR-ENT (n = 62) (50%) acquired by 2 weeks of postnatal age • (n = 69) (56%) infants had acquired MDR-ENT by discharge	C	PC	MDR-ENT (ENT=KP/EC)	3,86	Hospital	Human	0.50
OVID 0138	Min L. / 2015(494)	United States	Adult	Colonisation	(n = 111)	C	PC	DR-GN / MRSA / VR-ENTO	R-GN: 1,3,13,14,15, 16, (15)(shorter time to initial acquisition presented OR < 1) †; MRSA: 1,3,13,14,16, 22; VR-ENTO: 1,13,13, (1,3,16) †) (shorter time to initial acquisition presented OR < 1)	Hospital / Community	Human	0.67
OVID 1862	Minhas P. / 2011(495)	United States	Adult	Colonisation	• VR-ENTO (n = 19) • Non-colonized • (n = 747)	CC	PC	MRSA/VR-ENTO	1,2,3,9,31	Hospital	Human	0.71

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					• MRSA Colonized • (n = 35) • Non-colonized (n = 788)							
AS0008	Mitchel B.G / 2015(496)	International	NR	Transmission	• Events (n = 287) • Controls (n = 34,886)	M	OR	R-B	44	Hospital	Human	1.00
OVID 2160	Miyake M. / 2007(497)	Japan	NR	Infection	• MRSA cases (n = 49) • MRSA in oral cancer inpatients (n = 38)	C	I	MRSA / R-PA	2,3,11,12,13, 25,30,39,56,69,89	Hospital	Human	0.33
OVID 1162	Mody L. / 2007(498)	United States	Adult	Colonisation	• Residents with indwelling devices • (n = 100) • Control residents • (n = 100) • (14 nursing homes)	C (CS)	OR	MRSA	13	Hospital / Community	Human	0.50
OVID 0872	Montero M. / 2010(499)	Spain	Adult	Colonisation (Isolation)	• Non-PA (n=690) (44%) • S-PA (n = 532) (34%)	CC	OR	MDR-PA	1,2,3,42,44	Hospital	Human	0.57

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					• MDRPA (n = 345) (22%)							
OVID 0150	Montravers P. / 2015(500)	France	Adult	Colonisation (detected)	• Without persistent peritonitis (n = 122) • Persistent peritonitis (n = 98) • MDR strains (n = 63) • No MDR strains • (n = 110)	C	OR	MDR-B	12	Hospital	Human	0.83
OVID 2243	Morange-Saussier V. / 2006(501)	France	Adult	Carriage	• 468 swabs from 308 patients • MRSA (4.2%) • MSSA (11.4%)	CC	OR	MRSA / MR-B	1,9	Hospital	Human	0.86
OVID 0547	Morgan D.J. / 2012(502)	United States	Adult	Transmission	• 585 observed HCW–patient interactions, 180 were for VR-ENTO (n = 180) • MDR-AB (n = 167) • MRSA (n = 152) • MDR-PA (n = 86)	C	OR	MDR-B	46	Hospital	Human	0.83
OVID 1055	Morris S.R. / 2008(503)	United States	Adult	Transmission	(n = 63)	C	OR	FR-NG /MDR-GN	85	Hospital / Community	Human	0.33

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 2057	Mosqueda-Gomez J.L. / 2008(504)	Mexico	Mixed	Infection	• Cases (n = 17) • Controls (n = 104)	CC	OR	ESBL-KP	3,34	Hospital	Human	0.71
OVID 0434	Mossong J. / 2013(505)	Germany	Adult	Colonisation	• 19 LTCFs, 1962 residents (mean 103 per LTCF) • MRSA (n = 69)	C (CS)	OR	MRSA	2,3,15,31	Hospital / Community	Human	0.33
OVID 0208	Mozes J. / 2014(506)	Hungary	NR	Emergence (development of resistance)	160 bacterial isolates collected	C	CRC	CR-AB	3	Hospital	Human	0.67
OVID 2386	Nadesalingam K. / 2005(507)	United Kingdom	Mixed	Acquisition	• Cases (n = 15) • Controls (n = 30)	CC	PC	MRSA	2,3,24	Hospital	Human	0.43
OVID 0011	Nagy B. / 2015(508)	routine inspections at the airports of Vienna, Berlin, Frankfurt a.M. and Ljubljana	NA	Indirect transmission	The 600 food samples (The set of samples comprised 262 meat and meat products and 315 milk and meat products Another 18 samples were either fish, egg or bushmeat)	C	I	R-EC ; MDR-EC	4	Community	Human/Animal	0.33
OVID 1833	Nasa P. / 2012(509)	India	Adult	Emergence	• Overall (n=95) • ESBL-ENT (n=73) • Non-ESBL-ENT (n=22)	C	OR	ESBL-ENT	3,9	Hospital	Human	0.50
OVID 1666	Neulier C. / 2014(510)	France	Mixed	Colonisation	• Non-ESBL-ENT • (n = 2220)	C	OR	ESBL-ENT	1,31,33	Hospital	Human	0.83

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					• ESBL-PE (n = 135)							
OVID 2292	Nixon M. / 2006(511)	United Kingdom	Adult	Carriage	Colonised • MRSA positive • (n = 57) • MRSA negative • (n = 57) Infected: • MRSA positive • (n = 18) • MRSA negative • (n = 18)	CC	PC	MRSA	3,9,11,12,24, 35,61	Hospital	Human	0.43
OVID 0202	Nogueira Kd.a S. / 2014(512)	Brazil	Children	Infection	ESBL (n = 41) Non-ESBL (n = 164)	C	OR	ESBL-ENT	34	Hospital	Human	0.67
OVID 1260	Normanno G. / 2007(513)	Italy	NA	Indirect transmission	A total of 1634 samples (i.e., 993 meat products and 641 milk and dairy products)	C	P	R-SA	4	Community	Human/Animal	0.33
OVID 2330	Norstrom M. / 2006(514)	Norway	NA	Indirect transmission	Norwegian broilers: • 2001 (n=113) • 2002 (n =161) • 2003 (n =139)	C	OR	R-CJ	4	Community	Human/Animal	0.33

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					Humans infected in Norway: • 2001 (n = 84) • 2002 (n = 37) • 2003 (n=63) Humans infected abroad: • 2001 (n=129) • 2002 (n=110) • 2003 (n=144)							
OVID 0034	Noteboom Y. / 2015(515)	Netherlands	Adult	Emergence	(n = 213)	C	HR	R-PA	3	Hospital	Human	0.83
OVID 2248	Nseir S. / 2006(516)	France	Adult	Colonisation/infection	• MDR Bacteria • (n = 69) • No MDR Bacteria • (n = 788) • Bacteria Other Than MDR (n = 191) • No Bacteria (n = 597)	C	OR	MR-B	3,13	Hospital	Human	0.50
OVID 1926	Nseir S. / 2009(517)	France	Adult	Colonisation /infection	• MDR bacteria Yes • (n = 83)	C	OR	MDR-B	1,2,3,9	Hospital	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• No (n = 542)							
OVID 0584	Nseir S. / 2011(518)	France	Adult	Acquisition (ICU)	ICU-acquired MDR-PA: • Yes (n = 82) • No (n = 429) ICU-acquired A. baumannii: • Yes (n = 57) • No (n = 454) ESBL - producing GNB (n = 8) (6%)	C	OR	ESBL-GN / MDR-PA	ESBL-B:13,55 ; MDR-B: 3,12,44	Hospital	Human	0.83
OVID 0119	Nurjadi D. / 2015(519)	Thirteen centres (Amsterdam, Barcelona, Basel, Berlin, Hamburg, Helsinki, Munich, Paris, Rotterdam, Tübingen (two), Vienna and Würzburg)	Adult	Nasal carriage	• MRSA (n= 23) • MSSA (n=173)	C	OR	MRSA / MR-SA	5	Community	Human	0.67
SC0022	O'Fallon E. / 2010(520)	United States	Adult	Acquisition	• Present at baseline • (n = 66) • Acquired during study period (n = 68)	CC	OR	MDR-GN	3	Hospital / Community	Human	0.71

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• Cases (n = 29) • Controls (n = 29)							
OVID 0484	Olalekan A.O. / 2012(521)	Nigeria	Adult	Colonisation	374 HIV-infected patients and 370 healthy individuals contributed 125 and 77 SA strains, respectively.	C	PC	R-SA	2	Hospital / Community	Human	0.33
OVID 1233	Oliveira A.L. / 2007(522)	Brazil	Mixed	Infection	(n = 411)	C	OR	MDR-GN	1,3	Hospital	Human	0.50
OVID 1894	Orsi G.B. / 2011(523)	Italy	Adult	Acquisition	• Case patients (n = 38) • Control patients (n = 62)	CC	OR	ER-KP	1,2,3,13	Hospital	Human	0.71
OVID 1750	Orsi G.B. / 2013(524)	Italy	Adult	Colonisation (Isolation)	• Porin-ER-Kp patients • (n = 39) • KPC-CR-Kp patients • (n = 44) • Control patients • (n = 60)	CC	OR	ER-KP/KPC-CR-Kp	2,3,13	Hospital	Human	0.71
OVID 2039	Ortega M. / 2009(525)	Spain	Adult	Colonisation (Isolation)	EC (n = 4758)	C	OR	ESBL-EC/FR-EC	ESBL-EC:1,3,13 ; FR-EC: 1,3,13,33.1,83	Hospital	Human	0.83

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 0958	Ota K.V. / 2009(526)	Canada	Mixed	Infection	• QR isolates (695) • QS (688)	C (CS)	OR	QR-NG / CIR-EC	11,42	Community	Human	0.50
OVID 0945	Otsuka T. / 2009(527)	Japan	Children	Carriage	A total of 417 nasopharyngeal cultures were collected from 257 (252 included in final study) subjects belonging to group-2002–2004. In group-1996, 40 (1 nasopharyngeal and 39 throat) cultures were collected from 34 subjects.	C	PC	R-STR(p) / QR-NG	3,7,74	Hospital / Community	Human	0.33
OVID 0311	Ozgur E.S. / 2014(528)	Turkey	Adult	Infection	• Non-XDRAB (n = 100) • XDR-AB (n = 34)	C	OR	XDR-AB	22,24	Hospital	Human	0.83
OVID 1465	Ozkurt Z. / 2005(529)	Turkey	Mixed	Acquisition	• IR-PA (n = 40) • IS-PA (n = 93)	CC + C	OR	IR-PA	1,3,44,50	Hospital	Human	0.57
OVID 2327	Oztoprak N. / 2006(530)	Turkey	Adult	Infection	• Patients with MRSA infection (n = 21) • Patients without MRSA infection (n = 228)	C	OR	MRSA	3,13,34,44	Hospital	Human	0.83

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 1618	Papadimitriou-Olivgeris M. / 2014(531)	Greece	Adult	Colonisation	KPC-producing Klebsiella pneumoniae (KPC-Kp) - colistin resistant • Colonised patients (n = 62) • Non-colonized • patients (n = 192) KPC-producing Klebsiella pneumoniae Tigecycline-resistant • Colonised patients (n = 39) • Non-colonized patients • (n = 218) •	C	OR	KPC-KP	3,13,24,44,63	Hospital	Human	0.83
OVID 0071	Papadimitriou-Olivgeris M. / 2015(532)	Greece	Adult	Colonisation (upon ICU admission)	All patients: (n=481); KPC-KP (+) patients (n=59); VRE (+) patients (n=63); MRSA (+) patients (n=20)	C	OR	KPC-KP/VR-ENTO/MRSA	KPC-KP (at ICU):2,3,31,33,89 KPC-KP (during ICU admission): 2,3,12,44; VR-ENTO (at ICU):2,3,30,31; ;VR-ENTO (during ICU admission):2,31,44; MRSA (at ICU):	Hospital	Human	0.83

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
									22,31; MRSA (during ICU admission): 30,31,42			
OVID 1795	Park S.C. / 2012(533)	South Korea	Adult	Infection	• PDR (n=122) • Non-PDR (n = 217) • CAP (n=172) • HCAP (n=167) Type of pneumonia: Community-acquired • PDR: (n = 41) (33.6%) • Non-PDR: (n = 131) (60.4%), Health care associated: PDR: (n = 81) (66.4) • Non-PDR: (n = 86) (39.6)	C	OR	R-B	3,13,24	Hospital / Community	Human	0.67
OVID 1572	Park SH. / 2015(534)	South Korea	Adult	Acquisition	• CA-ESBL group • (n = 75) • CA-non-ESBL group (n = 225)	CC	OR	ESBL-EC	3,11,30	Community	Human	0.71
OVID 1869	Park Y.S. / 2011(535)	South Korea	Adult	Acquisition	• Cases (n = 33) • Controls (n = 66)	CC	OR	XDR-PA	22,36	Hospital	Human	0.86

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OVID 0856	Park Y.S. /2010(536)	South Korea	Adult	Acquisition	• Cases (n = 26) • Controls (n = 52)	CC	OR	XDR-AB /MR-SA	3,22	Hospital	Human	0.57
OVID 1081	Parker C.M. / 2008(537)	United States and Canada	Adult	Infection	• MDR-B (n = 75) • No MDR (n = 664)	CC	OR	MDR-B	24,34	Hospital	Human	0.86
OVID 0140	Pascual V. / 2015(538)	Spain	Adult	Infection	• Cases (n = 214) • Controls (n =428)	C	OR	AmpC-EC	3	Hospital / Community	Human	0.83
OVID 0431	Pasquale T.R. / 2013(539)	United States	Adult	Emergence	• Early-onset (n = 42) • Late-onset (n = 92)	C	PC	MDR-B in MRSA	3,31	Hospital	Human	0.50
OVID 1642	Patel S.J. / 2014(540)	United States	Mixed	Infection	• Cases (n = 103) • Controls (n = 195)	CC	OR	XDR-GN	2,3	Hospital	Human	0.86
OVID 1392	Pena C. / 2006(541)	Spain	Adult	Acquisition	• Cases (n = 103) • Controls (n = 103)	CC	OR	ESBL-EC	3,13,54	Hospital	Human	0.71
OVID 1000	Pena C. / 2009(542)	Spain	Adult	Acquisition	394 patients had CR-PA 246 (62%) non-ICU patients were included in the present study	C	OR	MDR-PA / MDR-STR(p)	3,13,33.1	Hospital	Human	0.33
OVID 0712	Pena C. / 2012(543)	Spain	Adult	Infection	151 nosocomial episodes	C	OR	XDR-PA	3	Hospital	Human	0.67
OVID 0218	Peng Y. / 2014(544)	China	NR	Infection	Overall prevalence of MDR-PA was 54.0% (188/ 348)	CC	OR	MDR-PA	3,13	Hospital	Human	0.71

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OVID 0879	Perez F. / 2010(545)	United States	NR	Infection	(n = 75)	C (CS)	PC	CR-AB	36	Hospital	Human	0.33
OVID 0659	Peters P.J. / 2011(546)	United States	Adult	Colonisation	• MRSA colonization (n=79) • MSSA colonization (n=180) • SA colonization (n=341)	C	OR	MRSA	31,72,81	Hospital / Community	Human	0.67
OVID 1269	Playford E.G. / 2007(547)	Australia	Adult	Infection	• 66 of 1431 (4.6%) patients admitted for ≥48 hrs acquired CR-AB • CR-AB infection occurred in 34 patients (52%), including pneumonia (19 patients), bloodstream (seven), surgical site (four), urine (three), and unknown site (one).	CC	OR	CR-AB	3,13,35,44	Hospital	Human	0.43
OVID 0720	Pollett S. / 2012(548)	Peru	NR	Indirect transmission	Susceptibilities were reviewed for a total of 4,652 non-duplicate isolates	C	P	R-CJ	4	Community	Human/Animal	0.67

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OVID 1056	Pop-Vicas A. / 2008(549)	United States	Adult	Colonisation	• Total (n = 84) • Colonized with MDR-GN (n = 43) • Not-Colonized with MDR-GN (n = 41)	C (CS)	OR	MDR-GN / (PNR/TRS-R) - STR(p)	2,15	Hospital / Community	Human	0.33
OVID 1497	Pop-Vicas A.E. / 2005(550)	United States	Adult	Colonisation	• Case patients (n = 55) • Control patients (n = 55)	CC	OR	MDR-GN	3,9,11	Hospital / Community	Human	0.71
OVID 0959	Presi P. / 2009(551)	Switzerland	Mixed	Indirect transmission (food)	320 chicken from 160 flocks, 100 pigs (one animal per herd), 100 cattle (one animal per herd) and 500 calves from 129 herds	C	PC	R-B	4	Community	Human/Animal	0.50
OVID 1146	Price L.B. / 2007(109)	United States	Adult	Carriage	• Poultry workers • (n = 16) • Community referents (n = 33)	C	OR	GR-EC/MDR-EC	8	Community	Human/Animal	0.67
OVID 1915	Quintero B. / 2011(552)	Venezuela	Children	Colonisation	• Children = 250 • Str(p) colonization • (n = 71) • SA colonization • (n =141)	C (CS)	OR	R-GP	92	Community	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• Co- colonization • (n = 39)							
OVID 0862	Rattanaumpawan P. / 2010(553)	United States	Adult	Infection	• Cases (n = 251) • Controls (n = 263)	CC	OR	FR-GN	1,2,3,24,42,43	Hospital	Human	0.86
OVID 1891	Rattanaumpawan P. / 2011(554)	United States	Adult	Acquisition	• Cases (n = 136) • Controls (n =139)	CC	OR	FR-ENTO	1,2,3	Hospital	Human	0.86
OVID 1760	Rettedal S. / 2013(555)	Norway	Children	Colonisation	• Colonized infants • (n = 44) • Non-colonized • (n = 55)	C	OR	ESBL-KP	3,86	Hospital	Human	0.67
OVID 1984	Reyes K. / 2010(556)	United States	Adult	Colonisation/Infection	• Patients with VR-ENTO (n = 329) • Patients with VR-ENTO and MRSA (n = 81)	C	OR	VR-ENTO + MRSA	3,31,94	Hospital	Human	0.67
OVID 1648	Roberts M.J. / 2014(557)	varied geographical origin, including six from North America, two from Europe and one from Northeast Asia	Adult	Infection		M	OR	FR-B	3,45	Hospital / Community	Human	0.96

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OVID 1413	Rodriguez-Bano J. / 2006(558)	Spain	Adult	Colonisation/Infection	• Case patients (n = 47) • Control group 1 • (n = 94) • Control group 2 • (n = 85)	CC	OR	ESBL-EC	3,13,45	Hospital	Human	0.71
OVID 1989	Rodriguez-Bano J. / 2010(559)	Spain	Mixed	Infection	• Case patients (n = 95) • Control group A • (n = 190) • Control group B • (n = 188) • Case Patients with Community-Onset Bacteremia Due to ESBL-EC compared with Patients with Community-Onset Sepsis (Control Group A) and Patients with Community-Onset Bacteremia Due to Non-ESBL–EC (Control Group B)	CC	OR	ESBL-EC	3,13,33.1	Hospital / Community	Human	0.86

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 0733	Rogers B.A. / 2012(560)	Residing in Australia	NR	Carriage	274 EC isolates from 102 participants	C	OR	MR-EC	5,7	Community	Human	0.50
OVID 1654	Rogers B.A. / 2014(561)	Six geographically dispersed tertiary centers in Australia (n = 5) and New Zealand (n = 1) participated	Adult	Infection	• Cases (n = 91) • Controls (n = 94)	CC	OR	ESBL-EC	3,5,43,33.1,45	Hospital / Community	Human	0.71
OVID 2072	Rogers M.A. / 2008(562)	United States	Adult	Infection	All: 56,182 ; Annual Incident rate of antibiotic - resistant infections 12.7 per 1000 person	C	OR	R-B	1,2,9,11,13,30,42	Hospital / Community	Human	0.50
OVID 2078	Rogers S.N. / 2008(563)	United Kingdom	Adult	Acquisition	• Total (n = 287) • MRSA (n = 39)	C	OR	MRSA	2	Hospital	Human	0.50
OVID 1312	Roghmann M.-C. / 2006(564)	United States	Adult	Colonisation	• Total (n = 84) Colonization With FR-GN • Yes (n = 20) • No (n = 64)	C (CS)	PC	FR-GN	3,13,35	Hospital / Community	Human	0.33
OVID 1637	Romaniszyn D. / 2014(565)	Poland	Adult	Colonisation	Nasal swabs from 193 residents were obtained. Overall in PPS, 56 residents (29.0%) were colonized with SA,	C	OR	MRSA	11,22,42	Hospital / Community	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					MRSA (n = 23)							
OVID 0936	Rooney P.J. / 2009(566)	Northern Ireland	Adult	Carriage	• Faecal sample: (n = 294) • Total care homes (16) • MDR-EC were cultured from 119 (40.5%) of these specimens.	C	OR	MDR-EC / R-STR(p)	3,45	Hospital / Community	Human	0.17
OVID 0855	Rosengren A. / 2010(567)	Sweden	NA	Indirect transmission (food)	43 farm dairies out of 52 (83%) that met the inclusion criteria, participated in the survey. Of participating dairies, 77% used pasteurized milk and 93% used starter culture. Fresh cheese was the predominant cheese type (52%), followed by Camembert (24%) and Chevre (15%).	C	P	R-B	4	Community	Human/Animal	0.67
OVID 0994	Routh J.C. / 2009(568)	United States	Mixed	Emergence (increasing prevalence)	7,100 and 9,985 urine cultures from 1997 and 2007; For the multivariate analysis: 74 patients with urine cultures positive for MRSA in 2007 to 2 randomly	C	PC	MRSA	1,11,13	Hospital	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					selected, equal size groups of patients with MSSA and EC bacteriuria							
OVID 0864	Routsi C. / 2010(569)	Greece	Adult	Acquisition	• CS-AB (n = 66) • CR-AB (n = 30)	C	OR	CR-AB	13,31	Hospital	Human	0.83
OVID 0558	Ruppe E. / 2012(570)	France	Adult	Carriage	• All patients (n=500) • ESBL-negative subjects (n=467) • ESBL-positive subjects (n=33)	C	OR	ESBL-ENT	3	Hospital	Human	0.83
OVID 0154	Russo A. / 2015(571)	Italy	Adult	Colonisation (isolation)	• LIN-R (n = 38) • LIN-S (n = 40) • Control (n = 90)	CC	HR	LR-SA	1,3	Hospital	Human	0.86
OVID 1652	Sadowy E. / 2014(572)	Poland	NA	Indirect transmission	428 isolates mainly identified	C	P	R-ENTO	6	Community	Human/Environment	0.33
OVID 0568	Sanchez-Romero I. / 2012(573)	Spain	Adult	Acquisition	• Case patients • (n = 55) • Control patients • (n = 55)	CC	OR	CR-KP	3,13,36	Hospital	Human	0.86
OVID 1602	Satlin M.J. / 2014(574)	United States	Adult	Emergence	• VR-ENTO (n = 39)	C	HR	VR-ENTO	2	Hospital	Human	0.50

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					• No VR-ENTO • (n = 199)							
OVID 2358	Sax H. / 2005(575)	Switzerland	Adult	Carriage	• Derivation cohort • (n = 672) New MRSA-positive case (n = 31) • MRSA negative (n = 641) • Validation cohort (n = 350) New MRSA-positive case (n = 48) • MRSA negative • (n = 302)	C	OR	MRSA	1,3	Hospital	Human	0.83
OVID 0400	Schaumburg F. / 2013(576)	Gabon, Central Africa	Children	Carriage	200 hospitalised children • ESBL-ENT (n = 90); • K-pneumonia (n=67) ; • *E. coli* (n=30) • *E. cloacae* (n=10)	C (CS)	OR	ESBL-ENT	1,11,24	Hospital	Human	0.50

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OVID 0379	Schelenz S. / 2013(577)	United Kingdom	NR	Emergence (change in resistance levels)	• Total significant bacteraemia episodes (914) over a 14 year period • Episodes attributed to patients with: haematological malignancies (473) • with solid cancer episodes (441) •	C	I	R-GN	3	Hospital	Human	0.67
OVID 0530	Schlackow I. / 2012(578)	United States	Adult	Emergence (incidence)	• Total cases: (n = 2240) • Susceptible: (n = 1728) • Resistant: (n = 512)	C	OR	R-EC	1,28,102	Hospital	Human	0.67
OVID 0507	Schoevaerdts D. / 2012(579)	Belgium	Adult	Colonisation	• Study population • (n = 337) • ESBL-ENT negative (n = 298) • ESBL-ENT positive • (n = 39) • MRSA negative	C	OR	ESBL-ENT / MRSA	ESBL-ENT: 13,22,73; MRSA:16,22,56	Hospital	Human	0.83

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• (n = 296) • MRSA positive • (n = 24)							
OVID 1963	Schreiber M.P. / 2010(580)	United States	Adult	Infection	• Total (n = 190) • HCAP (n = 94) • CAP (n = 96) • Resistant Organism • (n = 60) • No Resistant Organism (n = 130)	C	OR	R-B	2,9	Hospital / Community	Human	0.50
OVID 2129	Schwaber M.J. / 2008(581)	Israel	Adult	Colonisation (Isolation)	• CR-KP (n = 48) • CS-KP (n = 56)	CC	OR	CR-KP	3,22,34	Hospital	Human	0.86
OVID 0616	Schweickert B. / 2011(582)	Germany	NR	Acquisition (nosocomial)	• Total patients: (n = 228,703) • Total MRSA cases (n = 4279) • Total ICUs (140)	C	I	MRSA	44	Hospital	Human	0.50
OVID 2268	Seguin P. / 2006(583)	France	Adult	Infection	• MDR-B negative • (n = 79) • MDR-B positive	C	OR	MDR-B	24	Hospital / Community	Human	0.83

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					• (n = 14)							
OVID 0934	Seidman J.C. / 2009(584)	India	Children	Carriage	• 121 students • 120 stool samples • 119 *E.coli* samples tested • Resistant >=1 (n = 75) (63%) • (n = 38) (32%) were MDR	C (CS)	OR	MDR-EC/ R-EC	7	Community	Human	0.50
OVID 1935	Sheng W.H. / 2010(585)	Taiwan	Mixed	Infection	Colonization: • CR-AB (n = 30) • CS-AB (n = 30) Infection: • CR-AB (n = 91) • CS-AB (n = 97)	C	PC	CR-AB	3,24,31,33	Hospital	Human	0.83
OVID 1999	Shi S.H. / 2009(586)	China	Adult	Infection	• Non-MDR (n = 82) • MDR (n = 70)	C	OR	MDR-GN	2,12	Hospital	Human	0.67
OVID 0800	Shi S.H. / 2010(587)	China	Adult	Infection	• Total LT recipients • (n = 475) • Not infected (n = 418) • Infected (n = 57)	C	OR	MDR-B / CIP-CON-SA	2,12,13	Hospital	Human	0.83

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OVID 0924	Shigehara K. / 2009(588)	Japan	Adult	Infection	(n = 170) (FR-EC (n = 39) FS-EC (n = 131) ESBL-EC (n = 6) non-ESBL-EC (n = 164))	C	OR	FR-EC/ESBL-EC	R-EC: 1,3 ; ESBL-EC: 1	Hospital	Human	0.50
OVID 0417	Shilo S. / 2013(589)	Jerusalem	Mixed	Acquisition	• CR-KP (n = 135) • CS-Kp (n = 127)	CC	OR	CR-KP	3,12,13,33	Hospital	Human	0.57
OVID 1688	Shindo Y. / 2013(590)	Japan	Adult	Infection	• Total patients (n = 1,413) • CAP (n = 887) • HCAP (n = 526)	C	OR	R-STR(p)	1,2,3,13,15,56	Hospital / Community	Human	0.83
OVID 0177	Shoai Tehrani M. / 2014(591)	France	Mixed	Acquisition	• All patients (n = 219) • Patients with resistant strains (n = 39)	C	OR	R-GN	12	Hospital	Human	0.67
OVID 1031	Shorr A.F. / 2008(592)	United States	Adult	Infection	• Pathogen (n = 289) • No Resistant Pathogen (n = 350)	C	OR	R-B	1,2,9,33	Hospital	Human	0.50
OVID 2212	Skiest DJ / 2007(593)	United States	Adult	Infection	• MRSA (n = 119) • MSSA (n = 71)	C	OR	MRSA	3,45,75	Hospital / Community	Human	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 2266	Skippen I. / 2006(594)	United Kingdom	Mixed	Infection	• Cases (n = 50) • Controls (n = 50)	CC	OR	ESBL-ENT (ENT: KP/EC)	3,24,34	Hospital	Human	0.71
OVID 1985	Slama K.B / 2010(595)	Tunisia	NA	Indirect transmission (food)	79 food samples of animal origin (26 of poultry, 28 of sheep, 14 of beef, 10 of fish, and 1 of horse)	C	P	R-EC	4	Community	Human/Animal	0.50
OVID 0086	Smith J.M. / 2015(596)	United States	Adult	Emergence (predictor of resistance)	• Cases (n = 26) • Controls (n = 75)	CC	OR	R-GN	3	Hospital	Human	0.43
OVID 0508	Smithson A. / 2012(597)	Spain	Adult	Emergence (prevalence)	• All patients (n = 153) • QS-EC (n=101) • QR-EC (n=52)	C (CS)	OR	QR-EC	3,45	Community	Human	0.83
OVID 0647	Snyder G.M. / 2011(598)	United States	Adult	Colonisation	• Singly colonized (n = 42) • Co-colonized (n = 11)	C	PC	MR-ENT	15	Hospital / Community	Human	0.33
OVID 1736	Sohn K.M. / 2013(599)	South Korea	Adult	Carriage	(n = 127)	C	HR	VR-ENTO	2,3,9,12	Hospital	Human	0.83
OVID 1994	Song J.Y. / 2009(600)	Korea	Adult	Colonisation	• VR-ENT colonized • (n = 34) • Non-colonized • (n = 34)	CC	OR	VR-ENTO	3,9	Hospital	Human	0.71

