Delivery of a novel intervention for vector control: Learning frameworks to support complex decisions

Mary Megan Quinlan

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Imperial College London
Centre for Environmental Policy
Faculty of Life Sciences

Declaration of originality

I declare that this thesis, **Delivery of a novel intervention for vector control: Learning frameworks to support complex decisions**, is entirely my own work and where material could be construed as the work of others, it is fully cited and referenced, or appropriate acknowledgement is given.

Preferred citation

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Disclaimer

This research is entirely the opinion and findings of the author. Nothing in this study reflects official policies or opinions of the project studied, Target Malaria, nor of the funders.

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* These publications are available through Open Access.
** A copy of this publication appears in full in Appendix 4.

Abstract

Malaria remains a serious public health challenge, particularly in sub-Saharan Africa where initial progress from use of bed nets or indoor spraying is faltering in the face of insecticide resistance and other challenges. Vector control is a critical component for eliminating malaria. Consequently, there is increasing demand for novel approaches to mosquito vector control. This study focuses on moving one innovation – employing released modified mosquitoes to target their own species – from an external discovery laboratory through the early phases of evaluation and delivery into disease affected countries. A stepwise approach (contained studies, confined studies, pilot field studies) is considered best practice, in order to build knowledge on safety and efficacy while also increasing capacity of the decision makers. In reality, a diverse range of decision makers must make judgements about novel interventions in the face of uncertainty and lack of direct experience.

To date, considerations regarding partnership with researchers in a disease endemic country and establishing the standards for containment studies are barely mentioned in the literature on genetic strategies, which focuses instead on national frameworks and biological criteria for the field study phase. This thesis raises the question of what constitutes good practices and supportive decision tools in this scenario, using action research, interviews and literature review and testing of some early prototypes.

The researcher confirmed the value of simple frameworks to organise information, document evidence and inform future decisions, particularly when identifying appropriate research partners. Benchmarking the point at which to transfer a research organism to a partner can support those addressing the series of complex decisions unique to novel malaria interventions with more confidence and transparency. Learning tools are only effective when balanced with commitment to provide the resources and time for their use, and for ongoing skill development to face the challenges of such complex decisions.

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Acronyms and abbreviations

This list also includes acronyms and abbreviations from the Appendices, but not those that appear only in citations, which are defined in the References Section.

AAALAC	Association for Assessment and Accreditation of Laboratory Animal Care International
ACL	Arthropod Containment Level
Ae.	*Aedes* mosquito genus
AHTEG	Ad Hoc Technical Expert Group
AMANET	African Malaria Network Trust
An.	*Anopheles* mosquito genus
AU	African Union
BCA	biological control agent
BMGF	Bill & Melinda Gates Foundation
BSL	biosafety level
CAPA	Corrective Action Preventive Action report or template
Cartagena Protocol	Cartagena Protocol on Biosafety to the Convention on Biological Diversity (CBD)
Cas9	CRISPR associated protein 9
CDC	Centers for Disease Control and Prevention (USA)
CEP	Centre for Environmental Policy, Imperial College London
CIRAD	Centre de Coopération Internationale en Recherche Agronomique pour le Développement (France)
CoA	certificate of analysis
CRISPR	clustered regularly interspersed palindromic repeats
DALY	disability adjusted life year
DEC	disease endemic countries or disease endemic country
Defra	Department for Environment, Food and Rural Affairs (UK)
DNA	deoxyribonucleic acid
EC	European Commission
EFSA	European Food Safety Authority

EIA	Environmental Impact Assessment
EIR	entomological inoculation rate
ELSI	ethical, legal, social implications
EMPHASIS	Effective Management of Pests and Harmful Alien Species – Integrated Solutions (EC project)
ESC	ethical, social and cultural
ESFRI	European Strategy Forum on Research Infrastructure
EUCLID	Europe China Level for IPM Demonstration (EC project)
FAO	Food and Agriculture Organization of the United Nations
Fera	Food and Environment Research Agency (UK)
FNIH	Foundation for the National Institutes for Health (USA)
FP7	Framework Programme 7
GCGH	Grand Challenges in Global Health
GLP	Good Laboratory Practice
GM	genetically modified
HACCP	Hazard Analysis Critical Control Point
HSE	Health and Safety Executive of the UK
IACUC	Institutional Animal Care and Use Committee (USA)
IAEA	International Atomic Energy Agency
IBC	institutional biosafety committee
ICEMR	International Centers of Excellence in Malaria Research
ICGEB	International Centre of Genetic Engineering and Biotechnology
ICREC	Imperial College Research Ethics Committee
IICA	Inter-American Institute for Cooperation on Agriculture
INRA	Institut National de la Recherche Agronomique, France
IP	intellectual property
IPPC	International Plant Protection Convention
IRS	indoor residual spraying
IRSS	Institut de Recherche en Sciences de la Santé, Burkina Faso

ISBGMO	International Symposium on the Biosafety of Genetically Modified Organisms
ISO	International Organization for Standardization
ISPM	International Standard for Phytosanitary Measures, under the IPPC
ISTR	International Society for Third-Sector Research
IVCC	Innovative Vector Control Consortium
JRCO	Joint Research Compliance Office, Imperial College London
KARI	Kenya Agricultural Research Institute
LLIN	long-lasting insecticidal nets
M&E	monitoring and evaluation
malERA	malaria eradication research and development agenda, of the Malaria Eradication Scientific Alliance (MESA); malERA Refresh is a renewal of the same initiative
MosqGuide	A WHO/TDR project run by Imperial College London, CEP, that ended in 2012
MPAC	Malaria Policy Advisory Committee, of WHO
MRTC	Malaria Research and Training Center, Mali
MTA	Material Transfer Agreement
Nagoya Protocol	Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity
NASA	National Aeronautics and Space Administration
NASEM	National Academies of Sciences, Engineering, and Medicine (USA)
NBA	National Biosafety Authority
NBF	National Biosafety Framework
NGO	non-governmental organisation
NIAID	National Institute of Allergy and Infectious Diseases (USA)
NICE	National Institute for Health and Clinical Excellence (UK)
OECD	Organisation for Economic Co-operation and Development
OIE	World Animal Health Organisation
PAMCA	Pan African Mosquito Control Association
PCR	polymerase chain reaction

PhD	Doctor of Philosophy
PI	principal investigator
PPE	personal protection equipment
Q	question (in online survey)
QA	quality assurance
R&D	research and development
RIDL®	release of insects carrying a dominant lethal, a name no longer used
SDG	Sustainable Development Goals
SIT	sterile insect technique
s.l.	sensu lato
SOP	standard operating procedure
spp.	species (plural)
s.s.	sensu stricto
SWOT	strength, weakness, opportunity, threat
T&C	terms and conditions [of the authorising permit]
TDR	Special Programme for Research and Training in Tropical Diseases, WHO
TRL	technology readiness level
UK	United Kingdom
UN	United Nations
UNIDO	United Nations Industrial Development Organization
USA, or US	United States of America
UVRI	Uganda Virus Research Institute
VCAG	Vector Control Advisory Group of WHO
VCTR	Vector-based Control of Transmission: Discovery Research (a GCGH programme)
WHO	World Health Organization
WHOPES	WHO Pesticide Evaluation Scheme
WTCR	Wild Type (field caught) Colony Record

Preamble

The scope of this research is an examination into the decision making processes, barriers and enablers involved in the delivery of a novel intervention for human disease vector control, specifically looking at the early primarily lab-based phase in delivery. The research documents the context of why additional and novel interventions are needed, focusing on the case for control of malaria vectors. It should be emphasized, however, that this thesis does not consider nor debate the appropriateness of any single intervention, but rather begins from the premise that further innovations are needed in order to achieve a reduction in malaria and that such innovations are or will be available, at least in the initial stages of a product development pathway.

The researcher studied ways to support decision makers, whether or not the decisions were taken to proceed with a novel intervention. The researcher's unique access to situations of positive decisions towards progressing through the first steps in delivery is not intended to disparage similarly informed and deliberated decisions to not progress, which may have been taken in other cases or may arise.

Despite the researcher's involvement with the Target Malaria consortium, the thesis is not an authorised history of that initiative nor is it intended to endorse or oppose any of the current or feasible upcoming interventions in vector control, or other methods for reducing malaria transmission. The aim is to explore how complex decisions may be supported and facilitated, in the face of the challenge of a disease that takes human life on an hourly basis.

Therefore, this is not the place for a synopsis of the years of debate over technologies mentioned, including genetic modification, or the pros and cons regarding specific approaches such as gene drive. Equally, this research does not intend to selectively promote the usual top down, externally driven technology transfer described in the study. The researcher intentionally narrowed her scope to a frequent scenario in seeking new interventions: an external source of novel technology offered for delivery to countries that could potentially benefit enormously if the uncertainty and novelty itself can be evaluated and managed to their satisfaction. Throughout the study, the researcher seeks to clarify what could comprise good practices in the initial steps for delivery of a new vector control intervention. Although the example is for a specific area of public health, she concludes with observations on what may apply to similar cases of areawide control.

THE PROBLEM

Chapter 1. Why Add a Novel Intervention for Vector Control?

1.1 Scope of this research

Vector control is one of the key interventions for reducing human diseases that are transmitted through a vector insect. Innovations in vector control are considered essential to maintain recent gains against mosquito vectored diseases such as malaria, as discussed below. Innovations may arise from increased technical knowledge and additional technologies[1], improved production and delivery of interventions, or other types of increased operational capacity. Methods for enhanced coordination of policy makers also can contribute to improved decision making related to vector control (Mutero et al., 2014).

To justify adding a novel technology to field programmes that interface with the public in affected areas, however, researchers and governmental decision makers must be able to first answer key questions about the target disease incidence and provision of treatment. Then they must demonstrate the efficacy and safety of the proposed intervention and determine if it can be successfully delivered where and when needed, before establishing reliable, cost effective and consistent production of the intervention. Furthermore, they need to determine if it will be accepted by the relevant stakeholders. This study considers aspects of efficacy and safety and the ability to deliver where and when needed, although from the perspective of early phase delivery. Partnership and transfer of externally initiated technology at an early point in development allows further research and co-development within targeted geographic regions, rather than a final product delivery.

The introduction of a novel vector control intervention interfaces with numerous technical, social, political and biological issues, creating a complex landscape for decision making (WHO/TDR, 2010; Knols & Louis, 2006). Across this landscape are a number of decision makers who either move the innovation forward towards use in vector control campaigns, often at a national level, or delay or block the innovation, possibly due to lack of capacity, resources, clear authority or political will (WHO/TDR, 2017). Not all innovations are appropriate to the conditions of any given disease endemic country (DEC), and therefore not

[1] To simplify, in this paper the word ‘technologies’ actually refers to approaches, technologies, techniques or enabling tools and services. The researcher uses the term ‘intervention’ to mean the intentional application of an approach, technology, technique or other planned activities. A novel intervention refers to the application of a new, innovative technology as discussed further in Chapters 2 and 3.

all should be adopted. Failure to take informed decisions, however, is a poor reason for lack of progress towards use of novel interventions that could make a significant difference in the battle against vectored diseases.

This study focuses on the example of innovations in mosquito vector control that are developed outside the geographic area of future use, and on malaria as the example mosquito vectored disease[2]. Research was restricted to the early primarily lab-based phases of delivery of new, additional interventions for reducing malaria transmission, in this instance through novel vector control. The researcher classified early phases of delivery as: identification of research partners, decisions around transfer of research organisms between laboratory environments, and a number of decisions about conducting research in containment prior to studies under field conditions, along with the appropriate permissions to do so. (The originating step of actually discovering a potentially useful innovation is taken as a starting point for the study, as is a functioning health care system able to diagnose and treat malaria cases and monitor trends on a national level. These are major topics in and of themselves, making such assumptions, or restrictions to the scope, imperative in order to progress research on a more specific point in the delivery process.)

The overarching aim of the research is to assess: **How can learning systems improve the process of decision making around the delivery of a novel vector control intervention?**

In the context of this study, the term 'learning system' has been defined to mean:

A distinct and described framework or structure that has a rationale based on defined questions or objectives,

- Which will hold existing knowledge but also new and future knowledge (in whatever relevant format, such as literature, study results, or experiences) in a coherent and accessible manner
- Which also allows or promotes new knowledge for improvement (e.g. evidence supported conclusions, new interpretation) to be generated because of the system

[2] When mentioning malaria in this thesis, it refers to infection with *Plasmodium falciparum*, which is the most prevalent cause of malaria in humans globally, and overwhelmingly the most important species of the pathogen in Africa. Various sources suggest that at least 90% of all cases of malaria occur in sub-Saharan Africa (e.g. WHO, 2017a) and these are overwhelmingly this type of malaria.

- Which is structured for flexibility and robustness, allowing for different conclusions or learnings, depending on the information entered and differing criteria[3], and
- Ideally, providing knowledge that can be acted on by the user/learner

The approach of frameworks or analytical tools incorporating learning systems for increased effectiveness will be elaborated on in future chapters, in accordance with the title of this study, **Delivering a novel intervention for vector control: Learning frameworks for complex decisions**.

A number of new interventions are under development for early stage deployment against vectored disease, and these innovations frequently originate externally from the disease affected areas. Literature on novel technologies for mosquito vector control generally relates to decisions regarding regulation and field studies or deployment. The central assertion of the study is that improved decision support during the early stage of delivery of genetic strategies for mosquito control can produce significant impact in the absence of existing experiences, procedures or regulations. This study particularly draws on experiences with an international not-for-profit research consortium, Target Malaria[4]. The Target Malaria consortium was created for developing and sharing a novel intervention to vector control using transgenic mosquitoes.

1.2 The need for vector control in fighting vectored diseases

From the time that the role of mosquitoes as vectors of serious human diseases was identified, the importance of controlling the vector species has been known (Cox, 2010). Vector control[5] has been a cornerstone of public health programmes for mosquito vectored diseases for both prevention and control objectives (Oaks et al., 1991). Box 1.1 describes what is meant by mosquito vectors.

[3] The researcher as co-author in Mumford et al. (2016) offers one of many examples that illustrate this type of approach, in this case with a list of indicators for plant health innovations without necessarily resulting in a single 'correct' outcome.

[4] More information about this project can be found at https://targetmalaria.org. This thesis is the author's interpretation and understanding of the reported work, however, and is not representing any authorised version of events.

[5] The WHO Global Malaria Programme (2016: p.23) defines malaria vector control as 'measures of any kind against malaria-transmitting mosquitoes, intended to limit their ability to transmit the disease'. The same glossary definition further states that successful *vector contro*l would result in a reduction of malaria transmission by reaching the point where vectoral capacity is sufficiently low to interrupt transmission.

Vector control can be done on a small scale by individual citizens for an anthropophilic species of mosquito, for example those that vector dengue, yellow fever, chikungunya and Zika. In that instance, one of the most important control methods for *Aedes aegypti* and *Ae. albopictus* is still individual and neighbourhood efforts at source reduction: vigilance against standing water in containers or small reservoirs in urban, peri-urban and agricultural areas that provide a site for larval development (WHO, 2016b). Space spraying is appropriate for knocking out the adult life stage in densely populated areas or for a limited area and time span. It is not feasible for malaria vector control in most instances, although it is used extensively as an approach (fogging) in urban areas for dengue control, for example (Matthews, 2011). For malaria, however, the main vectors in Africa are a limited group of species that evolved in more open country with adaptations to humans as a key but not unique source of blood meals for biting females (White et al., 2011).

Box 1.1 What are mosquito vectors?

There are a number of human and animal diseases that are vectored by mosquitoes. The principal mosquito vector species considered in this study are in the *Anopheles* genus, although there are examples and lessons from the *Aedes* genus (which includes species that vector serious human diseases such as dengue, yellow fever, chikungunya and Zika). The *Anopheles* genus includes all of the species capable of vectoring the various types of malaria. Of the around one hundred Anopheline species that can vector malaria to humans, the key vector species in sub-Saharan Africa are those in the *An. gambiae* complex (s.l. or sensu lato); *An. funestus* is also an important secondary vector in some settings.

The researcher interviewed mosquito researchers working primarily with *An. gambiae* s.s. (sensu stricto), *An. coluzzii* (formerly known as *An. gambiae* M molecular form) and some laboratory strains of *An. gambiae* s.l. Other related species, such as *An. arabiensis*, may have been captured in field baseline studies. More details on these and other vector species can be found at VectorBase (https://www.vectorbase.org/), a National Institute of Allergy and Infectious Diseases (NIAID) Bioinformatics Resource Center.

Only female mosquitoes can bite, and only those already infected are able to transmit malaria. This means that a female mosquito must blood feed at least twice to transmit malaria: first to bite an infected person (or animal) – in order to become infected – and then, after several days, a second person to transmit the disease. Malaria is not transmitted to eggs laid by an infected mosquito or to male mosquitoes through mating. Because of this, additional care is taken with female mosquitoes and many areawide release programmes will seek to avoid release of female mosquitoes.

Some aspects of determining efficacy and safety of public health interventions, including vector control along with feasibility of delivery, are international and some are grounded in regional or even local area conditions. The World Health Organization (WHO) leads the

international process for evaluating new interventions for public health, or more specifically vectored human diseases, with inclusion of a new approach or technology as an official recommendation in guidelines being the ultimate endorsement (WHO, 2012a). The WHO evaluation process before recommending new health-related interventions can be categorised by the questions[6]:

1. Is it safe?
2. Does it work?
3. Does it work for me?

WHO endorsement is very important in the delivery of a new intervention, because most national vectored disease and mosquito control programmes are guided by the WHO guidelines and recommendations on related issues (Beier et al., 2008), even though working within their own relevant national authorities and legislative frameworks. Therefore, novel interventions are under scrutiny at global through to national and often regional or local levels. There is a need for vector control that is considered safe, effective and available at each of these points from macro to meso or micro levels.

Despite challenges to controlling malaria vector populations, the WHO was still stating fairly recently that malaria control could be enhanced 'through a concerted effort to optimise the use of currently available tools, **particularly vector control**' (emphasis added - WHO, 2015: p.7).

1.3 Why malaria continues to kill

National malaria vector control programmes in sub-Saharan Africa have relied upon only a few activities against mosquitoes, with long-lasting insecticidal nets (LLIN) being a key tool in recent years. Targeted residual spraying including inside houses (indoor residual spraying or IRS) is based principally on the concept of transmission from night-biting mosquitoes indoors (Coulibaly et al., 2015; Matthews, 2011). The reality is that malaria vectors are also outdoors biting and resting, which presents one of the key gaps in the current home-based technologies (Zhu et al., 2017; malERA Consultative Group on Vector Control, 2011). Vector populations are known to adapt to day biting when under control pressure (Russell et al., 2013). Larvicide and larval habitat control can be effective when the location of habitats is 'few, fixed, and findable' (WHO, 2013a; WHO Global Malaria Programme, 2012b: p.3). Recent research on

[6] The expression of the WHO approach in this manner arose from discussions based on the current publication at that time (WHO Global Programme on Evidence for Health Policy, 2003) within the MosqGuide Project, a WHO/TDR project run by Imperial College London and appeared in its unpublished *Module 4 Data Usage*. See Mumford et al. (2009) for more about that project.

male swarms has shown that targeting males during this localised behaviour can be very effective as vector control on the scale of a small village (Diabaté & Tripet, 2015). Improvements to these methods have been incremental, however, and insufficient to address the challenges. Trapping of adult mosquitoes, used mainly for monitoring of populations, can provide some control in small areas but is not appropriate for larger areas or national campaigns. Improvements in attractants and lures may make trapping more effective in the short term but will not have a significant impact on overall control programmes (Matthews, 2011).

At this stage in malaria vector control, small area control is insufficient or unsustainable. Furthermore, impacts of individual and small area interventions occur at the local level (Giardina et al., 2014), and do not always translate to a reduction of risk of malaria on the national scale. The reliance on individual access to control measures contributes to inequities within national programmes (Braveman & Tarimo, 2002). There are even greater inequities between countries, however (Miguel et al., 2018). Those countries experiencing internal political conflict, economic recession or large movements of populations due to these issues suffer a greater health burden in contrast to other, more stable countries in disease endemic zones (Head et al., 2017). The Global Technical Strategy for Malaria (WHO, 2015: p.8) further states that 'Given that reaching this level of coverage [required] will be operationally difficult, **further innovations in tools and approaches are needed** for elimination of transmission in areas where transmission rates are high; they are also needed in areas and for population groups that are presently hard to reach with current interventions' (emphasis added).

In this context, therefore, malaria continues to be a significant killer, with deaths and the costs of illness being most severe among children in sub-Saharan Africa. The Sustainable Development Goals (SDG) [7] specify malaria as a key health challenge, which exacerbates poverty and hampers development, following on the earlier Millennium Declaration by the General Assembly of the United Nations, which called for stopping and reversing malaria by 2015 (United Nations, 2000).

There has been meaningful progress against malaria. This century, after peaking around 2004, deaths in Africa due to malaria were decreasing annually. This is largely due to

[7] The SDG have been touted as 'the first universally agreed upon secular plan for the future of the planet and all people' (NASEM, 2016a: p.2). They are the result of three years of negotiation among all 193 member states of the United Nations (UN).

Goal 3.3, paraphrased as 'the end of malaria epidemics by 2030', falls under the higher level Goal 3. Ensure healthy lives and promote well-being for all at all ages (UN Statistical Commission, 2017; United Nations, 2015). The Target Malaria vision, a world free of malaria, is a goal similar to the SDG 3.3, as shown in Figure 1.1.

interventions aimed at the mosquito vector (insecticide impregnated bed nets, or LLIN as the preferred term, and residual insecticide spraying of houses) and drug treatment of infected individuals or priority groups (Howitt et al., 2012; Murray et al., 2012; WHO Global Malaria Programme, 2012a; WHO, 2011; Kilian et al., 2010). The expansion of these interventions put many countries on track for reducing malaria incidence by as much as 75% compared to earlier levels this century (WHO, 2015; WHO, 2005). Surprisingly, an escalation of currently recommended interventions to a level of 90% coverage[8] is still not expected to achieve malaria elimination in many countries (Walker et al., 2016; Griffin et al., 2010).

The WHO technical strategy for malaria concludes (WHO, 2015: p.5) that the 'gains achieved are fragile and unevenly distributed' or inequitable, with multiple factors posing barriers to success. Key among these factors are increasing insecticide resistance in mosquito vector populations and drug resistance to treatment of malaria (Hemmingway, 2017; Ranson & Lissenden, 2016; WHO, 2016a; WHO MPAC & Secretariat, 2015; Hemmingway, 2014; Ranson et al., 2011; Ranson et al., 2009).

It is now recognised that the progress of recent years was based on the 'imperfect application of imperfect tools' (Alonso & Noor, 2017: p.2532). Indeed, 2016 was the first year in over a decade that, in the words of the director of the Global Malaria Programme, Pedro Alonso, 'we can confidently say we have stopped making progress' (Maxmen, 2017: n.p.). Globally cases of malaria were at an estimated 216 million in 2016 with over 445,000 deaths, which represents an estimated 5 million more cases than the previous year (WHO, 2017a). Although the causes of this increase are not proven (Alonso & Noor, 2017), it is a setback that was anticipated. This is disappointing news at a time when there is a declared commitment to not only reduce cases but to eliminate malaria[9].

Figure 1.1 shows the researcher's summary of changes considered necessary to achieve malaria elimination, beyond those countries already certified as being malaria free (drawing on WHO, 2017b; Doumbia et al., 2012; Alonso et al., 2011). This includes the addition of **new, sustainable, cost-effective interventions for reducing malaria transmission**[10], which

[8] Universal coverage of LLIN is recommended.

[9] Elimination of malaria in this context refers to the end of malaria globally. The term may also be used to indicate a defined area is free of malaria.

Collins et al. (2019), with the researcher as co-author, addresses the scenario of eliminating the main vector species to the local, regional or even continental level as one means towards elimination of malaria.

[10] Target Malaria, a project that was significant source for the research presented here, evolved the consortium's mission statement from this statement, in bold, to a more specific one shown in Table 4.3.

could be new interventions for vector control, new drug treatments (especially those effective against resistance), and/or more cost-effective methods for preventative treatment of targeted populations.

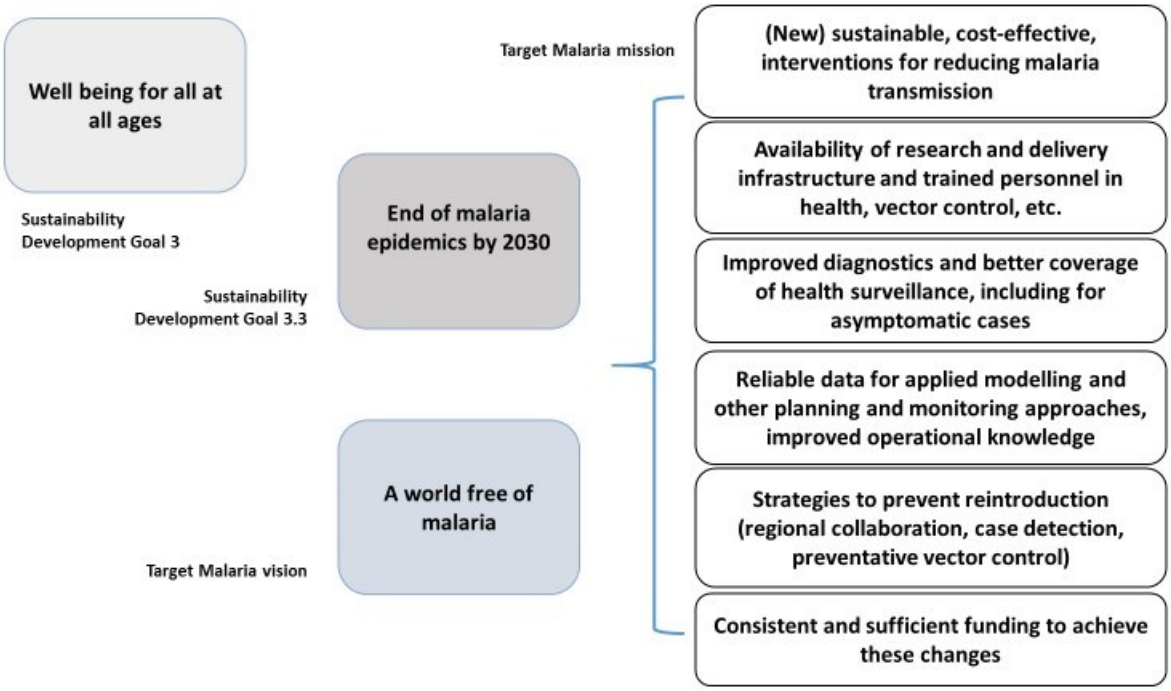


Figure 1.1 Changes that may be needed to contribute to a world free of malaria including new, sustainable, cost-effective interventions reducing malaria transmission

In all cases, researchers and practitioners (those carrying out mosquito control) agree that a combination of methods, integrated into a coordinated package, is the only way to succeed against malaria (e.g. WHO, 2017b; WHO, 2015; Doumbia et al., 2012; van den Berg et al., 2012; Alonso et al., 2011; Raghavendra et al., 2011). They also agree that additional interventions must be incorporated alongside the existing options from the planning stage onwards, in an integrated and coordinated manner. Integrated models that include epidemiology, economics, health systems and other key factors may result in different operational strategies and funding allocation than analysis at the level of individual interventions (Tediosi & Penny, 2016). This is particularly true under a policy to eliminate malaria, rather than a policy to reduce or delay disease incidence (Macias & James, 2015; Beier et al., 2008).

Vector control remains an essential part of any mosquito-vectored disease control or elimination programme, in tandem with other interventions such as drug treatment of the disease. Malaria elimination plans all include vector control as a significant component. Today

many believe that malaria can only be reduced or eliminated by the addition of a novel vector control intervention, in combination with the existing disease control efforts (Walker et al., 2016; WHO, 2016a; Sinden, 2015; Kittayapong, 2006). To win against malaria, there is a call for the international community to act quickly (Alonso & Noor, 2017: p. 2533): 'Faster innovation and smarter investments in research and development will accelerate the availability of new tools with proven efficacies'.

1.4 The complexity of introducing a novel intervention

The process if introducting a novel intervention for vector control is complex for a number of reasons. The international process for evaluating novel vector interventions as a category was only recently established. Existing national regulatory frameworks are generally not suited to truly novel interventions; nor are they always accommodating of areawide control. The use of any living organism as a product, such as by release of laboratory mosquitoes, presents complexity. Decisions regarding vector control extend beyond technical considerations to include social, ethical, political and funding concerns; sometimes societal perceptions have as much impact as evidence about potential risks and benefits. The novelty of the proposed interventions itself increases complexity, due to the lack of direct experience with the risks associated with a stepwise approach to research (Obonyo et al., 2011; Aultman et al., 2000) and potentially high levels of uncertainty regarding the delivery of the intervention. Finally, there are challenges to link vector control outcomes with impact on disease incidence throughout the early phase of research and field studies. The aspects of complexity unique to transgenic mosquitoes for this purpose are covered further in Chapter 2.