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 0999	Souli M. / 2009(601)	Greece	Adult	Colonisation	• Total patients • (n = 370) • Rectal swabs (370) • Environment specimens (106) • VRL-ENTO(f) Positive (n = 5) • VRL-ENTO(f) negative (n = 15)	C (CS)	OR	VLR-ENTO(f)	1,2	Hospital	Human	0.50
OVID 2274	Srinivasan S. / 2006(602)	India	NR	Infection	• Total SA isolated (150) • MRSA strains (50).	C	PC	MRSA	1,2,3	Hospital	Human	0.50
OVID 0998	Sritippayawan S. / 2009(603)	Thailand	Children	Infection	Total patients admitted to ICU (n = 347)	C (CS)	OR	MDR-B ; MDR-PA	3,54	Hospital	Human	0.50
OVID 0536	Steensels D. / 2012(604)	Belgium	Adult	Carriage (Faecal)	• CIR-S (n = 178) CIR-R (n = 58) • CIR-R-EC (n = 52) • CIR-R-Other (n = 6)	C	PC	FR-EC	2,3	Hospital / Community	Human	0.50
OVID 0121	Sun J.D. / 2015(605)	China	Adult	Acquisition	EC isolates with: • IHEC (n = 83) • Non-IHEC (n = 249)	CC	OR	R-EC	42,66	Hospital	Human	0.71

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
OVID 1824	Sung Y.K. / 2012(606)	South Korea	Adult	Infection	Total (n =556) • Resistance (negative) (n =283) • Resistance (positive) (n =209) Nosocomial infection (n =396) • Resistance (negative) (n = 167) • Resistance (positive) (n = 172) Community infection (n =160) • Resistance (negative) (n =116) • Resistance (positive) (n =37)	C	OR	R-ENT	1,3,9,*(1.1)	Hospital	Human	0.67
OVID 1035	Tacconelli E. / 2008(607)	Italy	Adult	Colonisation	• Total (n = 514) • Infected (n = 137) • Colonised (n = 120)	CC	OR	MDR-AB / FR-NG	2,3,12,13,15, 31,33	Hospital	Human	0.57
OVID 0926	Tacconelli E. / 2009(608)	Italy	Adult	Acquisition	• Total sample: 896 participants • Nested study sample (n = 715	C	RR	R-B / MDR-EC	2,3,11,24	Hospital	Human	0.50

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					inpatients at risk of acquiring ARB colonization among those starting antibiotics. (42 cases and 673 controls)							
OVID 1221	Tam V.H. / 2007(609)	United States	Adult	Infection	• CR-PA (n = 18) • CS-PA (n = 33).	CC	OR	CR-PA	24	Hospital	Human	0.71
OVID 0774	Tam V.H. / 2010(610)	United States	Adult	Acquisition	• Susceptible (n = 84) • Resistant (n = 25)	C	PC	MDR-PA	2,3,22,24,30, 39,101	Hospital	Human	0.67
OVID 0244	Tan M.W. / 2014(611)	Singapore	NR	Emergence (predictor of resistance)	• Total non-repeat AB. tested 4,341 • Non-susceptibe isolated (3,414)	C	CRC	CR-AB	3	Hospital	Human	0.33
OVID 1940	Tangden T. / 2010(612)	Sweden	Mixed	Acquisition	• ESBL negative • (n = 76) • ESBL positive • (n = 24)	C (CS)	PC	ESBL-EC	5,47	Community	Human	0.50
OVID 0436	Taylor S. / 2013(613)	Canada	Adult	Carriage (Faecal)	• Total (n = 865) • CIR-GN (n = 166) • All other growth (n = 684)	C	OR	CIR-ENT (ENT=KP/EC/PA)	2,3	Hospital	Human	0.83

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OVID 1643	Tedja R. / 2014(614)	United States	Adult	NS	• Total (n = 107) • MDR (n = 49) • non-MDR (n = 58)	C	OR	MDR-B	1,3,24	Hospital	Human	0.33
OVID 1669	Tekin R. / 2014(615)	Turkey	Mixed	Infection	• Uninfected Patients • (n = 60) • Infected Patients • (n = 30)	CC	OR	MDR-AB	12,13,22	Hospital	Human	1.00
OVID 0343	Ternes Y.M. / 2013(616)	Brazil	Children	Colonisation	• Admission (n = 45) • Discharge (n = 244)	C	OR	CON-SA	24	Hospital	Human	0.67
OVID 0529	Thiebaut A.C.M. / 2012(617)	France	Adult	Emergence (correlation)	• Total patients (n = 893) • Rectal swabs (3,453)	C	CRC	ESBL-CRE	3	Hospital	Human	0.67
OVID 2177	Thomas S. / 2007(618)	United Kingdom	Adult	Carriage	(n = 162)	C	OR	MRSA	31	Hospital / Community	Human	0.67
OVID 2331	Toltzis P. / 2006(619)	United States	Children	Carriage	Patients colonised by pneumococci (n = 221)	C	OR	AZ-R-STR(p)	88.1	Community	Human	0.50
OVID 0225	Tsai M.H. / 2014(620)	Taiwan	Mixed	Infection	• All (n = 15) • Persistent infection • (n = 10)	C	PC	CR-PA	11	Hospital	Human	0.50

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					• Re-infection (n = 5)							
OVID 0307	Tsai M.H. / 2014(621)	Taiwan	Children	Acquisition	• MDR-GN (n = 70) • Non-MDR-GN (n = 306)	C	OR	MDR-GN	2,3	Hospital	Human	0.67
OVID 0122	Tsao F.-Y. / 2015(622)	Taiwan	Adult	Carriage	• Total (n = 360) • MRSA (n = 73) • Non-MRSA (n = 287)	C	OR	MRSA	11,16	Hospital / Community	Human	0.67
OVID 1595	Tsu J.H. / 2015(623)	Hong Kong	Adult	Carriage	• Total (n = 371) • Antimicrobial-resistant rectal flora carriage (n = 199) • ESBL/FR-B (n = 152)	C	OR	MR-ENT	3,30	Hospital / Community	Human	0.83
OVID 1607	Tukenmez T.E. / 2014(624)	Turkey	Adult	Carriage (Faecal - pre-biopsy)	• Pre-biopsy faecal culture (n = 400) • ESBL-ENT (n = 75)	C	OR	ESBL-ENT	3,30,31	Hospital / Community	Human	0.83
OVID 1845	Tumbarello M. / 2011(625)	Italy	Adult	Infection	• MDR (n=40) • Non-MDR (n=66) • Controls: (n=212)	CC	OR	MDR-PA	3,13,89	Hospital	Human	1.00

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					Nosocomial onset of infection: • MDR (n = 38) • Non-MDR (n = 54)							
OVID 0528	Tumbarello M. / 2012(626)	Italy	Adult	Infection	• MDR-PM (n = 36) • Non-MDR-PM • (n = 63) • Controls (n = 100)	CC	OR	MDR-PM	1,3,9,13	Hospital	Human	0.86
OVID 0149	Unger H.W. / 2015(627)	Papua New Guinea	Adult	Colonisation (detected)	• SPCQ (n = 436) • SPAZ (n = 418)	CC	PC	MAR-SA	3	Hospital	Human	0.71
OVID 1898	Valles J. / 2011(628)	Spain/Argentina	Adult	Infection	• CA-B (n = 343) • HCA-B (n = 131) • Hospital associated-B (n = 252)	C	OR	R-B	33.1,83	Hospital / Community	Human	0.67
OVID 1613	Van Aken S. / 2014(629)	Sweden	Adult	Emergence (predictor of resistance)	• Total (n = 210) • ESBL (n = 70) • Non-ESBL (n = 140)	CC	OR	ESBL-EC	31	Hospital	Human	0.71
AD003-CDC	Van Cleef, B. A. / 2011(630)	European Union	NA	Indirect transmission	43 laboratories in 23 European countries	C	CRC	MRSA - livestock	8	Community	Human/Animal	0.50

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OVID 0145	van Hoek A.H.A.M. / 2015(114)	Netherlands	NA	Indirect transmission (contamination)	• 1216 samples analysed originated mostly from The Netherlands (724) • Vegetables from: • Spain (290), Italy (93), Germany (53), France (24), Egypt (20), Morocco (8), and Belgium (4). • In total 583 (47.9%) conventional and 633 (50.1%) organic samples.	C	P	3GC-ENT	67	Community	Human/Environment	0.50
OVID 0421	Vandendriessche S. / 2013(113)	National database of the Belgian Federal Agency for the Safety of the Food Chain (FASFC),	NA	Indirect transmission (human carriage of zoonotic bacteria)	• On pig farms, nasal swabs were collected from 10 pigs of each production group (sows, piglets and fattening pigs) present. • On veal, dairy and beef farms, nasal samples were collected from 10 animals evenly	C	OR	MRSA	8	Community	Human/Animal	0.67

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					distributed over the farm. • Per broiler farm, 40 chickens from one flock were consecutively sampled in the nasal cavity and cloaca. • Nasal swabs were collected from 149 farmers and family members, originating from pig (n=25), veal (n=45), dairy (n=22), beef (n=21) and broiler (n=36) farms, and from a control group of 42 farmers and family members working and/ or living on 22 strictly horticulture farms, randomly selected from the FASFC database, where no animals were raised, but that grew cereal,							

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					fruit and/or vegetables.							
OVID 1454	Van't Veen A. / 2005(631)	Netherlands	Adult	Infection	• Cases (n = 7) • Controls (n = 14)	CC	OR	MDR-KP	44	Hospital	Human	0.57
OVID 1597	Vasudevan A. / 2014(632)	Singapore	Adult	Colonisation/infection	• No GN Infection/colonization (n = 1398) • R-GN Infection (n = 76)	C	CRC	MDR-AB	2,3,12,34,50	Hospital	Human	0.50
OVID 0106	Velickovic - Radovanovic R.M. / 2015(633)	Serbia	NR	Emergence (development)	• EC (n = 1045) • ENT (n = 53)	C	CRC	CFT-R-EC	3	Hospital	Human	0.50
OVID 0055	Vergara-Lopez S. / 2015(634)	Spain	Adult	Acquisition (infection)	• Cases (n = 27) • Controls (n = 45)	CC + C	OR	MDR-KP	34	Hospital	Human	0.71
OVID 1904	Vernaz N. / 2011(635)	Switzerland	NR	Emergence (incidence of resistance over time)	The monthly average incidence of R-EC 0.15 (range 0–0.41) clinical isolates per 1000 patient days.	C (T)	CRC	R-EC	3	Hospital / Community	Human	0.50
OVID 0069	Vibet M.-A. / 2015(636)	France	NR	Emergence	Non-duplicate ENT isolates (13,496)	C	CRC	ESBL-ENT	3	Hospital	Human	0.67
OVID 0984	Vigil K.J. / 2009(637)	United States	Adult	Infection	• Cases (n = 58) • Controls (n = 115)	CC	OR	MDR-EC	1,2	Hospital	Human	0.86

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OVID 1316	Volonakis K. / 2006(638)	Greece	Children	Carriage	A total of 2851 healthy pre-school children aged 1–6 years were included in both studies	C (CS)	OR	PN-R-STR(p)/ERT-R-STR(p)	3	Community	Human	0.50
OVID 2339	von Baum H. / 2005(639)	United States	Adult	Infection	• MRSA (n = 189) • Candida (n = 80) • VR-ENTO (n = 31) • ENT (n = 13)	C	OR	VR-ENTO/ 3GC-ENT	VR-ENTO: 25,36 3GC-ENT: 2,13,91	Hospital	Human	0.33
OVID 1123	von Gottberg A. / 2008(640)	South Africa	Children	Emergence	• non-susceptible • (n = 9) • susceptible (n = 1745)	C	RR	LR-STR(p)	33.1,38	Hospital	Human	0.50
OVID 0201	Voor In 't Holt A.F. / 2014(641)	15 countries	Mixed	NS	3,966 patient cases (ranging from 5 to 345 cases per publication)	M	OR	CR-PA	2,3,13,24,33, 104	Hospital / Community	Human	0.85
OVID 1337	Walsh C. / 2006(642)	Ireland	NA	Indirect transmission	• EC O157:H7 isolates (257) • Non-O157 EC (O111 and O26) isolates (31) from a variety of clinical and veterinary sources.	C	PC	MDR-EC/MR-EC/AMR	4	Community	Human/Animal	0.50

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OVID 2127	Wang F.D. / 2008(643)	Taiwan	Adult	Infection	• MRSA (n = 851) • MSSA (n = 297)	C	OR	MRSA	11,12,13,24,36	Hospital	Human	0.50
OVID 1745	Waturangi D.E. / 2013(644)	Indonesia	NA	Indirect transmission	40 samples of ice cubes	C (CS)	PC	R-VC	6	Community	Human/Environment	0.50
OVID 0605	Webster D.P. / 2011(645)	United Kingdom	Mixed	Infection	Study1: Case-control: • Outbreak strain (n=12) • Non-outbreak strain KP (n=40) Study 2: • All BSIs: all (n=2516) • EC (n=2070) • KP (n=446) • Admission BSIs: all (n=1386) • EC (n=1220) • KP (n=166)	CC	PC	MDR-ENT (ENT=KP/EC)	3,28,33.1	Hospital	Human	0.71
OVID 1446	Wendt C. / 2005(646)	Germany	Mixed	Carriage	• Cases (n = 163) • Controls (n = 1,543)	CC	OR	3GC-ENT	3,11,13	Hospital	Human	0.71

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OVID 0836	Wener K.M. / 2010(647)	United States	NR	Colonisation (Isolation)	Cases: • Non- ESBL (n = 444) • ESBL (n = 78) • Controls(n = 358)	CC	OR	ESBL-KP/MRSA	3	Hospital	Human	0.71
OVID 2015	Wibbenmeyer L. / 2009(648)	United States	Mixed	Carriage/infection	1.Case control study: • Cases (n = 132) • Controls (n = 264) 2. 61 patients were colonized or infected with MRSA or VRE on admission	CC + C	OR	MRSA/VR-ENTO/VRE/ MRSA	1,2,3,9,12,24, 54	Hospital	Human	1.00
OVID 0842	Wibbenmeyer L. / 2010(649)	United States	Adult	Acquisition	MRSA acquisition: • Cases (n = 33) • Controls (n = 33) VRE acquisition: • Cases (n = 61) • Controls (n = 61)	CC	OR	MRSA / VR-ENTO	3,13	Hospital	Human	0.71
OVID 2295	Wigglesworth N. /2006(650)	United Kingdom	Mixed	Colonisation (Isolation)	During the 12-month period of data collection, there were 845 infection control requirements for patient	C	CRC	MRSA	48,62	Hospital	Human	0.33

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					isolation, of which 185 (22%) were considered as failures to isolate within the first 24 h from the time of risk assessment.							
OVID 0216	Willmann M. / 2014(651)	Germany	Adult	Colonisation	• Cases (n = 31) • Controls (n = 93)	CC	OR	XDR-PA	3,13,69	Hospital	Human	0.86
OVID 2178	Worth L.J. / 2007(652)	Australia	Adult	Infection	• Cases (n = 14) • Controls (n = 45)	CC	OR	VR-ENTO(f)	2,3	Hospital	Human	0.71
OVID 0559	Wroe P.C. / 2012(653)	United States	Children	Carriage	Total (n = 1011)	C (CS)	OR	PR-STR(p)	11,74	Hospital / Community	Human	0.50
OVID 1910	Wu D. / 2011(654)	China	Adult	Infection	• Cases (n = 39) • Controls (n = 78)	CC	OR	CR-KP	3,33	Hospital	Human	0.86
OVID 0420	Wueppenhorst N. / 2013(655)	Germany	NR	Emergence (development)	H. pylori isolates (5296)	C	PC	R-HP	3,39	Community	Human	0.33
OVID 2341	Wyllie D.H. / 2005(656)	United Kingdom	NR	Infection	• Total admissions (54,749) • SA cases (n = 46) • MRSA cases (n = 37)	C	PC	MRSA	11,24	Hospital / Community	Human	0.17

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OVID 2148	Wyllie D.H. / 2007(657)	United Kingdom	Adult	Infection	The population with hospital exposure in the 365 days prior to 30 June 2001, 2002 and 2003 was 44,929, 45,716 and 46,173 respectively	C	I	MRSA	42	Hospital	Human	0.17
OVID 0701	Xia Y. / 2012(658)	China	Adult	Infection (outbreak)	• Cases (n = 7) • Controls (n = 19)	CC	PC	MDR-AB	2,3,13,34,82	Hospital	Human	0.57
OVID 1876	Yoon Y.K. / 2011(659)	South Korea	Adult	Carriage	• Case (n = 58) • Control group (n = 36)	CC	OR	VR-ENTO	3	Hospital	Human	0.71
OVID 0358	Yoon Y.K. / 2013(660)	Republic of Korea	Adult	Acquisition	• All (n = 112) • No subsequent bacteremia (n = 91) (81.2%) • Subsequent bacteremia • (n = 21) (18.8%)	C	OR	MDR-AB	3,69,89	Hospital	Human	0.50
OVID 0273	Young B.E. / 2014(661)	Singapore	Mixed	Colonisation	MRSA • No (n = 988) • Yes (n = 18) ESBL-ENT • No (n = 880)	C	OR	ESBL-ENT	3	Hospital	Human	0.67

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					• Yes (n = 124)							
AS0002	Zacharioudakis / 2015(662)	International	Adult	Colonisation	4,842 dialysis patients (0-437 cases colonised)	M	OR	VRE	1,2,3	Hospital	Human	0.96
AS0006	Zacharioudakis / 2014(95)	International	Adult	Infection	Evaluable sample size: 9-541	M	OR	MRSA	31	Hospital / Community	Human	0.89
OVID 1416	Zaoutis T.E. / 2005(663)	United States	Children	Infection	• ESBL (n = 35) • Non-ESBL (n = 105)	CC	OR	ESBL-ENT	3,50,54,89	Hospital	Human	0.86
OVID 2307	Zaoutis T.E. / 2006(664)	United States	Children	Infection	80 cases of SA infection in 2001, as compared with 235 cases during 2003	CC	OR	MRSA	33.1	Hospital / Community	Human	0.57
OVID 1777	Zarrilli R. / 2012(665)	Italy	Children	Acquisition	• Cases (n = 22) • Controls (n = 139)	CC	OR	XDR-AB	13,36	Hospital	Human	0.57
OVID 1537	Zavascki A.P. / 2005(666)	Brazil	Adult	NS	• Case (n = 93); • Study 1 (patients selected at random from the same unit): Control (n = 93) • Study 2 (IS-PA): Control (n = 65)	CC	OR	IR-PA	1,3,36	Hospital	Human	0.71
AS0005	Zervou / 2014 (HIV)(96)	International	Adult	Colonisation/Carriage	Total sample: 1325 - 1787	M	OR	MRSA	1,16	Hospital / Community	Human	0.93
AS0007	Zervou 2014 / (neonates)	International	Children	Colonisation/acquisition	12,284 screened neonates in 12 NICUs, 6	M	OR	MRSA	1	Hospital	Human	0.93

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	(667)				studies reported data on 7,107 children hospitalized in 6 PICUs. 1 study containing nonstratified data on 331 neonatal and pediatric patients.							
OVID 1541	Zhao SY. / 2016(668)	China	Adult	Carriage (faecal)	390 residents of the seven NHs (A–G) provided rectal swabs and ENT isolates cultured (457)	C (CS)	OR	ESBL-ENT	3,12	Hospital / Community	Human	0.67
OVID 0186	Zhao Z. / 2014(669)	China	Mixed	Colonisation	• CR-ENT colonized • (n = 20) • Not CR-ENT colonized • (n = 283)	CC	OR	CR-ENT	1,3,12,44	Hospital	Human	0.71
OVID 1716	Zheng Y.L. / 2013(670)	China	Adult	Acquisition	• CR-AB (n = 97) • CS-AB (n = 145)	C	OR	CR-AB	2,3,22,36	Hospital	Human	0.67
OVID 0565	Zhong L. / 2012(671)	China	Adult	Infection	(n = 153)	CC	OR	MDR-GN	3,13	Hospital	Human	0.71
SC0036	Zillich A.J. / 2006(672)	United States	NR	Emergence	A total of 448 hospitals (67%) responded to the survey	C (CS)	CRC	R-B	48,49,61	Hospital	Human	0.50
NEW 0173	Abernethy J./2017(166)	United Kingdom	Mixed	Emergence	Total (n = 1688)	C	PR	R-EC	1,3	Hospital/Community	Human	0.50

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NEW 0219	Ahn JH / 2017(673)	Korea	Adult	Infection	• Total community onset pneumonia (n = 1046) • CAP-DRPs (n = 105)	C	OR	R-B	13,15,33.1	Community/hospital	Human	0.83
Meta 5	Alevizakos M/2017(674)	Global	Mixed	Colonisation + Infection	• Patients with malignancy (n = 8391) • VR-ENTO pooled prevalence 20% (14%-26%)	M	RR	VR-ENTO	1,2,3,31	Hospital	Human	0.85
NEW 0335	Banach DB/2016(675)	United States	Adult	Colonisation	• VRE +ive (n = 27) • VRE -ive (n = 34)	C	OR	VR-ENTO	3,13	Hospital (Transplant unit)	Human	0.83
NEW 0089	Bencardino D. / 2017(676)	Italy	NA	Indirect transmission	No. Isolates of SA from egg shells (SA was identified from 27 out of 50 egg shells) (n = 34)	CS	P	R-SA	4	Community	Human/Animal	0.17
NEW 0079	Blanco N. / 2017(677)	United States	Adult	Transmission	• Total residents colonised with R-GN (n = 57) • Total residents not colonised with R-GN (n = 128) • HCW interactions per R-GN colonised resident (median = 17 (interquartile range, 12 to 21)	C (LTCF residents)	OR	R-GN	3, 109	Hospital (LTCF)	Human	0.67
NEW 0032	Bosch-Nicolau P./2017(678)	Spain	Adult	Infection	• CO-Acute Pyelonephritis (AP) (n = 287) • HCA-AP (n = 47)	C	OR	R-EC (R = Amoxicillin-clavulanate / Cefuroxime /	3,33.1,45	Hospital	Human	0.83

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								Cefotaxime /Ciprofloxacin)				
ASNEW 1	Bryce A./2018(54)	United Kingdom	Children	Infection	• Pathogens (n = 79) • Contaminants (n = 745)	C	OR	R-EC	3,11,41	Community (primary care)	Human	1.00
Meta 15	Bryce A/2016(53)	Global	Children	Infection	77,783 E coli isolates in urine.	M	OR	R-EC	3	Community (Primary care)	Human	1.00
Meta 212	Bryce A/2016(679)	Global	Children	Carriage	• R-EC isolates (OECD): 3864 • R-EC isolates (non-OECD): 6699	M	OR	R-EC	3	Community (primary care)	Human	0.96
NEW 0195	Campbell WR/2017(680)	United States	Adult	Infection	• Total military trauma patients (n = 2,699) • None/Non-MDR-GN (n = 2,454) • MDR-GN (n = 245)	C	PC	MDR-GN	3,12,22,31,36,54	Community/hospital	Human	0.67
Meta 18	Carmeli, Y/1999(681)	Global	Mixed	Infection	• Patients with hospital-acquired VR-ENTO (n = 586) - Cases (61% treated with vancomycin) • Controls (n = 1249, 26% treated with vancomycin)	M	OR	VR-ENTO	3	Hospital	Human	0.67
Meta 197	Carrara E/2017(682)	Global	Adult	Infection	73,595 patients	M	OR	ESBL-B/CR-B/MDR-GP/MDR-B	3	Hospital	Human	0.96

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NEW 0207	Chabah M/2016(683)	Morocco	Children	Infection	• Total (n = 157) • CR-ENT-infected patients (n = 34) • CS-ENT Infected (n = 123)	C (CC)	OR	CR-ENT (CPE)	3,13,31	Hospital (ICU)	Human	0.71
NEW 0196	Chaves L/2017(684)	Brazil	Adult	Infection	• Cases (n=29) • Controls (n=58)	CC	OR	CR-PA	3	Hospital (bone marrow transplant unit)	Human	0.86
NEW 0016	Chen C.-H./2017(685)	Taiwan	Adult	Infection	• All (n=152) • Cases (n=36) • Control (n=116)	C(CC)	PC	VRE-ENTO(f)	34,39	Hospital	Human	0.71
NEW 0066	Chervet D./2017(686)	France	Adult	Infection	• ESBL-ENT (n = 48) • Non-ESBL-ENT (n = 1088)	C (Community UTI)	OR	ESBL-ENT	2,3,11	Community	Human	1.00
NEW 0033	Chia L. / 0033(687)	United States	Adult	Infection	• Total Population (n = 59) • MDR-B +ve (n = 12) • MDRO-B –ve (n = 47)	C	OR	MDR-B	2,16	Hospital	Human	0.50
NEW 0043	Chiotos K./2017(688)	United States	Children	Colonisation/infection	• Cases (n = 63) • Controls (n = 126)	CC	OR	CR-ENT	3,12,36	Hospital	Human	0.71
NEW 0279	Cilloniz C/2016(689)	Spain	Adult	Infection	Total patients analyzed with community acquired pneumonia due to PA (n = 77) • MDR-PA (n = 22) • Non-MDR PA (n = 46)	C	OR	MDR-PA	3	Hospital (outpatient clinic - community acquired)	Human	1.00
NEW 0225	DiPippo AJ/2017(690)	United States	Adult	Infection	• Total leukemia patients (n = 139)	C	RR	R-ENTO(f2)	3	Hospital	Human	0.67

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					• Daptomycin non-susceptible (n = 16) • Daptomycin susceptible (n = 61)							
Meta 38	Dulon, M/2014(691)	Global	NA	Carriage	• No. of events (nursing staff): 143 • No. of event (other staff): 47	M	OR	MRSA	112	Hospital	Human	0.93
ECDC 2018	ECDC /2018(692)	Europe	NA	Indirect transmission	Variable	CS	P	R-Sal/MDR-Sal / R-EC /ESBL-EC/ R-CJ R/CC / R-ENTO(f) / R-ENTO (f2) /MRSA	4,8	Community	Human/Animal	0.50
ECDC/EFSA/EMA 2017	ECDC/EFSA/EMA 2017(106)	Europe	Mixed	Indirect transmission	Variable	CS	Partial Least Squares Path Modeling (PLS-PM). (Includes R2 and correlation coefficients)	R-EC/R-Sal/R-CJ	3,4,115	Hospital/Community	Human/Animal	0.50
NEW 0175	Egervarn M./2017(693)	Sweden	NA	Indirect transmission	5 sites (98 EC isolates tested for susceptibility)	CS	P	ESC-EC	6	Community	Human/Environment	0.33
Meta 240	Fasugba O/2015(694)	Global	Mixed	Infection	5 - 22679 UTI samples	M	P	CIP-R-EC	33.1	Hospital/Community	Human	0.96

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NEW 0224	Fernandez-Barat L/2017(695)	Spain	Adult	Infection	• MDR-PA (n=22) • Non-MDR-PA (n=42)	C	OR	MDR-PA	2	Hospital (ICU)	Human	1.00
Meta 46	Flokas, M/2017(696)	Global	Adult	Colonisation	9775 screened subjects	M	OR	ESBL-ENT	1,3,13,31,45	Hospital (LTCF)	Human	0.96
Meta 47	Flokas, M/2017(697)	Global	Children	Infection	347 patients to 9218 patients	M	RR	VR-ENTO	3,31	Hospital	Human	0.96
NEW 0129	Fox A./2017(698)	United Kingdom	NA	Indirect transmission	Raw meat samples from retail supermarkets (n = 124) includes: • pork (n = 63) • chicken (n = 50) • turkey (n = 11)	CS	P	MRSA /MDR-B isolates	4	Community	Human/Animal	0.33
NEW 0280	Freire MP/2017(699)	Brazil	Mixed	Acquisition + Infection	• Total patients undergoing Liver transplantation (n = 386) • Post-LT CR-ENT acquisition yes (n = 119), no (n = 206) • Patients with CR-ENT infection post-LT yes (n = 54), no (n = 324)	C	OR	CR-ENT	2,12,13,33.1	Hospital	Human	1.00
FSA 2016 - Survey	FSA/2016(93)	United Kingdom	NA	Indirect transmission	C. jejuni (230) C. coli (53)	CS	P	R-CJ/R-CC/MR-CC/MR-CJ	4	Community	Human/Animal	0.50
NEW 0292	Giacobbe DR/2017(700)	Italy	Adult	Infection	• Total CR-KP colonised cohort (n = 353) • CR-KP infection (n = 37)	C	HR	CR-KP	28,34,110	Hospital	Human	0.83