Box 1.2 describes what 'delivery of a novel intervention for vector control' means in the context of this study. Areawide control also may require the addition of multiple operational components, not only the introduction of a new technology. Box 1.3 explains the basic concepts behind areawide control and provides several examples of vector control innovations in development that would be delivered in an areawide approach, if successful and approved.

A WHO committee, the Vector Control Advisory Group (VCAG), was established in 2013 to consider proposed approaches that are based on new paradigms[11]. The intervention in

[11] The VCAG evaluates new vector control interventions when they are considered to be based on innovative paradigms (in contrast to innovative products based on established paradigms) (WHO VCAG, 2014). Insecticide treatment of walls, for example, is considered to be based on an existing paradigm regarding insecticide use, therefore the technique is evaluated by an existing committee and system (WHO Pesticide Evaluation Scheme, WHOPES, in this case).

The WHO develops recommendations on pilot studies or on health policy for national governments to consider and implement. After WHO guidance is completed, country policy should be aligned with any

development by Target Malaria, for example, fits this category of novelty (WHO VCAG, 2017a). In addition to novelty of the technology, the mode of delivery or field strategy for Target Malaria's future products is different from the current interventions using LLIN, IRS, use of larvicide or trapping. In most cases, such novel tools will challenge decision making in the existing national evaluation process.

Box 1.2 The delivery process for a novel vector control intervention

National governments may be asked to register new insecticides after international testing, evaluation by the WHO Pesticide Evaluation Scheme (WHOPES) or transfer study results following registration in key countries (e.g. the country of product production or a country in the same region of DEC). This works because the toxicology studies, in very broad terms, would be the same regardless of the location of insecticide use. Use of living mosquitoes in areawide control of a natural population, however, has been treated as something unique. It is true that genetics and phenotypic traits can vary within the same species, and therefore it is important to ensure mating compatibility between the transgenic mosquitoes to be released and the target population. Some studies, however, may be duplicative if repeated in similar settings. Macias & James (2015) raise this important issue of accepting study results from other locations, or transferability of results. The time required to repeat containment studies, rather than simply introgressing the modification into the local population, is time possibly better spent on addressing field issues. This requires, however, that the studies done are considered adequate by DEC governments and stakeholders.

At present, delivery of transgenic mosquitoes as a vector control intervention will require import and research permits through the National Biosafety Authority (NBA, used as a generic term for any country's regulatory authority). This begins with repetition of studies in containment facilities in each DEC, along with baseline studies of the target mosquito populations in the field. Confined field studies, and possibly pilot programmatic ones, will be completed and results analysed before the inclusion of an intervention in the ongoing national mosquito control programme is even considered. Further to this, funding for such an intervention will be analysed and may not be easily freed up from the existing expenditures, even if the novel intervention is more cost-effective. Some of the complexities of the final stage of delivery are discussed by Cisnetto (2017), also based on the Target Malaria consortium countries.

new developments or recommendations and, for products such as pesticides, national product registration is required (WHO VCAG, 2015).

Box 1.3 An areawide approach to vector control

Areawide control refers to an approach that attempts to control an entire population (over a specified geographic area and time period) rather than using methods that control individual insects (Lindquist, 2000). Areawide control of mosquitoes may be either through reduction of the population (e.g. by using an antagonistic fungus that will be carried through the population or through release of sterile males) or replacement of the population (e.g. to a population altered through an introduced infection or genetic trait). Both mechanisms present significant paradigm shifts for vector practitioners, regulators, health officials, funders and other decision makers accustomed to working on the level of the individual or small scale (Alphey et al., 2010; Whitten & Mahon, 2005).

Several innovations that may be used in areawide control of Anopheles mosquitoes are progressing to field application. GM fungus (Wang & Jacobs-Lorena, 2013) or bacteria (Wilke & Marrelli, 2015) are examples of a paratransgenesis approach to areawide control that would not require additional application for each vector species. Natural infection of malaria vector species of Anopheles with various strains of *Wolbachia* appears to be provide a promising alternative (Jeffries et al., 2018), but the extent to which this infection reduces malaria transmission is not yet established (Gomes & Barillas Mury, 2018) and technical and operational challenges require attention before this approach can be replicated (Niang et al., 2018).

Okamoto et al. (2014) proposed that transgenic mosquitoes, capable of vectoring dengue, be modified to resist transmission without linking this trait to a gene drive (described further in Chapter 2). They demonstrated using models that sufficiently high numbers of these GM mosquitoes mass reared and released would spread through a native population in a manner reducing the disease. This approach would require regulatory approval through the same channels of other biotechnology, but avoid the socio-political pitfalls of introducing a gene drive to open field populations.

Areawide control that relies on release of lab mosquitoes mating with targeted field populations has its greatest impact when resources can be allocated and planned beyond a short term horizon, and each component of the approach is well coordinated and delivered in a timely manner (Lindquist, 2000). This requires some autonomy for the unit or individuals leading such a campaign, and may complicate existing mandates and institutional roles. Hendrichs et al. (2007) add the components of communication with stakeholders and ongoing evaluation as further critical factors. A successful vector control programme also requires the capacity and resources to achieve the correct mix of vector control interventions (WHO/TDR, 2016; WHO, 2012b), a challenge already identified in the integrated vector control literature (e.g. Sinka et al., 2016; Chanda et al., 2008). This paradigm of areawide control of mosquitoes has been entering policy deliberations, however. For example, the WHO process for recommending novel approaches using areawide control against Aedes mosquito vectoring spp has been accelerated by the emergency health issues related to Zika (WHO, 2016b).

In many DEC, the national evaluation and regulatory pathway to introduce a new vector control intervention based on insecticides, including larvicides, is broadly established[12], although frequently starting from a national framework for agricultural use. If national frameworks do not cover pesticide registration for public health use, then international guidance is well established and recognised by nearly all countries. For example, until recently in West Africa pesticides for public health, including against mosquitoes, were regulated by referencing of WHO decisions rather than a national or regional process; but a public health use registration process is now underway (DPV & OMS, 2010; Sahelian Committee for Pesticides, 2009). There is also a clear pathway for introduction of new malaria treatments[13] (drugs and combinations of medications) and vaccines[14]. This is not the case, however, for many of the currently emerging innovations in vector control. The national process is not oriented towards an areawide approach, which tackles entire populations of a pest species at the same time.

Release of living organisms to combat a pest species presents a special case for regulation in all instances (Quinlan, 2014), but the use of mosquito releases poses particular issues in terms of risk assessment and regulation (Quemada, 2015). Despite these challenges, a number of innovative technologies for vector control are in development and, in the case of *Aedes* species (spp. for plural), are already included in national programmes (as noted in section 2.1). Several of these technologies involve the release of modified mosquitoes to target their own species in the field. Technologies under study or in field trials for mosquitoes are based on novel symbiosis, paratransgenesis, transgenesis or genetic modification, all of which either have undefined regulatory pathways or fall within an additional set of production process specific procedures for consultation and approval (Quemada, 2015; Mumford, 2012). Transgenic insects introducing a self-sustaining trait present even further complexity (Costero-Saint Denis et al., 2016). The characteristics of some of these innovations are described in recent compilations (Adelman, 2015; Benedict, 2014), including issues specific to gene drive which were considered by a consensus committee organised by the National Academies of Sciences, Engineering, and Medicine (NASEM, 2016b).

[12] Despite a decision framework, 'Many countries, even those with longstanding vector control programmes, lack capacity to regulate the availability and use of pesticides for vector control purposes' (WHO, 2013b: p.1).

[13] Historically it has not been feasible in DEC to use preventative prophylactics, although targeted use is employed for some groups, e.g. pregnant women (WHO Global Malaria Programme, 2012a). Therefore, drug interventions refer to post infection treatment, in this study.

[14] Although the regulatory pathway for vaccine trials and approvals is generally established, seeking to affect 'herd immunity' or aiming for different types of endpoints do not fit well in the existing regulatory frameworks (Birkett et al., 2013).

The efficacy of interventions in public health for disease control are often evaluated against disease incidence rather than only the reduction of target vector populations. This presents additional challenges when health systems (including diagnosis, treatment and reporting) are weak, data are lacking, and analysis is uncoordinated. Also, for early phase research, impact on disease also implies field application of an intervention to a scale at which such an impact could be detected, which may not be acceptable until several questions regarding safety are answered under more controlled conditions.

If a disease incidence or epidemiological impact (rather than only an indicator of impact on vector populations) is expected in initial trials, a raft of other players is involved. There are multiple complicating factors to demonstrating impact on malaria incidence, such as inadequate health systems, lack of intersectoral coordination, and mismanagement of programmes (Aregbeshola, 2016; Macias & James, 2015; Beier et al., 2008). Misdiagnosis of febrile diseases, for example, is a common barrier to understanding malaria incidence (Nankabirwa et al., 2009; Chandler et al., 2008).

With novel technologies, decisions are not limited to scientific and economic criteria (NASEM, 2016b; Antonelli et al., 2015; Nuffield Council on Bioethics, 2012). There are social and risk communication ramifications, since no one wants to be 'the first' or have his country serve as the proverbial 'guinea pig'. Choices may be skewed by public perception of and concerns with new technologies, even if the concerns are lacking evidence of harm or a pathway to harm or are not supported by established benefit/risk concepts. This has been observed by the researcher in the national- and state-level deliberations about the choice between two novel approaches to *Ae. aegypti* control based on either releasing a laboratory-induced infection of mosquitoes that is likely to persist and spread in the environment as a novel symbiosis (not previously in that species) or using a continual release of genetically modified (GM) mosquitoes for sterile insect technique (SIT), which by definition are designed to not persist in the environment (Flores & O'Neil, 2018; Carvalho et al., 2015; Alphey et al., 2013; Christodoulou, 2011). While both technologies offer viable solutions for the gap in control of that vector (Dickens et al., 2016), in some sectors the comparison has turned into a debate between 'natural' and 'GM' rather than the traditional criteria of efficacy, safety, feasibility and potential impact based on risk assessment related to avoiding persistence in the environment for novel releases (Quinlan, 2014; FAO/IAEA, 2006).

Government decision makers responsible for reviewing innovative technologies of this nature face complex and highly technical choices. Typically, a decision to approve import or to grant a permit for field testing for something truly novel cannot be made on the basis of acquired direct experience alone. Appropriate, and hopefully technology-neutral or balanced, advice

and training may be needed to supplement existing regulatory capacity. Similarly, those developing the health interventions outside DEC are often not familiar with the target country context for either research of this nature or the regulatory decision making process overall.

Each of these aspects of complexity require policy decisions, operational decisions, staffing decisions and so forth. To break down these complexities, the researcher identified the various participants in the process of evaluation and decision making moving from an initial discovery laboratory (presently presumed to be external to the malaria-affected countries, as is the case for Target Malaria), through the phase of import to and studies in containment in partner laboratories in sub-Saharan Africa, up to the point of application for field studies. An analysis of the decision makers appears in Chapter 2.

1.5 This research

This thesis describes aspects of the early phase of delivery of a novel intervention for vector control aimed at elimination of malaria. It assumes an appropriate technology has passed the proof of concept (to the degree that the theory works in the lab, while the field application would be a proof of the principle; e.g. James et al., 1999) and has been shown, at least within the limitations of the setting, to be safe and efficacious (Is it safe? Does it work?), at the level of a laboratory setting. Such a technology is therefore in the process of being evaluated for its appropriateness in the target setting and context (Does it work for me?), although several issues regarding safety and performance also are dependent on local factors and require additional study at target sites.

The research presented in this thesis considers how novel interventions for reducing malaria transmission are delivered, for the example of genetic strategies using transgenic mosquitoes. The researcher examines the decision process, focusing on how availability of infrastructure, trained personnel and various aspects of capacity are considered.

The researcher aimed to identify or develop learning frameworks to support the evaluation and early stage delivery of this type of novel intervention. She also sought to test the initial uptake of the decision support, albeit on a very small scale. The objective of the research was to improve effectiveness of the decision process surrounding delivery of a novel vector control intervention, while allowing different decision outcomes due to differing national objectives, priorities or contexts.

The overarching question posed in this study is:

How can learning systems improve the process of decision making around the delivery of a novel vector control intervention?

This question can be better answered with the following subquestions (with chapter numbers that address each):

- Is there a best practice for external innovators or discoverers of a novel intervention to find appropriate research partners in disease endemic countries? (Chapters 5)
- Will regulators be supported to make more effective decisions about import and use of novel interventions by using decision frameworks? (Chapter 6)
- How does benchmarking a point of readiness for use of containment facilities support effectiveness of this first step in the delivery of the intervention? (Chapters 7, 8)
- Is a product stewardship approach to identity maintenance and data management necessary to support decisions about safety and efficacy in containment studies, moving towards field studies? (Chapter 9)
- Can biosafety objectives and quality assurance in the containment phase be achieved more effectively if using harmonised procedures and tools for research in disease endemic country settings? (Chapters 8, 10)

The approaches to and methodologies for considering these subquestions are laid out in Chapter 4. Finally, the findings and discussion of how these various lines of study contribute to the pathway towards effective decision making in the delivery of a novel vector control intervention are presented in Chapter 11.

The thesis reporting on this research is organised into three broad sections:

- The Problem: context, participants and possible approaches
- Findings: study results and discussion of findings
- Conclusions: discussion of the study question and recommendations

The chapters in the first section (Chapters 1-4) cover the context of vector control in general (Chapter 1) and for the specific case of novel vector control (Chapter 2), as well as some general observations about innovation and novel interventions in related fields (Chapter 3). The types of decisions, groups of decision makers and the geopolitical scale are discussed in Chapter 2. The study is conducted using a combination of methodologies, described in Chapter 4 and in the chapters where reported.

In the second section (Chapters 5-10) a series of decision support and learning frameworks are described, and their development or adoption and validation are discussed. The outcomes

and lessons learned from trialling these are covered in this section. Finding well suited DEC research partners, Chapter 5, may be supported with defined criteria. Regulatory decision making for these scenarios is considered in Chapter 6. Laboratory and field studies on transgenic mosquitoes or other novel vector control approaches require robust procedures, advanced research capacity and additional facility preparation beyond that needed in other types of mosquito research, as discussed in Chapters 7, 8, 9 and 10.

In the final section of the thesis (Chapter 11), the findings are discussed, and specific recommendations are made to potential users of the frameworks. Finally, more general conclusions about novel interventions are shared, along with observations about additional research considerations. Relevant literature is cited in each chapter, with a complete bibliography appearing after Chapter 11. Appendix 5 is a 'road map' for the potential user of the frameworks or tools described in the thesis. Publications resulting from this study are listed at the beginning of the thesis. There is only one of the publications by the researcher resulting from the study which is not open access (available at no cost online); that one is reproduced with permission in full in the Appendices.

The current research context is of very limited uptake of this type of novel intervention for malaria control, and continual change and development in those interventions still under study. This does not encourage randomised studies on decision making and the impact of support frameworks, but other methods for testing theories were found to be applicable (shown in Table 4.3). Decision support at this early stage of roll out to African sites also can produce more impact in absence of other guidance or existing procedures. Careful planning can result in a framework and learning system that, when fully embraced, will allow decision makers to continually improve the decision process by taking advantage of the experiences in the DEC faced with the choice of employing this type of novel intervention.

1.6 Summary of the introduction

This chapter lays out a general context for malaria vector control and novel interventions during the period of the research: Why is vector control important? Why are novel interventions needed, given advancements in prevention and treatment of malaria in particular? Why is the process of introducing a novel vector control intervention so complex? Much of the chapter is relevant to any type of novel intervention that would reduce malaria transmission.

The next chapter provides more details around the question: What is unique to the introduction of transgenic mosquitoes? The scope of this study is on vector control as a means to reduce malaria transmission. Use of transgenic mosquitoes is only one possible novel intervention for

vector control, but it is the one considered in more depth by the researcher. An outline of the other chapters is provided in Chapter 1, as a guide to reading and using the thesis.

The researcher presents published literature with expert opinion and study results that indicate the need for additional vector control approaches. Novel vector control should supplement an integrated approach in conjunction with existing interventions. The introduction of novel technologies or interventions presents complex challenges across various disciplines. Decisions related to introduction of a novel intervention in vector control are not limited to technical criteria, as public perception, economic impact, implementation issues and many other criteria come into play. Furthermore, the regulatory pathway is often not defined or is ill suited, particularly when self-sustaining interventions are to be employed. Many of those tasked with making decisions, along the steps from discovery to field studies and eventual programmatic use, will have no direct experience with the novel interventions in question.

Chapter 2. Transgenic Mosquitoes as a Novel Intervention for Areawide Vector Control

2.1 Background for use of genetic strategies to control mosquitoes

For decades, species-specific areawide insect control has been used for suppression and eradication campaigns, principally for livestock and agricultural pests (Klassen & Curtis, 2005; Robinson, 1976). Traditional sterile release pilot or field programmes in Africa, for example, have taken place against various species of tsetse fly (Bourtzis et al., 2016), New World screwworm, Mediterranean fruit fly, date moth, codling moth, diamond-back moth and vector species of mosquitoes (*An. arabiensis* and *Ae. aegypti*) over some time period in several African countries including Burkina Faso, Ethiopia, Kenya, Libya, Mauritius, Morocco, Nigeria, Reunion, Senegal, South Africa, Sudan, Tanzania and Tunisia. Box 1.3 defines areawide control as a concept. Most if not all of these initiatives have been supported technically, if not also financially by the Joint FAO (Food and Agriculture Organization of the United Nations)/IAEA (International Atomic Energy Agency) Programme, Division of Nuclear Techniques in Food and Agriculture.

Curtis (2006) and Dame et al. (2009) document historical uses of genetics for vector control and Klassen (2000) describes some of the earliest areawide mosquito programmes, including one in West Africa using larval control based on research conducted over a hundred years ago. As early as the 1940s, the use of genetic factors of disease vector mosquito species has been considered an important approach to add to vector management (as described in Curtis, 2006; Curtis, 1968). Genetic approaches have employed radiation-induced rearrangements, sterility induced by irradiation and chemosterilants (Gato et al., 2014; Gato et al., 2013; Dame et al., 2009), natural symbionts (Bourtzis et al., 2016), paratransgenesis (Mancini et al., 2016) and other methods. Such programmes against mosquito populations targeted with a sterile male release approach (Gabrieli et al., 2014; Klassen & Curtis, 2005: Table 3; Benedict & Robinson, 2003), had rarely passed the research stage or pilot scale for releases up to a decade ago (Wilke et al., 2009). Various genetic strategies for mosquito vector control have been developed in recent years (McLean & Jacobs-Lorena, 2016; WHO/TDR, 2010; Sinkins & Gould, 2006; Christophides, 2005), however, and some are currently in a field release phase.

There are now several European cities or areas where sterile mosquitoes are being or have been used, in combination with other measures, to control incursions of *Ae. albopictus* (Bellini et al., 2013). Recent areawide approaches against mosquitoes have reached all regions where mosquitoes are vectors, supplementing the historical experiences noted above: the Americas (e.g. Carvalho et al., 2015 [Brazil]; Harris et al., 2012 [Cayman]; Facchinelli et al., 2011 [Mexico]; Beech et al., 2011 [Brazil and Panama]); Europe (Bellini et al., 2013; Bellini et al., 2007); Asia (e.g. Zhang et al., 2018; Branigan, 2015 [China]; Lacroix et al., 2012; Lee et al., 2013; Lee et al., 2009 [Malaysia]; NEA, 2016 [Singapore]); the Pacific (e.g. Bourtzis et al., 2016; O'Connor et al., 2012 [French Polynesia]) and Australia (Jiggins, 2017; Eliminate Dengue, 2015).

Early studies with an induced translocation strain of *Ae. aegypti* in Kenya (Lounibos, 2003; McDonald et al., 1977) demonstrated capacity to conduct such research in Africa. This example reached field testing, but the possible impact of chemosterilants on the environment was a major factor for stopping further efforts along this line at the time (Dame et al., 2009). Interest in applying genetically-based advances has been shown in sub-Saharan Africa, (Ferguson et al., 2008), including the research consortium working as Target Malaria[15], while acknowledging that further steps are needed for broad acceptance (Okorie et al., 2014; de Souza et al., 2013; Marshall et al., 2010) – as has been necessary in other settings and for each new innovation (Andrade et al., 2016; NASEM, 2017b).

Throughout the development of the novel genetic strategies for mosquito control, the Special Programme for Research and Training in Tropical Diseases (TDR), hosted by the WHO, has played an essential role in coordinating interactions among the leading experts in related biological, social and regulatory sciences and moving these discussions forward (WHO/TDR and FNIH, 2014; WHO/TDR, 2010; Knols & Louis, 2006; WHO/TDR, 1991). Over the past 15 years, an initiative under the Grand Challenges in Global Health (GCGH) of the Bill & Melinda Gates Foundation (BMGF)[16] led this approach towards implementation. This funding and the focus on a set of priorities in global health changed the landscape for developing new interventions against vectored diseases (Matthews & Ho, 2008).

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[15] More information about this project can be found at https://targetmalaria.org. This thesis is the author's interpretation and understanding of the reported work, however, and is not representing any authorised version of events.

The ability of gene drive to deliver a selected and desirable heritable trait for vector control (Burt, 2014; Galizi et al., 2014) is the basis for work in Target Malaria.

[16] This initiative is described at http://gcgh.grandchallenges.org/challenge/develop-biological-strategy-deplete-or-incapacitate-disease-transmitting-insect-population

The GCGH goal to control insects that transmit disease endorsed the concept that genetic and heritable biological control strategies for disease-transmitting insects could lead to a transformation in disease control (Burt, 2003). The resulting programme, managed by the Foundation for the National Institutes of Health (FNIH)[17] and titled 'Vector-based Control of Transmission: Discovery Research' (VCTR)[18], contributed to advances with innovative products appropriate for reduction and control of disease-vectoring mosquito species, including some employing laboratory reared transgenic mosquitoes.

A timeline of some of these initiatives supporting safe deployment of transgenic mosquitoes is described by the researcher as co-author in Beech et al. (2011) and Beech et al. (2009a). Despite this long history of scientific discussion and debate, the researcher has observed a sense of surprise even within the research sector at how quickly technologies were ready for testing and to move to field use. We can expect this pace to quicken even further, as discussed in section 2.3.

2.2 Stepwise approach to address risks of field release of novel interventions

Established best practice when working with any technology based on a novel organism that must be released into the environment in order to perform its function is to learn as much from laboratory studies in containment as possible regarding safety and efficacy, before proceeding to confined field trials and open release studies (WHO/TDR & FNIH, 2014; Marris & Jefferson, 2013). Box 2.1 explains the difference between containment and confinement, as defined by various sources. Predictions based on comparable situations, organisms or traits may be extracted from literature and modelling, to complement such studies.

Employment of genetic strategies for vector control adds further possibilities to progressing through a stepwise approach, including molecular containment, localised drives, reversibility and studies with inserted gene drives turned off to explore the ecological impacts without the drive operating (Mathematical Ecology Research Group, 2017; Akbari et al., 2015). Most guidance lays out the differences from a risk perspective between genetic strategies that may not persist in the environment and those that are self-sustaining and/or are designed to persist.

[17] Other solutions pursued under the GCGH programme are noted in this announcement: http://fnih.org/what-we-do/major-completed-programs/grand-challenges-in-global-health

[18] http://www.fnih.org/what-we-do/current-research-programs/vctr-discovery-research

Box 2.1 Contained vs confined in the stepwise approach

Containment is defined in related European Directives as 'to limit the contact [in this case of the GM organism] with and to provide a high level of safety for, the general population and the environment' (Directives 2001/18/EC and 2009/41/EC; European Parliament and Council, 2001; 2009), whereas the United Kingdom (UK) law defines containment in terms of physical, chemical or biological barriers (UK Parliament, 2000). A discussion of other possible differences between the terms, or use of terms, 'containment' and 'confinement' appears in WHO/TDR and FNIH (2014).

Mosquito research facilities (sometimes called insectaries, although that could refer to a specific portion of a research facility) may be entirely within containment or may have portions segregated to provide containment at a set, authorised level. Because isolation is one of the main aspects of containment, all activities relating to the studies in containment will need to occur within the containment area(s), for example: establishment of mosquito colonies, rearing of successive generations to achieve stock maintenance of colonies or strains needed over the period of the permit, studies using the colony mosquitoes and termination of the colonies when the studies are complete, or the permit authorisation period has ended. Unique aspects of containment labs for mosquitoes and other arthropods have been described in a recent guide by the Institute of Safety in Technology and Research (ISTR, 2017). Containment is generally considered to be achieved by physical features, complemented by operational procedures.

Confinement, on the other hand, relates to the isolation of the study strains or individuals through various means, or a combination of measures. This could be physical, such as a large cage either indoors or outdoors, or biological, such as by using a strain or trait that will die out or disappear from the population within a defined number of generations (non-persisting). Some consider ecological or geographic barriers also as legitimate confinement. Ecological confinement might be, for example, if a study took place in an area where natural seasonal weather would kill off any persisting individual mosquitoes or in a valley surrounded by mountains where the species does not survive. Geographic confinement may be along the edge of a species' natural distribution. The most commonly cited example is an island, surrounded by water without other islands nearby. In all cases, however, the proximity to an area (or season) where the species could survive and the possibility of emigration and immigration of mosquitoes to the site are significant considerations.

Those designed to rapidly replace a population with altered genetics, essentially replacing a population's native genome, are commonly referred to as 'gene drive'[19].

[19] Gene drive is a term relating to use of mechanisms to move particular genes, or portions of DNA, through a population in a non-Mendelian manner, so that more than the usual chance of 50:50 inheritance through mating occurs, thereby increasing the incidence of the driving element over time. These mechanisms occur naturally in the environment and have been referred to as selfish genes (Burt & Trivers, 2006). Gene drive has been harnessed in recent years as a means for delivery of a desired

International guidance, such as that from the International Plant Protection Convention (IPPC), about release of living insects for control of unwanted, locally established insect populations historically focused on whether the species to be released was considered native or exotic (e.g. IPPC, 1996). The general consensus, however, has shifted to consideration of risks posed by novel traits, rather than simply the region of origin of the introduction or the method for development in cases of modification (Kenya NBA & ISAAA-AfriCenter, 2019; Quinlan et al., 2006; IPPC, 2005a; Quinlan et al., 2003). Some countries continue to employ a parallel system for evaluating GM organisms, but regulation based on novelty of traits (versus originating technology) does exist – principally in Canada (Smyth, 2017). Countries where there is serious discussion about adapting the regulatory framework towards biorisks versus evaluating based on genetic medication include Kenya, Uganda, Malawi, South Africa, and Nigeria (Tonui, pers. comm., 2019), as well as Ghana (Okoree, pers. comm., 2018).There seems to be a further shift by policy makers in some countries to consider benefits of intentional introductions of biological material, against the risk (Heimpel & Cock, 2018; Wambugu, 2014; EFSA, 2013).

In contrast, others argue that the issues arising from novel characteristics, in particular from gene drive, may require different criteria for evaluation in stepwise studies. Marshall & Akbari (2015) describe the design characteristics to achieve an effective gene drive system and discuss the economic effectiveness of such an approach. By contrasting existing technologies against their criteria, other aspects of effectiveness linked to a gene drive approach are explored (Marshall & Akbari, 2015). Ostera & Gostin (2011) considered the issues relating to a new technology such as gene drive to be so unique as to call for a new international convention specifically addressing novel vector control. Others consider the existing guidance such as for risk assessment to be applicable to all current technologies, given that all guidance has indicated criteria for evaluation and decision making to apply on a case by case basis – implying that all cases can fit within the guidance frameworks by adjusting the estimated risk or management according to the novel traits (Turner et al., 2018; Quinlan, 2014).

Various international guidance documents now propose regulatory and development pathways for introduction of genetic strategies in mosquito vector species control. For example, an Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management was convened based on a mandate from the Parties to the Cartagena Protocol on Biosafety to the Convention on Biological Diversity (AHTEG, 2012; AHTEG, 2010), hereafter referred to simply as the Cartagena Protocol, to review and elaborate further

trait by linking portions of DNA with the driving mechanism. Esvelt et al. (2014) show a range of uses of gene drive including for conservation purposes.

voluntary guidance from the Protocol's annex for risk assessment to more specifically address high interest cases, including transgenic mosquitoes, when shipped across borders and for release. Training materials were prepared to support the development of risk assessments at the national level (CBD, 2014). This multi-year expert group process was completed in 2016 after the final report (CBD, 2016) was presented to the Conference of Parties (see also http://bch.cbd.int/onlineconferences/ra_guidance_references.shtml).

While these guidance documents are relatively new and untested, they are rapidly gaining recognition as authoritative resources (James et al., 2018; WHO/TDR & FNIH, 2014; EFSA, 2013; WHO/TDR, 2010; AHTEG, 2010; Benedict et al., 2008)[20]. One fairly unanimous conclusion is that a phased approach, beginning with studies in a containment facility and using confinement in early field studies, allows for more familiarity and experience for all participants in the process prior to field studies, thereby addressing one aspect of the novelty.

The associated stepwise reduction of uncertainty, through collection of additional data and analysis, may support understanding and assessment of both the possible hazards and the probability of these occurring in later phases, so that studies and biosafety or other risk management measures may be adjusted in response. On the other hand, additional experience or data may lead to new study questions or previously unidentified questions, which then begins the cycle over again in the laboratory, at least for those specific points. Another possible outcome, of course, is that safety is not clearly demonstrated in early studies. This would indicate that the technology should not progress further along the stepwise continuum, since exposure to the public and environment increases as well. Specifics of the case would determine whether further research in containment is appropriate or not. The tension at this point is that one may not observe the same outcome in a laboratory that is predicted in a model (Valerio et al., 2016), nor the same phenomena in a small study as could emerge in larger field studies[21].

Stakeholder input along the process of delivery of the novel intervention may also result in this loop back to address questions that are more amenable to laboratory research in the first

[20] In most instances, the guidance documents specific to genetic strategies for mosquito control were published after the point of convergence with this study, and therefore they have had varying roles in informing the study, or to the contrary, the work carried out in this study informed them.

[21] In the case of gene drive, this has led to a parallel research track of remediation or 'recall' using other molecular tools to counteract any unanticipated outcomes. Guidance on this line of research recommends this approach (Benedict et al., 2008), while also emphasizing options for incorporating safety into the development (James et al., 2018). Molecular approaches that could restrict gene drives spatially is one example of this built in approach (Dhole et al., in press). Marshall & Akbari (2018) call for research on this safety measure to be linked closely with ecological studies as well.

instance, or easier to study in that setting (Mumford et al., 2018). Although considered best practice, there have not been sufficient cases of full progression through the stepwise approach to field deployment for a proper study of the true advantages in relation to the resources required and delayed potential benefits from the intervention. The approach has been endorsed conceptually, but would benefit from further validation.

The researcher created Figure 2.1 to show the typical sequence of the recommended stepwise approach, which is to answer study questions at each step against previously considered thresholds or criteria, and then move on to the next step when appropriate. It is worth noting that the first step of studies in containment for transgenic mosquitoes is due to the lack of experience rather than any identified hazard, unlike for infectious disease or pathogen research. Figure 2.1 also clarifies that completion of initial studies in the DEC containment laboratory does not mean an end to activities there. In most instances, because the transgenic strain will continue to be regulated as a research organism until a commercial exemption or an open field permit is granted, the supply of mosquitoes for studies in the confined step and small field studies will necessarily come from the containment facility. This may even be the case for a pilot programme, depending on the size of the facility and of the pilot. Therefore, proper preparations for this containment laboratory establish the foundation of delivering a novel intervention from laboratory to field.

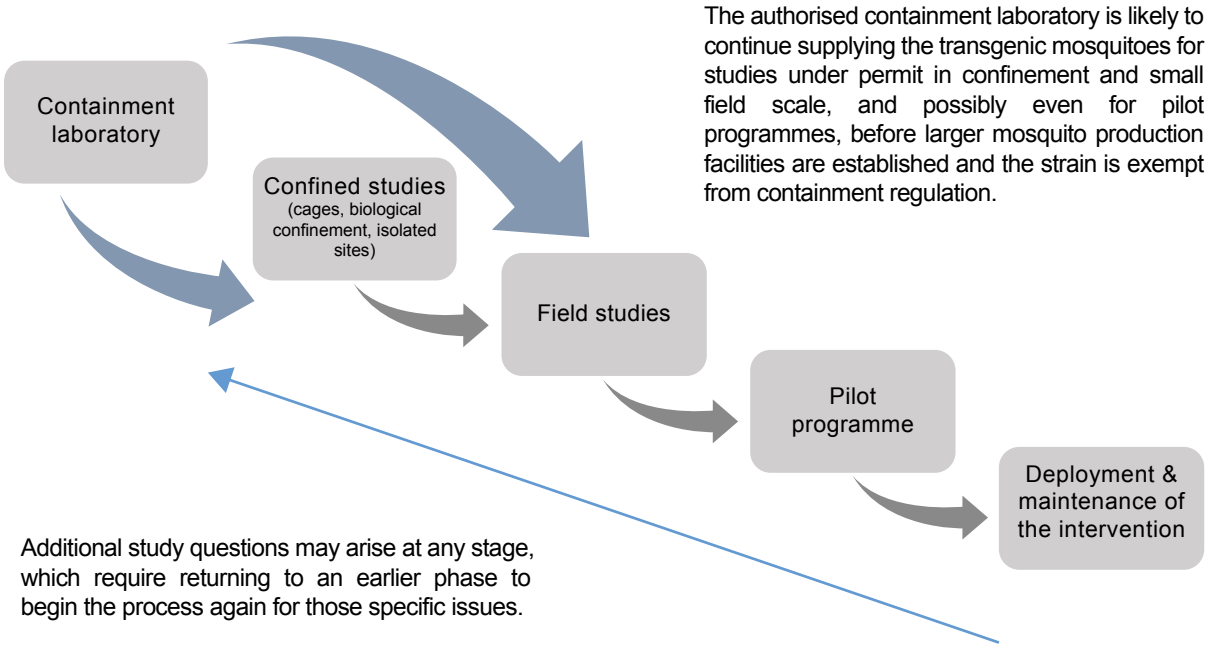


Figure 2.1 A phased approach to testing novel interventions for mosquito control

The same containment facility may play a role in research and development (R&D) and ongoing monitoring to determine and maintain the efficacy of the intervention, to conduct small

studies for operational improvements and possibly even to prepare the next generation technologies for the same intervention, i.e. additional strains of transgenic mosquitoes, anticipating possible development of resistance or reduction in performance. Such a laboratory will continue to support surveillance and monitoring of field activities, as well.

For mosquito research, the scale-up from initial laboratory studies could include working with larger colonies within containment facilities, small cage and larger cage studies either within laboratories or outdoors, and field studies with biological or geographical confinement when physical confinement is not feasible (NASEM, 2016b; Adelman et al., 2017b; WHO/TDR and FNIH, 2014; Facchinelli et al., 2013; WHO/TDR, 2010; Benedict et al., 2008). As described by the researcher and co-authors, containment studies allow for additional data about components of risk to be collected, to support decision making in regard to moving on to the next step (Mumford et al., 2018). Different stressors, complexity and scale limit the value of larger indoor cage studies, but they are important to parameterize models as well as provide stepwise data on key questions (Facchinelli et al., 2019).

Because of the novelty of genetic strategies for mosquito control, it may be important to design studies that will not only answer the questions aimed at progressing along the step wise approach, but also those that can reduce uncertainty related to lack of knowledge, unease due to lack of familiarity or similar. For instance, if there is societal concern, it is even more important to demonstrate the effectiveness of the risk management measures. This should include evidence of the effectiveness of the containment measures themselves, which may be of particular interest to regulators.

In addition to increased knowledge about the organism and the risk management, issues of feasibility, capacity to deliver (timing, quantity and cost), and performance under field conditions or with any local constraints in infrastructure or resources, stakeholder acceptance, and other localised criteria may be explored along the path of the stepwise approach, before a novel intervention can be integrated into an operational public health programme[22]. (This is equally true outside of Africa, as Kohl et al., 2016, describe for Europe.) These components relate to the third question of localisation in the WHO decision process described in Chapter 1 (Will it work for me?) but rely on national or local regulatory and research contexts to evaluate

[22] When these factors should be taken into account or included as study questions is not universally agreed. An unpublished study on efficacy of a range of novel vector control technologies under development revealed that most of the discoverer researchers contacted had not considered field efficacy criteria during the period of laboratory proof of concept of their approaches (Ng & Quinlan, 2013). This characteristic is probably changing with researchers having more experience with DEC settings and learning from DEC partners.

the results. As Wambugu states (2014, p.9): ‘the biosafety policy framework is a political process by design’.

Even beyond the WHO evaluation questions, national decision makers will need to gain familiarity with the new aspects of the innovation in order to feel confident to take final decisions, which is another reason to follow a stepwise approach. These individuals will face local stakeholders on a routine basis and must be prepared to defend decisions with clarity and conviction, whether approving or rejecting the novel intervention (Quinlan et al., 2016a; Wambugu & Kamanga, 2014). The first applications to reach regulators might be for each step of the phased process individually, or for single research strains, to support this process of familiarisation as well as the technical evaluation. With more experience, applications could become more streamlined. For example, in Brazil a research facility may obtain a permit for a research line, providing an annual report is provided on any studies carried out at that level of containment (see Library of Congress, 2015, for summary in English). Experiences with biosecurity challenges in Europe have led to the recommendation of forming ‘networks of experience and technical excellence’ (Mumford et al., 2017) to complement national capacities and fill gaps encountered in time-sensitive situations, such as to design field surveillance or for an application for import awaiting regulatory review. Other ways to support the capacity building process are discussed in Chapter 10.

2.3 Rapid changes in available technologies and related decisions

The amount of published literature on genetic strategies against mosquito vectors has increased considerably over the past five years, due to numerous recent publications regarding related research and also emerging lines of research related to social, regulatory and other factors supporting delivery of these technologies. The technologies currently under study for vector control embody a range of mechanisms and traits for achieving impact (e.g. Gantz et al., 2015). One approach is to introduce a desired characteristic to the native mosquito population, either to replace the population or reduce it, using a drive mechanism (Esvelt et al., 2014; Galizi et al., 2014; Burt, 2003). The United States (US) NASEM hosted a series of webinars and convened a working group specifically charged with reviewing technologies using gene drive, which underlies some of the strategies for novel interventions in vector control under development (NASEM, 2016b).

The example of one method of insertion of a gene drive is given by Ledford (2015: p.20 in chapeau), who states that this new gene-editing technology ‘is the biggest game changer to

hit biology since PCR' (polymerase chain reaction, an inexpensive way to sequence DNA). Indeed, the emergence of the CRISPR (clustered regularly interspersed palindromic repeats)/Cas9 (CRISPR associated protein 9) gene editing technology could revolutionise developments of transgenic mosquitoes (e.g. Gantz et al., 2015), along with other sectors of biotechnology (Ledford, 2016), despite difficulties regarding the intellectual property (IP) protection (Comfort, 2017).

While the present study does not address the technical methods behind genetic strategies, the researcher recognises that the challenges of decision making in this rapidly changing landscape are significant. Rapid changes in technology related to vector control require decision frameworks that adjust to new information and new technologies. The existing biosafety frameworks set up in response to the Cartagena Protocol, based on concepts of genetic modification at the time, may not even have a mandate to review some of the upcoming technologies and products (Oye et al., 2014). The pace of change in this sector poses a significant challenge to decision makers tasked with delivery of novel interventions[23].

2.4 Challenges to decision making for novel interventions

Innovation may offer greater opportunities for success, but also presents greater challenges as noted in Chapter 1. Researchers in the development phase often lack hard data and there may not be any institutional mechanism to facilitate a move from research to application (Carden, 2009). Transgenic mosquitoes as a vector control pose even greater complexity than other forms of innovation. The researcher considers there to be key bottlenecks to the delivery process: (a) the necessary knowledge and confidence around decision making and (b) efficiency in taking decisions. This is not surprisingly given the complexity and rapid changes described above.

While it might be possible for external researchers who have discovered or developed a novel technology for vector control to carry out necessary studies themselves in DEC, partnership with local researchers provides the local expertise and technical experience and the requirement of an institutional entity, in the first phase, to host the containment facility (James et al., 2018; Quinlan et al., 2018b). This entity and its accompanying availability of land for the construction, connection to water and electricity services, existing emergency and security

[23] O'Brochta et al. (in press) found the need for more guidance for biosafety officers tasked with decisions regarding appropriate containment or other risk management for a rapidly changing range of research using CRISPR.

services generally is a prerequisite to applying for a research or import permit from the NBA. Subsequent field studies also may require a local host.

Some initiatives, such as Target Malaria, have intentionally sought to co-develop novel technologies from early stages, rather than wait until further down the production development pathway. Either approach leads to new relationships to progress the delivery of the novel intervention.

The researcher developed Table 2.1 after an initial analysis of the problem as defined in Chapter 1 and 2, and supported by literature (see Table footnotes). (For research within the Target Malaria consortium, the categories of relevant decision makers were already defined prior to her study by their involvement in the work and availability.) Table 2.1 lays out types of decisions and the challenges for each of the participant groups along this pathway of delivery. It also states how each group is covered by the current study, which focuses on the early phase of the process of delivery.

To simplify more detailed concepts, the researcher refers to participants in these decisions as:

- Discoverer or Novel Researcher: referring to the originator, in this study assumed to be external to the countries where the intervention would apply, i.e. not a DEC
- DEC Laboratory Researcher: those involved in lab studies or containment studies, however this included researchers within and outside of the study case institutions
- DEC Regulators directly related to decisions affecting early phase steps in delivery, in particular import and research (other regulators are involved in other steps and aspects of delivery)
- DEC decision makers for uptake: those who would evaluate a technology to include in a public health programme, oversee its delivery or monitor its performance
- Funders
- International and regional policy makers, such as WHO Committees

Another group that influences decisions are those living in affected areas. These include initially those near a containment research facility and those in villages or areas where early studies are conducted. These decision influencers are sometimes legally recognized, through requirements for consultation or ethical committee review of consent, and other times are included at the discretion of the research team. As the novel technology progresses along the steps towards field release, the definition of stakeholders generally expands to include the general public of the country. In some cases, even foreign individuals or entities may be recognized as stakeholders through this consultation process, although influence of country-

external stakeholders can derail decision processes where it is not clear whose opinion matters in the national context (Quinlan et al., 2016a).

Table 2.1 Decision makers for introduction of novel vector control for public health

Title used in this study	Description of this group	Types of decisions made	Challenges	Inclusion in this study
Discoverer or Novel Researchers	Individual researchers, research teams and technical and science leaders (e.g. departmental lead) in originating institutions – assumed to be external to the DEC for this study In some cases, a different group within an institution oversees transfer of technology or licensing to those developing the intervention further (intermediary bodies)	Decisions about timing and stage of development when partnerships should be sought Decisions about intellectual property (IP) protection, collaboration style and shared liability/benefit Style of partnership for progressing to DEC testing	Novel interventions may appear viable over years of research and then fail at a later stage of development; costs to develop may be too high for potential market Inexperience with commercial operations, product development or mechanisms for funding Lack of guidance on finding DEC partners Decisions on timing may be determined by funding or resources for product development within a university or research institution, rather than the best timing and approach for the concept/product Peer reviewed publications may compromise protection of IP 'Founder syndrome', loss of control of research and possibly IP. Sense of long term investment when actually only beginning of product development	Online global survey; insights from European projects on plant health; interviews with French innovation and research institutions

Title used in this study	Description of this group	Types of decisions made	Challenges	Inclusion in this study
DEC laboratory researchers (containment studies)	Individual researchers, research teams and technical and science leaders (e.g. departmental lead) in DEC research institutions Top management of research institutions or their advisory bodies Institutional committee leaders for science, ethics, biosafety or other relevant institutional bodies that review the proposed work	Decisions about participating in novel research that may require additional human resources and investment [a] Decisions about staff and facility availability and commitment to dedicated use of facility/staffing resources versus institutional priorities or research needs Decisions such as ethics or research review about work of close colleagues	Investment of significant time and resources, from across the research institution, possibly without having ownership or control over the direction of the technology. Possible conflicts of interest due to limited staffing Alternatively, taking control of decisions away from the originator [b] Multiple research collaborations require response and reporting to various funders and can divide attention among different partners' priorities Preparation for research on novel interventions that never arrive for testing [c], creating a sense of frustration and 'false start'	Guided interviews with leaders of lab research teams in the Target Malaria project to evaluate and validate the specific tools and framework trialled Other DEC lab researchers facing similar challenges or opportunities, to verify the differences that might occur in other settings
DEC Regulators and other official entities	Regulators, in particular the National Biosafety Authority (NBA) for GM technologies Vector control public sector National experts from scientific associations or professional societies, who	Appropriateness of technology for the national context. Risk and benefit issues in the context of existing interventions Granting import and study permits; possibly facility certification; agreement to move from containment to confined field study	The lack of experience when an intervention is novel may lead to avoidance of final decisions Need for decision makers to defend decisions to all stakeholders Accepting other country's study results, e.g. regarding safety, may not be anticipated	Guided interviews with Regulators from various East and West African countries Published literature

Title used in this study	Description of this group	Types of decisions made	Challenges	Inclusion in this study
	may serve on committees or be called on for advice in evaluation of proposals	Validity of study design, in the cases where this is reviewed on a national level	in the regulatory framework Lack of individual authority to determine requirements for studies and on public consultations	
DEC decision makers for uptake	Those who evaluate, approve or register, and approve or allocate funding for programmatic uptake of new technologies for ongoing, large scale vector control	Priorities for health spending Compatibility with other technologies in ongoing vector control programmes Confirmation of safety and efficacy Feasibility of costs and delivery Appropriate existing policy and regulatory framework for evaluation and approval	Historic alignment of authorities and institutional frameworks; lack of authority to decide about interventions that present a paradigm shift in approach Competing demands for public health funds When genetic modification is involved, decisions are dominated by NBA rather than sectoral authorities, e.g. public health, agriculture External funder's agendas and preferences are considered to exert too much influence on national policy making [d]	Not included in this study other than through published materials [e]
Funders	Funders may include those providing financial support at any step of the progression of the technology[f], for any component such as R&D, delivery or programmatic field	Compatibility of proposed intervention with Funder priorities and policies. Potential value, benefit and impact of the technology, and the time frame for these In what circumstances to apply the national regulations and	A lack of in depth knowledge of the issues and particularly of novel technologies Decisions may reflect outdated priorities and scientific thought, due to lag time between funding decisions and ultimate implementation National context may appear out of line with Funder standards or	Not included in this study, except for any materials related to the funder policy and process for the main project under study (for Target Malaria, initially FNIH and BMGF)

Title used in this study	Description of this group	Types of decisions made	Challenges	Inclusion in this study
	operations (or cross cutting such as for training, stakeholder engagement, etc.)	standards of the country of the funder, or international standards, in addition to that of recipient country[g]	preferences, potentially leading to imposition of Funder approaches or values on to what should be independent decision makers	
International or regional policy makers and sources of guidance	WHO and its regional bodies Similar recognised global health entities Regional bodies, such as the African Union Professional associations or societies (e.g. Pan African Mosquito Control Association - PAMCA), conference participants who reach consensus or raise issues	Decision to recommend novel technologies as research progresses through to sufficient evidence on which to make this claim Choice of best practices or standards for laboratory biosafety and operations, whether appropriate for all locations, and for all types of technologies	The bureaucratic process imposes long delays between committee or membership meetings Decisions can be derailed or postponed by questions or concerns from a minority Working groups are heavily influenced by those involved in the early stages of scoping or specification of topic, which may not represent less resourced countries Danger of imposing requirements that are not essential and/or appropriate to DEC conditions	Not included in this study other than through published materials

[a] Fleck (2016).
[b] Ramsey et al. (2014).
[c] Coulibaly et al. (2015).
[d] Göransson (2016a); Mutero et al. (2014).
[e] Decisions about programmatic uptake are not included for this study, but have been researched by others (e.g. Cisnetto, 2017).
[f] See footnote 6 (p. 26) about technologies.
[g] For example applying an approach to gene drive that has been agreed amongst some funders (Emerson et al., 2017).

The researcher recognizes the importance of these stakeholders and their potential contributions but has focused the study on those decision makers noted. This is in part because the researcher relied on information from Target Malaria for much of her study, and

stakeholder engagement is managed on a country basis by specialist teams within that consortium. The researcher could not easily visit with partner country stakeholders due to security restrictions from Imperial College and the general sense that additional people should not be visiting individuals already generously sharing their time with the consortium for more meaningful engagement.

Aside from Target Malaria, others with training in social sciences have considered these decision groups in various settings with appropriate expertise, and new approaches to this engagement are emerging (Bartumeus et al., 2019). Also, this topic was not included in the study because the decision processes of this group of stakeholders are not defined – or restricted – by law, regulation or institutional requirements. (Only input to public consultation is restricted.) The researcher, therefore, chose deliberately to focus her study on the decision makers in the more defined and structured roles of authority, to test the possible value of feedback within a learning framework for the sectors in which she already has considerable experience. This focus to the research scope would allow for more in depth study of an already broad topic.

This table is based on the researcher's observations during years of development work, as well as literature and the initial months of the researcher's formulation of study questions. It was checked against comments made by those interviewed later in the study, however. Chapter 4 describes the combined methods used for research of the role and experiences of some of these groups.

2.5 Effective decision making for delivery of novel interventions

Some key bottle necks of knowledge and confidence, and efficient decision making, were already noted. Multiple criteria must be met to achieve the most effective process of delivery of novel interventions, given the high complexity of issues. Box 2.2 describes what effectiveness could mean in the context of delivery of a novel intervention for vector control. Not surprisingly, some conclude that overcoming the biological and operational challenges for malaria eradication 'will depend significantly on how well major scientific disciplines can provide tools that can address complexity and sustainability' (Macias & James, 2015: p.425).

Various aspects of each step in the phased approach could be considered against a series of different specific criteria and related indicators to conclude that effective decision making has

been achieved. Describing these further would reveal the depth of the questions summarising the WHO approach to preparing guidance[24], discussed in Chapter 1.

Box 2.2 What is an effective intervention for vector control?

Effectiveness for vector control (versus decision making) consists of at least three different components, in the context of this research: efficacy, performance and efficiency. For this study, the term efficacy is the level of control achieved by the intervention, for example the number of adult mosquitoes killed compared to those surviving in the area of application of an insecticide. In that example, the efficacy drops when insecticide resistance develops. Performance relates to the efficacy achieved under field or other 'real life' conditions. Using the same example, this could be based on improper application of an insecticide, loss of efficacy from subsequent rainfall or insufficient or inappropriate active ingredient in the mix. Efficiency may comprise various factors: cost per control achieved, having a mechanism (e.g. public sector) and resources to pay, accessibility of the product and of qualified applicators, and having a product that fits within other activities in the area, which may also relate to efficacy and performance.

Effectiveness is sought not only for the interventions, but also for the decision process. The three aspects of effectiveness for a novel intervention might be translated into qualities relating to decision making such as: technical capacity to make an informed decision; ability and confidence to make the decision within the existing national legal and institutional frameworks; and ability to make the decision in an efficient and timely manner, which does not delay provision for public health, and without requiring extraordinary resources beyond those already programmed.

2.5.1 Current landscape for decisions on delivery of a novel intervention

Continuing with the simplified summary of the WHO questions, the first two on safety and efficacy of transgenic mosquitoes (Is it safe? Does it work?) are being oriented to some degree by development of international guidance and active scientific debate, with incremental contributions of data from those projects already publishing from containment studies and field trials. These leaves most of the technical influence on decisions in the hands of those working in that research sector. As Benedict & Quinlan (2018: p.1) state: 'it is the responsibility, first, or the vector biology research community to propose recommendations to meet the

[24] WHO (2012a) enters into this detail much more than the earlier guidance, WHO Global Programme for Evidence for Health Policy (2003), explaining the multiple perspectives and criteria to consider before making a recommendation.

requirements that promote and merit confidence in the efforts that are necessary for implementation of novel solutions.'

The process follows in the tradition of the Asilomar conference on recombinant DNA molecules (Berg et al., 1975) at which the most technically specialised and informed scientists sought to reach consensus on the appropriate steps towards safe application of a new technology[25]. This self governing approach (outlined in Chapter 2) is an issue of concern for some non-governmental organisations (NGOs) opposed to use of any GM technology, as well as some observers of the technology landscape (Rudenko et al., 2018; Ledford, 2016). Self governance lacks oversight external to the research community (unless invited) and is inherently a conflict of interest. From the perspective of those opposing use of transgenic mosquitoes, these researchers will focus on what science can achieve rather than what is the best means to achieving the objectives, in this case reduction of malaria transmission. This implies that other methods for reducing transmission that are more acceptable (e.g. pose lower risk) may be ignored, although one can argue that countries not researchers choose their own programmatic options.

In contrast, those participating in the process of defining guidance and standards for research in genetic strategies for mosquito control consider they are the only ones technically qualified to evaluate the emerging options, and they are highly motivated to maintain the reputation and gain trust for the area of research[26]. Mumford (2010) notes that a single entity may not hold all of the expertise, but that collaborative development of international guidance would save considerable resources in place of individual countries trying to do the same.

Clearly there is a role for both self governance and regulatory oversight. Adelman et al. (2017a) contrast self governance, soft governance (international guidelines) and federal governance for the US context. One of the most important contributions of the specific documents they categorise as self governance or soft governance (Adelman et al., 2017a: p.717) is the ability to keep pace with rapid changes in technology, with gene drive being one

[25] Gleim & Smyth (2018) provide an overview of the biotechnology publications that influences the European, US and Canadian regulatory systems from the late 1970s into the 1990s.

The mechanisms for including values-based input to decisions that are defined as science based in regulation are considered in Rudenko et al. (2018) specifically for gene drive products. It is notable that more than 40 years after the Asilomar conference, at least one multidisciplinary effort to consider biohazards, described by Gillum et al. (2017), states that it is doing what that first conference intentionally avoided: defining a more integrated view of biosecurity.

[26] The researcher has observed this, but it is also documented from the earliest discussions on molecular biology through to more recent forums (Adelman et al., 2017a; Cohen, 2013; Berg, 2004; Krimsky, 2001; Berg et al., 1975; and the series of meetings described in section 2.1.)

of their cases in point. This allows responsible researchers in a sector to guide or govern those less experienced, or perhaps more ambitious and less principled.

The third question posed in Chapter 1 (Does it work for me?) has significant impact on the possibility of effective delivery. Van den Berg et al. (2012: p.8) stated that 'Vector control is often not sufficiently adapted to local or changing circumstances because many countries lack capacity in decision-making for vector control.' The capacity required includes not only technical knowledge of both traditional and emerging influencing factors, but also an understanding of those factors in order to account for the preferences, needs and competing priorities of the local communities. One extensive literature review of health governance definitions and tools describes the emerging expectations to manage a range of relationships within a health system, moving from a control through collaboration and communication styles (Barbazza & Telo, 2014, e.g. Box 2: p.8). The researcher considers that relevant decision makers in DEC are increasingly asked to go beyond basic good governance, albeit in a generally top down decision process typical for public health, to a more holistic stewardship approach including engaging stakeholders beyond the traditional public consultation process (see for example Quinlan et al., 2016a). This expansion of authorities may imply a change in legal mandate and certainly a change in skills and training, often with no additional resources.

Significant progress has been made to strengthen international guidance for review of ethical, social and other criteria alongside the science for health interventions (e.g. Lavery et al., 2010; Tindana et al., 2007) and even for transgenic mosquitoes specifically (Kolopack et al., 2015; Lavery et al., 2008; Macer, 2003). These issues benefit from international debate, just as the scientific ones have. One cannot assume that an African perspective necessarily is a more 'ethical' one towards the approach to health research and community consent, either due to the lack of well trained ethics oversight or experience, or due to the universal desire to advance the health research with urgency (Parker & Kwiatkowski, 2016; Ndebele & Musesengwa, 2012; Nyika, 2009; Nyika et al., 2009a). The criterion of localisation or goodness of local fit (by nature of the technology or the extent to which the novel intervention can be tailored to local circumstances – does it work in the local conditions, is it cost effective, will it be accessible) ultimately should be judged by the various DEC decision makers, most notably those tasked with maintaining public health. This requires time and resources, and additional competencies among decision makers.

2.5.2 Factors affecting effectiveness

The researcher made a key assumption that there are novel interventions with at least potential efficacy as far as impact on malaria transmission, in order to explore for this study

the more restricted questions around how best to deliver such an intervention. A novel intervention may not provide the intended results, however, if there is inadequate or misdirected training and education, a failing health system and over bureaucratisation (Morens, 2008). Effectiveness of interventions also has been shown to change over time or under different conditions. The erosion of effectiveness of some of the standing vector control programmes is reviewed by Raghavendra et al. (2011), with the need for integrated control being one of the conclusions.

Effectiveness of a strategy for malaria vector control has been defined as achieving a stable elimination of malaria at selected trial sites. But this depends on selection of an appropriate field sites and finding suitable research partners, using the right technology and having a proper study design and implementation plan for release (Macias & James, 2015). The importance of the outcome of early field trials as a key decision point along the stepwise approach, shows the need for addressing multiple criteria simultaneously to support decision making regarding progression of a novel intervention.