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NEW 0379	Gilbert EM/2017(88)	United States	Adult	Transmission	(n = 119) were transmitted VR-ENTO	C	PC	VR-ENTO	3	Hospital	Human	0.67
NEW 0355	Giuffre M/2016(701)	Italy	Children	Colonisation	• MDR-GN Colonized (n = 332) • MDR-GN Non-colonized (n = 820) • ESBL negative (n = 198) • ESBL positive (n = 134)	C	OR	MDR-GN/ESBL-GN	MDR-GN: 34 ; ESBL-GN:3	Hospital	Human	1.00
NEW 0044	Giufre M./2017(702)	Italy	Adult	Colonisation	• ESBL (n = 279) • No ESBL (n = 208) • MRSA (n = 84) • No MRSA (n = 403)	C (PPS)	OR	MRSA/ESBL-ENT	ESBL-ENT: 15; MRSA: 9,15	Hospital (LTCF)	Human	0.67
NEW 0058	Godic Torkar K. & Drazetic M./2017(703)	Slovenia	NA	Indirect transmission	88 strains	CS	P	R-GN	6	Community	Human/Environment	0.17
NEW 0358	Harries M./2016(704)	Germany	Children	Carriage	• ESBL-ENT carrier Yes (n = 5) • ESBL-ENT carrier No (n = 219)	CS	OR	ESBL-ENT	3,4,8	Community (nursery)	Human/Animal	0.33
NEW 0248	Hefazi M/2016(705)	United States	Adult	Infection	Total acute myeloid leukemia patients (n = 203) • VR-ENTO colonised at HCT (n=73) • Not VR-ENTO colonised at HCT (n=130)	C	OR	VR-ENTO	2,11,31	Hospital	Human	0.83
NEW 0181	Igbinosa E.O./2016(706)	Nigeria	NA	Indirect transmission	• Vibrio prevalence rate of 60.7% (334/550) isolates from 56 fish pond samples	CS	P	ARGs	6	Community	Human/Environment	0.17

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					• Vibrio isolates tested for susceptibility (n = 167)							
NEW 0392	Ilyas S/2016(115)	Pakistan	NA	Indirect transmission	Bacterial isolates (n = 127)	CS	P	R-(KP/*Enterobacter* spp/EC/*Pantoea* spp./*Citrobacter* spp/*Shigella* spp./*Proteus vulgaris*)/ R-GP	67	Community	Human/Environment	0.33
NEW 0287	Ishida T/2017(707)	Japan	Adult	Infection	Total cohort (immunocompetent patients with pneumonia) (n = 1559) • R-B (n = 51) • Non-R-B (n = 654)	C	OR	R-B	1,13,22,54	Hospital	Human	0.83
NEW 0303	Jacmel L/2017(708)	France	Children	Infection	Total cohort of febrile urinary tract infections (n = 474) • ESBL+ (n = 22) • Non-ESBL (n = 452)	C	OR	ESBL-GN	1,2,3,45	Hospital (paediatric ED)	Human	0.67
NEW 0010	Jang H.M. / 2018(709)	South Korea	NA	Indirect transmission	Coastal acquaculture sites (n = 12)	CS	P	Antibiotic resistant genes (ARGs)	6	Community	Human/Environment	0.33

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NEW 0321	Jiang HL/2017(90)	Taiwan	Adult	Infection	• VR-ENTO (n = 48) • VS-ENTO (n = 142)	CC	OR	VR-ENTO	2,3	Hospital	Human	0.71
NEW 0329	Kanayama A/2016(710)	Japan	Adult	Colonisation/infection	• Cases (MDR-PA) (n = 14) • Controls (not MDR-PA) (n = 28)	CC	OR	MDR-PA	13,82	Hospital (LTCF)	Human	0.57
NEW 0222	Kantele A /2017(89)	Scandinavia	Adult	Colonisation	• Total cohort of ESBL-ENT colonised travellers (n = 90) • Co-resistant ESBL-ENT (n = 48)	C	OR	co-resistant ESBL-ENT	3,11	Community	Human	1.00
NEW 0342	Karaaslan A/2016(711)	Turkey	Children	Colonisation	Total cohort (n = 762) CR-GNB (n = 176) • CR-ENT (n = 72/176) • CR-non fermenter-GN (n = 138/176)	CC	OR	CR-GN/CR-ENT/CR-(non fermenter)-GN	2,3,11,12,13, 34	Hospital (Paediatrics)	Human	0.86
NEW 0166	Kashoma I.P./2016(712)	Tanzania	NA	Indirect transmission	Total samples (n = 537) including: • Unpasteurized raw milk (n = 284) • cattle dressed carcass swab samples (n = 253) Geographically different municipalities (n = 3)	CS	P	R-CJ	4	Community	Human/Animal	0.33
NEW 0099	Khawaja T. / 2017(713)	Finland	Mixed	Colonisation	• Patients (n = 1122) • MDR carriers (n= 333) • Non-carriers (n =789)	CS	OR	MR-B	3,5	Community	Human	0.67
Meta 195	Kim MW/2018(714)	Global	Mixed	Infection	6,998 subjects	M	OR	MRSA	31	Community	Human	0.81

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NEW 0249	Kim S/2016(715)	United States	Mixed	Transmission (outbreak setting)	• Cases (n = 15) • Controls (n = 89)	C (CC)	OR/P	CR-ENT	1,13	Hospital	Human	0.71
NEW 0284	Lee CH/2017(716)	Taiwan	Adult	Infection	• Total cohort (community-onset monomicrobial Enterobacteriaceae bacteremia) (n = 1141) • ESBL producer (n=65) • Non-ESBL producer (n=1076)	C	OR	ESBL-ENT	1,3,9,30,45	Hospital (ED)	Human	0.83
NEW 0094	Li L. / 2017(717)	China	Mixed	Indirect transmission	• Total (n =1422) • Pig exposed participants (n =244) • Controls (n = 1178)	Cross sectional	PRR	MR-CON-SA / MR-Staphylococcus epidermidis / MR-Staphylococcus haemolyticus	8	Community	Human/Animal	0.50
NEW 0297	Li Z./2016(718)	China	Adult	Infection	Total cohort of nosocomial meningitis and ventriculitis patients (n = 132) • MDR-B (n = 69) • Non-MDR-B (n = 61)	C	OR	MDR-B	39	Hospital (neuro-critical care unit)	Human	0.83
Meta 96	Lin D/2017(719)	Global	NA	Indirect transmission	187 MRSA isolates	M	P	MRSA	113	Hospital	Human	0.93
Meta 97	Lin, J/2016(117)	Global	NA	Indirect transmission	813 MRSA isolates	M	P	MRSA	114	Community	Human	0.93

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Meta 102	Liu, P/2017(720)	Global	Mixed	Infection	3,627 participants	M	OR	CR-KP	1,2,3,13,24,33,34,36,89	Hospital	Human	0.96
NEW 0164	Masse J./2017(721)	France	Adult	Acquisition (ICU)	ICU-acquired R-B • Yes (n = 204) • No (n = 389)	C	OR	R-B	13,36,44	Hospital (ICU)	Human	1.00
NEW 0127	McKinnell J.A./2016(722)	United States	Adult	Colonisation	C (ICU patients): Surveillance study	C (ICU patients): Surveillance study	OR	VR-ENTO	3,24	Hospital (ICU)	Human	1.00
NEW 0354	Metersky ML/2016(723)	United States	Adult	Infection	• No MRSA or Pseudomonas (n = 59,854) • MRSA (n = 641)	C	OR	MRSA	1,3,9,11	Hospital (Veterans Health Administration)	Human	0.67
NEW 0341	Moghnieh R/2016(724)	Lebanon	Mixed	Colonisation	• Total ICU patients (n = 257) • XDR-AB (n = 40)	C	OR	XDR-AB	3,13,44	Hospital (ICU)	Human	0.83
NEW 0378	Munier AL/2017(725)	France	Adult	Acquisition	Total cohort of burn unit patients (n = 86) • MR-AB colonization at admission (n = 9) • No MR-AB colonization (n = 52) • MR-AB acquisition (n = 25)	C	HR	MDR-AB	3,12	Hospital (Burn unit)	Human	1.00
NARMS 2015	NARM/ 2014(726)	United States	NA	Indirect transmission	Variable	CS	P	R-Sal/MDR-Sal/R-EC/MDR-EC/R-ENTO(f)/MDR-	4	Community	Human/Animal	0.50

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								ENTO(f)/R-ENTO(f2)/ MDR-ENTO(f2)				
NEW 0107	Nour I./2017(727)	Egypt	Children	Infection (Late onset sepsis)	• CR-GN (n = 58) • Carbapenem susceptible (n = 100)	CC - Neonatal ICU	OR	CR-GN	13	Hospital	Human	0.86
NEW 0069	Osimani A. / 2017(728)	Netherlands, Belgium, France, Thailand	NA	Indirect transmission	40 samples of retail-edible mealworm larvae	CS	P	ARGs	4	Community	Human/Animal	0.33
NEW 0145	Osinska A./2017(729)	United Kingdom	NA	Indirect transmission	R-EC isolates (n = 317) identified from following sites: • Upstream river water samples (n = 4) , • untreated wastewater samples (n = 4) • treated wastewater (n = 4) • downstream river water samples (n = 4)	CS	P	R-EC / MDR-EC	6	Community	Human/Environment	0.33
Meta 132	Ou, Q/2017(730)	Global	NA	Indirect transmission		M	OR	MRSA	4	Community	Human/animal	0.93
Meta 133	Ou, Q/2017(731)	Global	NA	Indirect transmission	93 studies included/ total samples NR	M	OR	MRSA	4	Community	Human/animal	0.93
NEW 0307	Ozsurekci Y/2017(732)	Turkey	Children	Infection	• CR-GN (n = 31) • CS-GN (n = 66)	C	PC	CR-GN	3,24	Hospital	Human	0.67

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NEW 0090	Papadimitriou-Olivgeris M./2017(733)	Greece	Adult	Infection	• CR-PA BSI (n = 46) vs CS-PA BSI (n = 38) • Non–infected patients (n = 258) vs CR-AB BSI (n = 129)	CC	OR	CR-PA / CR-AB	CR-AB: 1,3 ; CR-PA: 1,13	Hospital	Human	1.00
NEW 0021	Park GE / 2017(734)	South Korea	Adult	Infection	• Case (n = 61) • Control (n = 91)	CC	OR	TI-AB	3,89	Hospital	Human	0.86
NEW 0169	Patchanee P./2016(735)	Thailand	NA	Indirect transmission	• Total pork samples (n = 82) • Sal +ive (n = 34) • Sal strains tested for resistance (n = 45)	CS	P	R-Sal	4	Community	Human/Animal	0.33
NEW 0290	Patriarca F./2017(736)	Italy	Mixed	Infection	• Total cohort of Hematopoietic Stem Cell Transplantation patients (n = 241) • MDR-GN infective episode (>=1) (n = 25)	C	HR	MDR-GN	12,31	Hospital (transplant unit)	Human	0.83
NEW 0015	Perez-Heras I. / 2017(737)	Spain	Children	Infection	• Total (n = 229) • EC (n = 208) • ESBL-EC (n = 21)	C	PC	ESBL-EC	2,13,24,42	Hospital	Human	0.67
NEW 0251	Pfeffer I./2016(738)	Israel	Adult	Carriage	• Total bowel surgery patients (n = 150) • ESBL-ENT carriers (n = 27)	C	OR	ESBL-ENT	2,3	Hospital	Human	0.83
NEW 0240	Pierri MD/2016(739)	Italy	Adult	Colonisation/infection	• All patients ICU admission following major surgery (n = 2,385) • MDR-AB (n = 14)	C	OR	MDR-AB	2109	Hospital (Cardiac surgery unit)	Human	0.83

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NEW 0318	Poole K/2016(740)	United Kingdom	Mixed	Carriage	• CPE +ive Case (n = 26) • CPE -ive Control (n = 592)	CS (nested CC)	OR	CR-ENT (CPE)	3,11	Hospital (inpatient)	Human	0.50
NEW 0179	Proia L./ 2016(741)	Spain	NA	Indirect transmission	4 stream sites	CS	P	ARGs	6	Community	Human/Environment	0.17
Meta 245	Righi E/ 2017(742)	Global	Adult	Infection	Total patients or no. of isolates NR, 6 studies included in meta-analysis	M	OR	CR-B	3	Hospital	Human	0.93
Meta 143	Salgado, C/2003(743)	Global	Mixed	Carriage	• 191 household contacts of 93 patients discharged from the hospital with nosocomial MRSA colonization • 3898 persons with healthcare contact • 4452 person without healthcare contact	M	RR	MRSA	1,7	Hospital/community	Human	0.59
NEW 0053	Salomao M.C./2017(744)	Brazil	Mixed	Colonisation	CR-KP +ive (n = 38) CR-KP -ive (n = 636)	C(CS)	OR	CR-KP	1,2,3	Hospital	Human	0.67
NEW 0229	Satlin MJ/2016(745)	United States	Adult	Infection	Total BSI in neutropenic patients with hematologic malignancies (n = 1,992 episodes) • Cases CR-ENT-BSI (n = 43) • Primary control group BSI (Not CR-GN) (n = 129)	C (CC)	OR	CR-ENT	2,3,28,34,89	Hospital	Human	0.86

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					• Secondary control group (CS-ENT-BSI) (n = 129)							
NEW 0190	Satwani P./2017(746)	United States	Children	Infection	n = 395 transplant patients	C	OR	R-GN / VR-ENTO	28	Hospital	Human	0.67
NEW 0019	Schill F./2017(747)	Europe (Germany (70%), Netherlands, Poland, Belgium, and Spain)	NA	Indirect transmission	Meat batches (n = 63 ; includes n = 189 fresh meat samples and n = 63 meat juice samples) - Fresh pork meat and meat juice samples	CS	P	ESBL/AMP-C-ENT	4	Community	Human/Animal	0.33
NEW 0228	Singh G/2016(748)	India	NA	Indirect transmission	Collected from 6 sites • Fruit juices (2 L each in sterilized bottles) • Street foods (25 g each except eggs) • Garnishing materials (25 g each)	CS	P (gene copies)	ARGs	4,6,67	Community	All	0.17
NEW 0288	Strysko JP/2016(749)	United States	Children	Infection	• ESBL (n = 76) • Uninfected (n = 380)	CC	OR	ESBL-ENT	2,5,43,45	Hospital (NICU)	Human	1.00
Meta 157	Tacconelli, E/2008(750)	Global	Adult	Carriage/infection /colonisation	24,230 patients	M	RR	MRSA	3	Hospital/community	Human	0.81
Meta 159	Tadesse, G/2015(751)	Ethiopia	NA	Indirect transmission	• Total samples (n = 6486) • Total animals (n = 1506) • Total isolates tested for susceptibility (n = 554)	M	P	R-Sal	4	Community	Human/animal	0.70

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Meta 202	Tang KL/2017(118)	Global	Mixed	Emergence	13 human studies for the meta-analysis	M	RD	R-B	115	Community	Human/Animal	0.93
NEW 0368	Tebano G./2016(752)	France	Adult	Emergence	• Total cohort lung transplant patients (n = 1046 strains) • R-B (n = 404 strains from 90 patients)	C	OR	R-B	3,13,34	Hospital	Human	0.83
NEW 0305	Thatrimontrichai A/2016(753)	Thailand	Children	Infection	Total cohort of neonates (n = 101) • CR-AB VAP (n = 63) • CS-AB VAP (n = 13) • Control group (VAP) (n = 25)	C (CC)	OR	CR-AB	1,3,12,13,51	Hospital (neonatal ICU)	Human	0.86
NEW 0108	Trinh T.D./2017(754)	United States	Adult	Infection (LRTI)	• Entire cohort (n = 200) • MDR-PA (n = 47) • Non-MDR-PA (n = 153)	C(CC) - LRTI patients	OR	MDR-PA	3,9	Hospital	Human	0.71
Meta 106	van Loon, K/2018(87)	Global	Mixed	Acquisition	Total number of participants NR	M	OR	CR-ENT	1,2,3,13,31,33,115	Hospital	Human	0.96
NEW 0323	Wang Q/ 2016(755)	China	Adult	Infection	• CR-ENT Infections (n = 94) • Non-ENT-infection (n = 93)	CC	OR	CR-ENT	3	Hospital	Human	0.71
Meta 173	Washam, M/2017(756)	Global	Children	Colonisation	13,252 infants	M	OR	MRSA	51,86	Hospital (NICU)	Human	0.89
NEW 0035	Wielders C.C.H./ 2017(757)	Netherlands	Adult	Carriage	• ESBL/pAmpC +ive persons (n = 109) • ESBL/pAmpC -ive persons (n = 2323)	C(CS)	OR	ESBL/pAmpC - ENT	5,56,108	Community	Human/Animal	0.33

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NEW 0003	Williamson D.A / 2018(758)	Australia	Mixed	Emergence	Salmonella enterica Serovar isolates (n = 58830)	C (L)	OR	MDR-Sal	5	Community	Human	0.67
NEW 0125	Wilmore S.M.S./ 2017(759)	Zimbabwe	Children	Carriage	• All (n=175) • ESBL-ENT -ive (n=151) • ESBL-ENT +ive (n=24)	C (HIV patients)	OR	ESBL-ENT	2,38	Hospital (HIV clinic)	Human	0.67
NEW 0136	Xu L./2016(760)	China	NA	Indirect transmission	Drinking water treatment plant sites (n = 2)	CS	P	ARGs	6	Community	Human/Environment	0.17
NEW 0122	Zhang Q./2017(761)	China	Adult	Infection	• AmpC-EC (n = 51) • Non-AmpC-EC (n = 197)	C (Cancer patients)	OR	AMP-C-EC	3,13	Hospital	Human	0.83
NEW 0365	Zhao S.-Y./2016(762)	China	Adult	Colonisation	• Total cohort with ENT (n = 457) • ESBL-ENT (n = 183)	CS	OR	ESBL-ENT	3,13	Hospital (LTCF/Nursing home)	Human	0.67
Meta 190	Ziakas, P/2013(763)	Global	Mixed	Acquisition	35,364 patients at risk	M	P	VR-ENTO	34	Hospital (ICU)	Human	0.93
Meta 188	Ziakas, P/2014(764)	Global	Adult	Infection	• 17,738 evaluable patients at risk • 589 MRSA-associated infections	M	RR	MRSA	31	Hospital (ICU)	Human	0.89
Meta 189	Ziakas, P/2014(765)	Global	Adult	Colonisation/infection	• MRSA colonisation in pre-transplantation patients (n = 2885) • MRSA colonisation in post-transplantation patients (n = 2342) • VR-ENTO colonisation in pre-transplantation patients (n = 1381)	M	P,RR	MRSA/VR-ENTO	2,12,31	Hospital (ICU/Transplant unit)	Human	0.93

Article ID.	First Author / Year [Reference]	Country	Sample type	Outcome	Sample size	Study type	Estimate reported	Resistant organism	Risk factor (code)	Setting type (Hospital / Community)	Reservoir Type	Quality score (0-1) (2 d.p)
					• VR-ENTO colonisation in post-transplantation patients (n = 1369)							

Appendix Table 4: Overview of risk factors identified and the risk domains created. R-B: resistant bacteria; S-B: susceptible bacteria

No. of risk factor code	Risk code	Risk domains with their respective risk factors	Total number of studies (Primary studies not meta-analysis)	Percentage of total primary studies out of 527	Mean quality score of risk domain and risk factor	Standard deviation of the mean quality score (SD)	Reservoir
Risk Domain 1							
Risk factor 1	2	Underlying disease	120	22.77%	0.66	0.18	Human
Risk factor 2	31	Previous R-B carriage/colonisation	34	6.45%	0.69	0.16	Human
Risk factor 3	22	Functional status score	22	4.17%	0.73	0.12	Human
Risk factor 4	30	Diabetes	20	3.80%	0.72	0.15	Human
Risk factor 5	16	Wound/skin lesions	17	3.23%	0.76	0.13	Human
Risk factor 6	45	Prior genitourinary infection/ Urological diseases	15	2.85%	0.71	0.19	Human
Risk factor 7	15	Immobility	13	2.47%	0.65	0.19	Human
Risk factor 8	50	Previous S-B infection	12	2.28%	0.62	0.17	Human
Risk factor 9	28	Prior infection (R-B/S-B)	9	1.71%	0.76	0.09	Human
Risk factor 10	89	Corticosteroid use / steroid hormone use	7	1.33%	0.76	0.22	Human
Risk factor 11	56	Gastric acid–suppressive agents / proton-pump inhibitors	6	1.14%	0.62	0.33	Human
Risk factor 12	35	Trauma admissions	5	0.95%	0.42	0.06	Human
Risk factor 13	83	Culture source	5	0.95%	0.60	0.25	Human
Risk factor 14	10	Smoking	4	0.76%	0.67	0.24	Human
Risk factor 15	47	Diarrhoeal symptoms	4	0.76%	0.67	0.24	Human
Risk factor 16	51	Birthweight	4	0.76%	0.67	0.15	Human
Risk factor 17	55	Unconsciousness	4	0.76%	0.81	0.06	Human
Risk factor 18	63	BMI	4	0.76%	0.67	0.20	Human
Risk factor 19	69	Blood test related indicators	4	0.76%	0.53	0.25	Human
Risk factor 20	38	Tuberculosis treatment/anti-retroviral therapy treatment	3	0.57%	0.50	0.17	Human
Risk factor 21	66	Bacteria retrieved from	3	0.57%	0.42	0.32	Human

		patient showing ESBL production					
Risk factor 22	71	Complication of bacteremia retrieved from patient	2	0.38%	0.44	0.19	Human
Risk factor 23	91	Burn patients	2	0.38%	0.60	0.37	Human
Risk factor 24	101	Patient with repeat cultures	2	0.38%	0.67	NA	Human
Risk factor 25	14	High arling score	1	0.19%	0.67	NA	Human
Risk factor 26	52	Factors increasing risk of abcess	1	0.19%	0.57	NA	Human
Risk factor 27	57	Maternal factors	1	0.19%	0.67	NA	Human
Risk factor 28	58	Patient being index case	1	0.19%	0.50	NA	Human
Risk factor 29	84	Bronchiectasis	1	0.19%	0.83	NA	Human
Risk factor 30	88.1	Absence of do not resuscitate order	1	0.19%	0.50	NA	Human
Risk factor 31	92	Received vaccination	1	0.19%	0.50	NA	Human
Risk factor 32	96	Allergies	1	0.19%	0.67	NA	Human
Risk factor 33	97	Neonatal complications	1	0.19%	0.50	NA	Human
Risk factor 34	100	Patient's timing of enrolment	1	0.19%	0.67	NA	Human
Risk factor 35	101.1	No prior positive urine culture	1	0.19%	0.71	NA	Human
Risk factor 36	104	Patient being treated in 'Prone position' during ICU procedures due to patient's clinical history	1	0.19%	0.57	NA	Human
Risk factor 37	110	Use of inotropic drugs	1	0.19%	0.83	NA	Human
Risk domain 2							
Risk factor 38	13	Invasive procedures (e.g catheterisation or tube feeding)	95	18.03%	0.69	0.18	Human
Risk factor 39	1	History of hospitalisation	78	14.80%	0.65	0.19	Human
Risk factor 40	12	Surgery	48	9.11%	0.72	0.18	Human
Risk factor 41	24	Length of stay (in hospital)	45	8.54%	0.69	0.18	Human
Risk factor 42	9	Non-home residence (transfer from long term care	41	7.78%	0.69	0.17	Human

		facilities/rehab /other)					
Risk factor 43	34	Stay in the ICU	31	5.88%	0.72	0.16	Human
Risk factor 44	33.1	Nosocomial acquisition / healthcare associated or attributed to healthcare	23	4.36%	0.63	0.25	Human
Risk factor 45	36	Ventilator use	22	4.17%	0.68	0.17	Human
Risk factor 46	33	Admission to the ICU	19	3.61%	0.70	0.17	Human
Risk factor 47	44	Colonisation pressure of resistant organisms in the hospital	19	3.61%	0.67	0.18	Human
Risk factor 48	61	Infection policy changes	4	0.76%	0.56	0.10	Human
Risk factor 49	82	Non-invasive procedures	4	0.76%	0.62	0.07	Human
Risk factor 50	46	Health care worker transmission	3	0.57%	0.67	0.33	Human
Risk factor 51	48	Hospital beds	3	0.57%	0.50	0.17	Human
Risk factor 52	109	Type of care in long term care facility associated with transmission on gown/gloves (e.g. bathing / dressing / bed pan changes)	2	0.38%	0.69	0.06	Human
Risk factor 53	49	Hospital status (e.g geriatric/trauma centre)	1	0.19%	0.50	NA	Human
Risk factor 54	62	Low isolation rate (of patients needing to be isolated)	1	0.19%	0.33	NA	Human
Risk factor 55	73	Outpatient clinic attendance	1	0.19%	1.00	NA	Human
Risk factor 56	93	Combined impact of mechanical ventilation + tube feeding	1	0.19%	0.83	NA	Human
Risk domain 3							
Risk factor 57	3	Prior Antibiotic (Abx) exposure /use	289	54.84%	0.68	0.16	Human
Risk factor 58	39	Inappropriate prescribing	8	1.52%	0.63	0.17	Human
Risk factor 59	115	Antibiotic use in animals	2	0.38%	0.38	0.08	Human/Animal

Risk factor 60	90	Maternal antibiotic exposure	1	0.19%	0.67	NA	Human
Risk factor 61	94	No antibacterial use	1	0.19%	0.67	NA	Human
Risk domain 4							
Risk factor 62	4	Food transmission (direct) + (indirect): (resistant zoonotic pathogens isolated from humans) + (resistant zoonotic pathogens found in meat products + broiler meat)	30	5.69%	0.46	0.14	Human/Animal
Risk factor 63	6	Water transmission	19	3.61%	0.33	0.13	Human/Environment
Risk factor 64	5	Travel abroad	15	2.85%	0.63	0.23	Human
Risk factor 65	8	Animal contact	14	2.66%	0.50	0.12	Human/Animal
Risk factor 66	7	Transmission from family member	8	1.52%	0.53	0.12	Human
Risk factor 67	75	Drug abuse + Homelessness	7	1.33%	0.55	0.17	Human
Risk factor 68	74	Day care attendance	5	0.95%	0.61	0.12	Human
Risk factor 69	32	Place/area of residence (urban / rural, building type)	4	0.76%	0.68	0.14	Human
Risk factor 70	40	Overcrowding (family/household size)	4	0.76%	0.42	0.22	Human
Risk factor 71	26	Education level	3	0.57%	0.72	0.10	Human
Risk factor 72	67	Environment reservoir: vegetable/fruits/salad (food transmission - non-meat related)	3	0.57%	0.33	0.09	Human/Environment
Risk factor 73	41	Socioeconomic status/ deprivation index	2	0.38%	0.75	0.35	Human
Risk factor 74	59	No family members	2	0.38%	0.83	0.24	Human
Risk factor 75	85	Sexual orientation	2	0.38%	0.50	0.24	Human
Risk factor 76	64	Out-of-pocket spending on health care	1	0.19%	0.17	NA	Human

Risk factor 77	72	Occupation	1	0.19%	0.67	NA	Human
Risk factor 78	81	Not using condoms	1	0.19%	0.67	NA	Human
Risk factor 79	87	Sauna use	1	0.19%	0.67	NA	Human
Risk factor 80	98	Time of year	1	0.19%	0.50	NA	Human
Risk factor 81	99	American football player	1	0.19%	0.50	NA	Human
Risk factor 82	102	Air temperature (5 degree increase)	1	0.19%	0.67	NA	Human
Risk factor 83	103	Children in nappies	1	0.19%	0.71	NA	Human
Risk factor 84	108	Residence proximity to farm	1	0.19%	0.33	NA	Human/Animal
Risk domain 5							
Risk factor 85	11	Age	61	11.57%	0.58	0.22	Human
Risk factor 86	42	Gender (Male)	23	4.36%	0.69	0.16	Human
Risk factor 87	43	Ethnicity	11	2.09%	0.66	0.20	Human
Risk factor 88	54	Gender (Female)	11	2.09%	0.74	0.15	Human

Appendix Table 5: Bottom tier of evidence on the Development of resistance: Human reservoir drivers