Effectiveness in the overall delivery process is not easy to measure or monitor. When considering a health system, the counterfactual of what would be occurring in terms of malaria and vector control is fairly well established, but not always easily compared. For example, a review of costs and cost-benefit comparisons among the principal malaria interventions concluded that the outcome would have to be presented across three dimensions: units of area (geographic area covered), impact on persons (such as mortality and morbidity), and by number of vector species controlled (MosqGuide, 2011). Literature reviewed for that report expressed impact on persons using a dozen different metrics. A conclusion was to express costs as (a) per person protected in the control area per year; and (b) cost per incidence/morbidity/mortality prevented per year, such as by using disability adjusted life years (DALYs), although Jordan et al. (2016) describe limitations of DALYs when a disease is often not diagnosed properly and the human response is variable, as is the case for malaria.

A gap analysis for improving a vector control system could support evaluation of the third WHO question on localisation and effectiveness (van den Berg et al., 2012). Sabet et al. (2017) offer a relevant guide to evidence mapping as a possible method to determine important gaps. Questions related to political commitment, legislation, infrastructure, resources, and expertise could be informative in this analysis. One aspect to consider, as already noted, is expertise for making evidence-based decisions. Additional aspects include: if research is designed to provide the evidence/data needed for decision making, if there is surveillance in order to know the outcomes and if the evidence is sufficient to determine effectiveness. The present study considers whether having a framework to support, document and possibly justify decisions

facilitates communication with other levels or sectors involved, without aiming to define gaps in the overall health and vector control systems. Organisation of data for evidence and comparison of the strength of evidence in various cases can be linked to learning systems to support better decisions in the future, but will always face the limitations of the public health system and malaria programmes.

Even after a decision is made to initiate research, those studying novel vector control face a multitude of challenges beyond the usual project-funded research ones, including[27]:

- Identifying the regulatory pathway for requesting government approval of import/participation in the research
- Adapting to a regulatory framework might not be designed for the purpose at hand
- The need to manage containment, through either physical or biological means
- Managing colony survival and monitoring for genetic drift, ensuring quality of the colonies used
- Achieving required documentation and records for potentially remote access and subject to international review (towards a recognised level of product stewardship, see Chapter 9)
- Expanding skills to cover augmentation of colonies to supply studies (see Figure 2.1)
- Developing and testing field release methodologies
- Managing expectations for what is often a long term commitment of resources and staff

These factors continue to present challenges over the course of the stepwise pathway towards programmatic uptake and require exceptional management capacity.

2.6 Understanding the geopolitical dimensions of decision making for novel interventions

The complexity and challenges of decision making along the steps from discovery to lab and field studies and eventual deployment, have been identified as hampering uptake of biotechnology in much of Africa (Keetch et al., 2014; Wambugu & Kamanga, 2014; Black et al., 2011; Ezezika et al., 2009). Complexity also arises within a biosafety framework from the interaction between policy formation and implementation; further complexities emerge as a policy is re-created and interpreted throughout its implementation (Hallsworth, 2011),

[27] These various demands on a country Principal Investigator (PI) were catalogued with Target Malaria colleagues.

sometimes coming through as attempts by stakeholders to engage on policy level issues when individual cases are under review (Quinlan et al., 2016a). The potential enablers and barriers to effective and efficient decision making have been explored across three different geopolitical scales: micro, meso and macro scale. The relationship of the decision makers identified in Table 2.1 to these scales is shown in Table 2.2.

Table 2.2 Various decision groups for delivery of a novel vector intervention, based on the example of transgenic mosquitoes, shown at geopolitical levels

	Early in delivery pathway	Time of initial involvement →	Later in delivery pathway
Micro	**Discoverers (lab or institute)**	**DEC Laboratory Researchers** (containment studies are the focus of this study, but this would include all DEC studies)	DEC lab or other facility for ramp up or ongoing larger scale production
Meso	[Discoverer country decision makers – research landscape]	**DEC decision makers – Regulators and others** (evaluating import of study strains, field studies and eventual field use)	DEC decision makers for uptake of a novel intervention, moving to programmatic use
Macro	[International policy makers – context of public health] Funders – R&D phase	International policy makers – evaluation of novel interventions Funders – delivery phase	International policy makers – recommended and endorsed interventions Funders – programmatic disease control, monitoring and evaluation (M&E)

Those groups in [ ] are not discussed in this study. Those in bold are the main focus of the study.

While one may be tempted to give the highest weight to macro level decision makers, even a small group working on a micro scale may contribute valuable tools that may lead to national or regional guidelines or general consensus across a sector. There are examples of previous efforts to harmonise or support transparent and appropriate practices for risk management in general, management of disease or infective agents and, to a lesser degree, for vector research (Beech et al., 2011, 2009a). For example, the Arthropod Containment Guidelines (American Committee of Medical Entomology, 2003) were developed in a US context. The original objectives are explained by Tabachnick (2006). These have since become a globally

referenced best practice. They were used in this study (Chapters 7 and 8), as well, to benchmark the expected characteristics of an Arthropod Containment Level 2 (ACL-2) facility, in particular, and are mentioned in several regulatory applications for mosquito research, of which the researcher is aware. Countless institutional versions of the same concept of a checklist for compliance in terms of containment and biosafety measures have been developed based on these guidelines. This has taken a micro and meso initiative through to a macro level of influence, with little alteration[28].

2.7 Summary of the main issues regarding use of transgenic mosquitoes as a novel intervention for vector control

A precautionary approach is appropriate for novel technologies or resulting novel organisms (including GM organisms), when beginning research and testing of novel approaches, because of the level of uncertainty[29]. Expertise and experience with the new traits, possibly from other scenarios, can greatly reduce uncertainty, however, and provide more accurate risk assessments than broad categorisation. Risk assessors can identify clear causal pathways of potential harm to strengthen the management choices. The estimated risk of these technologies may be reduced over time simply with additional experience if data accumulates to show no evidence of harm.

As the uncertainty, and *de facto* the 'novelty', decreases with more experience and handling of the novel organisms, the risk reduction will allow the responsible researcher to move on to confined field studies with greater biological knowledge, to face the different uncertainties of more natural ecological conditions and risk management relying on confinement measures[30].

A risk-based approach should clearly identify and document potential hazards, pathways or mechanisms for these to occur, probability of occurrence, and consequences – although containment facilities generally are described and classified by risk management measures

[28] In Chapter 7 the researcher suggests some revisions to the ACL guidelines to make them even more useful to a DEC or developing country context. There reportedly have been minor edits to the guidelines already, which are scheduled to appear in the March 2019 edition of the journal, *Vector-Borne and Zoonotic Diseases*.

[29] In this study, uncertainty regarding measurement and analysis is not discussed as much as uncertainty from a situation in which 'knowledge is incomplete, and where ambiguity and ignorance prevail' (Marris & Jefferson, 2013: p.25) due to the novelty of the research organism.

[30] All of the research presented in this thesis relates to transgenic mosquitoes without long term self-sustaining traits or gene drive, unless otherwise stated. The intention for Target Malaria is to move to those more cost-effective persisting options when possible (https://targetmalaria.org/our-work/), but this was not taking place over the period of this study.

(Quinlan, 2014: Box 18.1). Yeh et al. (2016: p.327) state that a risk-based approach can allow for 'system-wide analysis, taking into account mitigation and prevention, as determined by a comprehensive assessment that aligns the laboratory mission with biosafety and biosecurity'. A risk-based approach to managing containment of novel organisms is also the best framework for approaching the issue of worker and environmental safety throughout this stepwise progression (Kimman et al., 2008)[31]. (The limitations of a framework based strictly on risk parameters, however, is noted in Chapter 4.)

This research addresses several key components of introducing new vector control innovations to DEC from external research centres, and moving the technology through safety and initial efficacy studies within containment before commencing initial field studies. The context of vector control with transgenic mosquitoes is a subset of all existing vector control interventions, and sits also within the range of interventions for malaria control and elimination. Progress towards delivery is based on a recommended stepwise approach that accommodates more (and different) risk at each step, while simultaneously reducing the risk from the previous stage. The risk may be mitigated by reduction of uncertainty or by more informed or improved risk management, as well as by increased capacity of those involved.

The complexity of this decision making landscape is introduced from various directions: the complicated nature of vectored disease control, discussed here and in Chapter 1; the rapid pace of research in gene strategies and therefore the need for decisions; multiple actors involved in decision making and implementation (Table 2.1, Table 2.2) and uncoordinated or even competing objectives of the various entities (discussed further in Chapter 11); and multiple factors that impact the outcomes, making it impossible to have a direct line of causality from a single project, funder or indeed disease intervention, in terms of epidemiological outcomes. Basically, all of the types of complexity identified in Sheate et al. (2016) are inherent in the process of delivery of a novel intervention in vector control. Chapter 4 discusses the combined methods used by the researcher for conducting and presenting the research.

[31] This is also particularly relevant for novel technologies, since the approach of listing agents by level of risk is not as appropriate or efficient for emerging technologies offering greater complexity (Homer et al., 2013). Yeh et al. (2016) discuss replacing technique-based job descriptions for disease-based versions, for staffing in lower resource countries; they also note that a risk-based assessment is an important training mechanism.

Chapter 3. Characteristics of Introductions of Innovations in Related Fields

The story of delivery of a novel vector control intervention can bring insights to pathways of delivery for other innovations, particularly those employing living organisms or other interventions in public health.

3.1 Plant protection

As already noted, the International Standard for Phytosanitary Measures (ISPM) 3 (IPPC, 2005a) was revised to include sterile insects, pollinators and other living organisms used for beneficial purposes. Although this was aimed at plant protection specifically, as part of the framework of international standards under the IPPC (and previously as an FAO Code of Conduct), it has been referenced for work with other arthropods as well, including mosquitoes, because of the lack of consensus papers or guidance for that sector. In fact, until recently the mosquito research sector has been a fairly informal one, with much of the knowledge transfer going between colleagues and from educators to students rather than through coordinated rule making or guidance development, or consistent management frameworks (Kelly & Lezaun, 2017; Benedict et al., 2009). Therefore, possible lessons and even decision support from similar sectors was considered during the course of this study.

In addition to the regulatory guidance, experiences with ISPM 3 have shown that interest and support from individuals is crucial to initiate and maintain uptake of a guide or tool (see Box 3.1). This is an important lesson for introducing decision tools for innovative vector control, as well.

There are lessons of value for later stages of delivery of vector control as well. Plant protection product discovery, development and commercialisation is more complicated for biologically based products, in part because they do not fit the existing tools for business support, such as business plan templates (Quinlan et al., 2018c; Alden et al., 2017; Mumford & Quinlan, 2016). Useful planning and decision tools in this sector, prepared under the auspices of European Commision (EC) project funding, may apply to genetic strategy innovations as well. For example, plant protection products are sometimes developed by public sector research groups who hope for commercialisation but have no profit motive. Throughout the research sector in Europe, a similar form or template is widely used for declaring discoveries or prototypes with potential for patenting, and therefore for marketing with intellectual property

(IP) protection. This was found to be less applicable to biological products that are not easily protected by patenting or for initiatives in the public or not-for-profit sectors (Quinlan et al., 2018c; Quinlan & Tourneur, 2017). Materials that are enhanced but rely on existing technologies, tools or frameworks may be best 'protected' by promotion of a 'brand', which can be more easily protected, and by maintaining a high reputation (Alden et al., 2017).

Box 3.1 The importance of a champion

The use of ISPM 3 as a reference document when national regulations were lacking or very general has been documented by the researcher as co-author in Kairo et al. (2003; 2005). This standard is unusual among ISPMs, however, in that it focuses on the role of each party (exporting and importing) rather than entering into details about determination of risk or use of risk management. One of the findings of the various studies on ISPM 3 was that use of this guidance was greatly enhanced when there was a champion, or a person who consistently reminded others of its value in application to the circumstances. This role is not necessarily related to the person's job or position, but rather is defined by their consistent belief in and enthusiasm for use of the tool, guidance or technology.

The loss of one individual champion for sterile insect control of mosquitoes in Reunion was credited with the delays in putting that country behind Sudan in application of that areawide technology (Lees et al., 2015; El Sayed et al., 2009), although a negative experience with the release of a biological control agent in the same period also had an effect. The progression to the testing of sterile RIDL® (release of insects carrying a dominant lethal) mosquitoes in Panama, for example, was initially down to a single champion, who later was replaced by a new champion who would keep the strategy as an option over years of meetings and public consultations, as observed by the researcher through her work.

The importance of a champion for new decision support tools was found in the literature and current study, as noted in Chapters 5 and 10. When a tool is created by those affected, they are likely to use it, but introduction of a tool benefits from a champion.

3.2 Sterile insect technique

As already mentioned in Chapter 2, SIT has been applied as a type of genetic strategy on an areawide basis to some mosquito populations using irradiation, chemosterilants and, more recently, genetic modification to achieve sterility or strains that will not persist for long in the natural environment once released. One of the most significant ways that SIT is supported is through the Joint FAO/IAEA Programme in Nuclear Techniques in Food and Agriculture (http://www-naweb.iaea.org/nafa/index.html). This entity has provided technical support and some funding, but also a focal point for global and regional initiatives to research and define

best practices for the range of aspects involved in delivery of sterile insects, including: insect biology, development of strains, genetic sexing, mass production, shipping and packaging, field delivery, surveillance and management of field campaigns to name a few. Despite an historical focus on agricultural versus health topics, the FAO/IAEA Insect Pest Control Division is providing a similar forum for R&D for several species of mosquito, presently through a Coordinated Research Programme on handling, transport, release and male trapping methods (http://www-naweb.iaea.org/nafa/ipc/crp/ipc-mosquito-handling.html). Other aspects of mosquito research are not covered by any particular global entity, however. Guidance, such as the Arthropod Containment Guidelines (American Committee of Medical Entomology, 2003) has been developed through individual country professional associations, at conferences or other topic-specific meetings, albeit with geographically broader participation.

3.3 Biological control agents

The use of biological control agents (BCAs), particularly entomophagous ones, has focused on agricultural applications, although successes in forestry (Cock, 2003) and efforts to protect native plant biodiversity (Hight & Carpenter, 2016; Zimmermann et al., 2004; Habeck et al., 1990) are also known. Both SIT and release of BCAs have been cited as a model for considering persistence in the environment for gene drive mosquito control (Burt, 2014).

In earlier decades, BCAs were seen as environmentally positive in comparison with alternatives, which generally comprised chemical pesticide applications. Yet over time, and coinciding with the enactment of the Convention on Biological Diversity, there were increasing concerns over the impact of invasive species, including those not traditionally classed as pests by the IPPC or World Animal Health Organisation (OIE). Conservation of natural enemies is considered the most important part of applying biological control methods, particularly against invasive non-native introductions (EMPHASIS, 2016). Pressure on threatened or endangered species from introduced invasive species was clearly established in various settings, as was the impact on vulnerable ecosystems. An international system for identifying threatened species was established over 50 years ago (IUCN, 2017), although arthropods are not yet covered extensively compared to vertebrates (Knapp, 2011).

Quinlan et al. (2016b) describe this tension between biodiversity objectives and the use of BCAs. In fact, concerns over potential environmental impact have become so predominant that the use of BCAs was being stymied. Hickson & Slim (2012), describing the situation in New Zealand's business sector, noted other barriers to innovation in living organisms for commercial use as:

- Lack of mature technologies to move into field use
- Costs and estimated returns from use of the novel organism
- Unclear and/or costly regulatory requirements

This final point was found to apply for GM and non-GM organisms. This was specifically credited to the biodiversity legislative framework in that country (Hickson & Slim, 2012). During this period, the costs of gaining approval were increasing without similar support towards what might have been public good from the benefits of innovative organisms. Heimpel & Cock (2018) describe this period as one in which aversion to risk was the primary criterion for decisions in much of the world. Fortunately, they have noted another shift in paradigm recently, which is to consider benefit as well as risk. These underlying attitudes and paradigms can overflow to other sectors[32], especially when drawing on the same people for evaluation and decisions.

The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity, hereafter referred to as the Nagoya Protocol, seeks to curb biopiracy or exploitation of biological resources from one country by another, or by a private entity. However, the agreement was crafted from the perspective of private sector profits, which generally do not coincide with BCAs or SIT. Mason et al. (2018) proposed some steps towards compliance with the spirit of the Nagoya Protocol for a low- or non-profit sector, which may be relevant to early stages of genetic strategies, when introgressing or testing of local mosquito strains captured in areas that will be targeted for mosquito population control, as described in Box 3.2.

Chapter 9 discusses maintaining identity of a mosquito colony and ways to acknowledge a country's contribution to the genetic benefits, without extracting resources for the use of others.

3.4 Biopesticides

This shift to benefits seems particularly relevant to the public health sector, in which biopesticides are becoming more feasible as regulatory systems adapt. Biopesticides are sometimes categorised as BCAs but often come under a different regulatory framework.

[32] Similarly, negative experiences can colour the decision landscape for other sectors. When the negative experience is an event with serious consequences, the researcher has referred to these in other project settings as 'wild cards' that frequently alter the decision landscape for all sectors sharing any common attributes, even when the common factor is simply the involvement of the government or science.

Recent developments in use of mycofungicides for mosquito control are discussed in Lacey (2016).

Box 3.2 Possible method for compliance with the Nagoya Protocol for benefit sharing

Mason et al. (2018) have reviewed the requirements and intentions of the Nagoya Protocol and concluded some practical means for compliance in a low- or not-for-profit sector:

- Collaboration on what BCAs are available and how to obtain them
- Knowledge sharing through access to databases that reveal both successes and failures to those providing the genetic resource
- Cooperative research in source countries, with capacity building objectives
- Transfer of production technology to encourage small-scale production domestically, as an economic opportunity

This provides opportunities for shared research and capacity building, when significant financial resources are not expected to result.

The need for source country-based collaboration in research has grown already with the demand for more detailed risk assessments and environmental impact studies. Formalising this collaboration early, through detailed Material Transfer Agreements (MTAs), if not actual funding contracts, will support more benefits sharing. Mason et al. (2018) suggest that if patenting of individual strains of BCAs becomes more feasible in the future, the high costs of production and development may still make monetary sharing prohibitive for the usual small-scale operations producing these. Cock et al. (2016) have shown that reasonable agreements on such issues will prevent what is commonly a loss of benefits when domestic production is not successful, leading to the need to import the BCA back to the source country.

These observations appear to be a viable foundation for sharing of benefits for mosquito genetic resources as well.

Burkinabe regulators have approved a GM fungus for research in a containment laboratory and semi-field conditions to test it as a potential mosquito control agent (according to Bilgo et al., 2017), even before the applications for transgenic mosquito research were submitted. Although release of BCAs is more similar to future release of transgenic mosquitoes, the approach to evaluation and risk assessment for the GM fungus should provide a foundation for decision making by regulators in Burkina Faso, and those who learn from them.

3.5 Other novel biocides

One biocide, which has a function that relies on persistence in the environment in order to serve its function, is based on a zeolite clay carrier for silver ions as the active ingredient, to act as an antimicrobial by exchange of silver ions with sodium ions generated by moisture. Agion® began to be registered as a biocide in various countries in the 1990s. It is now used in a range of products including athletic shoes, clothing, refrigerators, air conditioning ducts and even building materials. The same concept is employed for water dispensers and in medical devices, such as catheters. While some of these applications are for health objectives, many could be categorised as amenity uses, for example to reduce odour.

Traditionally, the lack of persistence has been a preferred characteristic for some biocides, as with some classes of pesticides. This type of novel product makes a framework that favours the disappearance of the active ingredient as a positive characteristic unsuitable. Regulators faced with this type of paradigm shift generally find a way to accommodate the decision making in manners that are conceptually similar, if not biologically similar. In this instance, comparisons were made by some regulators to antifouling paint for preventing fouling of boat surfaces. This concept-based approach (versus exact precedence of a product) is another reason that regulation based on 'biorisks'[33], versus methods to achieve biotechnology, may be more appropriate in the long run.

3.6 Medical innovations as a model for decision making in public health

Many innovations are developed in the medical sector, including medical devices, diagnostics, and care delivery systems. In general, the pharmaceutical and vaccine sectors have a well-established pathway to testing, evaluation and registration. In contrast, the early assessment phase for medical innovations has not yet been supported with appropriate tools or common practices, according to recent reviews (Fasterholdt et al., 2017; Varabyova et al., 2017; Markiewicz et al., 2014).

[33] Wambugu (2014: p.5) has stated that the Cartagena Protocol should have been written to accommodate other types of biorisks, and should have provided 'clear scientific review guidelines' after the assumed dangers envisaged in the agreement did not occur. She further states that the Cartagena Protocol is the 'major barrier to adoption of agricultural biotechnology crops in Africa'. Certainly others in sub-Saharan Africa agree that the national frameworks driven by adoption of the Cartagena Protocol are not efficient for the current range of innovations in health, agriculture and other sectors.

Fasterholdt et al. (2017), covering a range of medical innovations, found that early assessment, if done at all, was based on a wide range of evaluation methodologies: cost-effectiveness analysis; scenario drafting or road mapping; review of strategic fit through weighted criteria, or strength, weakness, opportunities and threats (SWOT); other project management type approaches such as evidence mapping. Interestingly, of those published studies reviewed that did recommend iterative processes for evaluation, only one-fifth actually implemented the iteration themselves (Fasterholdt et al., 2017). There was also a lack of independence among the experts chosen when estimates of efficacy, for example, were elicited as part of the review. The lack of a consistent harmonised framework was identified as a major deterrent to early evaluations.

Similarly, a review focusing on early assessment of medical devices (Markiewicz et al., 2014) found that a wide range of methods for assessment had been reported in literature. Evaluations were generally performed at the prototype product development phase with potential manufacturers as the audience. This review supported conclusions of Varabyova et al. (2017) that the adoption of a more coherent and precise terminology and classifications of technologies, as well as the decisional systems in which they interface, would contribute to more rapid adoption of uniform systems for assessment that would, therefore, become more meaningful. Even more clarity on what 'early' implies for such an assessment ought to be harmonised and defined better across the related sectors (Fasterholdt et al., 2017).

Many of these observations on early assessment of medical innovations seem relevant to evaluation of other types of innovations aimed at complex public health issues. Emerging methods for early review of drugs for malaria control (e.g. Khoury et al., 2018) could radically reduce costs by eliminating those without sufficient promise much earlier. Ng & Quinlan (2013) found, however, for novel vector control researchers at the time that later stage field efficacy characteristics and indicators were not considered or well defined by many early phase researchers, who might be classed as Discoverers for this study.

For novel vector control, the WHO VCAG has begun the process of defining early phase and other sector-wide definitions. The use of independent committees to review choices in data, level of monitoring and analysis of results over the course of product development is considered best practice (WHO VCAG, 2017b).

3.7 Innovation as a catalyst for change

The climate change field talks about transformational adaptation in a way similar to paradigm shift. Although within a 'conceptual plurality' (Feola, 2015), Lonsdale et al. (2015) discuss the

concept of transformational adaptation as having: transformational or disruptive change rather than incremental; with changes becoming embedded in the system, rather than being transitory. Their review suggests an intensity of change, whether long standing or widespread or more localised. They explore various lines of thought regarding the components and conditions for transformational adaptation in relation to actions to mitigate climate change. On the other hand, innovations can be a way to cope with change.

Further research into how innovation in vector control can be a catalyst for change may be warranted.

3.8 Summary about related innovations

This study focuses on the early stages of delivery of a novel intervention for vector control, based on genetic strategies applied in an areawide approach. The future use of transgenic mosquitoes, in particular strains using gene drive, has been compared to use of BCAs including the cassava mealy bug natural enemy that was rolled out across much of the African continent (Zeddies et al., 2001). There are useful and important lessons from the BCA and biopesticides sectors, including the need to adapt regulatory frameworks to these innovations rather than require they fit within systems designed for chemical measures. Ideas for the role of each party (importing and exporting), best practices for material transfer, and proposed mechanisms for addressing the Nagoya Protocol on sharing benefits seem particularly relevant. The need for a central entity to host discussions towards consensus documents and some harmonisation of data collection and handling are useful lessons from the sterile insect technique sector.

These early stage studies under containment and the subsequent studies that rely on production of mosquitoes in containment will be the foundation for genetic strategies as a component of malaria control. Malaria elimination will require a step change from previous approaches. This clearly includes more integration of measures and more informed cross-sectorial decision making. Simply moving into areawide control requires a paradigm shift in terms of the geographic scale at which decisions are made, additional surveillance and monitoring, coordinated data collection and analysis and possibly the structure of the mosquito control programme. Many of these components of an integrated vector control approach are also critical for preparing for malaria elimination (James et al., 2014). Major changes in the approach to malaria control, such as use of genetic strategies, may provide the catalyst towards a paradigm shift in mosquito control.

Chapter 4. Research Methodologies: a Combined Methods Approach

4.1 Outline of the research

This chapter discusses methodologies employed for the research presented in this thesis, from the general approach and data collection, through to the approaches used for interpretation and/or validation of conclusions and frameworks. The main topics of the study regard:

- Selecting countries and partners for initial research (Chapter 5);
- Assessing unique factors of the regulatory context when importing and releasing a living organism which is also genetically modified (Chapter 6);
- Identifying facilities and import of novel organisms into regulated containment facilities for the research phase (Chapters 7); and,
- Choosing appropriate metrics and methods to determine readiness for the phased studies, such as training and facility audits (Chapters 8 and 9); and managing biosafety over time (Chapter 10).

The aim of the research was to identify or propose good practices for decision making, and structure frameworks and other methods or tools for supporting decision making by the various groups involved in the introduction of a novel vector control technology. The researcher used the example of genetically modified mosquitoes for malaria reduction or elimination. Where possible, learning systems that have some added feature to support new knowledge will be the objective of the study.

To address these research topics, different methods were combined at different times, as explained below. The researcher's ability to frame or validate any theories, however, is restricted due to the limited number of cases progressing along the delivery pathway during the period of her study and due to limited access to initiatives that are in progress. (The researcher also will argue later that few initiatives are moving through the early delivery steps with such consciousness as to allow study by an external researcher, but rather are reaching each milestone on a very ad hoc manner.) Therefore, more qualitative methods, combined to fit the research questions and opportunities for access, were considered to allow a focus on the early phase of delivery of novel interventions in vector control.

The primary methods employed were:

- Literature review and analysis of experiences from other settings involving novel interventions and delivery of innovations;
- Identifying project management tools and Theories of Change to better represent the research context and specific pathways towards delivery of a novel vector control intervention;
- Interviews of researchers producing innovations and an online survey of those involved in disease or vector control innovations;
- Convening an ad hoc focus group followed by an interactive symposium about experiences of regulators and those participating in public engagement on biotechnology decisions, supplemented by interviews with regulators from East and West Africa;
- Action research to develop theories and frameworks from within an example project, and reintroduce these to the ongoing project as an initial validation;
- Interviews with country-level Principal Investigators (PIs) in the focus project, to clarify and reflect on insights gained through action research;
- Iterative development of frameworks to represent the findings and support future decision making;
- Analysis of results, summary and recommendations.

Other methods that supplement these for particular points in the research are described in the relevant topic sections.

Table 4.1 is a timeline of key activities shown as administrative, data collection and research milestones, that were conducted as part of the research (general timing of literature reviews appears in Table 4.2). Research was conducted as a part time student. Due to personal injury and family bereavements, the researcher had time gaps in her research comprised of: 13 May through 10 August 2012 (fracture preventing computer use), 12 March 2014 through 30 September 2014 (emergency family leave) and March through August 2018 (not official, family leave). These periods, therefore, show less activity.