Risk factor description	No. of estimates extracted
Day care attendance	9
Inappropriate prescribing	9
Corticosteroid use / steroid hormone use	8
Drug abuse + Homelessness	8
Bacteria retrieved from patient showing ESBL production	7
Infection policy changes	7
Blood test related indicators	6
Gastric acid–suppressive agents / proton-pump inhibitors	6
Non-invasive procedures	6
Culture source	5
Gestational age	5
Trauma admissions	5
Birthweight	4
BMI	4
Diarrhoeal symptoms	4
Overcrowding (family/household size)	4
Patient with repeat cultures	4
Place/area of residence (urban / rural, building type)	4
Smoking	4
Unconsciousness	4
Complication of bacteremia retrieved from patient	3
Education level	3

Risk factor description	No. of estimates extracted
Hospital beds	3
Tuberculosis treatment/ART treatment	3
Burn patients	2
Factors increasing risk of abcess	2
High arling score	2
No family members	2
Socioeconomic status/ deprivation index	2
Absence of do not resuscitate order	1
Air temperature (5 degree increase)	1
Profession: American football player	1
Bronchiectasis	1
Combined impact of mechanical ventilation + tube feeding	1
Health care worker transmission	1
Hospital status (e.g geriatric/trauma centre)	1
Low isolation rate (of patients needing to be isolated)	1
Maternal antibiotic exposure	1
Maternal factors	1
Neonatal complications	1
No antibacterial use	1
No prior positive urine culture	1
Not using condoms	1
Occupation	1
out-of-pocket spending on health care	1
Outpatient clinic attendence	1
Patient being index case	1
Patient being treated in ‘Prone position’ during ICU procedures due to patient’s clinical history	1
Patient’s timing of enrolment	1
Received vaccination	1
Sauna use	1
Sexual orientation	1
Type of care in long term care facility associated with transmission on gown/gloves (e.g. bathing / dressing / bed pan changes)	1
Use of inotropic drugs	1

Appendix Table 6: Odds ratio overview by infection and colonisation category

Overall	OR >1 - <2	OR ≥2 - <3	OR ≥3 - <4	OR ≥4 - <5	OR ≥5 - <6	OR ≥6 - <7	OR ≥7 - <8	OR ≥8 - <9	OR ≥9 - <10	OR ≥10 - <12	OR ≥12 - <14	OR ≥14 - <16	OR ≥16 - <18	OR ≥18 - <20	OR ≥20
Patient clinical history (n = 147)	16%	34%	22%	15%	7%	8%	8%	3%	5%	3%	3%	4%	2%	3%	5%
Health care contact (n = 184)	24%	35%	27%	20%	12%	7%	6%	4%	3%	5%	4%	2%	4%	1%	9%
Antibiotic use (n = 189)	15%	32%	20%	13%	16%	7%	10%	3%	4%	5%	7%	4%	1%	2%	8%
Community level factors (n = 34)	21%	29%	29%	12%	12%	9%	3%	9%	0%	3%	3%	3%	3%	6%	15%
Patient demographics (n = 54)	28%	37%	19%	11%	6%	2%	4%	0%	2%	2%	4%	4%	0%	0%	2%
Comparison of top two outcomes from the review															
Infection	OR >1 - <2	OR ≥2 - <3	OR ≥3 - <4	OR ≥4 - <5	OR ≥5 - <6	OR ≥6 - <7	OR ≥7 - <8	OR ≥8 - <9	OR ≥9 - <10	OR ≥10 - <12	OR ≥12 - <14	OR ≥14 - <16	OR ≥16 - <18	OR ≥18 - <20	OR ≥20
Patient clinical history (n = 53)	19%	36%	17%	15%	9%	6%	8%	4%	6%	4%	6%	0%	2%	0%	6%
Health care contact (n = 73)	26%	30%	27%	26%	12%	3%	5%	3%	5%	10%	4%	1%	3%	0%	8%
Antibiotic use (n = 69)	6%	32%	20%	13%	17%	7%	9%	1%	4%	6%	12%	4%	0%	0%	6%
Community level factors (n = 7)	14%	14%	29%	0%	0%	0%	14%	0%	0%	0%	0%	0%	0%	14%	14%
Patient demographics (n = 18)	33%	33%	22%	6%	6%	0%	0%	0%	0%	6%	0%	0%	0%	0%	6%
Colonisation	OR >1 - <2	OR ≥2 - <3	OR ≥3 - <4	OR ≥4 - <5	OR ≥5 - <6	OR ≥6 - <7	OR ≥7 - <8	OR ≥8 - <9	OR ≥9 - <10	OR ≥10 - <12	OR ≥12 - <14	OR ≥14 - <16	OR ≥16 - <18	OR ≥18 - <20	OR ≥20
Patient clinical history (n = 40)	15%	33%	30%	18%	8%	3%	10%	8%	10%	5%	0%	15%	0%	3%	8%
Health care contact (n = 39)	23%	36%	21%	15%	15%	15%	5%	3%	3%	3%	3%	0%	8%	0%	13%
Antibiotic use (n = 40)	23%	38%	20%	5%	15%	0%	15%	8%	0%	8%	3%	3%	3%	3%	10%
Community level factors (n = 12)	25%	25%	50%	17%	8%	25%	0%	8%	0%	8%	0%	8%	0%	8%	8%
Patient demographics (n = 16)	13%	44%	13%	13%	13%	6%	6%	0%	6%	0%	13%	6%	0%	0%	0%
Comparison of Gram-positive and Gram-negative bacteria type															

Gram-positive	OR >1 - <2	OR ≥2 - <3	OR ≥3 - <4	OR ≥4 - <5	OR ≥5 - <6	OR ≥6 - <7	OR ≥7 - <8	OR ≥8 - <9	OR ≥9 - <10	OR ≥10 - <12	OR ≥12 - <14	OR ≥14 - <16	OR ≥16 - <18	OR ≥18 - <20	OR ≥20
Patient clinical history (n = 50)	18%	36%	26%	12%	6%	10%	8%	4%	2%	6%	0%	6%	0%	0%	6%
Health care contact (n = 52)	27%	42%	25%	6%	12%	0%	4%	0%	4%	0%	4%	4%	2%	0%	10%
Antibiotic use (n = 42)	17%	26%	21%	17%	7%	7%	5%	5%	5%	5%	2%	7%	0%	0%	5%
Community level factors (n = 13)	23%	38%	31%	23%	8%	8%	0%	15%	0%	0%	0%	0%	0%	8%	15%
Patient demographics (n = 23)	35%	30%	17%	0%	4%	0%	4%	0%	4%	0%	0%	9%	0%	0%	4%
Gram-negative	OR >1 - <2	OR ≥2 - <3	OR ≥3 - <4	OR ≥4 - <5	OR ≥5 - <6	OR ≥6 - <7	OR ≥7 - <8	OR ≥8 - <9	OR ≥9 - <10	OR ≥10 - <12	OR ≥12 - <14	OR ≥14 - <16	OR ≥16 - <18	OR ≥18 - <20	OR ≥20
Patient clinical history (n = 88)	15%	27%	24%	15%	6%	8%	8%	2%	7%	2%	6%	3%	2%	3%	6%
Health care contact (n = 111)	22%	31%	24%	22%	14%	11%	8%	5%	4%	6%	5%	1%	5%	2%	8%
Antibiotic use (n = 130)	15%	31%	20%	12%	18%	7%	11%	3%	3%	5%	9%	2%	1%	2%	9%
Community level factors (n = 19)	16%	26%	26%	5%	11%	5%	5%	5%	0%	0%	5%	5%	5%	0%	16%
Patient demographics (n = 27)	19%	48%	19%	15%	0%	0%	4%	0%	0%	4%	7%	0%	0%	0%	0%

Appendix II. Appendix for Chapter 3

Intervention strategy

Impact of strategies on antibiotic use – Study design RCTs / systematic reviews/ meta-analysis:

Search 1:

(systematic review[Title/Abstract] OR meta-analysis[Title/Abstract] OR meta analysis[Title/Abstract] OR meta-regression[Title/Abstract] OR meta regression[Title/Abstract] OR randomized OR randomised)

AND ((antibiotic dispensing[Title] OR antibiotic use[Title] OR high prescribers[Title] OR prudent use[Title] OR antibiotic prescribing[Title] OR antimicrobial prescribing[Title] OR antimicrobial stewardship[Title]))

AND ((((primary care OR general practice OR GP general practitioners OR hospital or acute or intensive care or emergency or nursing or long term care or healthcare setting or food-producing animal or meat* or water* or soil* or livestock or vet* or farm* or agri*))

AND ((((impact[Title/Abstract] OR effect[Title/Abstract] OR affect[Title/Abstract] OR effectiveness[Title/Abstract] OR outcome[Title/Abstract] OR efficacy[Title/Abstract] OR consumption[Title/Abstract]))

AND (prevent[Title/Abstract] OR control[Title/Abstract] OR reduc*[Title/Abstract] OR restrict*[Title/Abstract] OR prudent use[Title/Abstract] OR improv*[Title/Abstract] OR consump*[Title/Abstract]))

AND (intervention[Title/Abstract] OR antibiotic prescribing[Title/Abstract] OR antibiotic use[Title/Abstract] OR antimicrobial use[Title/Abstract] OR antimicrobial prescribing[Title/Abstract] OR infection prevention[Title/Abstract] OR infection prevention control[Title/Abstract] OR antimicrobial stewardship[Title/Abstract] OR consump*[Title/Abstract] OR antibiotic stewardship[Title/Abstract])))))))

Impact of strategies on antibiotic use and/or infection control specific to antibiotic resistant population– Study design: systematic reviews/ meta-analysis:

Search 2:

(((((((antibiotic resist*[Title/Abstract] or antibiotic-resist*[Title/Abstract] OR antibiotic resistance[Title/Abstract] or antimicrobial resist*[Title/Abstract]))

AND (((meta-analysis[Title/Abstract] OR meta analysis[Title/Abstract] OR meta-regression[Title/Abstract] OR meta regression[Title/Abstract])) AND

((((impact[Title/Abstract] OR effect[Title/Abstract] OR affect[Title/Abstract] OR effectiveness[Title/Abstract] OR clinical outcome[Title/Abstract] OR efficacy[Title/Abstract] OR consump*[Title/Abstract] OR infect*[Title/Abstract] OR coloni*[Title/Abstract] OR length of stay[Title/Abstract] OR LOS[Title/Abstract]))

AND (prevent*[Title/Abstract] OR control[Title/Abstract] OR decreas*[Title/Abstract] OR reduc*[Title/Abstract] OR restrict*[Title/Abstract] OR impact[Title/Abstract] OR improv*[Title/Abstract]))

AND (intervention[Title/Abstract] OR antibiotic prescribing[Title/Abstract] OR antibiotic use[Title/Abstract] OR antimicrobial use[Title/Abstract] OR antimicrobial prescribing[Title/Abstract] OR infection prevention[Title/Abstract] OR infection prevention control[Title/Abstract] OR decontamin*[Title/Abstract] OR antimicrobial stewardship[Title/Abstract] OR antibiotic stewardship[Title/Abstract])))))))

Scoping search:

Search 3:

OR (((((((antibiotic resistant or antibiotic resistance or antibiotic-resistant)) AND (((meta-analysis[Title/Abstract] OR meta analysis[Title/Abstract] OR meta-regression[Title/Abstract] OR meta regression[Title/Abstract])) AND

((((impact[Title/Abstract] OR effect[Title/Abstract] OR effectiveness[Title/Abstract] OR clinical outcome[Title/Abstract] OR efficacy[Title/Abstract])) AND (prevent[Title/Abstract] OR control[Title/Abstract] OR reduce[Title/Abstract] OR restrict[Title/Abstract] OR impact[Title/Abstract] OR improve[Title/Abstract]))

AND (intervention[Title/Abstract] OR antibiotic prescribing[Title/Abstract] OR antibiotic use[Title/Abstract] OR antimicrobial use[Title/Abstract] OR antimicrobial prescribing[Title/Abstract] OR infection prevention[Title/Abstract] OR infection prevention control[Title/Abstract] OR antimicrobial stewardship[Title/Abstract] OR antibiotic stewardship[Title/Abstract])))))))

OR ((((systematic review OR meta-analysis[Title/Abstract] OR meta analysis[Title/Abstract] OR meta-regression[Title/Abstract] OR meta regression[Title/Abstract] OR randomized OR randomised))

AND ((antibiotic dispensing[Title] OR antibiotic use[Title] OR high prescribers[Title] OR prudent use[Title] OR antibiotic prescribing[Title]))

AND ((((primary care OR general practice OR GP))

AND ((((impact[Title/Abstract] OR effect[Title/Abstract] OR effectiveness[Title/Abstract] OR clinical outcome[Title/Abstract] OR efficacy[Title/Abstract])) AND (prevent[Title/Abstract] OR control[Title/Abstract] OR reduce[Title/Abstract] OR restrict[Title/Abstract] OR impact[Title/Abstract] OR improve[Title/Abstract]))

AND (intervention[Title/Abstract] OR antibiotic prescribing[Title/Abstract] OR antibiotic use[Title/Abstract] OR antimicrobial use[Title/Abstract] OR antimicrobial prescribing[Title/Abstract] OR infection prevention[Title/Abstract] OR infection prevention control[Title/Abstract] OR antimicrobial stewardship[Title/Abstract] OR antibiotic stewardship[Title/Abstract])))))))))

AND "last 10 years"[PDat]))

Final search: (Search 1 OR Search 2 OR Search 3) limited to last 10 years

Mapping of objectives:

Appendix Table 7: Overview of stakeholder websites checked (Assesed between 01.05.2018 – 01.06.2018)

No.	Examples of key institutions in the global antimicrobial regime (Building upon Hoffman *et al*., 2015 paper)	Included (y/n (reason))	Policy document for AMR or including strategies related to AMR
1	World Health Organization (WHO)	y	y
2	Roll Back Malaria Partnership	n (population scope)	
3	STOP TB Partnership	n (population scope)	
4	Joint United Nations Programme on HIV/AIDS (UNAIDS)	n (population scope)	
5	United Nations Children's Fund (UNICEF)	y	y
6	United Nations Office on Drugs and Crime	y	y
7	United Nations Development Programme (UNDP)	y	y
8	Food and Agriculture Organization of the United Nations (FAO)	y	y
9	Joint FAO/WHO Codex Alimentarius Commission	y	y
10	United Nations General Assembly	y	y
11	United Nations Security Council	y	n
12	Global Fund to Fight AIDS	n (population scope)	
13	Tuberculosis and Malaria	n (population scope)	
14	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use	y	n
15	World Bank group	y	n
16	World Organisation for Animal Health (OIE)	y	Y
17	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products	y	y
18	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S)	y	n
19	World Trade Organization (WTO)	y	n
20	Consultative Group on International Agricultural Research (CGIAR)	y	n
21	OECD (incl. G7 and G20 commitments)	y	y
22	Global Health Security Initiative	y	y
23	Alliance for the Prudent Use of Antibiotics	y	y
24	Action on Antibiotic Resistance (ReAct)	y	y
25	Antibiotic Action Team	y	y

26	Health Action International (HAI)	y	y
27	Médecins Sans Frontières (MSF)	y	n
28	Innovative Medicines Initiative	y	y
29	European Platform for the Responsible Use of Medicines in Animals	y	Y
30	European Federation of Pharmaceutical Industries and Associations	y	y
31	International Dairy Federation (IDF)	y	y
32	International Federation for Animal Health	y	IFAH no access: Health for Animals website provides overview of commitments
33	International Federation of Pharmaceutical Manufacturers & Associations	y	y
34	International Hospital Federation	y	n
35	International Meat Secretariat	y	n
36	International Poultry Council	y	n
37	World Farmers' Organisation	y	n
38	World Medical Association	y	y
39	International Pharmaceutical Federation	y	y
40	World Health Professions Alliance	y	y
41	TATFAR	y	y
42	EU	y	y
43	ECDC	y	y
44	EMA/EFSA	y	y
45	EFSA	y	y
46	UK DH/PHE	y	y
47	World Alliance Against Antibiotic Resistance (WAAAR)	y	y
48	European commission	y	y
49	ARC	y	y

Appendix Table 8: Policy objectives of key stakeholders mapped to WHO objectives

Organisation abbreviation	Awareness	Surveillance + research	IPC	Antibiotic use / diagnostic	Investment / new antibiotics, vaccines, diagnostics	interdisciplinary cooperation	helping other stakeholders with frameworks / implementation	Governance / regulation / financial incentives
World Health Organization (WHO)	1	3	1	2	-	1	1	-
United Nations Children's Fund (UNICEF)	-	-	1	-	-	-	-	-
United Nations Office on Drugs and Crime	-	-	-	-	-	-	-	-
United Nations Development Programme (UNDP)	-	3	-	1	2	2	3	-
Food and Agriculture Organization of the United Nations (FAO)	1	2	1	2	-	1	2	1
Joint FAO/WHO Codex Alimentarius Commission	1	4	3	6	-	-	1	4
United Nations General Assembly	1	1	1	1	1	1	7	1
World Organisation for Animal Health (OIE)	5	3	1	2	1	5	9	-

Organisation abbreviation	Awareness	Surveillance + research	IPC	Antibiotic use / diagnostic	Investment / new antibiotics, vaccines, diagnostics	interdisciplinary cooperation	helping other stakeholders with frameworks / implementation	Governance / regulation / financial incentives
International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products	-	-	-	-	-	-	-	-
OECD (incl. G7 and G20 commitments)	-	2	3	3	-	4	2	-
Global Health Security Initiative	-	3	-	-	2	4	2	-
Alliance for the Prudent Use of Antibiotics	1	2	1	1	1	-	-	-
Action on Antibiotic Resistance (ReAct)	3	1	-	1	1	-	2	-
Antibiotic Action Team	1	-	1	-	1	-	-	-
Health Action International (HAI)	-	-	-	1	-	-	-	-
Innovative Medicines Initiative	-	-	-	1	5	-	-	-
European Platform for the Responsible Use of	2	1	2	2	-	2	1	-

Organisation abbreviation	Awareness	Surveillance + research	IPC	Antibiotic use / diagnostic	Investment / new antibiotics, vaccines, diagnostics	interdisciplinary cooperation	helping other stakeholders with frameworks / implementation	Governance / regulation / financial incentives
Medicines in Animals								
European Federation of Pharmaceutical Industries and Associations	-	-	-	-	-	-	-	-
International Dairy Federation (IDF)	-	2	3	3	-	-	1	-
International Federation of Pharmaceutical Manufacturers & Associations	1	1	-	7	2	3	1	-
World Medical Association	2	2	1	-	-	-	2	-
International Pharmaceutical Federation	3	1	-	4	2	1	2	-
World Health Professions Alliance	1	1	2	2	1	1	1	-
TATFAR	1	1	1	1	1	1	1	-
EU	1	3	2	4	1	4	1	1
ECDC	2	4	-	-	-	-	-	-
EMA/EFSA	1	1	1	-	-	-	-	-
EFSA	1	2	-	-	-	-	1	-
UK DH/PHE	1	2	1	2	1	1	-	2
World Alliance Against Antibiotic	1	1	1	1	1	1	1	1

Organisation abbreviation	Awareness	Surveillance + research	IPC	Antibiotic use / diagnostic	Investment / new antibiotics, vaccines, diagnostics	interdisciplinary cooperation	helping other stakeholders with frameworks / implementation	Governance / regulation / financial incentives
Resistance (WAAAR)								
European commission	2	3	1	2	2	3	1	2
Total objectives/actions specified	**34**	**50**	**29**	**50**	**26**	**36**	**43**	**13**

Appendix Table 9: Individual policy details (1/2)

Stakeholders	Awareness: education/training of healthcare professionals	Surveillance + research	IPC: Community : Food (meat products)	Antibiotic use / diagnostic
World Health Organization (WHO)	1) WHO will provide international leadership and coordination to raise awareness - World antibiotic awareness day	1) GLASS 2) GASP 3) CAESAR (along with European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the National Institute for Public Health and the Environment in the Netherlands (RIVM).)	1) WHO recommendations/guidelines	1) WHO list of essential medicines 2)List of critical medicines
United Nations Children's Fund (UNICEF)	-	-	1) WASH : Campaign	-
United Nations Office on Drugs and Crime	United Nations General Assembly (UNGA)	UNGA	UNGA	UNGA
United Nations Development Programme (UNDP)	-	1) Invests in building an evidence base to improve our understanding of the drivers of disease emergence, including climate change, environmental degradation and urbanization, and for tracking progress towards control of these threats 2) Fosters	-	1)Strengthens medicines regulation and stewardship programs across the human and animal health sectors to ensure the quality and safety of medicines and preserve the effectiveness of existing and new therapies

Stakeholders	Awareness: education/training of healthcare professionals	Surveillance + research	IPC: Community : Food (meat products)	Antibiotic use / diagnostic
		research in infectious diseases and in the development of new class of antimicrobial agents, point of care diagnostics and new vaccines for both human and animal sectors. 3) invests in research to develop new, affordable, available and more effective countermeasures and health technologies to prevent, diagnose, treat and minimize the impact of these threats ensuring a full social return on public investments		
Food and Agriculture Organization of the United Nations (FAO)	FAO Action plan: Focus Area 1) Improve awareness on Antimicrobial Resistance and related threats - Raising awareness (among veterinarians, value chain actors including producers and the public) about AMR -	Focus Area 2: Develop capacity for surveillance and monitoring of Antimicrobial Resistance and antimicrobial use in food and agriculture - 1) Strengthening food and human surveillance systems for AMR and the quantities of all antimicrobials being used at the national level 2) Supporting research to generate data on the prevalence and trends in AMR, as well as supporting risk assessment, risk management and risk communication in the AMR area	1) - Reducing the need for antimicrobials in animal husbandry, by improving animal health disease prevention and good practices along the chain	Focus Area 3: Strengthen governance related to antimicrobial use and Antimicrobial Resistance in food and agriculture - 1) Improving regulatory frameworks based on internationally agreed principles and standards (Codex, OIE) Focus Area 4: Promote good practices in food and agriculture systems and the prudent use of antimicrobials. 2) Developing appropriate policies/guidance on the prudent and responsible use of antimicrobials in animal husbandry
Joint FAO/WHO Codex Alimentarius Commission	1) Foodborne AMR Risk Communication 2) Responsibilities of the	1) Preliminary Foodborne AMR Risk Management Activities 2) Foodborne AMR Risk	Antimicrobial drugs are powerful tools for the management of infectious	1) Comply with the ethical obligation and economic need to maintain animal health. 2)

Stakeholders	Awareness: education/training of healthcare professionals	Surveillance + research	IPC: Community : Food (meat products)	Antibiotic use / diagnostic
	veterinary pharmaceutical industry	Assessment Foodborne AMR Risk Management 3) Surveillance of Use of Antimicrobial Agents and AMR Microorganisms and Determinants 4) Responsibilities of the regulatory authorities	diseases in animals and humans. This Code and existing guidelines for the responsible use of antimicrobial drugs in foodproducing animals include recommendations intended to prevent or reduce the selection of antimicrobial resistant microorganisms in animals and humans in order to: 1) Protect consumer health by ensuring the safety of food of animal origin intended for human consumption. 2) Prevent or reduce as far as possible the direct and indirect transfer of resistant microorganisms or resistance determinants within animal populations and from foodproducing animals to humans. 3) Prevent the contamination of animal derived food with antimicrobial residues which exceed the established MRL.	Responsibilities of the regulatory authorities 3) Responsibilities of the veterinary pharmaceutical industry 4) Responsibilities of wholesale and retail distributors 5) Responsibilities of veterinarians 6) Responsibilities of producers
United Nations General Assembly (UNGA)	1)UN GA declaration	1)UN GA declaration	1)UN GA declaration	1)UN GA declaration
World Organisation for Animal Health (OIE)	Improve awareness and understanding: 1) OIE initiatives seek to increase awareness and	Strengthen knowledge through surveillance and research: 1) Support Member Countries in developing and implementing	1) risk management,	1)Encourage implementation of international standards: Support individual Member Countries in their efforts to

Stakeholders	Awareness: education/training of healthcare professionals	Surveillance + research	IPC: Community : Food (meat products)	Antibiotic use / diagnostic
	understanding among Member Countries, veterinarians, farmers, stakeholders and citizens, organizing and conducting workshops, conferences and symposia. 2) Expand the portfolio of OIE guidance, educational and scientific reference materials. Collaborate with WHO and FAO 3)research and risk management, 4)Engage Member Countries through regular training of Focal Points on Veterinary Products, establishing direct links and support processes. 5)Ensure that well-trained veterinarians and veterinary para-professionals are at the forefront of national and regional efforts to improve animal health and welfare and the stewardship of antimicrobial products through training initiatives at international, regional and national workshops and conferences.	monitoring and surveillance systems. 2) Build and maintain a database for collecting and holding data. Enhance the development, use and functionality of WAHIS. 3) Guide and support research into alternatives to antibiotics.		implement OIE international standards for prudent use of antimicrobials and to combat AMR in animals taking into account their respective social, economic and cultural circumstances. 2)Disseminate and encourage adoption of the recommendations in the OIE List of Antimicrobials of Veterinary Importance.
International Cooperation on Harmonization of Technical Requirements for	same as OIE	same as OIE	same as OIE	same as OIE

Stakeholders	Awareness: education/training of healthcare professionals	Surveillance + research	IPC: Community : Food (meat products)	Antibiotic use / diagnostic
Registration of Veterinary Medicinal Products				
OECD (incl. G7 and G20 commitments)	-	1) Commit to put in place and strengthen their national surveillance systems to monitor antimicrobial resistance and antibiotic consumption and to provide this data to GLASS and the OIE database on antimicrobial use regarding animals; 2)Establishing a cross-sectoral forum where governments can discuss, develop and coordinate new strategies for prudent antimicrobials use in human, animal and plant health. OECD can provide the background evidence for the discussion and assess, beforehand, the potential effectiveness and cost-effectiveness of the innovative policies under discussion	1) Request WHO, FAO, OIE and the OECD to develop targets and goals to promote appropriate use of antimicrobials in the human health, animal health and plant health to prevent infections; 2)Task OECD in collaboration with WHO, FAO and OIE to establish a G20 platform to identify cost-effectiveness of different practices to support countries to adopt responsible and prudent use of antimicrobials and prevent the spread of infectious diseases 3)Discussing alternative approaches for treating and containing livestock diseases, based on the experience of those countries that have taken steps to reduce use of antibiotics	1) Commit to put in place innovative policies to promote a higher uptake of diagnostics in the human sector; 2) Request WHO, FAO, OIE and the OECD to develop targets and goals to promote appropriate use of antimicrobials in the human health, animal health and plant health to prevent infections; 3)Task OECD in collaboration with WHO, FAO and OIE to establish a G20 platform to identify cost-effectiveness of different practices to support countries to adopt responsible and prudent use of antimicrobials and prevent the spread of infectious diseases
Global Health Security Initiative	-	1) To share surveillance data from national public health laboratories and information on real or threatened contamination of food and water supplies along with information on risk mitigation strategies to ensure safe food supplies. 2)To further support the World Health Organization's	1)Discussing alternative approaches for treating and containing livestock diseases, based on the experience of those countries that have taken steps to reduce use of antibiotics	-

Stakeholders	Awareness: education/training of healthcare professionals	Surveillance + research	IPC: Community : Food (meat products)	Antibiotic use / diagnostic
		disease surveillance network and WHO's efforts to develop a coordinated strategy for disease outbreak containment. 3)To improve linkages among laboratories, including level four laboratories, in those countries which have them.		
Alliance for the Prudent Use of Antibiotics	1) APUA is part of a national coalition to promote passage of the STAAR (Strategies to Address Antimicrobial Resistance) Act.	Economic Cost of Antimicrobial Resistance and Misuse Resistant infections are a major cause of morbidity, mortality, and disability with associated economic impacts on health care costs and lost productivity. 1) APUA engages in systematic evaluations to determine the economic burden of resistance on society and to compile evidence that can help guide clinical and regulatory action. These studies provide policymakers with evidence on the factors impacting the cost of drug resistance, the economic burden of drug resistance on the health care systems, and the cost effectiveness of various interventions. Antibiotics in Animals and the Impact on Resistance APUA works with diverse stakeholders to gain consensus on controversial policy issues. 2) APUA is currently conducting an update to the FAAIR report and	Improving Sanitation and Hygiene to Control Infectious Disease 1) APUA advocates for the responsible use of hygiene agents so as to promote infection control, while reducing misuse of agents such as triclosan that could potentially compromise the effectiveness of antibiotic resources.	Accelerating Access to Antimicrobials and Diagnostics 1) APUA works with the Infectious Diseases Society of America (IDSA), the American Medical Association (AMA), and the Society for Healthcare Epidemiology of America (SHEA) to promote U.S. public policy and legislation that will maintain incentives for pharmaceutical antibiotic development and appropriate use.

Stakeholders	Awareness: education/training of healthcare professionals	Surveillance + research	IPC: Community : Food (meat products)	Antibiotic use / diagnostic
		investigating implementation and effectiveness of the EU Ban on antibiotics for growth promotion in agriculture.		
Action on Antibiotic Resistance (ReAct)	1) ReAct's Generating and Translating Evidence (GATE) Programme is a focal point for sharing and disseminating key information on antibiotic resistance related to health and sustainable development. The GATE translates scientific evidence into policy action on national, regional and global levels. The problem is large and ReAct cannot address the issue alone. We strive to equip our extended network with the knowledge and tools needed to take action on antibiotic resistance. - 2) Increase visibility of ABR in the global health dialogue together with global and local stakeholders - 3) Initiate debate about the need for rational use, affordable drug pricing and equitable access to antibiotics	1) ReAct's Generating and Translating Evidence (GATE) Programme is a focal point for sharing and disseminating key information on antibiotic resistance related to health and sustainable development. The GATE translates scientific evidence into policy action on national, regional and global levels. The problem is large and ReAct cannot address the issue alone. We strive to equip our extended network with the knowledge and tools needed to take action on antibiotic resistance.	-	1) Initiate debate about the need for rational use, affordable drug pricing and equitable access to antibiotics
Antibiotic Action Team	1) Helps raise AMR related awareness, Antibiotic action champions.:	-	1) We urge everyone to use existing antibiotics wisely and we promote the importance of	-

Stakeholders	Awareness: education/training of healthcare professionals	Surveillance + research	IPC: Community : Food (meat products)	Antibiotic use / diagnostic
	Antibiotic Action is a global public awareness initiative to inform everyone about drug resistance. We work with a wide variety of people, including professionals as well as the general public.		infection prevention and control.	
Health Action International (HAI)	-	ARC	ARC	1) Safe, effective, affordable and quality-assured medicines for everyone, everywhere.
Innovative Medicines Initiative	-	-	-	1) develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators; where possible, reduce the time to reach clinical proof of concept in medicine development, such as for cancer, immunological, respiratory, neurological and neurodegenerative diseases;
European Platform for the Responsible Use of Medicines in Animals	1) Engaging and communicating 2)Sharing knowledge by developing awareness campaigns	1) supporting transparency on the use of vet meds, such as surveillance of use and resistance monitoring	1) Promoting animal health and welfare 2)Working together to reach the highest achievable level of animal health (e.g. nutrition + housing)	1) Facilitating coordination and exchange of information on best practice together with national responsible use initiatives; 2)advocating for availability of vet meds as well aas access to innovative medicines and diagnostic tools
European Federation of Pharmaceutical Industries and Associations	same as DAVOS Declaration	same as DAVOS Declaration	same as DAVOS Declaration	same as DAVOS Declaration

Stakeholders	Awareness: education/training of healthcare professionals	Surveillance + research	IPC: Community : Food (meat products)	Antibiotic use / diagnostic
International Dairy Federation (IDF)	-	1) IDF-Standing Committee on Animal Health will continue to monitor and report new research results, in comparison with historical data, to alert the dairy industry of confirmed changes in antimicrobial resistance among mastitis pathogens. 2) Competent authorities in effectively controlling the manufacture, registration, supply and use of antimicrobial agents, and in having effective systems in place to monitor for potential problems such as antimicrobial resistance	1) • Appropriate and coordinated responses to prevent and control spread of resistance by management of therapeutic regimes will be proposed by the IDF if an emergence of antimicrobial resistance among mastitis pathogens is confirmed. 2)The guide highlights the role of: • Dairy farmers in managing animal health and husbandry practices to minimize the occurrence and spread of disease 3) Food (dairy and meat) processing companies in setting clear specifications for the raw products they source and in verifying and monitoring farmer compliance	1) IDF Guide to Prudent Use of Antimicrobial Agents in Dairy Production - Veterinarians providing expert advice to ensure that the most appropriate treatments are used correctly 2) Pharmaceutical companies in ensuring that antimicrobial agents are properly manufactured, assessed, labelled and then only sold through regulated distribution channels 3) Competent authorities in effectively controlling the manufacture, registration, supply and use of antimicrobial agents, and in having effective systems in place to monitor for potential problems such as antimicrobial resistance
International Federation of Pharmaceutical Manufacturers & Associations	1) recognizing this requires concerted efforts from many stakeholders, through continued provider and patient education	1) sharing of surveillance data with public health bodies and healthcare professionals	-	1) Improve access to high-quality antibiotics and ensuring that new ones are available to all 2)Reduce the environmental impact from the production of antibiotics, including a review of the companies' manufacturing and supply chains, and work with stakeholders to establish a common framework for assessing and managing

Stakeholders	Awareness: education/training of healthcare professionals	Surveillance + research	IPC: Community : Food (meat products)	Antibiotic use / diagnostic
				antibiotic discharge; 3)Help ensure antibiotics are used only by patients who need them, 4)an examination of the companies' promotional activities, 5)and collaboration with stakeholders to reduce uncontrolled antibiotic purchase; 6)Improve access to current and future antibiotics, vaccines, and diagnostics 7)working to reduce the prevalence of substandard/counterfeit antibiotics in high-risk markets;
World Medical Association	1) Support the concept of joint educational efforts between human medical and veterinary medical schools; 2)WMA resolution for AMR	1) Individual governments to cooperate with the World Health Organization (WHO) to enhance the effectiveness of the WHO's global network of antimicrobial resistance surveillance. This will foster the collection, quality and sharing of data; the monitoring of progress in combating antimicrobial resistance; the establishment of appropriate formularies; and scientific support for interventions. 2)Support cross-species disease surveillance and control efforts in public health, particularly the identification of early disease and outbreak trends;	1) Encourage joint efforts in clinical care through the assessment, treatment, and prevention of cross-species disease transmission;	-

Stakeholders	Awareness: education/training of healthcare professionals	Surveillance + research	IPC: Community : Food (meat products)	Antibiotic use / diagnostic
International Pharmaceutical Federation	1)Advocate the creation and increased awareness of national, regional and international electronic platforms that triangulate, in real time, trends in antimicrobial use and resistance within and between the human, animal and environmental health sectors in order to allow early warning of emerging resistance in any/all sectors to inform strategies for containment and to prevent transmission between and within sectors. 2)· Develop and support educational campaigns on the responsible use of antimicrobial medicines aimed at the public. 3) · Develop and support educational campaigns on the responsible use of antimicrobial medicines aimed at those involved in food production as well as health care, veterinary and environmental health professionals	1)Promote the establishment and/or strengthening of sustainable AMR and antimicrobial use surveillance systems in all health care settings.	-	1)Promote cooperation among countries and professional organisations in the development and use of indicators to monitor responsible antimicrobial prescribing, dispensing, use and disposal practices. 2)· Support the development and uptake of rapid and reliable diagnostic and susceptibility tests. 3)· Promote the role of the pharmacist in the sustainable production of, access to and the responsible use of antimicrobial medicines, including selection, procurement, distribution, compounding, use and disposal. 4)· Promote responsible production of antimicrobial substances and antimicrobial medicines, including waste disposal and waste water handling, and encourage the selection and procurement of medicines produced in an environmentally acceptable way in tenders/reimbursement systems.
World Health Professions Alliance	1) AMR factsheet	1) Encourage research on poor quality medicines. There are very few studies on the prevalence of substandard drugs with sufficient methodology including random	1) “Integration of prevention of antimicrobial resistance into all health systems and practice” as outlined in the report will require considering	1. Emphasize the importance of the emergence of antimicrobial resistance as a consequence of the problem of counterfeit and/or

Stakeholders	Awareness: education/training of healthcare professionals	Surveillance + research	IPC: Community : Food (meat products)	Antibiotic use / diagnostic
		sampling to evaluate the magnitude of the problem and design interventions.	the problem from the Universal Health Coverage perspective and the inclusion of medicines in the basic package of care for all people. It is well known, that individuals, who lack insurance, often turn to the Internet or buy drugs on the unregulated black market. The practice can increase the spread of substandard antimicrobials and ineffective treatments that will negatively impact populations' health and escalate healthcare costs. 2) The WHO-led global action plan should clearly articulate a strategy to improve the rational use of antimicrobials in human medicine and the use of antibiotics only for the treatment of infection in animals.	substandard antimicrobial medicines, especially for diseases that are treated with combination therapy, such as tuberculosis, malaria and HIV. Most treatment failures may be due to administration of counterfeit medicines even when some bacterial agents are still susceptible to common antibiotics. This may jeopardize the public's confidence in their healthcare providers as well as in government agencies involved in drug distribution. Healthcare professionals prescribing practices may also be affected due to false reports of drug resistance and result in prescribing higher priced drugs that are believed not to be counterfeit. In this regard, we underscore the need to promote increased surveillance, regulatory and legal measures along with public awareness campaigns and interventions related to good manufacturing practices to combat the problem. 2) The WHO-led global action plan should clearly articulate a strategy to improve the rational use of antimicrobials in human medicine and the

Stakeholders	Awareness: education/training of healthcare professionals	Surveillance + research	IPC: Community : Food (meat products)	Antibiotic use / diagnostic
				use of antibiotics only for the treatment of infection in animals.
TATFAR	TATFAR overarching aim	1) Outcomes to date have included better communication protocols and joint publications on existing methods of surveillance and antibiotic prescribing in member states. - Cooperate in the development of methodology for measuring and reporting the consumption of antimicrobials per species in veterinary medicine	2. Better prevention of healthcare- and community-associated drug-resistant infections	TATFAR works in areas of (1) appropriate therapeutic use of antimicrobial drugs in medical and veterinary communities
EU	(a) Better evidence and awareness of the challenges of AMR - EU antibiotics awareness day	1)(a) Better evidence and awareness of the challenges of AMR 2) Improve knowledge on detection, effective infection control and surveillance 3) Close knowledge gaps on AMR in the environment and on how to prevent transmission	1) Better prevention and control of AMR 2) Better addressing the role of the environment	1) Develop new therapeutics and alternatives 2) Develop new preventive vaccines 3) Develop novel diagnostics 4) EU prudent use guidelines
ECDC	1) ECDC reports 2)Joint EMA/EFSA/ECDC reports - JIACR reports (EFSA, ECDC, EMA and the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) have also published a joint scientific opinion on antimicrobial resistance focused on infections that can be transmitted to humans from	1) EARS-NET and 2) ESAC-NET 3)HAI-NET 4) AMR research	EU action plan	EU action plan

Stakeholders	Awareness: education/training of healthcare professionals	Surveillance + research	IPC: Community : Food (meat products)	Antibiotic use / diagnostic
	animals and food (i.e., zoonoses).)			
EMA/EFSA	1) ESVAC reports	1) European Medicines Agency - European Surveillance of Veterinary Antibiotic Consumption (ESVAC)	1)EMA and EFSA Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety (RONAFA)	1)EMA and EFSA Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety (RONAFA)
EFSA	1) EU summary report AMR in zoonotic indicator bacteria from animal, human and food	1) EFSA monitors and analyses the situation on antimicrobial resistance in food and animals across Europe. The Authority is assisted by the Task Force on Zoonoses Data Collection: a pan-European network of national representatives of EU Member States, other reporting countries, as well as the World Health Organization (WHO) and World Organisation for Animal Health (OIE). 2) EFSA's Scientific Panels assess the risks of antimicrobial resistance and provides scientific advice on control options at the request of risk managers or on its own initiative. This work has included risk assessments by the Panel on Biological Hazards on antimicrobial resistance in the food and feed chain and the public health significance of MRSA in animals and food focusing on the specific type of	-	-

Stakeholders	Awareness: education/training of healthcare professionals	Surveillance + research	IPC: Community : Food (meat products)	Antibiotic use / diagnostic
		MRSA found in food-producing animals. The Panel on additives and products or substances used in animal feed assesses the safety of animal feed additives, including the risks related to antibiotic resistance where micro-organisms are involved.		
UK DH/PHE	1. improve the knowledge and understanding of AMR,- Antibiotic guardian campaign	5. Better access to and use of surveillance data - Fingerprints AMR 6. Better identification and prioritisation of amr research needs	1. Improving infection prevention and control practices	2. Optimising prescribing practice 4. Developing new drugs, treatments and diagnostics
World Alliance Against Antibiotic Resistance (WAAAR)	Promotion of awareness of all the stakeholders - including the general public - of the threat represented by antibiotic resistance	-	-	In addition, WAAAR has called on UNESCO to recognize the concept of antibiotics as an 'intangible cultural heritage'. WAAAR has been particularly active in France, where many of its members are based.
Europeon commission	Communication, Education and Training - 1) Improve awareness raising on the appropriate use of antimicrobials - - 2) Improve communication on AMR to the public.	Improving monitoring and surveillance in human and animal medicine - 1) Strengthen surveillance systems on AMR and antimicrobial consumption in human medicines 2) Strengthen surveillance systems on AMR and antimicrobial consumption in animal medicines 3) Reinforce and co-ordinate research - Promote efforts to	Preventing microbial infections and their spread - Strengthen infection prevention and control in hospitals, clinics, etc.	Making sure antimicrobials are used appropriately both in humans and animals - 1) Improve awareness raising on the appropriate use of antimicrobials -2) Introduce recommendations for prudent use of antimicrobials in veterinary medicine, including follow-up reports

Stakeholders	Awareness: education/training of healthcare professionals	Surveillance + research	IPC: Community : Food (meat products)	Antibiotic use / diagnostic
		analyse the need for new antibiotics in veterinary medicine		

Appendix Table 10: Individual policy details (2/2)

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
World Health Organization (WHO)	-	1) gained further political and intersectoral backing to address antimicrobial resistance through the UNGA and build the consensus and partnerships needed to implement the global action plan.	1) WHO ACTION PLAN - This includes taking specific actions under each of the five objectives in the GAP and supporting countries in developing and implementing national action plans on AMR.	-	Human
United Nations Children's Fund (UNICEF)	-	-	-	-	Human
United Nations Office on Drugs and Crime	UNGA	UNGA	UNGA	UNGA	Human
United Nations Development Programme (UNDP)	1)Fosters research in infectious diseases and in the development of new class of antimicrobial	1) Facilitates full, universal and sustained compliance with the International Health Regulations (2005) and	1) Renews efforts to craft policies and regulatory frameworks to address more directly the multi-sectoral	-	Human

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
	agents, point of care diagnostics and new vaccines for both human and animal sectors. 2)invests in research to develop new, affordable, available and more effective countermeasures and health technologies to prevent, diagnose, treat and minimize the impact of these threats ensuring a full social return on public investments	aggressively adopts strategies and approaches that recognize that multi-sectoral responses are vital 2) Removes the professional, bureaucratic and cultural barriers, as well as the obstacles inherent within social, economic and political processes, that silo human health, animal health and the environmental sectors from effective multi-sectoral partnership and actions	responses to emerging infectious diseases and antimicrobial resistance 2) Strengthens medicines regulation and stewardship programs across the human and animal health sectors to ensure the quality and safety of medicines and preserve the effectiveness of existing and new therapies 3) Reaches across the public and private sectors and civil society to fully harness their collective power for change		
Food and Agriculture Organization of the United Nations (FAO)	-	1) - Strengthening national and international interdisciplinary cooperation and developing holistic strategies and action plans	1) - Developing appropriate policies/guidance on the prudent and responsible use of antimicrobials in animal husbandry 2) Improving regulatory frameworks based on internationally agreed principles and standards (Codex, OIE)	Focus Area 3: Strengthen governance related to antimicrobial use and Antimicrobial Resistance in food and agriculture - 1) Improving regulatory frameworks based on internationally agreed principles and standards (Codex, OIE)	Human/ Animal / Environment

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
Joint FAO/WHO Codex Alimentarius Commission	-	-	1) Comply with the ethical obligation and economic need to maintain animal health.	1) Responsibilities of the regulatory authorities 2) Responsibilities of the veterinary pharmaceutical industry 3) Responsibilities of wholesale and retail distributors 4) Responsibilities of veterinarians 5) Responsibilities of producers	Human/Animal
United Nations General Assembly	1)UN GA declaration	1)UN GA declaration	1) UN GA declaration 2) Creation of IACG 3)To coordinate mapping of the actions being taken by UN agencies – and other organisations and key stakeholders – towards achieving measurable results, and to identify opportunities for collaboration, as well as gaps, redundancies and duplication. 4) To support	1) UN GA declaration	All

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
			the implementation of the UNGA Political Declaration and the GAP and link them to the SDGs by championing and advocating for action against AMR at the highest political level. 5) To promote, plan and facilitate collaborative action to align activities so that gaps are closed and resources are optimally distributed. 6) To explore the feasibility of developing global goals and ambitions related to AMR for UN agencies, component members and, where appropriate, other stakeholders, for priorities set out in the declaration. 7) To report regularly on progress and on IACG meetings and issue a full report to		

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
			the Secretary-General during the 73rd session of the UNGA, keeping member states, stakeholders and the governing bodies of the FAO, OIE and WHO fully apprised of progress.		
World Organisation for Animal Health (OIE)	1) Identify and pursue opportunities for public-private partnerships in AMR	Improve awareness and understanding: 1) OIE initiatives seek to increase awareness and understanding among Member Countries, veterinarians, farmers, stakeholders and citizens, organizing and conducting workshops, conferences and symposia. 2) Expand the portfolio of OIE guidance, educational and scientific reference materials. Collaborate with WHO and FAO 3) Identify and pursue opportunities for public-private partnerships in AMR 4) Ensure that well-trained veterinarians and veterinary para-professionals are at the forefront of national and	Strengthen knowledge through surveillance and research: 1) Support Member Countries in developing and implementing monitoring and surveillance systems. Support good governance and capacity building: 2) Provide assistance and leadership to Member Countries as they develop and implement National Action Plans and policies. 3) Provide tools and guidance to assist Member Countries in their AMR risk-assessment initiatives associated with antimicrobial agents and use in animals. 4) Work	-	Human/Animal

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
		regional efforts to improve animal health and welfare and the stewardship of antimicrobial products through training initiatives at international, regional and national workshops and conferences. 5)Strengthen multilateral support for implementation of OIE standards among policymakers, our cooperation partners and donors to contribute to a well-coordinated international effort in the fight against AMR.	alongside Member Countries to ensure Veterinary Services have the capacity to implement OIE standards, taking advantage of their engagement in the OIE PVS Pathway7 . 5) Support Member Countries to develop and modernize legislation governing the manufacture, marketing authorisation, importation, distribution and use of veterinary products. 6)Encourage implementation of international standards: Support individual Member Countries in their efforts to implement OIE international standards for prudent use of antimicrobials and to combat AMR in animals taking into account their respective social, economic and cultural circumstances. 7)Disseminate and encourage adoption of the recommendations in the OIE		

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
			List of Antimicrobials of Veterinary Importance. 8)Build on the success of the OIE standards development work programme to continue to advance for the animal sectors our comprehensive framework of quality, science-based standards that support the Global Action Plan on AMR. 9)Collaborate with WHO and FAO to support the development of a comprehensive and aligned framework of international standards and guidelines across human health, animal health, agriculture and the food chain.		
International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary	same as OIE	same as OIE	same as OIE	same as OIE	Human/Animal

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
Medicinal Products					
OECD (incl. G7 and G20 commitments)	-	1) Request WHO, FAO, OIE and the OECD to develop targets and goals to promote appropriate use of antimicrobials in the human health, animal health and plant health to prevent infections; 2)Task OECD in collaboration with WHO, FAO and OIE to establish a G20 platform to identify cost-effectiveness of different practices to support countries to adopt responsible and prudent use of antimicrobials and prevent the spread of infectious diseases 3)Establishing a cross-sectoral forum where governments can discuss, develop and coordinate new strategies for prudent antimicrobials use in human, animal and plant health. OECD can provide the background evidence for the discussion and assess, beforehand, the potential effectiveness and	1) Confirm their commitment to tackle AMR, based on the principles of the 'One-Health' approach and in agreement with the Global Action Plan on AMR. This requires developing and strengthening national action plans; and providing capacity building support to other countries; 2) Developing good practices and national action plans.	-	All

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
		cost-effectiveness of the innovative policies under discussion 4)Discussing alternative approaches for treating and containing livestock diseases, based on the experience of those countries that have taken steps to reduce use of antibiotics			
Global Health Security Initiative	1) To explore joint cooperation in procuring vaccines and antibiotics. 2)To engage in a constructive dialogue regarding the development of rapid testing, research in variations of vaccines, and our respective regulatory frameworks for the development of vaccines	1) To explore joint cooperation in procuring vaccines and antibiotics. 2)To engage in a constructive dialogue regarding the development of rapid testing, research in variations of vaccines, and our respective regulatory frameworks for the development of vaccines, and in particular smallpox vaccines. 3)To improve linkages among laboratories, including level four laboratories, in those countries which have them. 4) To agree on a process for international collaboration on risk assessment and management and a common language for risk communication.	1)To further support the World Health Organization's disease surveillance network and WHO's efforts to develop a coordinated strategy for disease outbreak containment. 2)To share emergency preparedness and response plans, including contact lists, and consider joint training and planning.	-	Human

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
Alliance for the Prudent Use of Antibiotics	Accelerating Access to Antimicrobials and Diagnostics 1) APUA works with the Infectious Diseases Society of America (IDSA), the American Medical Association (AMA), and the Society for Healthcare Epidemiology of America (SHEA) to promote U.S. public policy and legislation that will maintain incentives for pharmaceutical antibiotic development and appropriate use.	-	-		Human
Action on Antibiotic Resistance (ReAct)	1) Identify, develop and seed innovative solutions for R&D of new antibiotics and diagnostics	-	1) Develop and advocate national/regional policy solutions to address the challenge of antibiotic resistance 2) Develop local training and education programs on ABR and assist with their implementation	-	Human
Antibiotic Action Team	However, we desperately need new treatments for infections and 1) we	1) Antibiotic action champions.: Antibiotic Action is a global public awareness initiative to	-	-	Human

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
	recommend enhancing global efforts to discover these treatments.	inform everyone about drug resistance. We work with a wide variety of people, including professionals as well as the general public.			
Health Action International (HAI)	ARC	ARC	ARC	ARC	Human
Innovative Medicines Initiative	1) improve the current drug development process by providing support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products; 2) develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators; where possible, reduce the time to reach clinical proof of concept in medicine development, such as for cancer, immunological, respiratory, neurological and neurodegenerative	-	-	-	Human

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
	diseases; 3) increase the success rate in clinical trials of priority medicines identified by the World Health Organization; 4) develop new therapies for diseases for which there is a high unmet need, such as Alzheimer's disease and limited market incentives, such as antimicrobial resistance; 5) reduce the failure rate of vaccine candidates in phase III clinical trials through new biomarkers for initial efficacy and safety checks.				
European Platform for the Responsible Use of Medicines in Animals	-	1) Engaging and communicating 2)Facilitating coordination and exchange of information on best practice together with national responsible use initiatives;	1) Developing best practice frameworks on responsible use of vet meds and advocating for more availability of vet meds		Human/Animal
European Federation of Pharmaceutical Industries and Associations	same as DAVOS Declaration	same as DAVOS Declaration	same as DAVOS Declaration	same as DAVOS Declaration	Human

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
International Dairy Federation (IDF)	-	-	1)IDF Guide to Prudent Use of Antimicrobial Agents in Dairy Production	-	Human/Animal
International Federation of Pharmaceutical Manufacturers & Associations	1) Invest in R&D that meets global public health needs with new innovative diagnostics and treatments 2)establishing new business models that balance access needs, appropriate antibiotic use, expanded vaccine coverage and adequate return to companies	1)and collaboration with stakeholders to reduce uncontrolled antibiotic purchase; 2) including working with stakeholders to strengthen global health systems and address access bottlenecks; 3)Explore new opportunities for open collaborations between industry and the public sector to address challenges in the research and development of new antibiotics, vaccines, and diagnostics, recognizing the value these bring to society.	1)establishing new business models that balance access needs, appropriate antibiotic use, expanded vaccine coverage and adequate return to companies	-	Human
World Medical Association	-	-	Support collaboration between human and veterinary medicine 1) Engage in a dialogue with the World Veterinary Association to discuss strategies for enhancing collaboration between human and veterinary medical professions in	-	Human

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
			medical education, clinical care, public health, and biomedical research. 2)Encourage National Medical Associations to engage in a dialogue with their veterinary counterparts to discuss strategies for enhancing collaboration between human and veterinary medical professions within their own countries.		
International Pharmaceutical Federation	1)· Promote the discovery and development of new cost-effective antimicrobial medicines by advocating for reform of reimbursement systems and novel incentive mechanisms that recognise the value of novel antibiotics and delink access and availability from return on investments and profit. 2)· Encourage the discovery and development of novel	1)Promote cooperation among countries and professional organisations in the development and use of indicators to monitor responsible antimicrobial prescribing, dispensing, use and disposal practices.	1)Facilitate and encourage the consideration of AMR information by regulatory agencies during the approval process for novel medicines 2)· Endorse the termination of use of critically important antimicrobial medicines in animals6 for growth promotion purposes as well as the reduction of use for prophylaxis and metaphylaxis by advancing biosecurity and good animal husbandry practices instead.	-	All

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
	treatment modalities and vaccines.				
World Health Professions Alliance	1) Involve the pharmaceutical industry as part of the solution. The need for antimicrobial medicines will be greater than ever with the emergence of multidrug resistance in common pathogens, new infections and the potential of using multi-drug resistant agents in bioweapons. Yet, the development of these agents is declining globally. Solutions are needed for encouraging and facilitating the development of new antimicrobial agents to meet global health needs.	1) A multisectoral and multistakeholder action plan should include education, regulation and surveillance of antibiotics use internationally.	1) AMR factsheet	-	Human
TATFAR	1) Strategies for improving the pipeline of new antimicrobial drugs.	1)TATFAR overarching aim	Providing recommendations for EU-US collaboration	-	Human/Animal
EU	1) Develop new economic models and incentives	1) Better coordination and implementation of EU rules to tackle AMR 2) A stronger EU global presence 3) Stronger	1) Developing a global research agenda	1) Better coordination and implementation of EU rules to tackle AMR	All

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
		bilateral partnerships for stronger cooperation 4) Cooperating with developing countries			
ECDC	EU action plan	EU action plan	EU action plan	EU action plan	All
EMA/EFSA	-	-	-	-	Human/Animal
EFSA	-	-	technical specifications for organisms identification	-	Human/Animal
UK DH/PHE	4. Developing new drugs, treatments and diagnostics	7. Strengthened international collaboration	-	1. Quality premium 2. CQUIN targets	All
World Alliance Against Antibiotic Resistance (WAAAR)	-	WAAAR calls for a holistic policy response and outlines ten suggestions for action, including improved awareness and education, better diagnostics, new drug development models and better stewardship and infectious disease control measures	-	-	All
Europeon commission	1) Developing new effective antimicrobials or alternatives for treatment 2)Research and Innovation-Promote unprecedented collaboration to bring new antimicrobials to patients	1) Cooperating with international partners to contain the risks of AMR 2) Promote unprecedented collaboration to bring new antimicrobials to patients 3)Develop and/or strengthen multilateral and bilateral	Develop and/or strengthen multilateral and bilateral commitments for the prevention and control of AMR	1) Strengthen EU law on veterinary medicines and on medicated feed 2) Introduce legal tools to tighten prevention and control of infections in animals	All

Stakeholders	Investment	Strengthening interdisciplinary/multisectoral cooperation	Helping other stakeholders with frameworks/ implementation/policy development/supporting governance	Governance: regulatory changes	Reservoirs which policy / strategy / objective is impacting *Takes account of Appendix Table 9 policies as well
		commitments for the prevention and control of AMR		in the new EU Animal Health Law	

Appendix Table 11: Overview of interventions identified from the targeted review of randomised controlled trials

Reference no. for interventions	Intervention	Control (Reference)	Target stakeholder	Efficacy of interventions	Adverse events	Translation of interventions into WHO GAP objectives	Risk domain targeted
Stewardship related interventions							
2	Audit and feedback (of antibiotic use)	Usual care (152–154,766–769)	Clinician	• Appropriate antibiotic use: OR: 2.03 (increased odds vs. usual care) • Duration of antibiotics: Median reduction 7 days • Increased adherence with quality indicators: 3% to 7%	• Length of stay: NS • In-hospital mortality: NS • Clinical improvement at or after discharge: NS	Intended target: Antibiotic use	Antibiotic use

Reference no. for interventions	Intervention	Control (Reference)	Target stakeholder	Efficacy of interventions	Adverse events	Translation of interventions into WHO GAP objectives	Risk domain targeted
				• % difference in antibiotic use: Not significant (NS) to -9.21% • Average expenditure per prescription: NS • Long term (>12 months) impact of interventions: NS			
3	Delayed prescribing / post-dating delayed prescribing	Immediate prescribing (770)(771)	Clinician	• Re-consultation rates for cough: Incident rate ratio: NS* to 0.22 • Change in antibiotic use: NS *(for patients who were NOT prescribed antibiotics for cough in previous 2 years))	-		Antibiotic use