Table 4.1 Timeline of PhD activities for research and thesis

Approximate timing	Key activity	Link to thesis
Administrative milestones *(note part time status affects timing)*		
1 October 2010	Official registration for part time study	–
February 2011	Initial plan of study (NB: main supervisor changed after this date due to leaving College, plan was then somewhat revised)	–
1 June 2011	Early stage assessment	–
October 2010 through November 2013	Transferable skills and presentations requirements met	–
March 2016 through September 2016	March 2016 internal departmental ethics approval for 2nd phase research; submission to Imperial College Research Ethics Committee (ICREC) administrative office for ethics approval; revisions of application by request; notification of decision by Coordinator of ICREC	–
September 2016	Late stage assessment and MPhil upgrade report and meeting Revision of statements of research questions	–
1 May 2017	Writing up away from College approval (not related to employment)	–
January 2018	Compilation of publications and posters related to PhD presented to date	Appendices 3, 4
2 February 2018	Examiners copy submitted for their review	–
20 April 2018	PhD Viva	–
February 2019	Resubmission following major corrections	–
Data collection and research milestones		
October 2010 through April 2011	Definition of problem and research questions	Chapters 1 and throughout
October 2010	Draft criteria for partner identification used to summarise characteristics of potential DEC partners with Target Malaria (precursor project)	Chapter 2, 4, 5; Appendix 2 draft
December 2010	First meeting with potential DEC partners of Target Malaria	Chapter 5, 6

Approximate timing	Key activity	Link to thesis
October 2010 through December 2011	Literature review focusing on regulatory criteria, GM context, genetic strategies, malaria, similar biological businesses and partner criteria	Chapters 1 -3, Chapter 4 and related chapters where topics are reported
January 2012	Second meeting with potential DEC partners of Target Malaria	Chapter 5, 6
February 2013	Entire project team meeting of Target Malaria, initial definition of need to benchmark facilities readiness and document mosquito strains	Chapter 7, 9
May 2013 September 2013	Facilities readiness meetings with Target Malaria teams	Chapter 7
November 2014	Symposium format for collecting regulators' perspectives on case by case decision making and frameworks for public input; presentation to conference on facilities readiness concepts	Chapter 6
December 2014 – December 2015	Further definition of approaches and methods; review of initial findings, framing of further questions; literature review on WHO, etc. update on genetic strategies	Chapter 4, entire thesis
2015	Audits of West African facilities	Chapter 8
2016	Interviews with French institutions (Aug/Sept 2016 for the majority, initial enquiry into topic supported by the Erasmus + grant)	Chapter 5
December 2015 – February 2016	Development of interview and survey instruments; identification of participant groups for online survey	Chapter 5; Appendix 1
February 2017	Interviews with East African regulator and other DEC research labs external to Target Malaria	Chapter 5, 6, 8, 10
March 2017	Intensive training Theory of Change	Throughout thesis, Chapter 11
January – June 2017	Online survey of Discoverers in vector control research	Chapter 5
November 2017	Interviews with West African regulators	Chapter 6
November 2017	Interviews with country level PIs for final thoughts and to 'exit' the study	Chapter 5, 7, 8 and 9
2016-2017	Preparation of publications on facilities readiness, in conjunction with those who took up the concepts	Chapters 7 and 9; Appendix 4

Approximate timing	Key activity	Link to thesis
2017-2018	Writing up research, additional literature review as needed to be up to date and better interpret or support conclusions	Entire thesis; Appendix 5
June 2018 through January 2019	Additional literature review on culture of self reporting; on social science methods not selected or to clarify those used; update of all key literature topics	Chapter 10; Chapter 4; all other chapters

Following emergency family leave in 2014, the researcher reviewed her results to date and formulated a second phase of research that involved interviews and a survey. This additional research was approved by the Departmental ethics process in March 2016, in line with what is now termed a non-health research track and in line with the review of many similar studies. The researcher, however, took the precaution to submit to the health research track for ethics approval. After a submission and repeated revision to meet the demands of the Coordinator's office for the Imperial College Research Ethics Committee (ICREC) that Office notified that the research would not fall under a health research remit and could proceed without the application passing to the ICREC itself. In the past year (2018), an improved ethics procedure was created at Imperial College London so that now there is a Science, Engineering and Technology Research Ethics Committee (SETREC) for non-health related studies. If this study were to begin again, that more suitable procedure would apply. The researcher and her supervisors consider that nothing in the new procedures would have altered or limited her research as it was laid out and conducted, had they been available at the time of application.

The terms of data management and storage also were set out in the ethics application in 2016, in line with requirements of the time. A retrospective review by the researcher has confirmed that this study was also in compliance with the principles set by the Data Protection Act 2018 and General Data Protection Regulations (Europe).

4.2 Philosophy of the research

4.2.1 Overview of multidisciplinary and combined methods approach

Policy research has a history of grappling with the effects of the political landscape and structural barriers to taking up new knowledge, even that commissioned by the same political units (Leff, 1988). Policy researchers find that complexity due to the multiple elements of the problem poses a frequent challenge (Sheate et al., 2016); this is in addition to complexity

arising from the general lack of information and data relating to decision making in this sector, described in Chapter 2.

The nature of decision making in relation to an issue as complex as the introduction of a novel vector control intervention led the researcher to consider a variety of approaches from various disciplines, to address the study objectives, including political or public policy science, organisational science, systems thinking and similar. The degree to which institutional structure, in aspects such as specialization and hierarchy, determines a shift in policy when new knowledge is introduced is discussed by Daviter (2015). This issue is of particular interest, since the study aims to introduce learning systems that by definition are only effective in systems where learning is feasible. The present study encompasses decision makers both inside public sector structures and outside them. The African and European research institutions providing cases for study are themselves a variety of governmental, semi or fully autonomous and private foundation organisations. This broad range of structures reduces the value of relying entirely on organisational research theory for this study, although aspects are valuable in framing the questions and analysis. Contributions from organisational management research are noted in the discussion of action research, below.

The limited number of individuals actively involved in the area of study during the period covered by the thesis makes use of grounded theory methods less valuable. Other social science approaches considered did not fit the opportunity for learning as well as action research.

A multidisciplinary approach using qualitative methods can offer greater access to complexities (Torrance, 2012), as is often are employed in policy research. The current study sits primarily a level below formal policy, however, at the level of effective implementation of regulations, institutional rules and project practices (i.e. complexity arising from multiple actors involved, possibly with conflicting interests). Such research, spanning different organisational or decision making levels and different sectors, requires a combination of approaches employing diverse methodologies from more than one discipline (Sheate et al., 2016: Table 5.2).

Therefore, this largely qualitative research is aiming to narrate a story and fill in details of opportunities for improved effectiveness for similar situations of novel introductions. The quantified aspects of the research related to ranking of responses in the online survey or, to a lesser degree, interviews and to those frameworks that employ yes/no criteria, such as membership in an intergovernmental organisation or submission on time of a report on implementation of treaty responsibilities.

Some would consider this as a mixed methods approach, combing qualitative and quantitative studies in a pragmatic manner to explain what is and may be happening in decision making for introduction of novel interventions for a very specific aspect of public health. Drawing on the mixed methods literature, of the five purposes of using mixed methods stated by Green et al. (1989), the researcher for this thesis was seeking to (a) complement and (b) expand learning from the various methods as well as gain clarification of results among methods, rather than specifically aiming at (c) corroboration or (d) initiation to reframe the questions; (e) development of results, by using one method to inform the other, was an aspect when considering what to ask in interviews and the survey. Using the taxonomy of mixed methods from Creswell & Plano Clark (2011), the researcher was closely aligned with an exploratory design working from general observation and qualitative methods that led to more quantitative approaches such as a guided interview or survey. Early definitions of mixed methods worked from a perspective of gaining better insights and more reliable validation by allowing a combination of quantitative and qualitative methods to address an issue from different perspectives, which is now sometimes called multimethod research (Burke Johnson et al., 2007). The concept of 'triangulation' was believed to lead to both reduction of error or uncertainty, but also possible new insights when different methods presented an apparent paradox. Torrance (2012) considers triangulation as a key element of mixed methods, but the term has fallen into disfavour by some more recently (Morgan, 2019) due to the variety of interpretations.

The researcher's work, however, was not entirely sequential and different subquestions (outlined in Chapter 1) were approached differently. Given the debates within the field of mixed methods research, and the fact that the researcher is not herself a social scientist, she chose to consider her approach as a combined methods approach, rather than mixed methods *per se*.

Like action research, however, many authors imply a philosophical underpinning to the choice of mixed methods, almost more so than a common definition and strict criteria for the approach (Burke Johnson et al., 2007; Greene, 2006). This might be summarised by Torrance's (2012; p.120) conclusion that: 'the process of producing and using new social knowledge is as important as the knowledge itself'. Learning and improvement rather than unbiased observation and reporting are at the heart of this study.

4.2.2 The action research approach

Much of the study related to experiences with Target Malaria and for this the researcher relies on 'action research', in which the researcher herself is interacting with the other participants

and the process itself[34]. The researcher specifically gained insights into partnerships, the decision point of when to proceed with import of a novel research organism (facilities readiness) and the use of audits and colony pedigree records (discussed in Chapters 5, 7, 8, and 9) in the course of action research beginning simply with how to proceed in this early phase of delivery.

Action research is distinctive as a research strategy because it is an interactive and iterative process that may involve collaboration between a researcher, or researchers, and those carrying out the activities or process under study, even from early stages of defining desired outcomes. In this study, the researcher had a unique access to the development of an international research consortium from the time of initial contact between the Discoverers or technology developers and the potential partners from DEC research institutions (see Table 4.1).

Arising primarily from social sciences, governance and organisational research, and even activism (Abraham & Purkayastha, 2012), the action research approach evolved as research in the 'real world' in which people and processes are not operating under experimental conditions. Its strength is in recognising that in real world situations, numerous factors are at play but the study questions must still be subject to legitimate scrutiny. Gayá Wicks & Reason (2009) argue that this legitimacy is established in the first steps of setting up such a study, by the nature of the initial communications and how they affect the 'communicative space', although this may be from a starting point of a request for an intentional study or from a stance of entering a new setting or community with an openness to learn and question. (The latter was how the researcher first began this study.) Drawing on action research from operational management and industrial settings, Coughlan & Coghlan (2002: p.237) explain how the researcher must present interpretations and incrementally formed theories back to participants in a manner that is 'open to testing and critique'.

The action research approach (as articulated in modern publications) has been employed for two decades in education, community and health initiatives, agriculture, sustainable natural resources management and youth development among other fields (Flood, 2017; Dick, 2010; Dick, 2009; Dick, 2006; Dick, 2004). A similar line of development occurred in industrial and operational studies, including research to enhance group performance (Coughlan & Coghlan,

[34] The various components of the study outside of the action research approach are described further below. Bradbury Huang (2010) emphasises that describing actions is not the same as action research; the presence or absence of meaningful relationships and participation appears to be a good indicator as to whether the study is within that method or using a different method for results. The researcher submits that this criterion was met and she has used this approach.

2002). Much more discussion on the theory behind it began to emerge ten years ago (Dick, 2009). There is as much a philosophy as a methodology behind the application of action research and consideration of the ethical context of the study and the participants' values is required (Coughlan & Coghlan, 2002).

Burns (2014) describes a spectrum from individuals reflecting on their own practices to seek improvement, through to system wide learning. These themes appear again in the interpretation phase of the current study as well, through consideration of enablers and barriers to the steps along the pathways under study. What is meant as action research in this study would fall towards the centre of Burn's (2014) continuum, as a 'group reflection on group endeavour' (which he calls cooperative inquiry) or 'community based generation of knowledge for community action' (participatory action research – this is distinguished from action research in which a facilitator has the main power of being the common element across various inquiries; although the current research is not a geographic community but rather a research consortium community). Action is the goal, but action that is based on knowledge arising from community learning, rather than being imposed entirely from external or hierarchical sources. This type of research can only take place within the context of relationship.

Figure 4.1 shows the interface of the key components of action research (adapted from Gaventa & Cornwall, 2001), but also the cyclic nature of the data collection, analysis and feedback steps in action research (adapted from Coughlan & Coghlan, 2002)[35].

One benefit of an action research methodology especially relevant to this study is that it allows capacity building and increase of skills in the course of addressing a particular problem or issue (SDRN, 2011), rather than awaiting the conclusion of research in order to apply the learning gained. The researcher relied on detailed records of each interaction, discussions between key events and consortium internal review of her theories as they arose and were developed.

In addition to the approach of extensive documenting the progression of knowledge development and evolution, the researcher has the added unique benefit of long term engagement with the consortium to allow for new ideas or input, follow up conversations and

[35] Although the steps of a learning history approach are not dissimilar (e.g. interviews for data collection, 'jointly told tales', consideration of enablers and barriers, etc.), Kleinsmann & Valkenburg (2008: p.373, Figure 1), among others, represent this in a linear fashion – moving from data collection and processing to analysis. Coughlan & Coghlan (2002) suggest that not only is it a cyclic process, but one must go through the cycle at least twice to achieve action research.

other opportunities to refine the work subsequent to the formal completion of the action research phase.

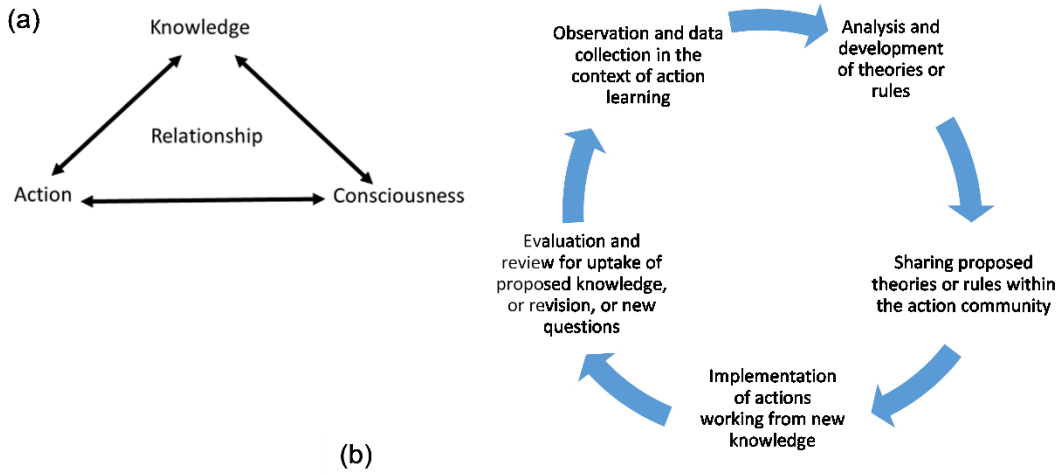


Figure 4.1 Main components (a) and the cyclic nature (b) of action research

Action research often gives pragmatic criteria more weight than theoretical ones, in terms of declaring research successful and valid (Reason & Bradbury, 2001). Or as Greenwood & Levin (2007) suggest in regard to action research, the value of pragmatic research is whether the specific community involved acts on the results. This is one reason it is employed in development projects, when implementation study questions are presented but funding streams, work plans and deadlines do not allow for a pre-implementation study phase. This is particularly the case when a project or initiative involves situations with significant emphasis on highly efficient use of resources. In this approach, the research focuses on how to achieve a desired outcome or change, rather than being purely observational of this process. The action research methodology addresses the need to deliver evidence towards answering study questions, while also producing results.

4.2.3 The researcher as facilitator

Early in the study, the researcher considered using metrics of trust and confidence as part of the context for decision making on vector control. Ideally, if there are competing values and motives between the researcher and the participants, these would fade into the background as trust is built by identifying and striving for common goals (SDRN, 2011; although see discussion of trust in Box 4.1). The common goals and larger societal values underlying participation in a health related project such as vectored disease control supported this

relationship among participants[36]. External stakeholders, however, such as regulators, would need to trust the research teams in order to proceed with objective review and evaluation of applications for import and contained studies of the research mosquito strains. (Community engagement was key to this process, but is not discussed in this study.) Box 4.1 explains why this line of enquiry on trust and confidence was left aside, despite presenting a rich field of inquiry.

In this study, the researcher became a type of facilitator for a highly technical process – preparation to deliver a novel intervention in vector control, a particular field of expertise for which she was a relative novice. The vantage point of an observer who was engaged but external to the research team, however, was useful for identifying principles or rules of the process and extracting or highlighting lessons from the acknowledged experts. This is what Wadsworth (2001) referred to as being a facilitator of co-researching, but is referred to as co-learning in this study, or co-development in regard to the Target Malaria products.

The method also can expand knowledge beyond the fields of expertise of the main actors. Pålshaugen (2004) considers how an action researcher, acting as a facilitator, can enter into the language of the group under study, sometimes literally by choosing particular words, to provide 'supplementary' not 'superior' knowledge. The researcher, in the current case, presented a vocabulary to the acting group in order to achieve an agreed way of talking about 'the way forward' and subsequently for organising the results of several of the steps in delivery of the novel intervention (for example, see Quinlan et al., 2018a).

While pure observational research aims to avoid influence on the study outcomes, there are situations in which the researcher is present and participating, leading to possible influence of outcomes. This participatory research also provides an opportunity for more in depth review of a process and outcomes, in realistic settings and situations. The researcher as facilitator, in fact, can identify the differing objectives or areas of particular interest that naturally arise within a group of people, and support more intentional discussion across these including where groups have blind spots to the realities of others (Reason, 2006).

[36] Such work in a DEC inevitably involves people who have been affected by the target disease, who then unconsciously become the awareness raising agents for those entering research from other geographic or disease free areas. This very process, though subtle, could be observed in the current study as described, for example, in Chapter 7 regarding preparations for contained studies.

Box 4.1 Trust and confidence as indicators of the decision making landscape

After DEC partner selection for Target Malaria (although the project was not yet named as such), the researcher started developing a joint approach to preparing containment facilities, procedures and staff for the first known import of a GM mosquito to Africa. Import of the research strain into a containment facility was considered an important foundation for a number of activities in the process of delivery of the intervention. (In fact, following the stepwise approach, the first strain was for training, not as a potential product. This was described in a poster at a MESA - Malaria Eradication Scientific Alliance - meeting in 2017: Sylla et al., 2017, shown in Appendix 3). At the first project activity aimed entirely at preparing facilities (Entebbe, May 2013), the researcher already had a proposed theory of 'the way forward' based on initial discussions with colleagues. This theory involved two concepts:

Confidence, defined as a belief based on experience or evidence, that certain future events will occur as expected.

Trust, considered to be a willingness to make oneself vulnerable to another, based on the judgement of similarity of intentions or values, and in expectation of beneficial outcomes.

The first concept was presented as something that could be increased by delivering against specific performance criteria; a more evidence-based set of being. Confidence was created based on historical experience with an entity, or with a premise (e.g. science, or genetic modification). The objective was to put in place what was needed to achieve confidence in terms of people, such as regulators, relying on the project to control the person's exposure to any hazard or risk. The presence of trust allows one to establish a record of experience, underpinning confidence. Trust, on the other hand, began with shared values, morality, social relations and so forth. Trust generally is offered as a choice among alternatives, rather than offering trust to all. The specific actions taken are less important than the framework of shared values. The proposed theory then was to set up a system that would provide the evidence needed to generate confidence within the team (confidence about their own competence to carry out the work) and between the team and regulators (confidence that the preparations for import were adequate and appropriate and would guard against risks). An initially unconscious objective was to do the same between the DEC teams and the central Discovery team. This theory was not stated as such, but was rather presented at the start of a four day meeting.

The researcher found, however, in an informal poll of participants that trust and confidence did not reflect expected outcomes based on those definitions. Trust was high, but so was confidence. In fact, confidence has been found in other projects to track up and down based more on the realisation of the additional skills and learning needed, than on the reality of capacity (Quinlan et al., 2016c: p.9). From that experience and initial reactions, the researcher realised that additional training in Target Malaria – which in fact would reveal the difficulty of working with the type of strain used in the project – could even cause confidence to drop, just when competence would rise.

Further consideration of trust appears in the discussion of partnerships (Chapter 5), however, and the terms continued to be used in later meetings on facilities readiness by those who had participated at the first one. The researcher's conclusion was to seek to measure preparations against agreed technical concepts and benchmarks, rather than considering individual perceptions of readiness (Quinlan et al., 2016c: pp.18-19). To this end, the researcher proposed the framework described in Quinlan et al. (2018a) and Chapter 7 comprising the three themes of compliance, colony utility and defensible science, and drafted a checklist for facility audits, as discussed in Chapter 8.

The researcher's facilitation in this study was more an act of bringing energy to an inquiry on 'the way forward', which inevitably is determined in large groups or projects but possibly with less consciousness of the process or in an entirely hierarchical manner. Facilitation was an act of shining a light on what was being learned, which aligns with the awareness or consciousness aspect in Figure 4.1a, then articulating or developing theories and sharing them back in the action community, shown in Figure 4.1b.

In this instance, the cycle of observation, analysis and testing took anywhere from minutes to years, depending on the issue at hand. This is because the study did not present a single all-encompassing theory, rule or framework, but rather a series of smaller contributions relating to individual issues or decisions (making the Theory of Change schematic, discussed below, particularly useful to achieve an overview of comprehension).

4.3 Background for collecting and interpreting data

The need for higher quality data in policy studies is balanced against the need to include 'all available evidence', when various sources can provide input but possibly at different levels of prestige or acceptance, to support proper evaluation (Lenihan, 2013). That review (Lenihan, 2013) and others (Baldwin & Black, 2016) warn of the separation of data into different domains, which can make access for multidisciplinary studies problematic. Another review states that including all types of decision makers (in this case in a health related theme) allowed for 'better understanding of how cross-cultural and …system variation impacts' uptake of evidence-supported recommendations (Wallace et al., 2012: p.343).

The research presented in this thesis is at the interface between decisions at the level of national policy and straight empirical research around the laboratory practices and processes associated with novel technology development. It relates to the effectiveness of the decision process more than improved efficacy of the technology, so that it is largely-operational research to improve knowledge on interventions, tools or strategies that enhance programme effectiveness (Durrheim et al., 2002). As already noted, technological advances must be coupled with feasibility of implementation, which inherently requires multidisciplinary approaches (Pattanayak & Haines, 2017).

Decision making is considered at various levels, however, including international, regional, national and local. The present study is working within a complex environment of competing or, at the very least, uncoordinated objectives expressing varying weight in terms of influence on final decisions. This led to a more cyclic approach of considering the way forward and

effectiveness (e.g. Box 2.3), while simultaneously seeking clarification of objectives and the appropriate targets for monitoring success[37].

This context led the researcher to choose a range of data sources. This study includes a wide range of sources and topics, which required various methods. Some limitations of this choice, and of the methods themselves, are discussed later in this chapter.

4.3.1 Analysis from observation and experiences

The first aim for this study was to document the current state of play of the larger issues of a novel vector intervention as robustly as possible (started in Chapter 2, e.g. Table 2.1), including the various layers of decision making and how the considered responses of each participant related to each other.

Data or observations, unique to the research presented here, relate principally to personal experiences and opinions, reflecting a particular period in time and phase and progress of the laboratory research (referred to as the delivery phase, see Box 1.2) in a specific project, the Target Malaria consortium. Theories and proposed good practices derived from the research were then returned to the project for use and feedback. Additional rigour was applied for some components of the study by testing against other frameworks, existing practices, other cases or approaches.

4.3.2 Literature review

The researcher relied on past experience and extensive literature review to define the problems and explain the context for delivery of a novel intervention. Published and unpublished literature also directed the selection of methodologies and informed the interpretation of findings. Parts of the overall literature review are incorporated into each chapter, rather than as a combined separate chapter, due to the complexity and range of topics touched on or influencing the research. Dividing it this way was considered to be more user friendly.

[37] It should be noted that there were clear objectives and targets for the project studied, just as there were for the other decision groups (e.g. National Biosafety Committees). The tension of objectives was because of the mixing among primary objectives related to health (malaria), and those related to biodiversity (biosafety framework), biotech product development, scientific discovery and academic prestige and so forth. The Logic Model (such as described in HM Treasury, 2011) behind the Theory of Change was therefore developed in line with the project's approach, rather than the entire range of options for the delivery of a novel intervention.

Literature about uptake of the results of the research was also searched. The period of the study coincided with the re-emergence of an emphasis on evidence to support analysis, interpretation and decision making in the policy realm, as well as in health research. The 'evidence' literature generally reinforced the plan to use learning frameworks rather than attempt to find common factors that could be accommodated into a framework that limits variability of data or responses.

Much of the literature was collected over time opportunistically, as issues arose, then complemented by a more directed search (dates of which are shown). The use of key word searches was not effective for the exploratory nature of the study, until a specific subtopic was queried. Defining key words for a search at the beginning of the study would have eliminated the majority of literature, which was found through various means described below. Instead, the researcher took advantage of numerous and sometimes unique opportunities interacting with the researchers in the sector under study, and ancillary sectors such as the OECD biotechnology team, to identify the most important texts for each topic. Table 4.2 summarises the themes reviewed in published literature.

One method applied to the literature review across the topics was to follow up on references cited by the most relevant papers and to monitor Research Gate for publications of related interest. Research Gate also allowed the researcher to follow particular authors of interest, and to see who was reading her publications related to this thesis, thereby introducing her to possibly new sources of related research. Greenhalgh & Peacock (2005) established that for complex policy questions, for example, protocol-driven electronic searches will fail to identify a significant portion of valuable literature when used in isolation. They found that 'being alter to serendipitous discovery can substantially increase the yield and efficiency of search efforts' (Greenhalgh & Peacock, 2005: p. 1065); the greatest return was from following up on references or later citations of key articles. They also concluded that existing knowledge and personal contacts such as through academic networks could contribute more efficiently than an electronic search using terms defined at the beginning of the study. Over the course of a decade of working on innovative vector control, including attending meetings and conferences on the topics, the researcher has met many of the authors appearing in the references list at the end of the main thesis. This personal contact has further enhanced literature review and understanding.

Table 4.2 Summary of literature review for this study

General topic searched (or specifics sought after particular information was identified)	**Approximate timing of main review and primary approach for searching**
Vector control and emerging genetic strategies for mosquito control	2010-2019: ongoing check on work by key researchers in the field; Google scholar searches related to key words from this research and reference follow up from key articles
WHO and other institutional structures and procedures for health intervention evaluation	2010-2019: list serve subscriber to Roll Back Malaria and WHO malaria topics. Targeted search for terms of reference and reports from new VCAG. Upon annual publication or reporting on routine meetings
Malaria control and eradication of malaria	2011-2018; directed word search and following key journals, e.g. *Malaria*
Drivers of change in vector control such as pesticide resistance and climate change	2012-2017: searching for review format articles, following researchers focused on these issues (e.g. Hemmingway)
Product development (vaccines, pharmaceutical, medical devices, etc.)	2010 – 2015: attended meetings of Wellcome Trust researchers, Imperial College speakers; followed journals such as *Health Policy*
Site and partner selection in North-South research partnerships	2011-2017; same as genetic strategies for site selection but little was found on partners; sustainable development literature and targeted review of FAO and other UN agency publications
Biotechnology and innovations; national innovation systems	2011-2015; literature was identified in advance of Erasmus + interviews (e.g. OECD), that gave ideas for the PhD study, but also suggested from those interviews
Ethics, community engagement and the role of review boards	2014-2016; targeted search on ethics review in Africa; correspondence with Wen Kilama and following AMANET
National biosafety frameworks and Institutional Biosafety Committees	2010-2012; Biosafety Clearing House webpage; targeted search and leads from interviews
Laboratory design, audit checklists and laboratory biosafety	2013-2019; suggestions from Target Malaria colleagues, interviews with both Discoverer and DEC labs; targeted search for audit and laboratory biosafety
Action research, complementary methods such as Theory of Change	2012 – 2017; added when clarified as the key method for the study
Policy research, uptake, evaluation, implementation	2016-2018: attended conferences on plant health, biological businesses, and DfId and Defra workshops; some ideas from participating in Newton Fund project reviews

Other approaches to policy research (not selected)	2018-2019; to better set the context of approaches that were chosen
Project planning and management methodologies	2016-2018; follow up on methods used over years for various funders, e.g. FAO, USAID
Learning systems, checklists and report card templates; risk and risk-based frameworks	2010–2017; routine reading on risk frameworks; following key authors in department (CEP); targeted searches on learning systems
Traditional biological control, areawide pest control and introductions of beneficial organisms	2010- 2019; routine reading on biocontrol and areawide control; attended international and European conferences on both topics
Genetically modified crops and historical issues related to genetic strategies	2010-2012; extensive literature provided through contacts at the ISBGMO meetings, and from a small group seminar at CEP focusing on alternative perspectives
Regulation of genetically modified organisms and other biotechnology, particularly in Africa; Cartagena Protocol and other international frameworks	2010-2018; extensive searches in 2010-2011 for figures in Chapter 5, which are described there
Health systems, evidence for health decisions and introduction of new health interventions	2011-2013; after internal searches [innovation; malaria; Africa] within some key health journals, the researcher set up notifications for citation of a few key articles. This continued to 2019 but became less valuable after the initial searches.
Enablers/facilitators and inhibitors/barriers to achieving policy implementation, or progressing a pathway of influence	2012-2016; policy seminars; follow up of references for key publications of relevance; training with the ISEAL
Organisational culture, capacity and training	2014-2019; meeting with Sandia Labs; ongoing reading on capacity development for malaria or similar networks; follow up on organisational culture literature from seminars
Trust and credibility	2010- 2015: The researcher is a member and has been trained by ISEAL on issues such as credibility of standards. This line of study was abandoned by the researchers for her particular research questions, but is recommended for future work (Chapter 11)
Interview and survey methods	2015-2016: The researcher acknowledges her supervisors' particular contribution to this enquiry on methods.