Reference no. for interventions	Intervention	Control (Reference)	Target stakeholder	Efficacy of interventions	Adverse events	Translation of interventions into WHO GAP objectives	Risk domain targeted
6	IT Decision support	Usual care (772)(773)(774)(154)	Clinician	• % Adjusted Mean Difference reduction in antibiotic use: -9.69% to -1.85% • Adjusted OR of antibiotic use following intervention: 0.64 • Reduction in antibiotic prescription rates: NS to 4% to 15% reduction	-	Intended target: Antibiotic use	Antibiotic use
23	Displaying poster-sized commitment letters in examination rooms	Usual care(775)	Clinician / Patient	% reduction in-appropriate prescribing: -19.4%	-	Intended target: Antibiotic use Awareness	Antibiotic use
26	Patient education	Usual care / Patient education regarding immunisations (compared to patient	Patient	OR: NS to 0.27 - reduced odds of antibiotic use for patients with	-	Intended target: Antibiotic use	Antibiotic use Demographics* (the

Reference no. for interventions	Intervention	Control (Reference)	Target stakeholder	Efficacy of interventions	Adverse events	Translation of interventions into WHO GAP objectives	Risk domain targeted
		education on RTIs and antibiotics) (151)(145)(770)		Indian ethnic origin Incident rate ratio: NS *(for all other patient groups)		Awareness	results happened to impact health-seeking behavior in a certain ethnic group)
28	Clinical education intervention	Usual care (776)(146)(147)	Clinician	% reduction in antibiotic prescribing: NS to -7.70%	-	Intended target: Antibiotic use Awareness	Antibiotic use
29	Performance related pay	Usual care (777)	Clinician	% reduction in antibiotic prescribing: -6 to -6.60%	-	Intended target: Antibiotic use	Antibiotic use
32	Decision support	Printed decision support vs usual care (773)(778)	Clinician	Reduced odds of antibiotic use: OR = 0.57 Increased odds of improvement in	Length of stay: NS	Intended target: Antibiotic use	Antibiotic use

Reference no. for interventions	Intervention	Control (Reference)	Target stakeholder	Efficacy of interventions	Adverse events	Translation of interventions into WHO GAP objectives	Risk domain targeted
				appropriate antibiotic use: OR = 2.4	Reconsultation rate: NS Return within a month with sore throat = NS		
		Clinical score decision support vs delayed prescribing(155)	Clinician	Reduced risk of antibiotic use: Risk ratio = 0.71; 29% reduction in Ab prescribing	Hazard ratio of duration of clinical symptoms recovery: 1.30 Reduction in severity of symptoms: Adjusted mean difference -0.33 - -0.30		
33	Procalcitonin and pyuria-based algorithm	Usual care (779)	Clinician	Median duration of antibiotics: 7 vs 10 days (usual care)	Mortality: NS Infections: NS	Intended target:	Antibiotic use

Reference no. for interventions	Intervention	Control (Reference)	Target stakeholder	Efficacy of interventions	Adverse events	Translation of interventions into WHO GAP objectives	Risk domain targeted
					Recurrent infection: NS Rehospitalisation: NS	Antibiotic use	
34	PCR test	Usual care (144)	Clinician	Median (hours) between test and on-target therapy: 5 vs 25.5 (usual care) On-target therapy: NS to 87.5% vs 31.8% (usual care)	Infections: NS Mortality: NS	Intended target: Antibiotic use	Antibiotic use
4	CRP test	Usual care(780)	Clinician	Change in antibiotic prescribing: NS	-	Intended target: Antibiotic use	Antibiotic use
Bundled interventions							

Reference no. for interventions	Intervention	Control (Reference)	Target stakeholder	Efficacy of interventions	Adverse events	Translation of interventions into WHO GAP objectives	Risk domain targeted
7	ASP bundle	Performance feedback / training meeting / guideline / reminders / committee meeting attendance vs Audit and feedback (NS)(768)	Clinician	Appropriate antibiotic use: NS to 7% increase	-	Intended target: Antibiotic use	Antibiotic use
		Rapid review by multi- disciplinary antimicrobial stewardship team vs Standard of care(781)		Relative hazard of receiving appropriate versus no treatment in intervention group relative to control group HR: 1.58 (time to culture from draw) to 1.95 (24 hours after blood culture)[20]			

[20] (Only appropriate treatment outcome reported in the table, paper also reported optimal treatment and active treatment outcome results)

Reference no. for interventions	Intervention	Control (Reference)	Target stakeholder	Efficacy of interventions	Adverse events	Translation of interventions into WHO GAP objectives	Risk domain targeted
1,2	Bundle: Guideline + Audit feedback	Usual care (782)(145) /	Clinician	Reduction in prescribing rate: NS to -8.61% Incident rate ratio of antibiotic prescribing rate: 0.47 – 0.97 Cost savings due to lower antibiotic use: £92,356 (2016)	-	Intended target: Antibiotic use	Antibiotic use
		Audit + feedback without behaviour change message (766)		-6.10% reduction in prescribing rate			
1,2,26	Bundle: Guideline + Audit feedback + Patient education	Usual care (145)	Clinician / Patient	Incident rate ratio of antibiotic prescribing rate: 0.98	-	Intended target: Antibiotic use Awareness	Antibiotic use

Reference no. for interventions	Intervention	Control (Reference)	Target stakeholder	Efficacy of interventions	Adverse events	Translation of interventions into WHO GAP objectives	Risk domain targeted
1,28	Bundle: Guideline + Clinician education intervention	Usual care(783)	Clinician	Adjusted risk difference at endline for overall antibiotic use: -29% Results were NS for multiple / broad-spectrum / intravenous antibiotics) Cost of antibiotics: -0.2% adjusted risk difference ; Result was insignificant for full prescription costs.	-	Intended target: Antibiotic use Awareness	Antibiotic use
2, 26, 28	Bundle: Audit + feedback + Patient eduction + Clinical education intervention	Usual care (150)	Clinician / Patient	Reduction in overprescribing for RTIs: -16% Change in antibiotic prescribing: Overall (1st year): -7.6% versus -0.4% (Control group) macrolides and amoxicillin/clavulanate -12.7% versus +2.9% (Control group)	-	Intended target: Antibiotic use Awareness	Antibiotic use

Reference no. for interventions	Intervention	Control (Reference)	Target stakeholder	Efficacy of interventions	Adverse events	Translation of interventions into WHO GAP objectives	Risk domain targeted
				Overall (2nd year): -4.3% versus +2% (Control group) macrolides and amoxicillin/clavulanate -7.8% versus +6.7% (Control group)			
2,28	Bundle: Audit + feedback + Clinical education intervention	Usual care (769)	Clinician	Decreased odds of prescribing: OR = 0.64 – 0.72 % change in prescribing: 5% increase to -30% decrease	-	Intended target: Antibiotic use Awareness	Antibiotic use
2,6,23,26	Bundle: Audit feedback + IT decision support + Display of commitment letter + Patient education	Usual care (784)	Clinician / Patient	Overall antibiotic prescribing: 88.8% vs 62.3% (control group) Antibiotic prescribing for RTI: 87.1% vs 64.3% Antibiotic prescribing for GTI: 94.7% vs 52.4%	-	Intended target: Antibiotic use	Antibiotic use

Reference no. for interventions	Intervention	Control (Reference)	Target stakeholder	Efficacy of interventions	Adverse events	Translation of interventions into WHO GAP objectives	Risk domain targeted
24,26	Bundle: Clinician + Patient communication + Patient education	Usual care (780)	Clinician / Patient	Total prescribing rate : 1.95 (increase)	-	Intended target: Antibiotic use Awareness	Antibiotic use
24,26,4	Bundle: Clinician + Patient communication + Patient education + CRP test	Usual care (780)	Clinician / Patient	Total prescribing rate : NS	-	Intended target: Antibiotic use Awareness	Antibiotic use
26,28	Bundle: Patient + Clinician education	Usual care (148)(149)	Clinician / Patient	Percentage reduction in use: NS (Tetracycline/ Penicillins/ Sulfonamides and trimethoprim/ Quinolones) to -9.37% (Macrolides) Rate ratio (of reduction in antibiotic use): 0.65 – 0.78	Reconsultations : NS New RTI consultation: NS Hospital referrals: NS	Intended target: Antibiotic use Awareness	Antibiotic use

Reference no. for interventions	Intervention	Control (Reference)	Target stakeholder	Efficacy of interventions	Adverse events	Translation of interventions into WHO GAP objectives	Risk domain targeted
28,3	Bundle: Delayed prescribing + Clinician education	Usual care (785)	Clinician	Dispensing rate: NS	-	Intended target: Antibiotic use Awareness	Antibiotic use
31,32	Bundle: Rapid diagnostics (viral infections) + Printed decision support	Usual care / Delayed prescribing (Risk ratio: 0.73; 27% reduction in Ab prescribing, Symptom severity: -0.30 to -0.33 reduction in mean difference on symptom severity scale; Time to symptom resolution = NS; Return within a month with sore throat = NS) (155)	Clinician	Reduced risk ratio of antibiotic use: 0.73	Reduced mean difference in infection rate: -0.30 Duration of infection: NS Reconsultation: NS		Antibiotic use

Reference no. for interventions	Intervention	Control (Reference)	Target stakeholder	Efficacy of interventions	Adverse events	Translation of interventions into WHO GAP objectives	Risk domain targeted
6,3	Bundle: IT decision support + Delayed prescribing	Clinician education intervention (-1.6% reduction in absolute prescribing rate) (785)	Clinician	Absolute reduction in dispensing rate: - 1.60%	-	Intended target: Antibiotic use	Antibiotic use
6,32	Bundle: IT decision support + Printed decision support	IT decision support alone (NS) (773) (Gonzales R 2013)	Clinician	Change in antibiotic use: NS	-	Intended target: Antibiotic use	Antibiotic use

Abbreviations: [ASP =Antibiotic stewardship program; CRP = C-Reactive protein; GTI =Gastrointestinal tract infections ; HR: Hazard ratio; IT: Information technology; NS = Not significant; OR = Odds ratio, PCR = Procalcitonin Testing ; RTI = Respiratory tract infection, WHO GAP = World Health Organization Global Action Plan]

Appendix III. Appendix for Chapter 4

Appendix Table 12: Updated parameter list for expanded *E. coli* bacteraemia with resistant and susceptible infected population

Symbol (parameter in model)	Parameter description	Value in model	Method of deriving the value used in the model	Assumptions (Reference)
N	Total population size	100,000	Total population = 100%	Simulation of 100,000 people from an English population perspective
N_h	Percentage of the total population in hospital	0.24%	Average of Q1(June 2016) - Q4 (March 2017) hospital bed data used (Total number of hospital beds in 2016/17) / (Total England population in 2016/17) = 130457.0206 / 55268067 =0.24% 0.24% of total population are in hospital.	NHS England. Average number of available and occupied beds open overnight by sector. (https://www.england.nhs.uk/statistics/statistical-work-areas/bedavailability-and-occupancy/bed-data-overnight/) (176)

Symbol (parameter in model)	Parameter description	Value in model	Method of deriving the value used in the model	Assumptions (Reference)
N_c	Percentage of the total population in the community	99.76%	1 – Nh	(176)
α (alpha)	Rate at which those in the community enter the hospital	8.02×10^{-4} per day	Total number of admissions in England in 2016-17 / Total population in England in 2016-17 = 16,546,667/55268067 = 0.2994 Per day rate = 0.2994/365 = 8.02×10^{-4}	Finished Admission Episodes (FAEs), which is the first episode in a spell of care – proxy for total number of admissions in England (https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2016-17) (177)
l	Rate at which those hospitalized return to the community	Option 1: 0.20 per day	Option 1: Average length of stay = 4.9 days Hospitalised returning to community = 1 / 4.9	Option 1: NHS digital: Average length of stay = 4.9 days Option 2: Not published source - Appendix: Nichola Naylor thesis Inverse of the expected length of stay for *E. coli* bacteraemia = 1/3.87 (closest to original model value = 3.15 days) (Methodology provided in: (168) Option 3: Nuffield Trust Mean length of stay in 2012/13 for England overall = 5.2 (https://www.nuffieldtrust.org.uk/chart/mean-length-of-stay-in-uk-hospitals) (786) Option 4: Eurostat Hospital discharges and length of stay statistics - In-patient length of stay (days) for all causes in 2015 for United Kingdom = 6.8 (787)

Symbol (parameter in model)	Parameter description	Value in model	Method of deriving the value used in the model	Assumptions (Reference)
b (bdr)	Background death rate	3.38×10^{-5}	Inverse of life expectancy = (1/81)/365	(169,179)

Symbol (parameter in model)	Parameter description	Value in model	Method of deriving the value used in the model	Assumptions (Reference)
ε (eps)	Proportion that acquire resistance during each antibiotic treatment	0.0667 per treatment	Average of all incidence of resistance per antibiotic tx = 5.6% + 1.9% + 9.2 % + 8.6 % + 10.0% + 4.7 % + 11.8 % + 13.4% + 2.5% + 3.3% 2.4% = 6.67%	Option 1: Proxy assumption: Recent ECDC report states: For resistance to *E. coli* the strength of correlation with antibiotic use is strongest for human antibiotic use compared to animal antibiotic use. Since this model is modelling R-*E. coli* overall and not only ESBL-EC we are assuming a greater proportion of resistance is acquired due to antibiotic use compared to other sources in England so using only the lowest of the incidence rates (which was previously used for the ESBL-EC model (179)) would be an underestimation. Thus, an average of all the incidence rates identified in the original case study has been taken. The values for TB have not been included. (The same references were also identified as the main acquisition of resistance from antibiotic use parameter in a recent scoping review Ramsey et al. (160)) Option 2: Using transmission rates and infection rates (*E. coli* in England) to calculate the rate of resistant acquisition = 0.0004 per treatment, **this value resulted in little to no resistant bacteria colonisations in the original and the new model so Option 1 was chosen instead** to keep in line with methodology used in the original model and similar transmission models prior to that (Ramsay et al. (160)) Option 3: ECDC does not provide the exact values of number resistance divided by overall population. The probability estimates have been estimated from the graphs – actual values not provided. ECDC/EMA/EFSA – JIACR 2nd report (2015: EU/EEA values): Figure 9: Probability of resistance for 1 unit DDD/1000 inhabitants per day consumption of cephalosporin = 0.20

Symbol (parameter in model)	Parameter description	Value in model	Method of deriving the value used in the model	Assumptions (Reference)
				Each unit (per 1 DDD per 1,000 inhabitants and per day) increase in consumption of fluoroquinolones was associated with 56% (38% to 69%) higher probability of resistance in invasive *E. Coli* isolates Figure 16: Probability of resistance to fluoroquinolones in human invasive *E. coli*, EU/EEA per 1 unit DDD/1000 inhabitants per day consumption of cephalosporin = 0.22 The multivariate analyses showed that for resistance to 3rd-generation cephalosporins in invasive *E. coli* from humans, there was a significant direct effect of the consumption of 3rd- and 4th-generation cephalosporins in humans, and hospital consumption appeared to have the greatest weight. No significant effect of the consumption of 3rd-generation cephalosporin in food-producing animals or the corresponding resistance in commensal *E. coli* from food-producing animals was observed. (106) Original method: Using incidence rates per antibiotic treatment as a proxy for acquisition rate: For the ESBL-EC original study (179) the mean of the lowest estimates (0.8% and 1.9%) and the proportion that acquire resistance was set to be 1.35%. 1)Fish *et al*., 1995: 173 studies of 8 antibiotic classes and 225 individual treatment: resistance occurred in 5.6% of all treatments 2)Lew *et al*., 2008 (TB) : The cumulative incidence of acquired drug resistance with initially pan-sensitive strains was 0.8% (95% CI, 0.5% to 1.0%) compared with 6% (CI, 4% to 8%) with initially single drug–resistant strains and 14% (CI, 9% to 20%) with initially polydrug-resistant strains. 3)Choi *et al*., 2008 : The overall incidence of the emergence of antimicrobial resistance during antimicrobial therapy was 1.9% (14/732). Resistance to broad-spectrum cephalosporins, cefepime, extended-spectrum, penicillin, carbapenem, fluoroquinolones, and aminoglycosides

Symbol (parameter in model)	Parameter description	Value in model	Method of deriving the value used in the model	Assumptions (Reference)
				emerged during treatment in 5.0% (11/218), 0% (0/20), 2.0% (2/100), 0% (0/226), 0% (0/153), and 1.1% (1/89) of patients, respectively. 4) D Milatovic and I Braveny 1987: Mean resistance rates were calculated to be 9.2 % for broad spectrum penicillins, 8.6 % for second and third generation cephalosporins, 10.0% for latamoxef, 4.7 % for imipenem, 11.8 % for ciprofloxacin and 13.4% for aminoglyeosides. range of overall incidence = 4.7% to 13% (179) Additional studies identified: 5)Raum *et al*., 2008: On average 20% increase in prevalence of resistant *E. coli* following 1 day of abx therapy (Since this was not measuring the incidence of new *E. coli* acquisitions this was not included) (788) 6) Hurford *et al*., 2012 (using data from Juan 2005): Modelling study linked antibiotic use and antibiotic resistance in an intensive care unit setting. (2.5% - 3.3%) per treatment following 1 day of treatment. (180,789)
ω_c (Wc_all)	Rate of antibiotic exposure in community	0.0018 per day	0.0018 0.67 per person per year ~ (0.67/365) per person per day	Shallcross *et al*., 2017 (163) Proxy for 2016-17: (Data from 2011-2013 from UK primary care cohort of 1 948 390 adults registered with 385 primary care practices) Overall antibiotics prescribed in community setting were used and not restricted to specific antibiotic classes. (To control for the confounding factor that over a period of time interaction is possible between prescribing one type pf antibiotic and

Symbol (parameter in model)	Parameter description	Value in model	Method of deriving the value used in the model	Assumptions (Reference)
				selection/co-selection of resistance for a different type of antibiotic – Koen *et al*., 2018 (218))
ω_h (Wh)	Rate of antibiotic exposure in hospital	0.24 per day	= 6229/25942 = 0.24 per day Total patients in NHS organisation: 50,778 Total overall AMU: 25942 Total for case study: Ciprofloxacin 707 Third-generation cephalosporins 535 Gentamicin 1566 Piperacillin/tazobactam 2262 Carbapenems 1159	Proxy for 2016-17 same source as (179) Antibiotics included ciprofloxacin, third generation cephalosporins, gentamicin, piperacillin/tazobactam and Carbapenems 1) recent England specific study (Naylor 2018 thesis – unpublished) has estimated the excess length of stay associated with resistance to at least one of these antibiotics (stated above) 2) to keep in line with the most up to date costing 3) currently no study measures the co-selection rate of resistance in the secondary care setting in England (in comparison data for England exists in the primary care setting (218)), Due to reasons 1-3 other antibiotic types were not included.
ncomo	Proportion of susceptible population (Cs) who have no comorbidities	Nc*0.653	1271513 / 1948390 = 0.653	Shallcross *et al*., 2017 (163) % of population without comorbidity in primary care population for 2011-2013 used as a proxy for 2016-17 proportion.
como	Proportion of susceptible population (Cs) with comorbidities	Nc*0.347	676877/1948390 = 0.347	Shallcross *et al*., 2017 (163) % of population with comorbidity in primary care population for 2011-2013 used as a proxy for 2016-17 proportion.
ω_{cn} (Wc)	Rate of antibiotic exposure in community for individuals without any co-morbidities	0.0013 per day	Per day rate from: (Total prescriptions over 3 years/ Total patients over 3 years) ((1830978.72/1271513)/3years)/365= 0.0013	Shallcross *et al*., 2017 (163) x y r

<table>
<tr><th>Symbol (parameter in model)</th><th>Parameter description</th><th>Value in model</th><th>Method of deriving the value used in the model</th><th>Assumptions (Reference)</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><th></th><th>Proportion split</th><th>Total patients</th><th>Total prescriptions</th><th>Prescription rate over 3 years</th></tr>
<tr><td>Comorbidities 0</td><td>65.3</td><td>1271513</td><td>1830978.72</td><td>1.44</td></tr>
<tr><td>Comorbidities 1</td><td>24.9</td><td>485168</td><td>1212920</td><td>2.5</td></tr>
<tr><td>Comorbidities 2</td><td>7.1</td><td>138725</td><td>552125.5</td><td>3.98</td></tr>
<tr><td>Comorbidities 3</td><td>2.7</td><td>52984</td><td>320553.2</td><td>6.05</td></tr>
<tr><td>Overall</td><td>100</td><td>1948390</td><td>3922732</td><td>2.013319715</td></tr>
</table>
</td></tr>
<tr><td>ω_{cc}

(Wcc)</td><td>Rate of antibiotic exposure in community for individuals with any co-morbidities</td><td>0.0028 per day</td><td>((2085598.7/676877)/3years)/365 days</td><td>Shallcross et al., 2017 (163)</td></tr>
<tr><td>β_h

(betah)</td><td>Transmission rate in the hospital</td><td>0.05</td><td></td><td>Gurieva et al., 2018 (173) : single-admission reproduction numbers (RA) = 0.047 (R-E. coli ICU setting)
For every colonised assuming there are 0.05 transmissions.
(~95% higher transmission level in hospital compared to community)</td></tr>
</table>

Symbol (parameter in model)	Parameter description	Value in model	Method of deriving the value used in the model	Assumptions (Reference)
β_c (betac)	Transmission rate in the community	0.0053		Haverkate *et al.*, 2018 (174): Index person to household transmission rate = 0.0053 per colonised per day For every colonised assuming there are 0.0053 transmissions.
c (Clear)	Rate of clearance of resistant bacteria in community	(1/401.5) per day	Based on most recent studies 2018/2017: the mean time provided in the 2018 study to losing carrier ship has been assumed as the clearance rate: 1.1 years = 401.5 days	Teunis *et al.*, 2018 (181): In carriers, the mean time to lose carriership was 1.1 (95% range 0.8–1.6) years.(does not include gene type) Jørgensen *et al.*, 2017 (790): The ESBL point prevalence of faecal carriage = 61% at 4 months, 56% at 7 months, 48% at 10 months, 39% at 13 months, 19% after two years, and 15% after three years or more. Original model (179) : 127 days assumed based on the mean time provided Birgrand et al.: French study: The median time to ESBL-E clearance was 6.6 months. Bruinsma et al..: Dutch study: The median times to clearance were around 1–2 months for all bacterial types

Symbol (parameter in model)	Parameter description	Value in model	Method of deriving the value used in the model	Assumptions (Reference)
i_c (inf)	Rate of infection in England (*E. coli* bacteraemia)		(73.9/100000/365) 73.9 per 100,000	Mandatory surveillance 2016-17 (165)
Inf_c	Rate of infection in community		0.16*73.9/100000/365	Mandatory surveillance 2016-17 (165)
i_h (inf_h)	Rate of infection in the hospital	2.5*inf_c	Higher rate of infection compared to the community setting estimated using Mandatory surveillance data.	Mandatory surveillance 2016-17 (165) 2) Boldt *et al.,* 2018 (791): Incidence of nosocomial infections = 3.5 (95% CI 2.0–6.1) per 100 patients rectally colonized with 3GCREB compared to 2.3 (95% CI 1.8–3.0, P = 0.213) per 100 3GCREB negative patients.
r_{inf} (rinf)	Decreased rate of infection by resistant organisms.	0.973	Gram-negative (*E. coli* resistant to ciprox and nalixic acid) mean value The mean relative fitness and 95% confidence intervals of antibiotic resistance mutations associated with a given species. A fitness value of <1 indicates a fitness cost in the absence of the antibiotic.	Reason for including a reduced infection rate: Melnyk *et al*., 2015 (182): Meta-analysis identified: We found a significant fitness cost of resistance mutations. Option 2: A reduced rate of infection of for resistant vs susceptible was calculated using the mandatory surveillance data and this accounted to around 0.8, however, after running the model, the infection rate per 100,000 per year was lower than the actual mandatory surveillance results. After applying the decreased infection rate from Melnyk 2015 the model provided the correct approximate resistant infections for England, therefore it was decided to use the literature value.

Symbol (parameter in model)	Parameter description	Value in model	Method of deriving the value used in the model	Assumptions (Reference)
μ_r (mur)	Proportion of infections with resistant bacteria that result in death	16.07%	Most recent estimates from Nichola Naylor thesis used.	Unpublished: Nichola Naylor thesis: Cumulative Incidence- % (95% CIs) *E. coli* bacteraemia resistant to at least one antibiotic 16.07 (14.73 - 17.52) Methodology presented in: (168) Option 2: Abernethy *et al*., 2015(792): Mortality was slightly higher in those with *E. coli* bacteraemia that was non-susceptible to carbapenems, cephalosporins or ciprofloxacin (MR range from 21.3 for cephalosporins to 25.0% for carbapenems), compared with those whose infection was susceptible to these antibiotics (MR range from 17.0 for ciprofloxacin to 18.1% for carbapenems).
μ_c (mus)	Proportion of infections with susceptible bacteria that result in death	14.33%	Most recent Naylor thesis used.	Unpublished: Nichola Naylor thesis: Cumulative Incidence- % (95% CIs) *E. coli* bacteraemia: 14.33 (13.74 - 14.94) Methodology presented in: (168) Option 2: Abernethy *et al*., 2015(792): Escherichia coli bacteraemia in England: Thirty-day all-cause mortality was 18.2% (17.8–18.7%) (5220/28 616). This equates to an MR of 10.34 per 100 000 population. Patients with community-onset infection had lower mortality (15.3, 95% CI 14.8–15.8%; 3179 deaths) compared with other onset categories.

Infection rate calculation using literature values:

Outputs of the original model:

Cs = Susceptible population in community

Crc = Population being colonised by resistant *E.coli* in community

Crh = Population being colonised by resistant *E.coli* in hospital returning to community

Hs = Susceptible population in hospital

Hrc = Population being colonised by resistant *E.coli* in community coming to hospital

Hrh = Population being colonised by resistant *E.coli* in hospital

Indicators from the original model:

Irc = Population infected with resistant *E.coli* in community

Isc = Population infected with susceptible *E.coli* in community

Irh = Population infected with susceptible *E.coli* in hospital

Irh = = Population infected with resistant *E.coli* in hospital

Actual inputs identified to fit the model to England specific values – *E. coli* bacteraemia mandatory surveillance data and Ann-Bouton paper:

Irc + Isc = 59.9 per 100,000

Irh + Ish = 14.06 per 100,000

Irh = 7.3 per 100,000

Ish = 6.7 per 100,000

Hri = Resistant infections in the hospital = (16.6 + 7.3) to be costed as hospital costs

His = Susceptible infections in the hospital = (22.2 + 6.7) to be costed as hospital costs

Community resistant and susceptible split based on ratio of community onset susceptible and resistant population:

Cri = Resistant infections in the community = 9.03 per 100,000 (after adjusting for infections admitted to hospital) to be costed as community costs

Csi = Susceptible infections in the community = 12.07 per 100,000 (after adjusting for infections admitted to hospital) to be costed as community costs

Appendix Table 13 Calculation and source for actual infection inputs to fit the model with

Per 100,000	Using proxy for		Rate per 100,000 person per year in England	(%) out of all reported *E. coli* bact	(%) out of hospital inpatients with *E. coli*	(%) out of total community acquired *E. coli*
Mandatory surveillance 2016-17						
Infection rate of *E. coli* bact (2016/17 dataset)	NA	*E. coli* bact	73.91741403	1		
Rate of hospitalisation for *E. coli* bact over 1 year per 100,000	Hospital infections (all: includes resistant + susceptible): Rate of hospitalisation for *E. coli* bact over 1 year per 100,000	*E. coli* bact admitted to hospital as inpatients	52.82781769	0.714687		
Rate of community *E. coli* bact not admitted to hospital over 1 year per 100000	Community infections (all: includes resistant + susceptible)	*E. coli* bact not admitted to hospital as inpatients	21.08959634	0.285313		
Rate of *E. coli* infections in hospital due to community acquisitions		Community onset *E. coli* bact for inpatients	38.76747962	0.52447	0.733846	
Rate of *E. coli* infections in hospital due to hospital acquisitions		Hospital onset *E. coli* bact for inpatients	14.06033807	0.190217	0.266154	
Rate of *E. coli* infections due to community acquisitions		Estimated: Community onset *E. coll* in admitted inpatients + *E. coli* bact in not admitted inpatients	59.85707596	0.809783		
Rate of hospitalisation for community acquired E. coli		Estimated: (Inpatients due to community acquired infections / Total community acquired infections) = 65%				0.647667
Ann-Bouton dataset						
Infection rate of *E. coli* bact (2012/2014 dataset)			62.39346947	1		
Rate of hospital onset resistant *E. coli* in hospital (using data from 2012-2014)			6.195069648	0.09929 = 10%		
Rate of community onset resistant *E. coli* in hospital (using data from 2012-2014)			13.99425333	0.22429 = 22%		
Ratio of community onset resistant infection to hospital onset resistant infection			2.258933979	0.036205		
Conversion to 2016/17 values by using % from Ann-Bouton dataset					**% out of total hospital onset R-*E. coli***	**% out of total community onset R-*E. coli* in hospital**
Rate of hospital onset resistant *E. coli* in hospital	Adjusted to 2016/17 values based	73.9 * 10%	7.339286178		0.521985	
Rate of community onset resistant *E. coli* in hospital		73.9 * 22%	16.57896293			0.276976

Rate of community onset susceptible *E. coli* in hospital	on *E. coli* bact rate per 100,000 2016/17 values	(Community onset *E. coli* bact for inpatients - Community onset resistant *E. coli* in hospital) = 38.8 - 16.6	22.18851669			
Rate of hospital onset susceptible *E. coli* in hospital		(Hospital onset *E. coli* bact for inpatients - hospital onset resistant *E. coli* in hospital) = 14.1 - 7.3	6.721051893			

(Highlighted values are the ones being used to fit the model)

Appendix Table 14: Weighted average infection rate calculation

		per 100,000 per year from mandatory surv adjusted with Ann-Bouton 2016	per colonised per year from transmission model	**Increased** rate of infection in the hospital (adjusted for susceptibility)	**Decreased** rate of infection in the community compared to overall infections (adjusted for susceptibility)	**Decreased** rate of resistant infection compared to susceptible (adjusted for setting)
inf	infEC	73.9	0.000739	-	1	
infc_r	infRc	9.03	9.03E-05	1	-	0.748136
infh_r	infRh	23.9	0.000239	9.03/23.9 = 2.646733	-	0.82699
infc	infSc	12.07	0.000121	1	12.07/73.9 = 0.163329	1
infh	infSh	28.9	0.000289	28.9/12.07 2.394366	-	1

Appendix Table 15: Multipliers for infection rates in the hospital and community

	*Weighted average of increased rate of infection in hospital	*Weighted average of decreased rate of infection in community compared to overall infection level	weighted average of infection rate of resistant infection compared to sus	
	v2	**v1**	**rinf**	comment

infh	((2.647*23.9) + (2.394*28.9)) / (23.9+28.9) = 2.5086			Weighted average of susceptible and resistant increased rate of infection in hospital
infc		0.163329		
rinf			0.805367	Melnyk 2015 value of 0.925 is being used instead to reach the mandatory surveillance infection level values. By using 0.805 the model was not able to predict the target infection level of 73.9 per 100,000 per year.