This approach has been used in business studies and is referred to as chain referral sampling, or 'snowball sampling' (Suri, 2011), and seemed to the researcher to be particularly

appropriate to the exploratory aspects of her broad range of literature reviewed. A more systematic review, such as described by the Centre for Reviews and Dissemination (CRD, 2008) was conducted on the key topics of genetic strategies for vector control. The standards proposed by CRD (2009) are in line with the seriousness of patient care and applications to health studies. There is in fact an increasing number of publications on innovative vector control interventions. Many of these are not included, however, because they are very specific to Aedes mosquitoes or other vector species. For this ongoing and systematic review, the researcher defined the parameters by: genetic strategies against vectors for malaria control, as a subset of all novel interventions affecting malaria transmission; and of genetic strategies for control of other types of vectors (including areawide control of insects and SIT). Another thread was malaria interventions in sub-Sahara Africa, as a subset of trends in malaria reduction and control. The initial review questions were:

- What are the current practices for decision making in this sector?
- Who are the decision makers (although this question was fairly well defined already through direct discussions)
- What are the barriers and enablers to effective delivery experiences by these decision makers?

A second thread was more specific to the interventions:

- What is unique about use of genetic modification or transgenic mosquitoes?
- Are there useful practices from comparable field interventions, such as biological control?
- Are there other interventions that are subjected to early phase review, to increase efficiency of the research towards impact?

This approach was not randomised, but rather purposeful and directed. The researcher believes that the bias introduced, first by only working with literature published in globally recognised journals and second by focusing on the higher impact journals, was tempered by the fact that many of the publications arose from a number of countries and research groups. Since Imperial College London is considered a lead university globally, the researcher also cross checked her selection of sources by attending lectures presented by the informal malaria network of the university led within Life Sciences and later, since October 2017, by the formalised cross-departmental malaria network (https://www.imperial.ac.uk/network-of-excellence-in-malaria).

In addition to the technical content of literature considered, articles discussing the impact of layout and presentation of material were also informative (McKinnon et al., 2015; Foster, 2014; NICE, 2007). For example, in an analysis from 20 systematic reviews for improving quality of patient care, the top five identified facilitators to uptake were identified: (i) usefulness to the target decision maker; (ii) that the study presented various perspectives (e.g. benefits, harms, costs); and that presentation of the systematic review was in (iii) an accessible format including a page with the take home message, as well as a short summary but also gave access to a longer detailed paper for further reading; (iv) that there could be training in the use of recommended actions and (v) peer-group support was demonstrated (Wallace et al., 2012). The value of simple checklists, based on deep underlying research and validation, has been established in other fields (Haynes et al., 2009; WHO, 2009; World Alliance for Patient Safety, 2008; Gawande, 2007), although use of such checklists also may improve with training.

The researcher acknowledges a significant bias to her literature searches relating to publishing in English. Although she read some literature in Spanish and French, the general search approaches greatly limit the results to those with titles in English and at least a summary or abstract in English, if not the entire article. This is not unlike the 'hit rate' of better known journals masking some important contributions in lesser known ones, but the chain referral approach can reveal some of those publications (Greehalgh & Peacock, 2005).

4.3.3 General project planning methods

A major component of this study was the observation and learning from a single project, as described in Chapter 2. Projects (which are initiatives with defined objectives, resources and time frames) are supported with tools or methods for advance planning, ongoing monitoring and evaluation (M&E). A number of existing management tools are employed by the project and were considered as complementary methods for this study including: working back from a shared vision to the activities required (Outcome Mapping), mind mapping (using MindGenius® software), problem formulation meetings, and development of checklists. For development and health related projects, these approaches have been supported, or at times required, by multilateral and national donors in order to verify the thought process in the planning of interventions and also to inform monitoring and evaluation. Domestic programmes, with internal government funding, may also be supported with these methods, including input from various projects.

Logical Frameworks, or logframes, achieve a similar representation by objective, but following a hierarchical structure based on assumptions regarding cause and effect. A recent training manual in Logical Frameworks (Umhlaba Development Services, 2017) provides a useful

history of the application of the method for problem analysis and project design, particularly in the development sector. Smith et al. (2012: p.21) describe this approach as a planning, monitoring and evaluation methodology 'that conceptualises an intervention in terms of a hierarchy of objectives that are linked in a cause-effect relationship: Activities result in outputs which result in outcomes that cause impact.' This is another methodology that can be used on its own, but also can be combined with other approaches. Frequently the emphasis of logical frameworks in use has been on project deliverables and deadlines or milestones, viewed in a more linear fashion. The method remains popular with funders as a way to determine that the proposed activities and resourcing should result in the desired outcomes. The uniform format makes it easy to use across multiple projects. This method implies a level of control and influence, however, with a listing of assumptions about what supports and, if not accomplished, may alter or delay results.

A Gantt chart may be created from a logical framework to show much more detail on roles, responsibilities and assignments; timing; and resources required as well as the linkages of various activities that influence each other. With current software support (e.g. Microsoft Project), a Gantt chart can be displayed at an overview level more similar to a Logical Framework, or narrowed down by a single objective or task. Project planning software permits one to go from the top level objectives to the most detailed level of activities. Gantt Charts also are frequently required by funders to determine the exact status of progress towards planned objectives through project implementation. The Target Malaria project operates against a detailed Gantt chart, which is continually revised and refined over the course of the activities.

Outcome Mapping methodologies, generally considered to be formalised about 20 years ago (Earl et al., 2001), were also reviewed as a progression beyond the Logical Framework approach in terms of elaboration of desired outcomes. The researcher was given the opportunity to informally survey thoughts on the highest level of desired outcomes at a Target Malaria project meeting in 2013. The statements reflected what project participants described as desired outcomes for the project by 2023 (ten years on). The researcher found that statements fell into four categories: product related outcomes, governance and regulatory related outcomes, stakeholder engagement outcomes and disease related outcomes, depending for the most part on the field of expertise of the respondent. This method was employed further by the researcher when leading country-level training, to elicit specifics regarding what would be desirable in case of a serious incident and to support disaster preparedness (after focusing heavily on prevention up to that time). This was followed through with detailed planning from the agreed desired outcomes (given a bad situation had in theory already occurred), back to the current period when preparations should be made. The method

helped clarify action items and equipment needs, and dispelled the idea that the consequences of a disaster cannot be mitigated. In both cases, albeit showing very distinct uses of the method, the outcomes could be located within the Theory of Change for the project (see 3.4), that was developed by the researcher over time and is presented in the discussion of the study, Chapter 11.

Literature and general project management tools contributed to the development of the context in which delivery of a novel vector control intervention would occur, specifically that being developed by Target Malaria.

4.4 Interviews, an online survey and a participatory symposium

Three approaches were employed to collect personal observations and collate experiences: guided or semi-structured interviews from parties external to Target Malaria[38], an online survey and a participatory symposium, in order to engage the largest cohort possible from each category of decision makers identified (see Chapter 2) to supplement and validate results from in depth action research within one research consortium, as described. Table A1.1, in Appendix 1, presents all documentation used for data collection through interviews and the survey.

4.4.1 Guided interviews

Guided interviews were employed as part of collecting information from DEC research laboratory teams outside of Target Malaria and to verify the researcher's perception of action research results from within the project. This approach was also used for Discoverers or potential sources of research innovations, focusing on the leading British institution for the focus project (Imperial College London) and French institutions, considered to represent cultural contexts in French West Africa for historical reasons. Guided interviews were conducted with DEC Regulators representing East and West African countries, both internal and external to those home to Target Malaria partner institutions.

Guided interviews are useful for exploring complex issues and to build a narrative to draw on for understanding barriers and enablers to each group's role and decisions involved (Creswell & Plano Clark, 2011). Questions were related to personal experience and opinions, reflecting

[38] A guided interview format, shown in Appendix 1, was also used to encourage final comments and to wrap up the process of action research within Target Malaria. These interviews (Table 4.1) took place with country level PIs and one management level participant from a country that did not continue within the consortium.

a particular period in time and in the phase and progress of the laboratory research. Guided interviews allowed the speaker to add more material, or take a different direction in narrative, than a written survey would have achieved, while at the same time ensured certain topics were covered and not forgotten in a free flow interview with no guidance.

DEC lab researchers

Guided or semi-structured interviews, both internal to the project and external, were designed to be a verbal exchange, to share experiences and personal opinions.

Within the Target Malaria project, those interviewed were at the country management level, and were staff who have worked within the project for some years. This included country PIs and one former project staff member at management level, thereby representing four countries. It was made clear before interviews that the specific responses would not be shared with the overall project management or third parties, including within the same research group. That said, some interviewees preferred to conduct the interview in the presence of others, and in those cases responses were heard. An email explaining the process and requesting an interview was sent to each project interviewee in advance, allowing some time to consider the request. Although participation in the project has been agreed under terms of a collaboration agreement, participation in this research was clearly identified as optional.

Similarly, staff from two DEC research institutions working with other types of innovative vector or disease control were interviewed to understand issues in research and implementation outside the Target Malaria project. These interviews provided personal opinions and experiences, within a context of institutional policies and practices that are either published or observed by the researcher. The same consent forms described below were adapted to the interviews for external parties. The outcomes and responses are anonymised or, alternatively, publicly available materials are cited to support conclusions first derived from external interviews and the survey.

DEC Regulators

Regulators were invited to participate in face to face interviews either at the margins of a regional workshop and training on the subject of novel vector control with transgenic mosquitoes, or with the researcher visiting the Regulator's office, following advance arrangements. The questions discussed appear in Appendix 1, along with other documents used for recruitment, information and consent (as explained below). Those interviewed at the

regional workshop were asked in person for the opportunity to interview, rather than by email, but were given at least a day to consider their consent before the interview took place.

Discoverers

In depth interviews took place with two researchers working in discovery labs providing innovative technology, involving vector control interventions. In addition, the Erasmus+ programme of the European Union supported the researcher's enquiry into partnership styles through interviews with three French and two international institutes working with novel interventions for health or agriculture, as a comparison with the British approach experienced within the study project. This contributed to her understanding and framing of this related questions for the PhD study. There was no attempt to use these parties as 'controls' but their experiences outside the process described for the project of focus contributed additional perspectives. The difference in cultural perspectives was also noted.

In these instances, and for the project-internal interviews, the written questions were offered in case that made the person being interviewed more comfortable, but no one preferred to only read them; therefore, the researcher asked the questions verbally. Each group or individual approached was given background on the study, an opportunity to ask questions or not participate. For each in person interview, a consent form was offered and the participant signed before the researcher asked questions. (Consent was given verbally in some telephone conversations or remote meetings using Skype software, although the offer was made to send a consent form in writing.) The recruitment email (if used), information about the study, consent form and questions for guided interviews also appear in Appendix I.

The time and place for the interviews were prearranged for the participant's convenience. Each interview took approximately 60 to 90 minutes. The interviews all took place in English, which was a point highlighted at the time of recruitment and in the consent form. The decision in advance was to exclude those not comfortable being interviewed in English, due to limitations in resources to have professional simultaneous interpretation and the need to fit interviews into busy schedules, so that the final timing of interviews was not always predictable. The choice of language was not an issue, as many who participated had advanced degrees from English-speaking universities or were already participating in English-speaking events at the time.

The respondents were told in advance that specific content of any response would be treated confidentially or in an anonymised manner. Notes and responses from the interviews were

treated as confidential material and will be destroyed within three years of completion of this study and/or published articles.

4.4.2 Online survey of Discoverers

An online survey was developed to understand how technology innovators, assumed to be located outside DEC for this type of innovation, have selected partners in DEC research institutes in order to take novel research further along the development pathway. The format of an online survey was chosen in order to reach the broadest range possible of respondents, with targeted emails and broad network requests going out to researchers in Europe, the Americas and Asia. Although the responses are not considered to be representative, due to self-selection of participation, the material provided further narrative to complement direct experiences from a single project and aimed to identify any obvious bias due to the limited number of countries involved in Target Malaria.

An online survey in English was developed using a Survey Monkey™ platform, with the direct link provided to potential respondents. This survey platform is well known and widely used, and economical for the researcher. Academics and researchers are accustomed to taking such surveys, and often respond as a professional courtesy. It is an efficient method for collecting a wide number of responses on a limited set of questions, without the opportunity for in depth discussion or verification.

The survey instrument (shown in Appendix 1) appeared online in a more streamlined, user friendly format that adapts to the answers provided. Respondents were allowed to skip or partially answer questions, according to a logical hierarchy.

The survey covered six topics relating to partner selection:

1. Overview of collaboration with DEC researchers (e.g. status of work – current or past)
2. Details about the respondent's role in partner selection
3. Criteria for selecting a country or site
4. What influenced partner selection
5. Outcomes to date from this partnership
6. Challenges, successes and recommendations

The questions covered both research and organisational topics, and were estimated to take 15 minutes on average to complete. A bar showing progress towards completion was displayed across the bottom of the screen, to encourage completion.

The pool of potential respondents is a fairly limited and well known set of people (identified by publications and participation in projects in the general subject of innovations in vector control), who are highly educated and able to respond in English. The researcher began to identify this pool through publications, grant awards and participation in related meetings. The plan was to contact approximately 200 potential participants with the aim of obtaining a minimum of 25 responses in order to include the material, although 25 was chosen as a number that would maintain some anonymity in the responses rather than for any statistical significance. An initial trial of contacting a sample of eight individuals with a recruitment email, however, was not considered successful. The approach was modified to contact individuals through networks of relevance to the study, so that the recruitment email referred to the researcher but originated from the network manager. All of the managers of the three networks (two formal and one ad hoc) agreed to send the online survey recruitment email, although one provided the emails for contacts whereas the others made contact directly with their networks.

Inclusion in the survey from within these networks was based on self-selecting consent to fill in the survey (through a pop up consent form requiring response prior to the survey opening). As reported in Chapter 5, a total of 50 researchers responded as self-identifying as someone working on novel approaches to vector control, although less than half answered all questions in full.

Online survey responses were collated by the Survey Monkey™ software, presenting results by respondent (anonymised by number) and by question. Simple percentage spreads were calculated for multiple choice or ranking questions. Those questions with fill in answers were collated using the exact wording from individual respondent records by the researcher, for her analysis of trends or key points. Results are discussed in Chapter 5.

4.4.3 Informal focus group and Symposium

The third approach was to convene a symposium[39] about best practices for regulators to engage with the public, at a biennial conference of the International Society for Biosafety Research Conference (ISBGMO) held in Cape Town, South Africa in 2014. This forum was chosen because of its long standing role in the sector (2014 being the 13th conference, generally occurring every two years) and its focus on regulators of biotechnology. The 2014 session was chosen because of anticipated higher participation of African delegates,

[39] Sheate et al. (2016) describe workshops as 'a series of meetings emphasizing interaction and exchange of information among a usually small number of participants' and identify the approach as an accepted method for evaluation of policy. A similar application may be used for a topical symposium.

compared to the ISBGMO conferences held in the United States of America, USA, (2012) or Mexico (delayed to 2017).

This issue of stakeholder engagement had been identified as one of the primary challenges for regulators, in part from discussions at an earlier ISBGMO conference (2012). The process of information collection began with an unstructured focus group activity in which the researcher asked the selected speakers specific questions about their experiences with stakeholder engagement, some months prior to the symposium using remote meeting and email discussion. This formed the basis for initial observations that were considered in the symposium. Speakers represented both North and South national regulators and an industry representative. The researcher worked with another convenor in the preparation and facilitation of the symposium[40].

Results of the symposium presenters' experiences were complemented with summaries of experiences from the symposium participants, which were elaborated on through follow up emails from the researcher. Finally the researcher added findings derived from literature about a European stakeholder consultation to complete the resulting published article (Quinlan et al., 2016a).

4.4.4 Approval and consent

The researcher prepared the survey and guided interview questions about experiences and opinions, and subsequently guided interview questions about the use of the tools and frameworks. The former was described and copies of all documentation appears in Appendix 1. The research related to vector control directly and to health systems only indirectly, and was not considered to be health research by the Imperial College London review process at that time (see note 4.1). Individual health matters were not discussed. No medical research was conducted under this study, according to the definition of the Imperial College Ethics Review Committee policies. The target respondents are well-educated professionals, over 18 years of age and familiar with the topics considered. The study did not involve any groups considered to be vulnerable.

The researcher used a project information sheet and consent forms for individual interactions (versus online), to ensure that participants understood the purpose and nature of the research. The researcher retains signed consent forms on file in a confidential folder until three years

[40] Joe Smith, formerly of the Office of Gene Technology Regulator Australia, was the co-convenor. The ISBGMO program committee also offered useful input for the initial selection of speakers, and thus of focus group members.

after the first publication of any interpretation of the responses, including this thesis, at which time the consent forms revealing the identity of each individual will be destroyed. The researcher asked whether the respondents' own institutions required ethics approval or a particular procedure, in order for them to participate in such interviews. In all cases individuals reported that their own consent was considered to be adequate acknowledgement of understanding the study.

There was no compensation or personal material benefits to participating in the research, beyond possibly basic hospitality of food or drink during the interviews. The benefits are for a larger community of researchers working to reduce or eliminate malaria, and other mosquito vectored diseases. Participation in such surveys or interviews is a common practice among colleagues in these fields, and would not be considered unusual. Therefore, the researcher considers that all steps were taken to demonstrate approval and consent for the research reported here.

4.5 Theory of Change as an organising method for the research

Action research has been described as studying multiple stakeholders in 'multiple inquiries connected horizontally and vertically' in order to understand what is needed to achieve the targeted objectives (Burns, 2014). Theory-based (versus simply logic-based) methods 'provide an overarching framework for understanding, systematically testing and refining the assumed connections (i.e. the theory) between an intervention and the anticipated impacts' (HM Treasury, 2011: p.57).

Participation and relationship are central to this methodology. For example, health behaviour research has shown that 'engaging the actors in the process is the best way to bring about change amongst them' (Darnton, 2008: p.20). Numerous aspects of delivery of a novel vector control intervention are not covered by this study, however, but can be acknowledged in an overview schematic.

Additional existing methodologies have been used for framing the challenges faced in delivery of a novel intervention in vector control, as well as for data collection, and in the presentation of the research in order to organise the contextual concepts and to reveal underlying assumptions[41] as well as possible links among the various levels of interventions. Key among

[41] In this context, the assumptions are what 'needs to be true for a causal chain to operate' (White, 2015), rather than assumptions related to the participants' pre-existing perspectives or attitudes. For example, the assumption at this phase of Target Malaria (and for this current study) was that a novel

these methodologies was the Theory of Change approach to graphically show the relationships and pathways of multiple actions, outputs and outcomes to longer term impacts, finally producing the long term change, in this case of ending malaria. (In this study, the delivery of a novel vector control intervention to reduce malaria transmission was considered to be an 'impact' because (a) this would have effect on the burden of malaria with or without the other necessary changes to achieve elimination of malaria and (b) there are various pathways and interventions that would contribute to this impact, with those identified for delivery of transgenic mosquitoes being only one.)

Comments from Smith et al. (2012: p.22) help to describe how the two methods of research, action research and Theory of Change, could relate [bracketed comments added by the researcher]: 'Theory of change provides a model of what an intervention needs to do to achieve the desired outcomes [a key starting point for action research]. Unlike a simple cause and effect model it articulates the mechanism by which action contributes to an outcome thus making assumptions explicit. The model of how an intervention is supposed to work can be monitored and evaluated to establish if the rhetoric matches up to reality.'

4.5.1 Theory of Change in relation to other project planning methods

While Theory of Change may reflect real life situations more accurately, with a variety of formats and representations possible, the lack of uniformity and structure in this method does require more attention from funders managing a portfolio of projects. Theory of Change provides more of an overview and allows for other sources of influence.

In a study of the outcome mapping methodology, the majority of cases reviewed appeared in developing country contexts and also during the planning phase rather than for monitoring and evaluation. Its application was found also in regional and global organisations, however (Smith et al., 2012). This same review identified criteria for when the methodology is most effective:

- Complexity and uncertainty exist about how results will be achieved
- Willingness to engage with the complexity
- Commitment of one or more champions to the method

Optional additional criteria for employing this method were funder support of the method; support from the implementing organisation or its executive; an organisation with a learning

technology exists and has achieved a proof of concept, and that progressing towards delivery required inclusion of DEC partners.

culture; appreciation for monitoring and evaluation at multiple levels and resources to implement the outcome mapping (Smith et al., 2012). These three required criteria were present in the current study, along with interest from the executive group of the project and resources in the form of the researcher.

Predictive quantitative models are used extensively for various aspects of genetic strategies, although primarily for biological and disease factors (e.g. Liu et al., 2014; Huang et al., 2007). While this type of method is outside the remit of the current study, the researcher participated in development of various plans based on models for answering questions regarding the best approach for field releases in Burkina Faso, if the technology proves efficacious and is approved (presented as a poster by Habbel et al., 2017, shown in Appendix 3). Darnton (2008) distinguishes models that aim to explain and possibly predict behaviour and the Theory of Change approach. The latter considers what change is needed and how to achieve it.

Despite the suggested application for future monitoring of activities, the Theory of Change was formed first from experiences with the project under study, as well as participants' experiences in other settings. Evaluation methods are generally considered to be retrospective, in the best case with historical reflection providing useful clues to better work in the future. Sheate et al. (2016) considered how evaluation of policy formation and implementation can contribute to the policy under study, in terms of improving the chances of success in reaching objectives, as well as improving future policy decisions. Evaluation can also be used to clarify objectives and appropriate indicators for the policy, and to provide accountability for use of funds, for example.

In this context the value of the Theory of Change approach is to recognise that multiple factors – including many outside the control of any single project or even a national programme – influence the delivery of a novel technology. The logic presented in this way permits the researcher to reach valid recommendations on best practices, despite other influences and potential areas for improvement in the overall delivery process. It would be difficult for the current study to collect sufficient evidence to prove or disprove a theory about decision making behaviour from the very limited participant pool. One form of validation, however, is to determine whether all aspects fit within a rationalised Theory of Change aiming towards the objectives of effective and efficient delivery of a vector control innovation (see validation of this Theory of Change in 4.4). The activities and outputs of the research instead are evaluated against the objectives, values and actions taken towards the desired change or long term outcome. Monitoring for any unanticipated impacts also is facilitated by the visual layout arising from this method.

4.5.2 Application of Theory of Change to this study

The researcher determined that all of the criteria for applying Outcome Mapping were also relevant to use of Theory of Change (paraphrased to be the presence of complexity, a willingness to engage, and a champion with commitment to a co-learning process). First, early discussions with selected DEC research partners made it clear that the complexity of the work at hand was recognised. Furthermore, the partnerships began in a deeply collaborative manner; the project would not be implemented using a 'service hire' approach. This was largely due to the objective of the project being a technology that would last beyond the research and development phase, rather than simply increased knowledge for others to apply. (A description of the nascent partnership and a typical continuum of transfer of decision making power in such a project appears in Chapter 5.) Project management tools were employed from early on, but became increasingly complicated themselves (e.g. from a table of deliverables to detailed Gantt charts) as the project grew and staff was hired for the role of management (beginning in 2012). It was accepted that multiple approaches and requirements to engage with the complexity of the work would be needed, and in fact several specific requirements across various objectives were included in the study project's Collaborators' Agreement (contract with partners). Finally, the champion was the researcher herself, although supported by the executive level of the project.

The Theory of Change map and discussion in this study draws largely on work by the voluntary standards sector, owing to the values based context of these examples. Research also benefited from the experiences of many of these organisations' work in developing country contexts. For example, the extensive work shown in the Theory of Change by Fairtrade International (2015) illustrates the multiple strands leading to related long term outcomes defined by its original vision and mission – statements that preceded the use of the mapping methodology by some years. Target Malaria similarly developed its vision, mission and value statements (outlined in Table 4.3) after the initial selection of DEC partners and several years after the research began in the GCGH initiative; these were first shared publicly in mid-2017.

In this final version, the mission has become more specific to the type of vector control intervention: genetic technologies to modify mosquitoes; the long term impact remained reduction of malaria transmission, however. This is what was used in the original mapping by the researcher.

Although each Theory of Change map is best created with stakeholders' involvement from the beginning, the researcher drafted those shown in the thesis before vetting them with Target Malaria researchers and revising according to comments. It was not a method already used

by participants in the project at the time and additional training in the tool would have been useful. One interesting result was that all of the wording and statements from the project vision, mission and values, which were developed separately through a representative working group across the project teams, was included in the Theory of Change, developed by the researcher independently, in similar if not the same words.

Table 4.3 Target Malaria project statement of vision, mission and values

Target Malaria
Vision, Mission, Values Statement

Vision - Our vision is a world free of malaria

Mission
We will develop and share new, cost-effective and sustainable genetic technologies to modify mosquitoes and reduce malaria transmission.

Values
We will:

- Achieve **excellence** in all areas of our work, creating a path for responsible research and development of genetic technologies
- We will **co-develop** both our technologies and the associated knowledge base
- Ensure our work is **evidence-driven** so we can deliver safe and effective technologies
- Be **open** and **accountable** in how we work, in our relationships and in our decisions

Figure 1.1 showed the overall position of the Target Malaria project's mission in regards to elimination of malaria. A more detailed Theory of Change underlying the example project, was prepared by the researcher retrospectively, as part of the iterative process of illustrating the decision support framework. The Theory of Change, presented in Chapter 11, evolved from individual pathway components that were the focus of this study, through to the researcher's initial complete version through the process of project validation and minor revision. The choice of what to focus in on for the study related primarily to an acknowledgement of the time line of the project, with the aim that all of the activities under study would have progressed sufficiently during the study to begin to demonstrate or disprove the value of the learning frameworks. With this selection, the researcher was able to participate in nearly all major

meetings, field visits, discussions or remote calls relating to the topic over the period of 2011–2017, before finalising this report of the experiences. The choice of the study components also can be explained by Figure 1.1 which highlights that ongoing importance of the containment facility in production of transgenic mosquitoes throughout the steps of testing and delivery of the new intervention (see also Mumford et al., 2018).

Finally, other schematics appear later in the thesis showing only a portion of the Theory of Change, namely specific pathways towards the delivery of a novel intervention, such as development of containment facilities. These align with the final, validated version but show more details at the level of activities.

4.6 Analytical perspectives

The analysis and interpretation of the study results arise from the methods described above for problem formulation and context, data collection through interviews and other means. To further organise the conclusions, however, the results are considered from two perspectives: (i) enablers and barriers to the desired uptake, change in situation and outcomes articulated, and (ii) the geopolitical scale of the person, organisation, role/function or activities observed. This is presented in the final discussion but noted in other chapters to organise the material.

4.6.1 Enablers and barriers

As already noted, action research involves co-learning and progress towards mutually held goals, in a way that reflects shared values. High participation in sharing knowledge for benefits of team outputs, when individuals might lose control and direct benefits from their contributions, can be tied to belief in the work as a public good (Carayannis et al., 2000). Studies from other fields have identified the impact of individual motivations and organisational and country culture on participation in knowledge sharing and enabling of the shared production outcome (Ardichvili, 2008). In many past studies, enablers/barriers were not explicitly identified in this manner. This classification may still be useful when reviewing literature without that exact analysis at the time, but with sufficient information about the design of the study and transparent results (e.g. for shared clinical decision making, as covered by a retrospective review: Gravel et al., 2006).

The concept of enabler and barrier also facilitates analysis at varying scales. For example, co-design of products in industry was found to depend heavily on the creation of a shared understanding of both the content and the process of product design, which could face barriers at the organisational levels and interfaces of the individual (the actor), project or company

(Kleinsmann & Valkenburg, 2008). For this study, the levels chosen were for the project, country and international scale in order to protect the anonymity of individual actors in the process, although data collected was often at that scale.

The methods already described for earlier phases of the study (data collection and validation) are also valid for supporting interpretation. In review of a Theory of Change, the nature of interventions, assumptions, etc. reveal the enabling or inhibiting aspects of each. Some of these interactions can be anticipated and draw on the wide literature on enablers and barriers. The National Institute for Health and Clinical Excellence (NICE, 2007) found that barriers for change in health care practices could be identified through interviews, questionnaires, focus groups, brainstorming with actors in the process and observation of practices.

Policy also can be reviewed (i) after the objectives are declared, to determine the best way forward; (ii) during implementation to determine progress against objectives and targets (monitoring); or (iii) from the perspective of effectiveness and efficiency during or after the implementation (evaluation) to see whether the benefits have been realised (HM Treasury, 2011).

In this study, the enablers and barriers were considered for those key pathways to change described in the Theory of Change figures.

4.6.2 Geopolitical scales

The organisation of information in line with the geopolitical scales for analysis further provides a context for discussing which factors are enabling the desired outputs or outcomes and which are posing barriers, as well as how these may interact across scales. This classification supported interpretation of the overall study into more easily understood conclusions and recommendations. It has also been argued that barriers, and thus enablers, to progress for complex issues can only be properly identified and understood using a 'multi-level perspective'[42] due to the interactions between levels (Burch, 2010). This could well be anticipated in this study, for example due to the impact of a regulatory instrument (national) on the outcome of a research team's participation as partners for novel research.