***weighted on actual infection levels. Highlighted cells have been used as multipliers**

Appendix Table 16: Final multipliers used to get model to generate English specific infections levels

Total population	100,000	
Inf = Infection rate per 100,000 yer year	0.000739	
infc	0.16*inf	v1*inf
infh	2.5*infc	v2*infc
infh_r	0.925*infh	rinf*infh
infc_r	0.925*infc	rinf*infc

Appendix Table 17 Model equations using R

```
#Model parameters which use the inputs from the inputted parameters.
eps = var_eps * eps # development of resistance on treatment
 wh = var_wh
 ncomo = var_ncomo
  #wh = var_wh * wc # treatment rate in hospital.
  betac = bh #Almorag 2018 modelling study
  betah = betah  # Dutch study
  infh = v2 * infc  #suscep hosp
  infh_r = rinf * infh #res hosp
  infc_r = rinfc * infc #res comm
#Model equations which run the model
Nc = A$Cs[ijk-1] + A$Crh[ijk-1] + A$Crc[ijk-1] #Total community population
Nh = A$Hs[ijk-1] + A$Hrh[ijk-1] + A$Hrc[ijk-1] #Total hospital population
 A$Cs[ijk]   = A$Cs[ijk-1]  + l * A$Hs[ijk-1]  - alpha*A$Cs[ijk-1]  - ((wcc * eps *(((como)*A$Cs[ijk-1]))) + (wc * eps * (((ncomo)*A$Cs[ijk-1])))) - betac*(A$Crc[ijk-1]+A$Crh[ijk-1])*((wcc *(((como)*A$Cs[ijk-1]))) + (wc *(((ncomo)*A$Cs[ijk-1]))))/Nc + infc_r * mur * (A$Crc[ijk-1] + A$Crh[ijk-1]) + infh_r * mur * (A$Hrc[ijk-1] + A$Hrh[ijk-1]) + infh * mus * A$Hs[ijk-1] + clear * (A$Crc[ijk-1] + A$Crh[ijk-1]) + bdr * (A$Crc[ijk-1] + A$Crh[ijk-1]) + hdr * (A$Hs[ijk-1] + A$Hrc[ijk-1] + A$Hrh[ijk-1])
 A$Crc[ijk]  = A$Crc[ijk-1] + l * A$Hrc[ijk-1] - alpha*A$Crc[ijk-1] + ((wcc * eps *(((como)*A$Cs[ijk-1]))) + (wc * eps * (((ncomo)*A$Cs[ijk-1])))) + betac*(A$Crc[ijk-1]+A$Crh[ijk-1])*((wcc *(((como)*A$Cs[ijk-1]))) + (wc *(((ncomo)*A$Cs[ijk-1]))))/Nc - infc_r * mur * A$Crc[ijk-1] - clear * A$Crc[ijk-1] - bdr * A$Crc[ijk-1]
 A$Crh[ijk]  = A$Crh[ijk-1] + l * A$Hrh[ijk-1] - alpha*A$Crh[ijk-1] - infc_r * mur * A$Crh[ijk-1] - clear * A$Crh[ijk-1] - bdr * A$Crh[ijk-1]
    # Hospital
  A$Hs[ijk]   = A$Hs[ijk-1]  - l * A$Hs[ijk-1]  + alpha*A$Cs[ijk-1]  - wh * eps*A$Hs[ijk-1] - betah*(A$Hrh[ijk-1]+A$Hrc[ijk-1])*wh*A$Hs[ijk-1]/Nh - infh * mus * A$Hs[ijk-1] - hdr * A$Hs[ijk-1]
  A$Hrc[ijk]  = A$Hrc[ijk-1] - l * A$Hrc[ijk-1] + alpha*A$Crc[ijk-1] - infh_r * mur * A$Hrc[ijk-1] - hdr * A$Hrc[ijk-1]
  A$Hrh[ijk]  = A$Hrh[ijk-1] - l * A$Hrh[ijk-1] + alpha*A$Crh[ijk-1] + wh * eps*A$Hs[ijk-1] + betah*(A$Hrh[ijk-1]+A$Hrc[ijk-1])*wh*A$Hs[ijk-1]/Nh - infh_r * mur * A$Hrh[ijk-1] - hdr * A$Hrh[ijk-1]
    # Indicators
    A$infEC[ijk] = inf * (A$Cs[ijk-1] + A$Hs[ijk-1] + A$Crh[ijk-1] + A$Crc[ijk-1] + A$Hrh[ijk-1] + A$Hrc[ijk-1])
    A$infRc[ijk] = infc_r * (A$Crh[ijk-1]+A$Crc[ijk-1])
    A$infRh[ijk] = infh_r * (A$Hrh[ijk-1]+A$Hrc[ijk-1])
    A$infSc[ijk] = infc * (A$Cs[ijk-1])
    A$infSh[ijk] = infh * (A$Hs[ijk-1])

#Input parameters - Inputs for the England case-study
como = 0.347 #new para #Shallcross 2017 #como = 1 (when changing overall prescribing)
  var_ncomo = 1-como #new para
  ncomo = var_ncomo
  alpha = 0.2994/365 #16 / 53 / 356 # hospitalisation rate per day. 15.5milion / 64 million
  l = 1/(4.90) # NHS data
  eps = 0.07 #0.0004 #0.07 #0.0667 #0.08 # Estimated... #average of incidence of Abr after Abx
  wc = 0.0013 #0.0215 ##Shallcross 2017 no-comorbidity prescription rate #wc = 0 (when changing overall prescribing)
  wcc = 0.0028 #0.029 #Shallcross 2017 with comorbidity prescription rate #wcc = 0.0018 (when changing overall prescribing)
  infc = 0.16*73.9/100000/365 #adjustment based on mandatory surv #v1 = 0.16
```

```
  betah = 0.05 #Almagor 2018 model: Low Abx scenario # 0.0078 #MOSAR Trial Boostma
2018 paper ICU setting
  bh = 0.0053 #Boostma 2018 Dutch household transmission rate per index
  clear = 1/402
 #v1 = 0.16 #0.19 #73.9 infections, 52.86 in hospital, 21.04 in community (because this
population includes comm acquired as well which will be adjusted in the end)
  v2 = 2.5 #2.5*0.17 #0.39 #adjustment based on mand surv and infection results from model
run
  rinf = 0.925 #Melnyk 2015 #0.8 mandatory surv decreased rate of inf compared to sus
  rinfc = 0.925 #Melnyk 2015 #0.8 mandatory surv decreased rate of inf compared to sus
  mur = 0.161 # Naylor thesis
  mus = 0.143 # Naylor thesis
  var_wh = 0.24 #PPS
  wh = var_wh
  var_eps = 1 # in baseset
```

Please refer to Appendix Table 12 for description of the parameters.

Results

Model (with addition of prescribing variation due to comorbidities)

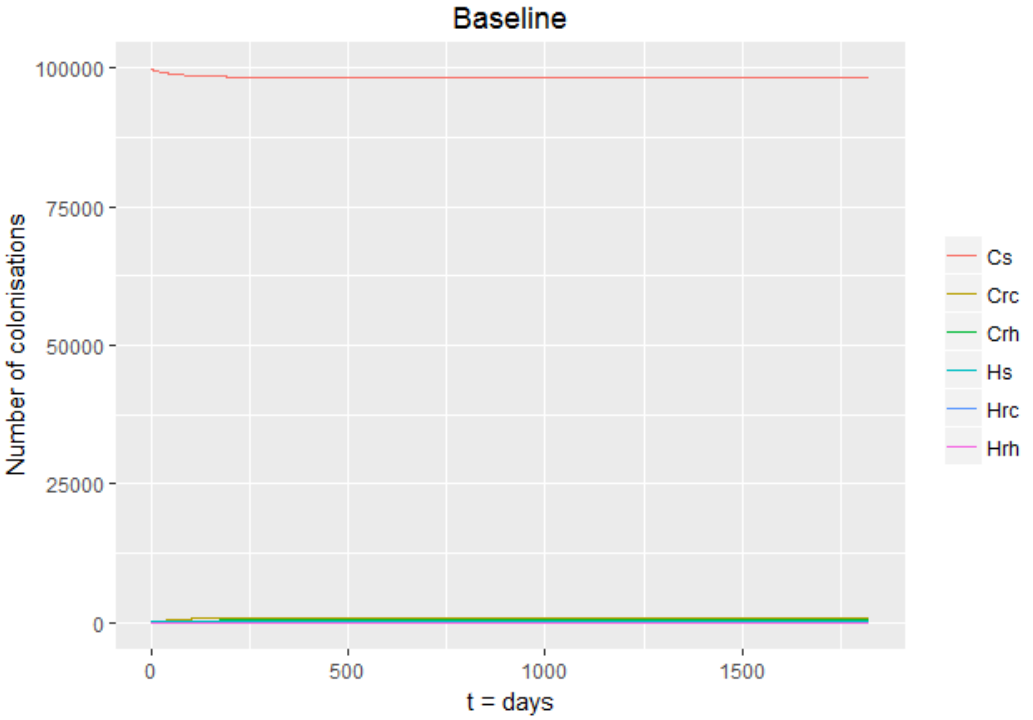

Figure 63: New model with comorbidity related prescribing difference in community

	From the original model over/under estimating susceptible population						
	Days	**Cs**	**Crc**	**Crh**	**Hs**	**Hrc**	**Hrh**
Baseline	365	98403.93	830.58	387.91	344.54	3.15	29.89
-1%	365	98412.16	822.34	387.92	344.57	3.12	29.89
-5%	365	98445.10	789.35	387.97	344.69	2.99	29.89
-10%	365	98486.29	748.09	388.04	344.85	2.83	29.90
-15%	365	98527.52	706.80	388.10	345.00	2.68	29.90
-20%	365	98568.78	665.48	388.17	345.15	2.52	29.91
5%	365	98362.80	871.78	387.84	344.39	3.30	29.88
10%	365	98321.70	912.95	387.78	344.24	3.46	29.88
15%	365	98280.62	954.08	387.72	344.09	3.61	29.87
	Adjusted model: Assuming susceptible pop remain stable						
	Days	**Cs**	**Crc**	**Crh**	**Hs**	**Hrc**	**Hrh**
Baseline	365	98403.93	830.58	387.91	344.54	3.15	29.89
-1%	365	98403.93	822.34	380.25	344.54	3.12	29.30
-5%	365	98403.93	789.35	350.35	344.54	2.99	26.99
-10%	365	98403.93	748.09	314.68	344.54	2.83	24.24
-15%	365	98403.93	706.80	280.90	344.54	2.68	21.64
-20%	365	98403.93	665.48	249.02	344.54	2.52	19.19
5%	365	98403.93	871.78	427.34	344.54	3.30	32.92
10%	365	98403.93	912.95	468.66	344.54	3.46	36.11
15%	365	98403.93	954.08	511.84	344.54	3.61	39.43

Figure 64: Original and adjusted model results showing impact of change in antibiotic use from baseline in community population

Appendix IV. Appendix for Chapter 5

Imperial College Healthcare NHS
NHS Trust

Service Evaluation Form

This form is to assure the Trust that Imperial based service evaluation projects have had local managerial discussion and assent. Projects will typically be locally based, evaluating service provision, delivery and interventions and for which publication of results is primarily internal. Once your project/study is approved you will receive an email with a unique ID number. This should be quoted in future correspondence relating to the project.

1. Project Title	(Office use only) Registration No:
Resource allocation decisions in implementation of interventions to control for health care associated infections with a focus on antibiotic resistant bacterial infections – Case study in Imperial Health Care Trust hospital(s)	199

Planned Start Date: 01/09/2017	Planned Completion date: 31/03/2018

Please summarize for our records the purpose of the service evaluation:

Rationale:

Rates of some drug-resistant infections in England have increased over the last 5 years (2010-2015), including an increased rate of *Escherichia coli* and *Klebsiella pneumoniae* bloodstream infections of 13.5% and 17.2% respectively. These rates have further increased to 4.6% and 9% respectively in the past year. A recent costing study conducted at the Imperial College Healthcare NHS Trust on a CPE outbreak estimated the total cost to an NHS hospital was nearly £1 million. Therefore, the health and economic burden of antibiotic resistant infections on society is an increasing cause for concern.

Compounding the NHS funding issues in light of the current economic and political climate in the United Kingdom, NHS hospitals have had to continually fight against health care associated infections which are either brought into hospitals setting from the community or harboured within the hospital environment. Drug-resistant infections in particular are an increasing threat to patients in hospitals as clinicians have limited therapeutic options to target these types of infections.

Following the implementation of a National AMR strategy in the UK in 2013, all Trusts around England are adopting the strategy's recommended measures and interventions. Individual trusts have some choice over what to adopt and it is important to understand how trust-specific financial, organisational and other socioeconomic factors influence these decisions. In particular, it is important to understand how costing-related decisions are being made, and what barriers are being faced during these decision making processes within hospitals to be able to target these life threatening infections effectively which are further increasing the economic burden on the NHS.

Aims:

The aims of this service evaluation are to explore the following questions:

a) Evaluate what interventions have been implemented in Imperial College Healthcare Trust (ICHCT) hospitals in line with the AMR 5 year strategy in England?

b) Evaluate what decisions have been made by ICHCT hospitals relating to the costs and resource use of interventions to control health care associated infections (HCAI), with a particular focus on AMR in line with national and local policy?

Please summarise for our records what the project will involve:
Interviews with staff regarding the cost and resource allocation decisions made in line with the AMR national and local policy, using a semi-structured questionnaire.

The key decision makers (participant list below) involved at a functional and operational level in the trust will be contacted to take part in interviews at their convenient time and location lasting between 20-30 minutes. No pressure will be placed on the subjects to answer questions. Subjects are free to decline / withdraw from participating in the study at any time.

Written informed consent will be obtained prior to the interview.

Proposed target participant list:
NHS staff in charge of costing evaluation and final signing off on business cases, namely those listed in the publicly available ICHCT board meeting notes held on 25.01.2017:
There are a number of boards, groups and committees that consider, recommend and approve investment; namely:
- Decision Support Panel (DSP)
- Capital Steering Group (CSG)
- Executive Operational Performance Committee (ExOp)
- Finance and Investment Committee (FIC)
- Trust Board
- NHS Improvement (NHSI)

2. YOUR DETAILS

Name: Anuja Chatterjee	**Position:** PhD student at NIHR HPRU
Email: ac6315@ic.ac.uk	**Telephone:** +447817543458

3. DOES THIS INVOLVE A CHANGE OF PRACTICE FOR THE FOLLOWING GROUPS

Nursing? *No*	**If yes, Nursing and midwifery Lead** Click here to enter text.
Medical staff? *No*	**If yes, Chief of Service/Divisional Lead** Click here to enter text.
Please give the name and date of the forum (e.g. Divisional Q&S Committee) where this project proposal was presented	Joint Meeting: HPRUs at Imperial College 16.03.17

Have any training issues been addressed and documented?	*Yes*
Have any costs/financial issues been addressed?	*Yes*
Does this project impact on other divisions?	*No*

If yes, please provide names and contact details for the member of staff consulted in each affected division:	Click here to enter text.

4. INFORMATION GOVERNANCE

Please refer to the Trust Information Governance intranet resources for further information. Source

Does the project involve the use of any patients or staff identifiable information?	*No*

If **NO**, proceed to section 4.

If **YES**, please complete the IG review form and attach the approved form along with the IG reference no.
InformationGovernanceAdvice@imperial.nhs.uk

IG Form Reviewed and approved by: *Click here to enter text.*	*IG Reference No:* *Click here to enter text.*

4. REVIEW

Manager Review (they will receive a copy of this form)

Name: Click here to enter text.	**Position:** Click here to enter text.
Email: Click here to enter text.	**Date Reviewed:** Click here to enter text.

Safety and Effectiveness Review

Name: Shianne Gerald	**Position:** Clinical Audit Administrator
Email: Shianne.gerald@nhs.net	**Date Reviewed:** 12/07/2017

From: Roper, Gary C
Sent: 21 June 2017 14:18
To: Chatterjee, Anuja
Subject: RE: Service evaluation protocol proposal

Hi Anuja

Is this the same project you described in you other email? If so it is service evaluation and does not need ethics approval.

Best wishes

Gary

Gary Roper
Head of Regulatory Compliance
AHSC Joint Research Compliance Office
Imperial College London and
Imperial College Healthcare NHS Trust
Room 215
Level 2, Medical School Building
Norfolk Place,
London W2 1PG

Tel: 020 7594 1872
E-mail: gary.roper@imperial.ac.uk
Website: www.imperial.ac.uk/clinicalresearchgovernanceoffice

From: Chatterjee, Anuja
Sent: 12 June 2017 10:51
To: Roper, Gary C <gary.roper@imperial.ac.uk>
Subject: Fw: Service evaluation protocol proposal

Dear Gary,
I am following up on the service evaluation enquiry I had made about a month ago.

We wanted to check if this piece of work would be considered as a service evaluation.
Look forward to hearing from you.

Best wishes
Anuja Chatterjee
PhD Student | NIHR Health Protection Research Unit | Imperial College London | 7th Floor Commonwealth Building,Hammers

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From: Chatterjee, Anuja
Sent: 10 May 2017 16:32
To: Roper, Gary C
Cc: Ward, Becky
Subject: Service evaluation protocol proposal

CA

Chatterjee, Anuja
Wed 10/05/2017 16:32
Roper, Gary C; Ward, Becky

Evaluation protocol outline.d...
27 KB

Dear Gary,

Hope you are well.
I am emailing to discuss a service evaluation I wish to conduct within the Imperial College NHS Trust (ICHCT) hospitals under Alison Holmes's supervision at the College.

This aim of this service evaluation is to evaluate:
1. What interventions have been implemented in ICHCT in line with the antimicrobial resistance (AMR) 5 year strategy in England?
2. What decisions have been made by ICHCT relating to the costs and resource use of interventions to control health care associated infections (HCAI), with a particular focus on AMR in line with national and local policy

Please find attached the protocol outline for your consideration which further details the specifics of this evaluation.

We believe that this project, interviewing ICHCT NHS staff on existing overarching management level decisions related to cost and resource allocation and avoiding any specific patient examples should not raise any particular ethical issues, but we would value your opinion on this project being classed as service development before proceeding further.

Look forward to hearing from you soon!
Best wishes
Anuja Chatterjee
NIHR Health Protection Research Unit | Imperial College London | 7th Floor Commonwealth Building,Hammersmith Hospital,W12 0HS| Mobile no: +447817543458

Participant sheet

Introduction to service evaluation:

Thank you for agreeing to take part in the service evaluation.

I am doing a service evaluation of the Trust, and I am looking at the different interventions that have been implemented in the Trust surrounding AMR. The challenges regarding these interventions, adoption and implementation surrounding them, and the resource allocation decisions surrounding them as well.

There are about nine or ten questions. Feel free to answer them if you can.

Question 1:

I would like to start with asking you what your job role is and what the priorities are within this job role.

Question 2:

In terms of the different risks that you see within the Trust around development and transmission of AMR, can you name some of the key ones?

Or

The different risks or challenges to basically tackling AMR that you see in the Trust.

Question 3:

In terms of the different measures that are being taken to tackle these superbugs, are you aware of them or do they come up in your meetings with the Trust?

- If participant is aware then discuss the specifics of the intervention (e.g. what they are, who is responsible for implementing, monitoring)

Question 4:

Are you aware of how decisions are made surrounding business cases, and do you play a role within this decision making process?

e.g. decision to approve implementation of an intervention related to AMR?

- If a decision maker for a business case, discuss how decision are made, is there a way to prioritise choosing one intervention over another.

Question 5:

What are some of the overall challenges the Trust is facing at the moment?

Question 6:

In terms of the challenges, because that brings me onto the challenges of AMR intervention and adoption at the Trust, can you think of some of them?

- If struggling for an answer to ask more specific questions by giving examples of business cases.

Question 7:

What are some of the pros and cons of the national initiatives related to AMR being implemented at the Trust?

Question 8:

Do you have any overall comments on how AMR is being tackled in the Trust at the minute, and what can be done more or better?

Table is in alphabetical order of the focused codes

Appendix Table 18: Thematic analysis to identify the challenges of tackling antibiotic resistance at the Trust

Initial codes	Focused codes	Quotes (Case number)
Working with the community (outside the Trust setting) Working with partner organisations	Communication (external)	"And I think the other challenge is about how we work in a different way with our partner organizations, because we've done a lot of work to make us as efficient as we can be, and there's probably still a lot more to do, but actually the boundaries between our organization and the community providers, mental health providers, and things like that, don't always work very well. And I think probably there's a lot we could do to make that more streamlined." (Case A003) "And then there was an interesting incident a little while ago when there was a mental health patient with CPE and he was seriously psychotic …. and the community care wouldn't accept. There was no, so the ways of looking after this individual were not sorted out." (Case A010) "[Related to delayed discharge into the community] We can't necessarily get them out the back end, and we want to discharge people because we can't necessarily get the packages of care." (Case B006)
• Meeting NHS performance targets • Working with contractors • Keeping IPC/AbR priority • Competing organisms	Competing priorities	"And then I think the only other challenge is, sometimes because of the way things are organised or the way NHS targets work, it can mean that differently people have slightly different agendas, and sometimes they conflict with one another. And finding a way to sort of bring those together can be a challenge." (Case A003) "The main one [challenge] probably is, even though in my small world it's my priority. It's got a lot of conflicting priorities in the trust as a whole. So if I go back

Initial codes	Focused codes	Quotes (Case number)
		to that nurse on the ward, or a consultant on a ward,… and say "This is terrible. This is a big problem. Armageddon. It's all going to go wrong in a few years, and we need to protect our future generations.[related to repurcussions of AMR+prescribing]" They are dealing with 16 other people coming in with their own agendas and sores, or pressure ulcers, or failure to rescue. Whole host of things that are the priority. And it [AMR + IPC] seems sometimes very flavor of the week, and for the ward staff it's very hard for us to keep our IPC agenda up there when they're faced with lots of people like me coming in and telling them "No, no, no. This is more important than IPC. This is what you need to focus on."" (Case A005) "And you have a contractor that's potentially looking to make money. As all contractors are, obviously, or they wouldn't do it. But what that might mean is that they may make decisions that, if it was in-house service, we might not make. In terms of, you know cutting services or we're not going to replace that domestic, we'll cover it elsewhere. Those types of things." (Case B003) "And you wouldn't want to spend time doing something that is clinically not important, yet is required by managers and by policy, rather than things that are important and not necessarily show up on manager's audits and records…You always have to prioritize." (Case A009) "I think there's a lot of issues with isolating patients, because you've got conflicting organisms to manage. So does the patient with colonization of CPE take precedence over isolating someone with an MSSA bacteremia, or a C. Diff, or ... so I guess the competing pressures for people are the access to side rooms." (Case A002) "[Regarding implementing AMR interventions] So, I think it's competing time tables… competing other priorities is definitely one thing." (Case A007)
• Useful (appropriate) + timely data feedback to stakeholders • Resource limitations and IT infrastructure • Identification of target patients	Data and evidence	"That data should be playing back to us so that you could send them back to me and say out of the nine consultants, I'm the eighth good at it [prescribing practice related], and actually I could be given support and help to improve and get better. When does anybody ever give me that data? They don't. They report it up centrally. People ask for action plans and action plans don't turn into action. We have to measure for improvement. This is so incredibly important and so deeply cultural. The culture of data in this country is they use it for regulation and for commissioning purposes and what we want to do is to use it to measure it for improvement and give the data to local teams…….over the year, we've had an

Initial codes	Focused codes	Quotes (Case number)
		electronic patient record. We still have no data from there to tell us and support us in our work." (Case A001) "[Regarding challenges on implementing AMS] it's identifying patients. It's okay where you've got your regular routes, but it's identifying the patients who can have an early intervention I think is quite challenging actually. So, I know that pharmacists had tried looking at pulling off a list of the patients on certain antibiotics. Which would be great, but they don't have the resources to do that every day. So you need to have a really good infrastructure with the IT, to be able to use the access. …. If I was able to log on in the morning to my site, and you know, pull up 5 wards or something of interest and say okay this person is on a target antibiotic, this ones on a target antibiotic. It would make life so much easier, as opposed to some of my colleagues who still having to go through a full list of patients in the ward before they get to the ward to, to see who's appropriate. So I think there is that lack of infrastructure as well. To help us prioritize who needs discussing most." (Case A007) "we can't get access to this data very easily. A lot of it is not readily available. The data are held in very different tables which are linked and you need to use a different specific software to access it and very limited people have access to this data and so there are a lot of access-related challenges in terms of using data I think within The Trust and not just specifically for antibiotics" (Case A008) "and also making sure that our data that we're producing is palatable to the everyday person on the ground, because we produce lots of data and that doesn't necessarily translate into practice." (Case A012) "The other thing is, as a commission, you need to understand and value the feedback. So there'd need to be a feedback circuit that allows us clinically to understand why we're using the system. What benefit does it bring to you, me, or the patient? So it's been clear about the benefits. Both the patient, both in terms of return on investment," (Case A014)
• Financial deficit • Not enough finances for flexibility of decision making in	Financial	"The third issue is the underlying financial deficit in the trust is such a problem that it stops a whole lot of other things during. That ability to spend a little bit of money to do something interesting and exciting will make a load of difference down the

Initial codes	Focused codes	Quotes (Case number)
the Trust/infrastructure maintenance		street is very hard to pull off. There is just not that flexibility around funding and money to unlock things." (Case A001) "we've got financial constraints and a deficit position that we have got to account to our regulators for." (Case A002) "the funding is looking at being cut rather than be expanded to try and reduce the deficit." (Case A007) "So we've got a whole stack of challenges in terms of processes. Process isn't working well enough, the management of those processes, the funding to support the infrastructure to support those processes, and then the systems that then support those processes. It's a huge headache and there's a chronic..." (Case A014) "Some of the challenges are financial, so having the finances to do all of the necessary works" (Case B002) "Oh. I think financially. So I think, probably, I know we're not paying our bills. We were on stop with one of our companies that we get chemicals from that we need. So I think they're trying to show that they are in a better financial situation than they are." (Case B004) "So they [private institutions]would take more risk because they are able to, because of financial reasons, because of the way, you know, governance's are carried out in those types of organizations. But we are very risk averse, particularly from a financial point of view, because of the financial position" (Case B001)
• Compliance of hand hygiene • Contracted out services	IPC efficiency	"I mean, one of the things that's very much on management mind at the moment is the basic quality of cleaning. we're not happy with the cleaning service that we're actually getting…I think something else that the board is quite exercised about is whether we have a strong enough compliance regime. So again, some of these things might not seem particularly superbug related, or infection, but again the basics, such as hand-washing. The danger sometimes is that you focus on some of the more exciting and innovative techniques such as deep clean and fancy chemicals and so on, and then you find out to your frustration, that 10%, 20% of staff don't feel it's always necessary to wash their hands between every patient interaction and so on. Or even some of the basic stuff like the "bare below the elbows" rules and so on." (Case B007)