The geopolitical classification applies to the policy context as well as the actors or participants. Table 2.2 shows how micro, meso and macro level decision makers address themes that continue through the local level – down to the level of the individual laboratory or research

[42] While taking on this term, it is not to imply a methodology encompassing the analysis of a global transition, as discussed by Geels & Schot (2007).

institution (micro), national or regional level (meso) and international level (macro), respectively. Analysis using these categorisations may help to avoid confusion from the number of decision makers and clarify the role and influence each has on the ultimate deployment of a novel health technology in the field. In general, as shown in Table 2.2, the breakdown of the categories in this study would be Micro: Discoverer and DEC labs; Meso: DEC Regulators or other setting a national context; and Macro: WHO committees and collaborators and international or multilateral funders. Each level is affected by and may influence the others, however, and many overlap into more than one category.

4.6.3 Approaches to testing and validation

The aim of this study was to create learning frameworks that can benefit the other initiatives, consortiums or projects developing novel interventions in vector control, or similar technologies. First, the choice of methods was tested. The use of an action research component of the study was found to be valid and valuable for informing these outputs.

The Target Malaria project, and the research consortium that preceded when the project was formalised, has a stated value of ‘co-learning’, meaning that no one is yet an expert in all aspects of the way forward, but rather the partners are all learning together. This attitude (and phrase) also has been established between the DEC research institutes and the national biosafety regulators, as well as between project advisors and DEC researchers. This statement was arrived at independently from the influence of the researcher, thereby further validating the use of action research as the overarching methodology for the study, since it took place within a context that encouraged the development of new knowledge to improve actions taken. Therefore, the study project was considered to be open to research with an action research methodology.

Taking an action research approach limits the possibility of randomised trials applying a policy or approach to some groups while maintaining a control, inasmuch as all participants are involved in the process.

Some of the theories developed through action research were immediately adopted. Several of the definitions and descriptions offered by the researcher for preparations of containment facilities, for example, became standard terminology for the Target Malaria project (Quinlan et al., 2018a). The external facilitator perspective also led to the researcher being asked to lead audits for three of the containment facilities ready for use during the time of the study, despite lack of formal credentials in the technical topics covered. These audits were based on checklists of questions the researcher developed, in coordination with the other auditors

(discussed further in Chapter 8). This and other uptake of results of action research further validates that the action research approach added value to the activities of the project's research consortium, while producing outcomes that stand up to external review as described below.

Another method used was to prepare logical models or components of Theories of Change, for each thread of the research. These were then assembled into a full Theory of Change focusing on the project. The practice of drafting a Theory of Change without full stakeholder participation was found to be acceptable given the impracticalities of trying to carry out the entire process with involvement of all stakeholders (Smith et al., 2012). The process of using this method and the outputs were validated by parallel initiatives of the project. Near the end of this research in 2017, for example, an external project advisor worked with a small group to prepare project statements on the Vision and Principles of the overall initiative. While this was late in the project and not widely inclusive, it was an attempt to choose wording for thoughts already crystallised in other fora over the ten years of the project's existence, and four years of collaboration with DEC partners. The project vision was found to align closely with the version of a Theory of Change developed by the researcher. In a final validation of the researcher's version for the project, the entire mapping of this theory was reviewed with various project members and some external experts.

Although outputs from this study could not be tested in other projects in the time frame of the research, suggestions for uptake are provided in Appendix 5. A key component showing the quality or value of an action research based study has been said to lie in the continuity of impact beyond the study (Bradbury & Reason, 2001). Mårtensonn et al. (2016) discuss a redefinition of quality in any type of multidisciplinary research. They conclude it should be (i) contributing, as well as (ii) credible, (iii) communicated and (iv) in compliance with requirements (e.g. ethics) for the field of study.

The researcher purports that the present study achieves all of these indicators for a quality study. One component of contributing is to be addressing timely issues relevant to the important questions of the day (Reason & Bradbury, 2001). Clearly, ending the burden of malaria counts among these important issues.

Approaches to testing and validation of the outputs from the study are summarised in Table 4.4, although generally described in more detail in each relevant chapter.

Table 4.4 Testing and validation of methods, and outputs of the current study

Issue, topic or output	Method(s) employed for validation	Discussion/ presentation of process	Output of study
Support for a Discoverer to select DEC research partners	Application of draft process and criteria to the Target Malaria project decision process (2010–2011; **4 initial research partners selected**) and insights from subsequent project experiences Comparison against subsequently published criteria from similar projects	Chapter 5 Proposed selection criteria	Tables for interested parties to apply as partners and a review template (Tables 5.2 and 5.3) List of published criteria ranging across multiple themes (Appendix 2) [a]
Best practices for partner selection and lessons learned	Online survey of Discoverers; their participation in survey and coherence of results (**50 respondents to survey**, between Jan 2017 and Jun 2017) Surveys of research scientists by other researchers published or presented at conferences	Chapter 5	Summary of best practices from participants [b] (Table 5.3)
Regulatory decisions about a novel intervention to be taken with confidence, transparency and in a timely manner	ISBGMO symposium for presentation of various cases and discussion with larger audiences (2014) Interviews with regulators from West and East Africa (**5 regulators interviewed**, Nov 2016 and Feb 2017) Specification for legal reviews, discussed with FAO Legal Department. **Legal reviews carried out for 4 countries**	Chapter 6 and Quinlan et al., 2016a peer reviewed published article	Proposed questions for consideration by DEC regulators [c] Quinlan et al., 2016a published article Proposed questions for legal issues additional to biosafety frameworks
Conceptual framework for facilities readiness	Meetings with all relevant participants aimed at facilities readiness to develop concepts Application of draft process and criteria to the Target Malaria subsequently Follow up interviews with **3 country PIs from Target Malaria and 1 former country management** level staff member(Nov 2016 and Feb 2017)	Poster presented at international conference (Appendix 3) Chapter 7 and peer reviewed article Quinlan et al., 2018a	Description and diagrams of key components of a method for determining the point of readiness of a containment facility (applied prior to import applications in 2 DECs) [d]

Issue, topic or output	Method(s) employed for validation	Discussion/ presentation of process	Output of study
Detailed steps towards facilities readiness	Process of preparing facilities within the Target Malaria project Follow up preparation of descriptive article describing process with the key participants from that project (remote meetings and emails, 2015–2017)	Chapters 7 and 8 and peer reviewed article Quinlan et al., 2018b Poster at PAMCA Oct 2017	Flow charts of steps to consider for planning and monitoring work [e]
Exploring the use of audits to benchmark facilities readiness	Process of conducting audits in refurbished and purpose built **facilities in 3 countries** (Apr and Sep 2015, May 2017) Follow up one year later in one country to review validity of single visit audit	Chapter 8	Audit checklist for project [g] (includes a number of items specific to project) Audit checklist for general use Confidential Target Malaria audit reports
Establishing clear identity of wild type strain of mosquitoes used in studies, and maintaining records from field collection onwards	Use of template by **3 labs in Target Malaria**, with various refinements over time (adding different events such as export from colonies 2015-2017) Comparison with forms used by suppliers of research strains	Chapter 9 Poster presented at PAMCA Oct 2016	Wild type colony record (WTCR) template and user guide [f] Target Malaria standard operating procedures (SOPs)
Using a database to check quality and consistency of operations and to populate risk models	Contribution to specification for bespoke database for insectary, review of use of database once provided Use of Insectary Database output from database to verify operations remotely	Chapter 9 Mumford et al., 2018	Description of bespoke database and which insectary indicators were chosen by the project

Issue, topic or output	Method(s) employed for validation	Discussion/ presentation of process	Output of study
Maintaining biosafety in a DEC laboratory setting, after initial training	Literature review Discussions with French institutes (Aug 2016) Discussions with Imperial College London Safety and Health professionals (ongoing)	Chapter 10	Recommendations for further study List of questions for review of SOPs [h]

[a] The researcher's list of ethical, legal, social issues criteria, Table 5.2, was discussed with colleagues throughout its development. Adrian Leach supported preparation of research/publication linkages and regulatory context maps.

[b] Zen Makuch and John Mumford provided extensive support and Valentina Cisnetto gave useful suggestions for the preparation and revision of the College ethics application.

[c] Joe Smith, co-convenor of the symposium at the ISBGMO, and all of the participants in that symposium gave food for thought and shared rich experiences as the basis for this output. Further acknowledgments appear in the *Frontiers for Science* article. DEC regulators, remaining anonymous, who agreed to be interviewed also contributed greatly to its development.

[d] Peter Raymond was the main partner with the researcher in discussing and developing these concepts in a coherent manner to launch the process in Target Malaria.

[e] James Mutunga provided valuable input to this process throughout. The flow charts, drafted by the researcher and appearing in the article, were revised by Lorna Clark based on her extensive experience in managing the facilities preparations for Target Malaria.

[f] Adrian Leach was the primary expert to translate the researcher's ideas into an operating template based on a platform of Microsoft Excel®. He was also the lead in incorporating learning and specific naming preferences from the WTCR into the Insectary Database, designed by Evgeniy Meyke of EarthCape, and in maintaining conceptual consistency.

[g] Mark Q. Benedict was the main collaborator on development of the researcher's audit checklist. Peter Raymond, Stef Hoyle and Lorna Clark also commented.

[h] These were developed in discussion with the Insectary Manager for Target Malaria's Burkina Faso facility, Moussa Namountougou, for a project-wide meeting in February 2017.

4.7 Systems for learning

The researcher's description of the term learning system appears in section 1.1. Such frameworks that structure questions, materials, or other parameters may provide valuable support to individuals called upon to make decisions. Given the complexities already noted – in the context for decisions, decision making and the decisions themselves – the objective of this research was to identify or propose learning frameworks which are able to support decision making and decision makers with a harmonised structure, but also to represent any

progression of thinking with additional experiences or new data. Johnson et al. (2017), for example, reviewed various 'report card' frameworks for complex systems and concluded that those most successful will have clearly defined goals, engage stakeholders, be flexible in implementation, be able to communicate effectively and be based on rigorous science. They also identify a useful system as one that can be initiated while knowledge is still under development, be refined as more knowledge is obtained, and aggregate and integrate information from disparate sources[43].

Though the definition of complexity in policy sciences is not harmonised (Johnson, 2013), one can compare some of findings of Hallsworth (2011) about devolved responsibilities in the United Kingdom (UK) to the context of a large international research consortium, or other multinational projects, wherein a central group is working to ensure accountability in the delivery of objectives or promised outcomes, but much of the decision making and nearly all of the encounters with national policies and regulations is occurring at the next level down. This supports the study approach of building systems or frameworks in the Target Malaria project, with the executive group playing a role of steward of these, while allowing latitude for the main decision makers and actors in the project to continue developing and learning, while working towards the defined objectives. The objective of a learning system is that knowledge is both applied, in its current state of the art, and generated for continual improvement.

Bradbury Huang (2010) considers the transfer of knowledge derived from action research to any new group as the point of departure from action learning, since the knowledge arising from the participation will by definition not be developed within a different group or setting. However, even within the same project (Target Malaria) additional staff joining later were not part of the action learning process. In this instance, working from a framework has benefits as long as those external to the development process find value in the structure as well (see also Chapter 10). There also is a wealth of material on options for capacity transfer; some examples appear in Chapters 5 and 10.

Frameworks can provide a harmonised methodology and criteria, an accessible and transparent record of the decision, and a context for repetition of decisions to achieve similar outcomes for similar conditions and data. If designed appropriately for this aim, frameworks also allow decision makers to recognise and emphasise any particular criteria of importance

[43] Their preference was to use Bayesian networks to achieve this, but similar characteristics can be found in other frameworks, or combinations of frameworks. The weakness of the current study outputs might be considered to be a lack of close integration into a single framework. The example provided by Johnson et al. (2017), however, was aimed at a single geographically defined area, thereby reducing the issue-related complexity described by Sheate et al. (2016).

to his or her own institution, country or region in relation to the targeted disease vector. For example, a country may have the policy of achieving equity in coverage of a disease prevention or elimination method across the national population or wish to focus on more vulnerable and underserved populations (Melamed & Samman, 2013; Barat et al., 2004).

The process of developing decision support materials and guidance has been studied in other contexts. Experience with other introductions of living organisms suggests that a user-friendly, technically robust decision support framework regarding the inclusion of genetically modified mosquitoes for vector control in public health programmes could reduce the resources and time expended in reaching a conclusion. The frameworks resulting from this study incorporated the principles and best practices drawn from historical methods for mosquito control, release of BCAs, sterile insect technique, and other public health interventions.

4.7.1 Risk-based frameworks

The idea of using risk-based tools is to benefit from best practices for identifying concerns and potential hazards, determining probability of a hazard, clear representation of estimated risk and justifiable linkage between risk and management measures. The risk-based approach still allows for uncertainty and encourages design of management measures in proportion to the estimated risk. It also encourages feedback mechanisms for using new data to reduce uncertainty and address particular questions about the innovation. Therefore, a risk-based approach is an efficient way to progress decision making while improving the certainty underlying decisions with each new experience. The underlying concepts of risk, uncertainty and risk mitigation are discussed in each chapter in more specific details relating to the objectives or topic.

Initially, the researcher aimed for risk-based frameworks, to build on her area of expertise and recent work in mapping risk. The risk-based approach has been applied by the UK Department for Environment, Food and Rural Affairs (Defra), but the potential for conflicting objectives and need for additional consideration of secondary adverse consequences was found lacking (Rothstein & Downer, 2012). For instance, it was difficult to translate the various types of risks into the same framework using the same risk metrics or scale; for example high, medium and low. Furthermore, Rothstein & Downer (2012) found that physical risks, legal risks and reputational risks were not treated with the same rigour, resulting in conceptual ambiguities that weakened the overall system. Most importantly, their study found that the system's allowance of 'selectively identifying hazards and assessing probabilities' permitted manipulation of the outcomes either purposefully, by advocacy groups (who might participate as stakeholders in a consultation, for example) or by decision makers who were influenced

with ‘subjective judgements’ or concerns over risks to their own departments or staff (Rothstein & Downer, 2012: p.795)[44]. A study of regulation based on risk frameworks versus problem-centred approaches (Baldwin & Black, 2016) identified similar challenges in identifying key issues, given the different drivers of risk and interactions among these drivers. The authors found that the mandate of the regulators, culture of their organisation and, at times, their loudest constituents generally determined what would be on the agenda in the first place, so that those risks given priority may not be the ones of most importance. Although these challenges may arise with other approaches, they reduced the value of attempting to operate under the parameters of strictly risk-based frameworks.

Over the course of the current study, as well, it became clear that some of its contribution was in the form of frameworks that did not include all of the components of risk, namely: hazard identification and initial categorisation, estimate of the probability and consequences, and development of risk management and communication options. This also is a generally qualitative rather than quantitative study, and some believe that more formal risk frameworks suggest quantification where only qualitative input was used. What emerged, therefore, were frameworks that supported parts of this overall risk methodology or could provide information for one of those parts, but which are not entirely risk based. This distinction will be described in the presentation of each framework.

In some regulatory systems, consideration of potential benefit against the possible risk is not allowed. By linking these two concepts during development of a learning framework, however, one potentially can reduce uncertainty and inform decisions from a perspective including both safety/risk and efficacy-effectiveness/benefit. The methodology therefore was adjusted towards systems for learning, in which a framework would be developed from literature review and the experiences with the main case under study.

The important characteristic is to allow different conclusions and decisions to emerge from the same framework, but at the same time provide consistency in the process and criteria for decisions. These learning frameworks then would be validated or tested and offered for use by the Target Malaria project, but also other initiatives. This approach aligned with the idea of those holding the central accountability for delivery acting more as ‘stewards of systems’

[44] The tendency of otherwise well informed and educated participants to be suspicious of quantitative approaches using the same expert judgement and opinion as other methods has been observed by the researcher in other projects and sectors. The belief seems to be that using quantification can be a way to ‘fool’ the consumer of the information into believing it is more accurate or evidence-based than descriptive or qualitative outcomes, simply by adding numbers.

(Hallsworth, 2011), rather than as the decision makers, and aimed for contribution without undue influence.

4.7.2 Presentation of frameworks

A final aspect of action research is to reflect on or review the process, with conscious evaluation of the initial findings. Some take this idea further to say the approach must involve observation, intervention and evaluation to comprise action research (SDRN, 2011). An important aspect of this evaluation is to communicate results in a manner that is comprehensible to those who participated in the process, but also to those who may benefit from that learning at a later date. As already noted, this was certainly relevant for Target Malaria, which more than doubled in numbers of staff, advisors and trained volunteers over the period of the study.

McKinnon et al. (2015) discuss the numerous studies and reviews that fail to organise and synthesise the evidence that is gathered. This leads to quality research conclusions that are not read by the target audience, let alone taken up. This component of communicating and validating research within the context of the user is critical. Supplementary interactive files will be available through project-based avenues, for viewing (e.g. PowerPoint presentations) or for use (e.g. in the form of Excel-based templates that require electronic files to be shared).

4.8 Summary of methodologies employed

The delivery of a novel intervention for vector control includes several aspects of complexity identified for policy evaluation (Sheate et al., 2016). The decisions involved cross over several policy and programmatic areas on the national level, and are influenced from micro through to macro level policies, institutions and organisations and players. While some argue that the final decisions on delivery should be squarely in the public health sector (Elves, 2017), at present many of the decisions for a novel intervention involving genetic modification are led by National Biosafety Committees or NBAs.

Outputs from this research began with an understanding based on literature, project management tools, experiences from other fields of innovation and biotechnology, the active international discourse on the technology in the main case studies, and the existing structures at the global, regional, national and, at times, very local scales for decisions about novel interventions. The assumptions surrounding objectives of each group (identified in Chapter 2) differed. The research began with the premise that a technology developer has either discovered or translated discovery to a potential solution, or responded to the demand for a

solution with discovery[45]. The study assumes at this time that the Discoverer is external to DEC and will need to find a research partner. The DEC regulator, on the other hand, has a different *raison d'être*, because of the need for evaluation against the regulator's legal mandate and regulatory criteria. For this group, it is worth noting that introducing frameworks to articulate the intended change of events is not aimed at promoting or advocating any intervention so much as supporting the decision processes surrounding the uptake. Indeed, a well-documented and justified conclusion to reject the opportunity for a novel intervention shows as much validation of the decision process as a decision to proceed. In the context of this complexity, a more intentional review and selection of methods to use in the study took place.

4.8.1 Limitations of the selected methodologies

Research employing various methods, particularly when largely qualitative presents some challenges to analysis and interpretation. Unless the methods truly investigate the same feature or aspect of a question, having more than one method adds data without necessarily adding clarity. It may be difficult to establish the quality of the research or compare it to other studies using different methods (Gravel et al., 2006). As already discussed, there is some development on how to judge qualitative research, albeit without unified support, and efforts are progressing to establish cross cutting quality criteria for research in general (Mårtensonn et al., 2016). While the researcher accepted limitations, or adjusted to them as situations prevented further site visits, she did so in the spirit of pursuing exploratory research rather than attempting to prove a theorem.

The research groups considered in this study cannot be considered truly static in the aspects studied, due to continual and multiple influencing factors such as various health and development projects, vector research and external funding. The time covered by the study led to 'snap shots' from very different points in the progression of the sector overall, although the researcher enjoyed the opportunity for long term and deep engagement. Furthermore, input from survey and guided interviews clearly skew the conclusions to fit with individual opinions from those who participate. Quantifying impacts of interventions due to overreliance on reporting only from those most engaged, and self-reporting of behaviour versus measurement of it, is more difficult when taken in an action research context (SDRN, 2011) but is possible through use of well-defined and tested tools (Martí, 2016).

[45] This push/pull dynamic itself is the topic of extensive literature in innovation, but appears only briefly in this study in the interpretation of enablers and barriers.

Regardless, the final outcomes of the main project studied, Target Malaria, are not known; the activities are ongoing, important milestones have been reached and it appears that the work will continue long past the point of this thesis report. This implies that new outputs and outcomes to the same study questions – from additional experiences, other research groups, or changes in opinion upon reflection from study participants – may occur beyond the time frame of this thesis, and therefore the impacts of the proposed frameworks may not be known even while the intended objectives remain the same (White, 2015). The researcher seized opportunities for targeted research within a relatively short and defined period for a sector in rapid flux, as explained previously.

Qualitative research also faces the danger of the facilitator having too much power or influence on outcomes. As Gullion & Ellis (2014: p.63) observe: 'Knowledge is socially constructed by those who have the power to do so' and action researchers must take special care to prepare interview techniques and other tools from the perspective of being allowed to document others' lived experiences, rather than overly interpreting them. Again, Burns (2014) defines the role of the facilitator/researcher as requiring a strict code of responsibility to ensure he or she is opening up inquiry, representing the various inquiries faithfully and allowing new threads to emerge. These challenges as a research methodology necessarily will influence which objectives are articulated and in what structure, so that desired outcomes become more process oriented and may lack definition of decision points or knowing when an objective is achieved. This should be anticipated, to maintain some discipline in the application of decision support. The personal history of the researcher always creates a perspective that cannot be eliminated. It is best to understand this perspective and accept its legitimacy, while recognising other perspectives could lead to other conclusions.

This raises a limitation imposed by the subject of the study, as much as any methodology. The debate about use of genetic modification is heated and ongoing. This study does not attempt to side step it as much as focus research to a different aspect of the public health intervention of interest. However, one must acknowledge that the topic will introduce limitations to the study. As Lub (2015; p.3) states: 'The fewer underlying assumptions of a particular research field are shared, the more difficult it is to defend the relevance of the research and the more difficult it is to reach a consensus on the validity criteria for that research'.

Methods to ameliorate an unavoidable bias of even considering this line of novel interventions include description and definition of end points throughout the research, to seek common ground on for at least some of the points in the stepwise progression, and the articulation of more widely agreed objectives aligned with the steps identified in a Theory of Change, just as described above.

While, based on experience, creating a Theory of Change and mapping outcomes allow for more in depth exploration of the study questions, in practice funders' agendas may also skew outcomes by setting the initial objectives or requiring particular indicators along the way. This tension also may be seen in requirements for Gantt Charts, logical frameworks or particular project planning and monitoring software choices. Smith et al. (2012) noted that funders may still require their preferred management method for reporting; this was confirmed more recently by a variety of organisations aiming to work with Theory of Change (pers. comms, anonymous NGOs in training course, 10 March 2017).

Another limitation is that the Theory of Change was prepared from a perspective of the Executive level stewards of the system for Target Malaria. This reflects a perspective held by the researcher of project objectives, deadlines and deliverables more than what might be valued or undeclared objectives of the other teams within the project. Gariba & de Hoop (2012) discovered a tension between Theory of Change methodology and the traditional approach to evaluation in many African contexts. They challenged their social scientist colleagues to elaborate further on this difference, but certainly one way would be to make it a more inclusive process. This approach could be the basis for future study.

While presenting their own limitations, methods that attempt to quantify opinions, as well as the guided interviews seeking to discover experiences and opinions, can mitigate some of these limitations of the overarching methodology of action research. These complementary methods were focused on data collection, to populate and test the descriptions and definitions of the context. Testing these outputs outside the context of the community generating them can provide validation for the value of these outputs as lasting contributions.

In this instance, it is important to remember that, to paraphrase Darnton (2008), what is developed in this study are not templates for the policies or decisions, but rather frameworks that serve to structure the decision process, as aids to thinking rather than for providing answers. For this reason, despite the limitations of the chosen methods, they appear to be those best suited to the objectives and context of the study.

4.8.2 Relationship among selected methodologies

This chapter elaborates on several approaches to the study questions, with a methodology of action research for the most unique contributions of the researcher. Kleinsmann & Valkenburg (2008) approach this type of narrative study through what they call the 'learning history', a method for studying systems within the action research approach, whereby the relationships among three phases of research – data collection, classification and data interpretation – are

shown in line with activities occurring during each phase. Yet others emphasise the cyclical nature of the process, as shown in Figure 4.1. Rather than dividing research into clear period of data collection, categorisation and interpretation, the researcher applied the cycle of inquiry several times on different issues or problems, in different sectors, while attempting to maintain an overview of the relationships and influences among them all. Although the present research does not enter into the relationships among actors at an individual level to the depth of the learning history method, the relationships among tasks as laid out are very similar to what has actually occurred in terms of phases of research. This focus on the systems level (Parent et al., 2007) is typical of a form of action research that may reveal possible enablers to better outcomes for specific challenges, while recognising the cultural context and multi-level influences. Furthermore, the focus at levels above that of the individual removes some of the necessity to investigate personal relationships, even though the concept of trust continues to be critical to the final outcomes of the study (as noted in various studies, e.g. Foster, 2014).

Both Theory of Change and outcome mapping focus on the contribution to a well-articulated and rational description of interventions with causal links to outcomes. While impact or attribution is de-emphasised, the linkages are not lost. These approaches allow for this study's consideration at various geopolitical levels with different stakeholders or participants without following each decision under study from beginning to end, along each strand.

Policy research for a complex issue, such as malaria vector control, faces a variety of drivers (including social, environmental and even physical, e.g. due to climate change), that may not be identified initially as influencing the study questions. This research is employing existing methods to create or adapt frameworks based on clearly stated criteria – sometimes including risk assessment and management – and globally recognised principles. Methods have been reviewed and considered within this context. Although health and health systems literature was reviewed, this is not health research in the classic sense of relating to an individual's health or disease treatment, but rather a study of decision making related to policy and interventions for vector control in public health. In particular, the emerging genetic strategies for vector control provide a rich field for research on decision making, which may inform policy and decision making for other novel interventions in public health and beyond.

FINDINGS

Chapter 5. Forming a Partnership with DEC Researchers for First Steps in Delivery of a Novel Intervention in Vector Control

5.1 The question of partnership

The interface between science and technology and society and its immediate needs is where meaningful scientific impact is believed to lie. For malaria research, partnership is critical to achieving this impact[46]. This study focuses on how partnerships are developed during the early steps in delivery of a novel intervention in vector control, including import of a research organism and studies in containment. Characteristics of field sites and national regulatory regimes have been the focus in other publications to date, whereas this study focuses on the steps prior to field studies.

This chapter explores how a discoverer or provider of an innovation in vector control, referred to as the Discoverer, may identify and form a partnership with a DEC partner suitable to progress an innovation or product for vectored disease or vector control, towards the intended field application and beneficial impact. The premise of this chapter – that the novel intervention is first discovered or developed outside sub-Saharan Africa before being further developed or tested there – is based on the examples available to the researcher and those studied. The researcher chose this scenario as a typical one, particularly true for innovations based on molecular biology (e.g. Black et al., 2011; Birhanu, 2010), although the amount of domestically developed biotechnology in Africa may have increased substantially in the most recent years. This scenario forming the basis of the current study is not meant to discourage a different model, in which the innovation or product is discovered and developed entirely within a DEC, in particular within sub-Saharan Africa for malaria control.

Clearly, there is a wide range of situations and objectives among Novel Researchers, even when limiting this study to vector control research. The point of entry for DEC partners (revisited later in Figure 5.7), in terms of the development phase of the intervention for example, and the objectives of the funders and/or external researchers will have a significant

[46] The researcher states this based on the ethical (Tangwa, 2017; Kilama, 2005), technical and material, and regulatory and logistical necessity (Quinlan et al., 2018b; Kolopack et al., 2015) of partnering with African researchers, already mentioned in this study, while acknowledging the overwhelming portion of research funding, and much expertise, that comes from external sources (Head et al., 2017; Nuffield Council on Bioethics, 2002).

impact on the style of the partnership. Despite these variations, in this chapter the researcher asks the relevant subquestion from Chapter 1:

Is there a best practice for external innovators or discoverers of a novel intervention to find appropriate research partners in DEC?

When considering partnerships, there is more published guidance regarding criteria relevant to field studies or an initial release in the stepwise progression. The Cartagena Protocol is interpreted as covering import of GM organisms for field release, whereas it does not impose requirements on countries for import into containment for research purposes (although a national biosafety framework may do so; there are proposals to revise the Cartagena Protocol in this regard, see further discussion in Chapter 6). As already implied in Chapter 2, however, the decision about DEC research partners in the early phase of containment studies could impact directly on the move to confined field studies and eventual programmatic use. This is because transferability of results from the early studies is not clearly established for research in genetic strategies.