Initial codes	Focused codes	Quotes (Case number)
		"One of the problems, for example, is we have may not have a workforce that will do what they are meant [related to IPC compliance]to do properly." (Case A014) "mentioned about our environment, cleaning, which is not adequate, in fact it's been dreadful, cleaning standards…..[related to infrastructure and hospital environment] ..it may be contract management because cleaning is outsourced and audits that were always very good but actually staff on the ground disagreed and that has been truly dreadful... But also truly dreadful environments." (Case A010) "But the most important thing is to clean. If you watch sometimes what the cleaners are doing, it's not quite as methodical as it should be." (Case B004)
• AbR + IPC: Lack of understanding • AMS: Lack of frontline staff engagement	Lack of engagement [Stakeholder engagement]	"…think one of the challenges is then to get them [AMR + AMS related messages] filtered back down, to the people who are doing the prescribing. And so I think that you probably need to target multiple levels at the same time…. I'm not convinced that appreciation is there, at the lower level of the people who are prescribing….. and if you aren't a clinician who's been involved in an outbreak, why would you think that you doing that IV to oral switch is so important." (Case A007) "How do you get them to buy into this [AMR]? And recognize that it's important and clinically significant. And how do you respect their professional judgment and decision-making when it comes to this?" (Case A009) "I think what is not so well perceived is engagement from our nursing staff." (Case A012) "but I also want to raise the issue about sepsis versus AMR. It was absolutely ridiculous that there was a patient safety alert sent out to trusts about sepsis and then one about antibiotic stewardship when they're all, it's the same thing, …, or they're part of the same thing, or wanting to set up separate databases. Major issues about thinking that these are completely different separate things." (Case A010) "So, sometimes when you're trying to say to someone else, "Well, have you taken everything out this room to clean it?" They'll say, "Yes, everything's out the room." But you'll go there and you'll say, "But, you've got all that stuff in there." … Education, communication [challenges]." (Case B004)

Initial codes	Focused codes	Quotes (Case number)
		“I still think there's a disconnect between IPC and stewardship, that there is not a connection that both go hand in hand. A few people get it, but actually you could argue that stewardship trumps IPC, so stewardship is the big thing, of which IPC is a pillar of that. I think that's a difficult message to get across to people.” (Case A012)
• Growing targets and initiatives • NHS funding mechanisms • NHS funding cuts •	NHS challenge (external)	“Huge, all sorts of initiatives but the service doesn’t get any bigger and the service actually has to put in a cost improvement programme. So the stuff that is being requested from the centre is going up and up but the local services are being asked to cut back and cut back.” (Case A010) “So I think lots of them stem from national challenges, and the biggest national challenge, in my opinion, is that the funding mechanism for the whole NHS hasn’t changed in the 70 years that the NHS has now been in existence.” (Case B005) “because of the financial position that we, and the rest of the NHS [are in].. all the financial issues, that you read about in the media to a certain extent, they are very true and we feel them like any other NHS organization is feeling them.” (Case B001) “I know we spend a huge of money in the NHS, but it's a chronic scenario, underfunding at the moment. Which is going to cause significant problems” (Case A014)
• CPE/CRE related outbreaks • “Organisational memory” due to impact (clinical + cost) of outbreaks	Outbreaks	“And the particular cause for concern at the moment, I think, is the number of cases of carbapenemase [carbapenamase producing organisms], so CP, which we have seen an increase in the number of patients with that organism. But then, of course, you've got to balance the ... we are screening actively for these patients. And so the argument is that if you screen for them, you'll find them…..But, the bit that from an organization perspective is really quite concerning is, we have definitely got episodes where we've transmitted that infection between patients and so CP” (Case A002) “I think the biggest issue for us at the moment is how we manage, I don't know whether to call it CRE or CPE” (Case A003) “The biggest one is CPE” (Case A006) “we have a particular challenge with controlling CPE at the moment” (Case A010)

Initial codes	Focused codes	Quotes (Case number)
		“oddly before the outbreak there was passing interest in it [AMR]. But once people saw the consequence of it and there were wards closed for ages and there was a cost to the organization in terms of scrutiny and time and interaction with external partners and loss of revenue, I think that got attention in a way that just talking in an abstract sense, I don't think would” (Case A004) “Internally as a trust, unfortunately it's like I analogized just before, we were hit by that train so we had a massive outbreak [CPE] and it did refocus or focus our efforts. Sometimes I think that was a good thing and that we've always got that organizational memory of "Do you remember?" You know, 18 months ago that's what happened, and people will go "Gosh, yeah. We don't want that to happen again." And will take what we're saying on board.” (Case A005) “But this a problem [AMR], this is a very expensive problem. Certainly, we did a cost analysis [CPE related] with looking at what the cost of a single outbreak was and worked it out, it cost the trust a million pounds predominately in bed losses….. That definitely hit home. That was ... You know they were like gosh that's a million pounds we could have done without losing. So I think the high level, there probably is that appreciation.” (Case A007)
• Winter pressure • High occupancy • Mismatch of patient activity and planned resources	Patient activity	“we also have overcrowding particularly in winter.” (Case A010) “High occupancy, being a regional or major receiving unit. So you take everything. Malicious attacks was quite high on the [inaudible 00:07:35] for the trust, and last year you'll be aware, we had a number of them.” (Case A013) “I mean, the hospitals are extremely busy… The fact that we have got two hospitals with A&E's, one of which is a major trauma center means that we are extremely busy anyway..” (Case B002) “we're seeing increasing numbers of people turning up at our doors, we're having to admit more people,” (Case B006) “This year, we're on a continuous black alert. I think we're probably keeping patients, not quite in corridors, but the next best thing. You know, in not the nicest environment. I was up on a ward where the ward was not big enough for six beds, and six chairs, and six lockers. So, you couldn't get to the wash hand basin if you wanted to. The poor patient couldn't have sat in the chair if he really wanted to.” (Case B004)
• Different metrics to measure patient activity	Pay conflict with commissioners	“So, I think that the bigger picture's not always looked at by the commissioners.” (Case B004)

Initial codes	Focused codes	Quotes (Case number)
• Patient activity planned and forecasted discrepancy		"if you think of patient activity, you're presenting clear data that shows, over the years activity has increased 10%. That's what auditor is telling us. We have instances, where even those kind of cases cannot be approved, because the first question that we will ask is, does the commissioner acknowledge that there's a 10% increase in activity? And have they acknowledged they pay for it?..... And nine times out of ten ... in fact, I've never come ... I've been here five years now, and I've never come across a situation where we've presented a case and the commissioner's agreed to pay for something up front, based on activity. Never." (Case B001) "So, that patient has come in, was that originally captured within what we're budgeting for or is that an additional activity, because they only pay a marginal rate for additional activity, rather than the activity we're planned for, so you get into a whole series of debates, and they [commissioners] will make a challenge back to us about "Well, we think that you over performed by X amount. Therefore, we're only going to pay you seventy percent of the tariff for this number of people." So, at each point of the kind of plan, the planning cycle at the start and then the in-year cycle, you get into these sorts of debates with the commissioners. Which, candidly, is a huge overhead on us as an organization and the CCG as an organization, which is part of issues with the systems as a whole, where you've got commissioners and providers and you've got that split. You just create that head-to-head relationship and that friction." (Case B006)
• Community structure • Ageing population	Population structure (external)	"I think that our population changes are a huge issue. The very transient mobile population we have. The huge inequalities," (Case A001) "And therefore, the demand based on the complexity of care and the aging population is really not one that is recognised in the current system. So how that translates into the Trust is that the payment that we get for care often doesn't really recognise the full complexity and the cost of care" (Case B005)
• Old infrastructure requires continuous rebuilding • High cost of maintenance • Impact of estate on cleaning + IPC	Quality of estate	"So I think one of the big issues for us is our estate and the cost to maintain it… And the cost to rebuild it… But I do think the estate issues here are probably a bit different to many other organizations." (Case A002) "There's a huge estates challenge for this trust. So the quality of our estate is very poor, and the cost to maintain it is huge,….. So there's a short, a medium, and a long term challenge around our estate. Essentially what the trust is trying to do is knock this hospital down and replace it with a new build. So that's a massive challenge." (Case A003)

Initial codes	Focused codes	Quotes (Case number)
		"quality of the estate.. have ward closing at very short notice because they've become unsafe" (Case A006) "working within an estate, working within buildings that are absolutely inappropriate in terms of providing safe care and a safe environment to take care of patients and to prevent the acquisition and transmission of organisms and particularly the concern about acquisition and transmission of highly resistant organisms….. I also mean the response to immediate needs and requests for repairs, refurbishment that take months, weeks, months, years to get done. So this is continuous and it's particularly bad at the moment." (Case A010) "it actually, it doesn't meet modern day standards at all, to say it's not fit for purpose, but it doesn't meet modern day standards. If we look at some of the buildings" (Case A013) "the trust is sort of falling apart at the seams, so estates, we've got a huge issue there." (Case A014) "all sites have got a challenging capital backlog maintenance burden….. You'll find that lots of flooring is close to, if not past it's- Service life. It's either cracked, breaking up, or has worn through in cases… Water hygiene is a big issue across the estate" (Case B002) "You've got high ledges, high ceilings. You've got all sorts of nooks and crannies everywhere. And it makes it really difficult to get clean. So often you have to put in an extra level of resource to be able to do that." (Case B003) "The biggest challenge for us is the age of the estate. The age of the estate, and the condition of it is very poor and makes delivering services in it very difficult" (Case B008)
• Time (staff) availability • Space (isolation rooms / bathrooms / sinks / toilets) • Impact of estate on resources (time/money/space) •	Resource availability	"That people are very, very stretched. They just don't have time to think and breathe and think differently about things. So on the one hand, you and I say, the biggest problem is there's no imagination, people aren't thinking differently. On the other hand, there is no space and time and support for them to think differently." (Case A001)

Initial codes	Focused codes	Quotes (Case number)
		“But we've got an old estate, so therefore, we've got an estate that was built a long, long time ago. So the numbers of bathrooms are restricted. And so the numbers of side rooms are restricted. So therefor, having access to isolation can be difficult. And I guess that's the balance that the operational teams are having to juggle day in and day out.” (Case A002) “And sometimes the lack of isolation facilities means that you're not able to use your capacity in the way that you would otherwise want to. Because if you've got somebody in a bay, with an infection that you need to isolate, and you can't move them, then you can't use that whole bay of beds…… really we're too small for the level of service that we're running.” (Case A003) “And it could be because that's a resource issue, both in terms of manpower and time and money.” (Case A004) “I think the major problem is we don't have enough space for the demand that comes in through the front door, and there doesn't seem to be an answer for that. And every day, this sort of abnormal situation becomes normalized” (Case A005) “But the reality is we cannot get medical review [Antibiotic prescribing related] of every medical inpatient seven days a week.” (Case A006) “But yet there’s not enough resources for proper teaching, team based what do you call it? Context specific teaching. For your teaching to be good and relevant it should be within the context and that’s, don’t, there are just not the resources, other competing targets….. but so much time is wasted on the issues around the estate” (Case A010) “So, I know that pharmacists had tried looking at pulling off a list of the patients on certain antibiotics. Which would be great, but they don't have the resources to do that every day ……We need an estate where you've got vastly increased numbers of side rooms” (Case A007) “So in terms of that, do we have enough estate, number one for capacity? We run at high occupancy…. we're quite fixed in infrastructure, if you think about it, whereas the demand is not.” (Case A013)

Initial codes	Focused codes	Quotes (Case number)
		"When you go up on the wards, you'll see that they are very limited in terms of storage and proprietary storage solutions within the stores…. The bed space is based on previous bed separation distances, so you've got more beds per square meter than you'd have on a modern hospital, so everything is constrained really." (Case B002)
• Quick fix solutions due to structure of the organisation • Cost improvement plans without future investment • National policy short term outlook: • CQUIN disadvantages • Junior doctor turnover • Reactive not proactive approach	Short term measures (One or two year planning)	"I think the [they ~ the organisation and also the commissioners and policy makers] often don't have enough long term sight in view. They in many cases don't properly understand the problem, so we have a big problem in the trust and we are great at jumping to solutions without properly understanding the problem…. SO antibiotic, antimicrobial resistance is a brilliant example of something that is not new, ….. In this, it's not a one to two year problem. This is going to be a massive problem over the decades ahead. Business plans and business cases are just not written up or thought about in that framework…… The problem with cost improvement and business plans and things ... The parameter by which you have to, they're designed to be done is …[prevents/stops] you from thinking differently because they're based on last year's plan. Last year's plan, you notice last year's plan plus five percent or minus five percent and I think that's part of the problem we've got." (Case A001) "In different ways that things are managed based on NHS England, NHSI [NHS improvement], they'll come out for example a CQUIN, it's there for a year, two years. In terms of the length of time people stay in a post, the effective government changes. They all have, they are short-term attempts at fixes. A short-term attempts at setting targets, and its not actually not the right, we don't have a long-term strategy that's fully funded or supported moving forward. That's not just us as a trust that, you know, the NHS, I mean, how is it that every year we have this strange thing called winter. That seems to happen every year, and yet it just seems to catch us out." (Case A014) "It's extremely difficult to deliver further CIPS without investment. If we had a newer estate, like with development, we would have assets that have a better breakdown history. It'd run longer between failures and then you wouldn't have as much reactive cost." (B002) "The NHS has been doing cost improvements for years and years and years. I guess, from some of the negatives that we find is that actually because we've been doing it for so long, you're kind of scraping the bottom of the barrel now in

Initial codes	Focused codes	Quotes (Case number)
		terms of what we can do to achieve….. If we want to continue making the levels of savings that we need to, we need to physically start changing how we deliver." (Case B003) "Yeah, I mean actually a couple of years ago we had to restructure the [redacted] team as part of the cost improvement program, which was one of the hardest things I've ever had to do actually. I had to downgrade [redacted] senior [positions] [redacted], ..which was very challenging actually. Because we had to then present this cost improvement as a good idea when I knew it wasn't. But obviously we had to do a cost improvement, and go in there and say we didn't have one wasn't an option. And what resulted is that [redacted] left ….which has had quite serious ramifications, …whereas the [redacted]people I had before were very, very experienced, so it actually had quite a big knock-on effect." (Case A005) "And so the other downside is for somewhere like this organization, the money isn't visible. So the CQUIN money, even if we meet it, has already gone into the budget of the organization because we're in such a financially difficult position. So it is again asking our team to do extra things, and the Trust to do extra things, it feels, but without any extra resource to do that. So there was a short-term injection for us to get out a pharmacist for a year, we've been able to do great things for that pharmacist. I'm sure [redacted]can talk to you about that... And now it looks likes like that person will not have their contract extended and therefore, to us it feels like we could meet this if we had X, Y, and Z, but the money actually isn't visible; it's going to disappear into the bottom line. So that, for us, has been a downside..." (Case A004) "We're not proactive; we're reactive ... planning forward, in fairness, the planning forward, the five years ahead and plus, it's locked up in this organization, the redevelopment discussions. It is uniquely difficult to secure capital in the NHS, and if you see where St. Mary's is at the moment to come up with a solution, working with a lot of acute services here." (Case A013) "We also, and we'll have to be honest, we have a work force whereby, the NHS and certain[redacted]behaved in a very reactive way. So we tend to react to problems, rather than be proactive, with a strategy moving forward that we just stick to…. Absolutely, So we're still on Black Alert. You know, where is the

Initial codes	Focused codes	Quotes (Case number)
		proactive planning that manages it, in a sensible and sustainable manner? ” (Case A014) “I don't think.. a CQUIN particularly helps for this [AMR/prescribing] sort of thing because all it does is gives you a short-term focus on a problem. And the big issue is generally, you're junior medical staff, who will only be here for usually half the life cycle of a CQUIN and then move on to another organization. So what generally happens with a CQUIN is, if we know we got a CQUIN coming up we will spend some the money on employing some more pharmacists to help the antibiotic stewardship but they don't become embedded in the system, so when the CQUIN ends you lose the pharmacists and instead of trying to tick that box for the short-term , it's almost like you should probably..[be] thinking about how you educate about the management of bacterial infection and also about the, why do you do antibiotic stewardship?.. And I think [this] is a very short-sighted approach to what is actually a big cultural problem” (Case A006) “Why your narrowing down your broad spectrum antibiotics is so important. We can try to do a little [bit] of education, but particularly when the junior doctors are changing so often.”
• Staff vacancies and turnover • Staff to patient ratios	Staffing	“Of course there are many, many challenges across the trust. If you look at the frontline nursing practice, challenges include shortage of staff and a lot of the time, people will have more ... Nurses will have more patients to care for…. The turnover is high, the vacancy rate is high” (Case A009) “we have a major problem with not enough doctors…. Churn [turnover] in senior leadership” (Case A010) “You have lots of change of staff, be that junior management or medium management, and again, the history is not retained. You don't have people coming in posts that worked their way up and have been there. I've been here a long time, ten years. I was in a meeting before your meeting where those people weren't even in the last meeting six months ago, half of them.” (Case B004) “…in many cases it's to work in environments which are far below what they, and we, would want. It feels a little bit like a ticking time bomb, it's just how long can we continue to squeeze that level of effort out of staff and then you compound that with Brexit and what it's doing to nursing and some of the decisions over the last five years that have reduced nursing education funding and reduced nursing education estimates and ... I mean, that's not so much a ticking time bomb as

Initial codes	Focused codes	Quotes (Case number)
		bomb that's almost going off just in terms of that demand management for the most part isn't flattening out demand. … We still have more people turning up for emergencies and so on than we did last year and that's creating ever more pressure on staff." (Case B007)
• Appropriateness of antibiotic prescribing • Behaviour differences when prescribing antibiotics • Culture difference across specialities related to antibiotic prescribing • Switch from paper to electronic prescribing • (and its impact on antibiotic prescribing)	Underpinning issues of antibiotic prescribing [Antibiotic prescribing]	"So, partly antibiotic stewardship. And that includes focusing antibiotics as soon as you got a cultural result. Adequate switch to, you know, an appropriate switch from IV to oral, but also use of our guidelines because one of the biggest issues facing the trust at the moment is actually getting people to follow the guidelines….. Because there is still a perception about some antibiotics are stronger than others as opposed to appropriate. …if we could get everybody to follow the policy. And it's almost a behavioural thing….. cultural … people don't like making changes to other people's patients unless they've been told to. But the reality is we cannot get medical review of every medical inpatient seven days a week " (Case A006) "Because we've recently in the last few years implemented a Trust-wide electronic prescribing and administration system. And while it's generally been going well, there are still a lot of problems [related to antibiotic prescribing] and I don't think they are problems that they weren't there before. I think some of them were probably there with the paper drug charts but it's become more visible with the electronic prescribing system and it's harder to work around occasionally with the electronic prescribing system." (Case A008)
• Estates and clinical teams • Finance and clinical teams • Organisation set up (hierarchies, senior leadership instability)	Within Trust communication barriers	"I suppose the challenges are because they're a different group of professionals from the group of professional with which I normally work. They speak a different language. They have different technical knowledge to me….But it means I have to trust that they are knowledgeable. And that has proved challenging….Well, it just ... it hinders progress. Because you have to spend a lot of time on picking what they're talking about. And you almost have to learn their language," (Case A004) "And sometimes the challenge around their very very expert role. May be they don't always see the patient consequence, or the reason why we're interested in a certain aspect, say of ventilation or water hygiene or anything like that. And I'm not saying that they're not experts in what they do, but they're managing sort of a water system in a hospital would be very different to managing a water system in a block of flats or somewhere. So it's getting that patient perspective and the health care element of it. It can be a challenge." (Case A005)

Initial codes	Focused codes	Quotes (Case number)
		“there are ... you know, just as there are communication issues and issues with silos, between say the finance director as a director and a service as a service. I'm aware that the nurse on the ground, for example, who may have a fantastic idea, may not necessarily know how to channel that idea up to the chief of service. That chief of service can now have a conversation with me. And so communication has to be improved.” (Case B001) “there's some instability at the higher level so in terms of directions and what's happening we may get information that things are going well but we don't really get a good sense of what is ... what we need to do to improve properly. I feel like we get mixed messages sometimes between what the situation is and what the situation they would like us to be in.” (Case A008) “So all this business about communicating and getting things done across divisions, what we need, to get things done if you have to go to each division it just doesn’t work. It’s not, you need one, this has to be trust wide. Many things are not just one division, they have to be agreed trust wide. So if you don’t have one person who can say, although it’s all supposed to be acting like they’re all CEOs is just really not so easy.” (Case A010)

Appendix Table 19: Thematic analysis to understand the resource allocation decision making processes at the Trust

Subthemes (In bold)	Key themes	Quotes
• **Clinical risk to patients outweighs financial viability** • **Meeting guideline and regulations**	Immediate concerns (patient/regulatory)	"Case B006: And then, you know, look, there are situations where these things go to the executive and we have to be honest and say to the exec ""Look, this is a circumstance because there's a real safety issue or a quality issue or the CQC have identified something, that we can't necessarily get this business case to stack up on its own merits, in terms of the benefits outweighing the costs, but we still think it's a good thing for the organization to be spending money on and investing in because the clinical outcomes that it will deliver or the risks that it will mitigate are worth the investment."" Case B007: So we try and develop systems where clinicians, as far as possible, can see the financial constraints. Like I say, they've got the ability if they think it's a patient safety, to just push straight though the financial constraints and say, ""Safety is more important,"" " Case A013: ...sometimes the clinical risk to patients will outweigh any kind of financial viability argument. Case A002: I guess decisions are not just based on finances, they're based on quality and specific issues that relate to quality. "Case A003: we would make sure that it ticked all the boxes in terms of guidelines and regulations and things that we've got to comply with. And we would also endeavor to make sure that our commissioners would be supportive of us doing whatever it is that the business case is for.
Bare minimum needs a financial position • Save money • Cost neutrality **Financial and longevity** • Focus shifting to two year as opposed to one year business plans **Quantifiable evidence due to scarce finances**	Strong financial argument	"Case A003: the easiest business cases are the ones where it's very clearly identifiable that you can make, that the business case pays for itself, so you get a return on investment in financial terms. Case B005: So all business cases have to have, at a bare minimum, a financial position. ...in any business case, you have to be able to demonstrate that the investment has a good return. So that's the first one. ....And there is a requirement that business cases don't add additional cost, so if you want to do something new, unless it is a real strategic priority and will then have a longer term effect, business cases shouldn't add costs to a system that's already really struggling.

Subthemes (In bold)	Key themes	Quotes
• Believable data - patient and financial level • Strong evidence is needed to support business case **Specific to a capital business case** • CQC framework - safe, effective, caring, reponsive, well led • Organisational matrix - Risk and return on investment		Case A013: to think about number 1: it's patient benefit and patient care and number 2: strategic alignment and number 3: financial viability. " "Case B005: So we have our own decision making tool that shows the comparative strategic attractiveness of each service, and that benchmarks them on productivity, on strategic fit, experience and outcomes and financial sustainability and longevity. Case B006: We're responsible for business planning, so we start to do more two year business plans than one year business plans as the NHS. So we're starting to think about future years. " "Case B001: But ultimately, for something to be approved, whatever that data is, it needs to be as fully quantifiable as possible, just purely because there's such scarce finance. Case B005: But in the current climate, you can only really make decisions based on really strong evidence and support.... Case B006: There is clearly a benefit from ensuring that we are able to bring beds back into use quicker and that we reduce the spread of infection. "
Case for change **Data generated from within the Trust** **Holistic return on investment**	Trust wide engagement (The three subthemes are elements to aid engagement)	"Case A002: But I think that prioritization takes place on a Trust-wide basis, looking at the available resource and the cost pressures from all areas. There's a process at the beginning of the year ... so at the moment ... as part of the business planning, where all of the divisions and corporate areas have got to put forward their cost pressures, which is where these business cases should also be playing into. And to get a decision made about what priorities across the Trust people want to fund. Because, the problem we have is, that funding only becomes available if people make savings elsewhere to be able to fund. So there is a prioritization process that has to be put in place. That said, I think it's done in a Trust-wide way. And the divisions have got to be absolutely included in that. Case A003: So yes, it goes out to the three divisions, and they consider it, give their feedback, and go, because otherwise, when it goes to the executive committee, if one of

Subthemes (In bold)	Key themes	Quotes
		the divisions hasn't agreed with it, they'll say, ""I'm not happy if this would be approved."" Then the whole thing has to go back round the loop again. " "Case B005: So all business cases have to have, at a bare minimum, a financial position. They have to have a case for change. They have to look at activity and they need to bring in some of the key safety measures. Case B006: So that's one business case that's come through, where there's a clear rationale for doing it. It probably stacks up in financial terms, but it all certainly will benefit the Trust from a clinical and safety perspective. " "Case A003: So if it's something that we've piloted in this organization, and we can see that it works, even if we're the only place doing it, that's reasonably strong evidence that expanding it would, or making it permanent would be a good thing. Case A007: So we really did have to put in the leg work to customize it [Microbiology lab technology to reduce culture turn around time business case-which was approved] to our population at this hospital. Case A004: You know, for example, we recently trialed an isolation pod in the Trust. And it worked great in the particular area that it was trialed. But there were no other places in the Trust where we think it would be useful. So there's no point in investing in that. You know? " "Case B005: ... but most business cases have to demonstrate that they will improve the financial position, the operational position or the patient experience and safety in its widest sense. So you would expect to see that your investment is delivering on all of those areas. It's very rare that in healthcare, you can separate out one from the other. So you would want to see a more holistic improvement and return on your investment across those measures. Case B001: So it's not all about the clinical stuff, or the operational stuff, all of that. It's all of that combined together, in order to be able to tell. If it does, then what it will come down to is how much money we have available to spend and the exec should be making that decision. "

Appendix Table 20: Standards for Reporting Qualitative Research

	http://www.equator-network.org/reporting-guidelines/srqr/	
	Standards for Reporting Qualitative Research (SRQR)*	**Page/line no(s).**
Title and abstract		
	Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	Section 5.5
	Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	NA
Introduction		
	Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	Section 1.2, Section 1.2.2.4, Section 1.3.3, Section 5.2.1
	Purpose or research question - Purpose of the study and specific objectives or questions	Chapter 1
Methods		
	Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	Section 5.2.1
	Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	Section 5.5.4
	Context - Setting/site and salient contextual factors; rationale**	Section 5.5.5
	Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	Section 5.5.2.2-5.5.2.4
	Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	Section 5.5.1

	Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	Section 5.5.2.2-5.5.2.4
	Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	Section 5.5.2.2-5.5.2.4
	Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	Section 5.5.2.2-5.5.2.4
	Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	Section 5.5.2.2-5.5.2.4
	Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	Section 5.5.2.2-5.5.2.4
	Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	Section 5.6.4 Section 6.2
Results/findings		
	Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	Section 5.5.3-5.5.5 Section 5.6
	Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	Appendix Table 18
Discussion		
	Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	Section 5.7
	Limitations - Trustworthiness and limitations of findings	Section 5.6.4 Section 6.2

Other		
	Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	NA
	Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	NA – Included as part of PhD project
	*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.	
	**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.	
	Reference:	
	O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014 DOI: 10.1097/ACM.0000000000000388	

Publications associated with thesis

Pouwels KB, **Chatterjee A**, Cooper BS, Robotham JVet al., 2019, Antibiotic resistance, stewardship, and consumption, The Lancet Planetary Health, Vol: 3, Pages: e66-e66, ISSN: 2542-5196

Chatterjee A, Modarai M, Naylor NR, Boyd SE, Atun R, Barlow J, Holmes AH, Johnson A, Robotham JVet al., 2018, Quantifying drivers of antibiotic resistance in humans: a systematic review, LANCET INFECTIOUS DISEASES, Vol: 18, Pages: E368-E378, ISSN: 1473-3099

Naylor NR, Atun R, Zhu N, Kulasabanathan K, Silva S, **Chatterjee A**, Knight GM, Robotham JVet al., 2018, Estimating the burden of antimicrobial resistance: a systematic literature review, ANTIMICROBIAL RESISTANCE AND INFECTION CONTROL, Vol: 7, ISSN: 2047-2994

Naylor NR, Uchegbu I, **Chatterjee A**, Robotham JVet al., 2017, Gambling with antibiotics: a novel approach for exploring antibiotic consumption decision-making, PUBLIC HEALTH, Vol: 151, Pages: 146-148, ISSN: 0033-3506

Lishman H, Aylin P, Alividza V, Castro-Sanchez E, **Chatterjee A**, Mariano V, Johnson AP, Jeraj S, Costelloe Cet al., 2017, Investigating the burden of antibiotic resistance in ethnic minority groups in high-income countries: protocol for a systematic review and meta-analysis, SYSTEMATIC REVIEWS, Vol: 6, ISSN: 2046-4053