A national biosafety framework (NBF) could allow for transferability of early phase results if there is a mechanism for evaluating and possibly accepting these results from studies conducted elsewhere, such as is done with toxicology studies (see Boxes 1.2 and 6.2, and Section 5.4). Once transferability is more clearly established, it would be possible to have centres of excellence for specific steps in the progression of genetic strategies (e.g. large cages in one location, for studies supporting field studies in a different location), while recognising that mosquito colonies may not represent their native counterparts until introgressed with the target population of mosquitoes and mass reared under more natural conditions (Mumford et al., 2018; Ng'habi et al., 2015). Until transferability, or the appropriate terms for transferability, of the results from preliminary studies in containment preclude the need for repetition of the same studies in every country considering use of the novel intervention, partnerships will need to be based on criteria and characteristics through ***each*** step towards deployment. The lack of research transferability is one of the most significant influencing factors regarding early phase partnership, at this time.

The researcher explored various aspects to partnerships for the purpose of answering the research subquestion on best practice for finding partners, primarily from the perspective of the Discoverer external to DEC. The research methods employed are described in Chapter 4, and included:

- A literature review to document the context for DEC researcher, summarised in this chapter (described in Chapter 4);
- Development of possible criteria from literature and analysis, evaluated in the context of an example project to introduce transgenic mosquitoes;
- Use of an online survey of researchers developing innovations related to vectored disease and vector control;
- Conducting interviews with institutions that have generated other types of innovations in biosciences or health and drawing on European projects supporting innovative biological products; and
- Supplementary literature review and further follow up individual interviews to test the criteria developed and supplement analysis.

In addition to analysis from directly relevant published papers, other literature about enabling innovation (discussed further in Section 5.6.1) was reviewed. General lessons for 'North-South' research partnerships, for example, also can be found in experiences with development assistance aimed at scientific capacity, reviews of historical research partnerships and networks, cases of private-public partnerships for technology or product development, and more commercial partnerships requiring a DEC validation or testing component. The question of how the type of partnership for research on and delivery of innovations in vector control affects the DEC partner is considered further in Chapter 10.

5.2 The 'right type' of partnership

The researcher considered to what extent general good practices could be agreed for research partnerships pursuing delivery of a novel vector control intervention. She investigated this from the perspective of related experiences and the literature review. Results of guided interviews with innovation researchers outside the focus project and an online survey of innovation researchers give further food for thought. The question of the 'right type' of partnership is important, when approaching the selection of a research partner to progress an innovation in vector control along the delivery path.

An early attempt to define good practice for 'North-South' research collaborations or partnerships (United Nations, 1979) recommended keeping with development priorities determined by the countries themselves; provide, as far as possible, for developing country participation, even when conducted in developed country institutions; provide for joint participation and control, when conducted in developing countries; and include a training component. While this guidance still rings true, more recent guidance puts forth good practice

as achieving the objectives of all parties, from 'North and South'. Imposing too many requirements for capacity building objectives can weaken the chances for success in the specific case of technology transfer[47]. This delicate balance frequently arises in the debate between improving national health systems versus single disease horizontal investments and management.

Bradley (2007) offers an extensive review of the literature on North-South research partnerships, concluding that 'most [published] studies analysed small teams of researchers from the same discipline, working for a limited period of time on a particular set of research questions' (p.14). These studies, therefore, may be less relevant to multidisciplinary teams or those working together over a longer time frame. She identifies three major types of partnerships (Bradley, 2007: pp.1, 13-14): those created for a project with a specific objective and time frame; those designed for capacity development; and general research networks (formal and informal). Many collaborations, needless to say, cross over these categories.

Innovative product creation in general has been studied for various sectors, including software development. Kleinsmann & Valkenburg (2008: p.371) state that 'the process of creating shared understanding [across the product development teams], might be as important as having shared understanding' when it comes to successful and efficient product development. This is due to the importance they found not only of successful transfer of relevant knowledge and experience among product teams, but also of an enhanced ability to communicate, a shared view of the task, and even the emergence of empathy for outcomes from the various disciplines required for product development, rather than the usual focus only on one's own criteria and objectives[48]. This more collaborative product development pathway would appear to create a good foundation for more integrated cross-disciplinary work, which, beyond product development, is increasingly expected for vector control initiatives (James et al., 2018).

These conclusions leave open the question of the degree of difference between collaborative research and product development. This distinction should be considered in depth at the point

[47] The researcher had observed over recent years projects where the expectations for scientific results (knowledge generation) were high, but then additional development-oriented expectations were added by the funder or by someone evaluating the project without integration of these in the funding phase. This trend sometimes causes frustration, in her perception, for those managing such projects or research networks for public health or malaria control, because they are faced already with challenging milestones. This expansion of mandate is noted for regulators as well.

[48] Enablers/barriers at the project level were found to emerge from less individualised characteristics, for example from the quality of the documentation on the product, the degree of freedom to operate within a task, and general project planning (Kleinsmann & Valkenburg, 2008). Company level enablers/barriers were found to relate more to organisation of resources and allocation of tasks.

of entry into the partnership (see Tables 2.2 and 5.7), necessitating some early clarification of objectives and preferred partnership style, as well as development of working agreements.

5.2.1 The role of each party

The success of other collaborations involving biological products or transfer of living organisms are known to be influenced heavily by the clarity of each party's role (NAPPO, 2007), as well as the presence of a champion for the process itself (Alden et al., 2017; Kairo et al., 2003). For introduction of BCAs[49], for example, an analysis of two developing regions – East Africa and the Caribbean – found that the need for someone who was dedicated to an internationally recognised and transparent process was key to maintaining the standard of care included in the ISPM 3, formerly an FAO Code of Conduct (Kairo et al., 2003). The ODI *Guidance Note on the Partnering Process* (2005) distinguishes this role of champion from the role of an internal facilitator, who demonstrates the ability to take into account the interests of each of the parties involved in partner negotiations. The *Note* provides a case study in which an NGO can step into the gap as a facilitating entity when a partnership is moving further into development, in this case with Phase II funding. The author has employed a similar approach in regional projects (Quinlan et al., 2016c: p.10) for disbursement of funds and procurement purposes, thereby moving the role of negotiator and enforcer for financial stewardship to a third party while maintaining the research agenda with the primary institutions providing the new techniques. What is clear is that the role of each party may evolve over the course of a partnership and assignment of roles and authorities in decision making will need to be consciously reviewed at each point. Furthermore, champions emerge, it is not a job assignment nor based on particular training.

5.2.2 Ownership of the research

The broader context of research partnerships is discussed extensively in what may be termed 'development' literature. There is a useful distinction between a research initiative with a 'North-driven' agenda and set of priorities, and that initiated with the perceived requirements for strengthening scientific capacity and achievement in 'the South' (Sieber & Braunschweig, 2005). Some question whether the context and skills needed to set a research agenda are

[49] The Kairo et al. (2003) study took place prior to the revision of ISPM 3, which in its present version (IPPC, 2005a) was expanded to include other beneficial insects such as pollinators or sterile insects to use in sterile insect technique. On at least one occasion, the revised ISPM 3 has been cited for decisions regarding sterile mosquito transport and release due to lack of guidance materials more specific to mosquitoes (Bellini, pers. comm., 2013).

themselves lacking in much of the DEC of Africa (Waiswa, 2015; Chu et al., 2014)[50]. Others argue that the perceived disparity in capacity is false, since partners are chosen among the most experienced and leading scientists of respected African institutions, whereas the partner from the developed context may be junior staff, for example, or unfamiliar with the broader research context, for instance of malaria research in the context of a DEC (Bradley, 2007).

In one regional analysis (Madikizela, 2013), Tanzania had the highest proportion of research funded by external funders (almost 50%) and the highest indication that complying with funders' priorities affects the choice of research. Put another way, nearly half the researchers responding to a survey (Göransson, 2016b) felt that external funders are not aligning to the national development goals. This could be due to poor evidence and evaluation of existing programmes for these objectives, but also because projects aim towards shorter term goals than national programmes. It is also possible that development assistance supports development goals, without the links of each activity being made obvious. Discussions about problem context and development of agreed Theories of Change or similar may address that apparent disconnect.

Regardless, the practice of 'extractive research' is fading, due to the expectations of funders, increasing demand by DEC institutions – if not their governments – for equitable roles in the research, and the recognition by researchers working in global health topics that local expertise provides more than a source of samples or data. Instead, recommendations for partnering talk of 'shared vision, trust, clear objectives …strong leadership on both sides, collaborative processes for prioritizing research topics..' (Sewankambo et al., 2015: p.6). One recommendation is simply to put more funding under management by DEC research partners, to allow different decisions and priorities to come through that avenue (Conway & Waage, 2010) and build management capacity through experience. Like researchers anywhere, the DEC research community values the 'freedom to formulate and pursue [one's] own line of research' (Göransson, 2016b: p.284). The reality of a project, initiative or consortium with a product outcome, however, is that individual research interests may not align with the required focus on R&D deliverables.

MTAs may be developed with more detail and precision to clarify roles and ownership. Clarification on ownership of data or samples also is a critical part of agreements for partnership. Some countries, such as Tanzania (NIMR, undated), even intervene with national

[50] Waiswa (2015) writes that: 'Countries will need people who can internalise evidence, policies, program performance, and design interventions that are equitably accessible, affordable, and have quality. This is a role that cannot be delegated to visiting foreign 'experts' as this is neither sustainable nor effective.'

frameworks for research review and data transfer. This data transfer agreement template for medical research was developed under an Act of Parliament requiring registration of all medical research.

5.3 Baseline for many DEC research settings

The researcher considered that a starting point for identifying an appropriate DEC research partner is to acknowledge the challenges faced in those research settings, regardless of the recognition and professional stature of the individual researcher or institution. The need to consider the overall socio-political context for researchers in DEC has been well established and is acknowledged by most funders (e.g. ODI, 2005). One review of an early bilateral grant programme, since abandoned, cited the lack of 'a true community of scientists', in which individuals meet each other and exchange ideas, as one of the main obstacles to enhancing research capacity in the South (Greene, 1991). Twenty-five years later, lack of postdoctoral training, lack of research groups, and lack of mobility to participate in conferences or interchanges are still recognised as gaps to sustainability of research in Africa and barriers to enabling contribution (Sewankambo et al., 2015; Waiswa, 2015).

Some cite the relationship between the scientific community and policy makers as a particular challenge for developing countries. Göransson (2016a) found the process of turning research findings into policy or as the basis for decisions was particularly weak in many developing countries, although a 'chasm' and mutual distrust between research and policy communities may occur anywhere. Other experiences suggest that the limited and overlapping pool of experts in smaller nations supports the co-learning approach, mentioned in Chapter 4, or construction of knowledge systems taking advantage of all expertise available (Kairo et al., 2005). The cultural context of any case in point can encourage the possibility of mutual respect developed in a small community and the pragmatic attitude of working together towards solutions offering benefit to the country, or distrust and competition among sectors.

Institutional structures at the national or meso level, also affect the research landscape. For example, although some African countries have research ethics committees dating back to the 1960s and 1970s, many still rely on a framework of the funder or its country, in particular from US Government sources (Kass et al., 2003). The national process of research ethics review in many developing countries is confronted with many challenges, funding being universally noted as one of the more important of these (Kass et al., 2007). The same published review reported that ethics criteria were being slanted towards the scientific, without experience in incorporating other criteria to the process. Operating procedures for committees

were often not in place at that time. There was virtually no monitoring of the research after review, so that the highlighted concerns were not addressed in the implementation of the research. As already noted in Table 2.1, avoiding conflicts of interest for national or institutional review bodies may be a challenge in situations where raising issues could result in losing funding or being considered uncooperative (Kass et al., 2007; Sugarman et al., 2007).

At the level of research institutions, weak administrative infrastructure and inadequate resources for this component have been identified as some of the main barriers to successful collaboration by developing country researchers for the past few decades (OECD, 2011; Gaillard, 1994; Greene, 1991). The transactional costs of exploring a partnership, developing a proposal and seeking funding for research can be very high. Possible ways to absorb these costs against other income, share the costs across entities, or justify the investment for potential return are mentioned in some literature reviews (ODI, 2005). Even when direct funding for DEC research institutions is approved, it often requires a lengthy process for contracting and to transfer funds (Gaillard, 1994). Those institutions that cannot manage the transactional costs of exploring and forming partnerships to seek such funding often will be left behind.

Funders are beginning to consider ways to finance these costs, in the form of early idea and exploratory grants, but even these require the inputs noted. For now, there can be some advantage to recognising that these costs can be high and are likely to occur as long as years before initial funding is secured for the corresponding research. Accepting this allows for better planning and resource allocation. Without some institutional support for those researchers preparing proposals or administering projects, it is too easy to reduce quality and effectiveness of the already secured projects and partnerships, by ‘stealing’ resources from them until the new funding is secured.

These are listed in Table 5.1 on the micro and meso level. The researcher compiled these and other relevant challenges in a developing country context from observation, drawing on years of experience working in around 50 countries, many lesser developed, on agricultural, environmental and public health development issues[51].

[51] It should be emphasised that, although identified in this study, this does not imply that these challenges were present (either as a whole, or individually) in any particular situation, project, country, or time period considered during the study. In particular, the researcher has not been aware directly of any instances that could be classed as bribery or corruption throughout her research.

Table 5.1 Example micro and meso level barriers for potential research partners to work on novel technologies in developing country contexts

Micro level – • unclear or unstaffed institutional system for procurement, rests on project level • some items procured locally are not quality controlled or authenticated, or simply not consistent in contents, concentration or labelling • international procurement of equipment or materials may be required, leading to additional costs, effects of transport and possible delays in customs • lack of institutional level training budget or programmes for ongoing enrichment, resulting in opportunistic rather than strategic continuing education and training • insufficient/under resourced institutional support for estates management, construction oversight, worker safety or other roles that might be covered at an institutional level in the 'North' • variety of employment terms and for staff, unclear or lack of administrative means for ensuring ongoing employment and/or incentives and rewards for increased capacity • limited opportunities for advancement or facilities and infrastructure for advanced research, leading to 'brain drain' to other countries	**Micro level –** (continued) • need for development of institutional committees to review studies (biosafety, ethics, etc.) or such committees are comprised of the researchers who themselves are in charge of studies under review • limited opportunities for internal institutional understanding or reviewing the novel technology • senior management may be pressured to use high profile projects for political capital, or to showcase the institute, rather than focusing on project objectives **Meso level –** • appearance of corruption, bribery or nepotism • need for greater transparency in some legal or regulatory topics, such as permitting • legal and regulatory frameworks that are not fit for purpose for the novel intervention • policy landscape for innovation and research that is not enabling for research with external partners, or novel product development • weak systems for protection of IP or for resolving contractual disputes • assignment of liability to the individual's level, lack of liability protection or insurance • unreliable or variable national infrastructure affecting micro level, e.g. electric supply

These examples of challenges facing developing country researchers will be true for much of sub-Saharan Africa and will exacerbate the challenges facing the range of decision makers along the pathway of delivery of a novel intervention in vector control (Table 2.1). Though it is especially challenging to work with complex or innovative lines of research, as discussed in Chapter 2, the conditions listed in Table 5.1 are not unique to that case.

One encouraging trend is the rise of multidisciplinary research initiatives (Bradley, 2007), even if deep integration remains challenging. The inclusion of social sciences has been found to

complicate collaboration, but is well established as vital for public health and vector control initiatives. Sonnenwald (2007) notes in general the increasing pressure from funders to have interdisciplinary teams for scientific research in general. The tendency to divide funds among different disciplines (e.g. social sciences and biological sciences) rather than creating true integration was identified in an earlier review of several bilateral and multilateral initiatives to support research collaboration (Gaillard, 1994). This tension among disciplines is as real as geographic cultural differences, and an important aspect to the context for a DEC researcher. Glowka (2002: p.52) concluded that: 'A more holistic approach to decision-making may result in a more accurate consideration of costs and benefits in the regulatory decision-making process.' This seems also to be the case for decision making at the micro level of a research team or institution. A more accurate picture of the barriers and enablers to improved vector control is sure to emerge if teams incorporate multidisciplinary experts and seek input from stakeholders early in the process of delivery, before reaching the point of moving from lab to field.

Other challenges are particular to health research or vector control. For instance, the general reduction in numbers of qualified vector entomologists has been identified as a barrier to malaria elimination campaigns globally. The researcher questioned whether networks focusing on tropical disease, such as malaria, may have a different paradigm in terms of partnership from the start[52]. Research in vectored disease control makes the need to work with affected countries, or at very least receive samples and data from affected countries, a given.

The online survey, reported in Section 5.5, provided some useful insights into the approach taken by individual Discoverers in the Americas, Europe and Asia, and suggests a more personal approach than might be anticipated. That stated, the researcher believes the institutional context and daily challenges for potential DEC research partners may not be adequately taken into account when considering criteria for finding a DEC partner. It would be rare that the researcher who creates a 'technology push' (finding a 'solution' and linking it with a problem, rather than knowing the problem and looking for solutions) is also the person who is deeply aware of or experienced with the pervading research context for any DEC researcher with aspirations and the achievements sought for forming a good partnership. Ways to address the challenges identified in Table 5.1 are considered in part in Chapter 10. Otherwise, the

[52] The conclusions about experts in vectored disease generally not being informed about novel strategies or that they consider 'existing opportunities to communicate with a non-scientific audience as inadequate to the task' from another study (Boëte et al., 2015) do not seem substantiated by this study or possibly by the data presented in Boëte et al.'s own paper.

context described was the backdrop for the current study when identifying possible best practices for finding a DEC-based research partner.

5.4 Proposed criteria for finding a DEC partner for research in novel vector control

When this study began in 2010 there was limited published literature addressing issues relating to DEC research partner identification or selection for novel vector control research. Most literature mixed useful criteria for design of a genetic strategy (e.g. stability of transgenes), with that for selection of a future field release site (e.g. high disease burden, potential for community consent). The researcher began with the premise that selection of field sites and evaluation of the potential for programmatic release requires review of country level, or possibly regional level, criteria. For containment studies, however, it seemed less clear. The researcher considered whether identifying DEC lab partners would be a micro level decision – to partner with an individual, a research team or an institution – or would require the addition of a number of meso level criteria, which themselves may be highly influenced by macro criteria (such as those relating to the influence of international guidance from the WHO or a WHO committee endorsement of any particular innovation, as noted in Section 1.2 and Beier et al., 2008).

Key publications at that time noted the need for capacity development among the potential research partners (Benedict et al., 2008; Knols et al., 2007; Touré & Manga, 2006), but gave no specific recommendations towards achieving that end. Descriptions of requirements for capacity generally stopped at the national or meso level, or simply noted the value of finding existing facilities at the micro level. Throughout the period of this study, there was no comprehensive listing of facilities or accompanying details about research teams already compiled for sub-Saharan Africa (in contrast, for example, to the SIT facilities, for which a directory is maintained by FAO/IAEA, referred to as DIR-SIT)[53].

Researchers working with genetic strategies who had ongoing partnerships shared their experiences in a meeting on use of novel mosquitoes, held in Geneva in 2009 (WHO/TDR, 2010). The researcher gained insights from projects led by S. O'Neill and A. A. James in particular, although those were working towards siting of large outdoor cages rather than containment labs, at the time. The need for early engagement with stakeholders was a key

[53] An overview of mosquito research capacity across Africa is now being developed by the Pan African Mosquito Control Association (see call for study, PAMCA, 2017).

message from both of these other initiatives; Ramsey (2010) raised some pragmatic questions as to how to do this in DEC settings. Ochanda (2010) touched on the need for capacity building and establishment of networks of scientists in DECs. Publications regarding field site selection and research facilities relevant to genetic strategies research are summarised in Section 5.7.

The basic biological criteria for choosing a field site seemed to be either broadly established (summarised in Section 5.7) or highly technical, relating to the specifics of the modification or drive mechanism, so that the researcher was particularly interested in criteria focused on governance, regulatory, biosafety and other 'soft' sciences (see Section 5.4.1). Taking into account those challenges reflected in Table 5.1 and based on her experience with development projects throughout the world around 2010, the researcher drew up an initial list of criteria for ethical, legal and social implications (referred to as ELSI) or ethical, social and cultural issues (ESC), presented in Table 5.2.

Table 5.2 Some early criteria considered by the researcher on governance and ELSI themes

General governance	
participating in international agreements	
federal system in place, local system in place to review technology	
experience with research and biosafety applications	
International	signatory Cartagena Protocol
UN agencies	IAEA status
	IPPC/OIE/FAO
Regional	member of regional group related to health issues
	regional group on disease control
	regional group on vector control
	existing mechanisms for consultation on open release
Federal	enacted Cartagena Protocol related legislation
	regulations or norms for implementation
	administrative framework for applications
	experience with review process
	experience with environmental assessment
	clear roles for decision making; coordination mechanisms
	national policy for dengue or malaria control
	funding mechanism for vector control
Local	area of local administration's authority well established
	issues affecting local site (e.g. zoning, ownership, infrastructure)
	evidence based and transparent decisions for vector control
	level of autonomy/independence in vector control decisions
	funding for vector control

Scientific culture, experience and capacity

- society's relationship with science
  - trust in researchers
  - trust in science
  - experiences with biotechnology or other innovations
  - opposition to GMOs
  - experiences with public consultation (see community involvement)
- educational and laboratory system
  - national programmes in disease and entomology
  - return of scientists to country
  - institutions dedicated to relevant research
  - personnel capacity within institutions
- international recognition of institution/staff
  - publications in peer reviewed journals
  - existing partnerships with Imperial College London* (or other leading universities)
- mechanisms for communicating scientific information
  - free press reporting accurately on science
  - basic comprehension of science; lack of intimidation by science
  - understanding of disease and role of vector
- examples of public influence on decisions, especially related to technology, health or science
  - locally based NGOs
  - relationship with international NGOs
- critical mass of people with time, income and education to participate
- motivated individuals (champions)

Ethics & individual concerns

- individuals potentially impacted by change to this technology
  - current vector control workers
  - people at proposed location of cage or lab trials
  - health care workers
- common societal priorities identified in national documents or programmes
  - integrated framework
  - poverty reduction plan
  - health plan
  - environmental plan
  - pesticide use plan
  - pesticide disposal
  - national biosafety framework
- national bioethics process for research on health
- institutional bioethics processes, some coordinated approach across institutions
  - possibility of research site benefiting from results
  - same communities, same country, altruistic choice

* The researcher's home institution

The ELSI criteria in Table 5.2 were subsequently compared against examples arising in the literature, in particular against Brown et al. (2014; including supplemental tables; see Appendix 2), although some of their criteria for site selection for release of genetically sterile *Ae. aegypti* were not relevant to *Anopheles*. Both the researcher and Brown et al. (2014) had mixed criteria in with potential indicators or objectives, however. Also, some criteria were easy to determine (e.g. membership of international and regional technical bodies) and others were more subjective (e.g. trust in science). A later revision of criteria, their usefulness and need for measurement are discussed further in Section 5.7.

5.4.1 Country level criteria

Despite the technical challenges noted during this period (Scott et al., 2002), malaria control with transgenic mosquitoes was considered 'a possibility in the foreseeable future' (Marshall & Taylor, 2009) and studies on transgenic mosquitoes in containment had been discussed as an appropriate first step. Within that context, the researcher agreed with the concurrent discussions that the first country level 'go/no go' criteria (requirements that had to be met) were related to the general disease and vector status of the DEC country. For malaria, the main health criteria were that malaria was endemic, and that it was considered a significant concern by the national government, if not society at large[54]. Ideally, evaluation of the existing health system, in particular the national capacity for effective disease surveillance and resources for disease control, would be a required criterion. A meaningful review of this nature was not feasible for the level of effort involved or the emphasis of this study on vector control rather than disease control[55].

[54] Although this seems an obvious criterion, in fact countries facing potential entry or spread of a disease that is not yet established or endemic may also choose to take action against an established vector population. This could be particularly important when the human population at large has not been previously exposed to this disease (referred to as a naïve population). An important forum among genetic strategy researchers (Alphey et al., 2002) noted resistance towards release of any transgenic mosquitoes that would not have direct impact on the vectored disease, while in reality most studies begin with evaluation of vector population impacts.

[55] The importance of disease impact rather than only vector population impact was not considered in this study to the level of detail that might be necessary past early phase. This point is critical, depending on the type of intervention or as the development of an intervention advances. As shown in Figure 1.1, measurable impact on transmission of malaria would require additional conditions in the country such as a good health system with adequate diagnostic capacity and health surveillance.

The potential for 'successful vector control' is challenging to determine, given the dearth of information to define that potential. Later, the researcher worked with Target Malaria to commission studies on the existing national programmes in mosquito control in recognition of the importance of this aspect (as also emphasised by Mnzava et al., 2006). In fact, if a country had already rolled out significant malaria control measures such as LLIN, or began doing so during the field studies, this could very much affect the results of any study and therefore the feasibility of using any given field site.

A further ‘go/no go’ country criterion was the status of the country with the funder, because of political restrictions on spending funds in some countries. At times, the call for applications for funding states clearly which countries are eligible. Sometimes, however, the researcher must review a funder’s policies to find this information. (If a Discoverer is seeking new funding for the delivery phase, the limitations imposed by funders could be reviewed to determine a fit with preferred partnerships, rather than vice versa.)

Working with colleagues, the researcher represented possible indicators of presence of what is considered the most important malaria vector species in Figure 5.1: reported presence of *An. gambiae* s.s. (actually representing *An. gambiae* s.s. and *An. coluzzii* using current taxonomic identities) at the country level. Figure 5.1a maps the presence of *An. gambiae* s.s. at the national level and Figure 5.1b the reported entomological inoculation rate (EIR) using data compiled from 2009[56].

The representations of issues underpinning decision making were somewhat deceptive at that time, even if the indicators were not later questioned. For example, the EIR map did not reflect the countries with the highest burdens from malaria – Chad, Central African Republic, the Democratic Republic of Congo (Head et al., 2017) and Sudan (Pasquale et al., 2013) due to the lack of data that was readily available. This corresponds to the findings of Head et al. (2017) that international funding for malaria research is not reaching the countries most affected by the disease. However, the next country level ‘go/no go’ criterion related to the challenges of difficult working conditions such as civil unrest, war, high security threats, lack of national infrastructure and so forth. For reasons of practicality, from the perspective of the researcher’s own host institution’s (Imperial College London) travel restrictions at the time, several countries were not considered as viable options for novel research in terms of access. Since that time, improved vector and disease transmission maps are available (e.g. Malaria Atlas Project, http://www.map.ox.ac.uk, following the method of Sinka et al., 2012; Gething et al., 2011). Therefore, data presented from 2009 should be treated as illustrative of the period and certainly not current.

[56] M.M. Quinlan, A.W. Leach, R.L. Carrasco and J.D. Mumford compiled both presence/absence and EIR data from a variety of sources readily available from published articles and through contact with some individuals working in the field. They also drew on Kiszewski et al. (2004) to determine where *An. gambiae* s.s. was recorded as absent, eliminated those countries (*An. gambiae* s.s. being a key vector) and then mapped individual species of the complex showing which vector species were prominent. Much of the information at the time was variable in presentation and reliability. Sometimes data was at a national level, so that maps showed status as covering the entire area within political boundaries, and other times it was more specific to the level of regions. A list of all of the sources by country is available upon request, but since that time much better materials are available as noted in the thesis.

Figure 5.2 shows upgraded maps of the dominant and secondary vector species for malaria in sub-Saharan Africa downloaded in 2017, although *An. coluzzii* is yet to be presented as a separate species in this series. Further data on presence/absence of key vector species are appearing in numerous publications along with details of the population genetics, phenotypes and so forth. Bhatt et al. (2015) have shown the impact of malaria control on a continental level from 2000 to 2015 using extensive compilation of field data, with interpretative and predictive modelling.

Early on, publications warned of the need for special consideration of introduction of a novel intervention when based on genetic modification but recognised that this would vary based on the cultural context of the country (Macer, 2003) as well as regulations. However, Macer (2003: p.15) states that 'there is no new intrinsic ethical dilemma from the modification of DNA structure in genetic engineering as it simply mimics the natural ways organisms use to change genetic structure', but recognises that some would consider a change in the purpose of an organism or any control by humans over nature to pose ethical concerns.

Focusing on the regulatory framework rather than cultural contexts, the main criterion discussed at the time was whether a country was a party to the Cartagena Protocol (considered to indicate the right landscape for decisions regarding the studies) or, to the opposite extreme, had banned the use of GM organisms in the country, which clearly discouraged consideration for partnership in research of transgenic mosquitoes. The researcher proposed a more sophisticated approach (such as Nang'ayo, 2006, used in his review regarding GM crops) to evaluate the status of decision making under the NBF.

There had been active and well-funded international capacity building activities from 2001 onwards to prepare contracting countries to meet their obligations under the Protocol. These were aimed at development of NBFs and Biosafety Clearing-House nodes, but many countries had not yet developed a functional system. Some countries, such as Côte d'Ivoire, fell under the category of being involved in preparations of a NBF without yet being a party to the Protocol. The opposite might also have been true, that a country could become a party to the Protocol without having any NBF, resources to develop or implement one, or clear intentions as to what to do next towards meeting the new obligations.

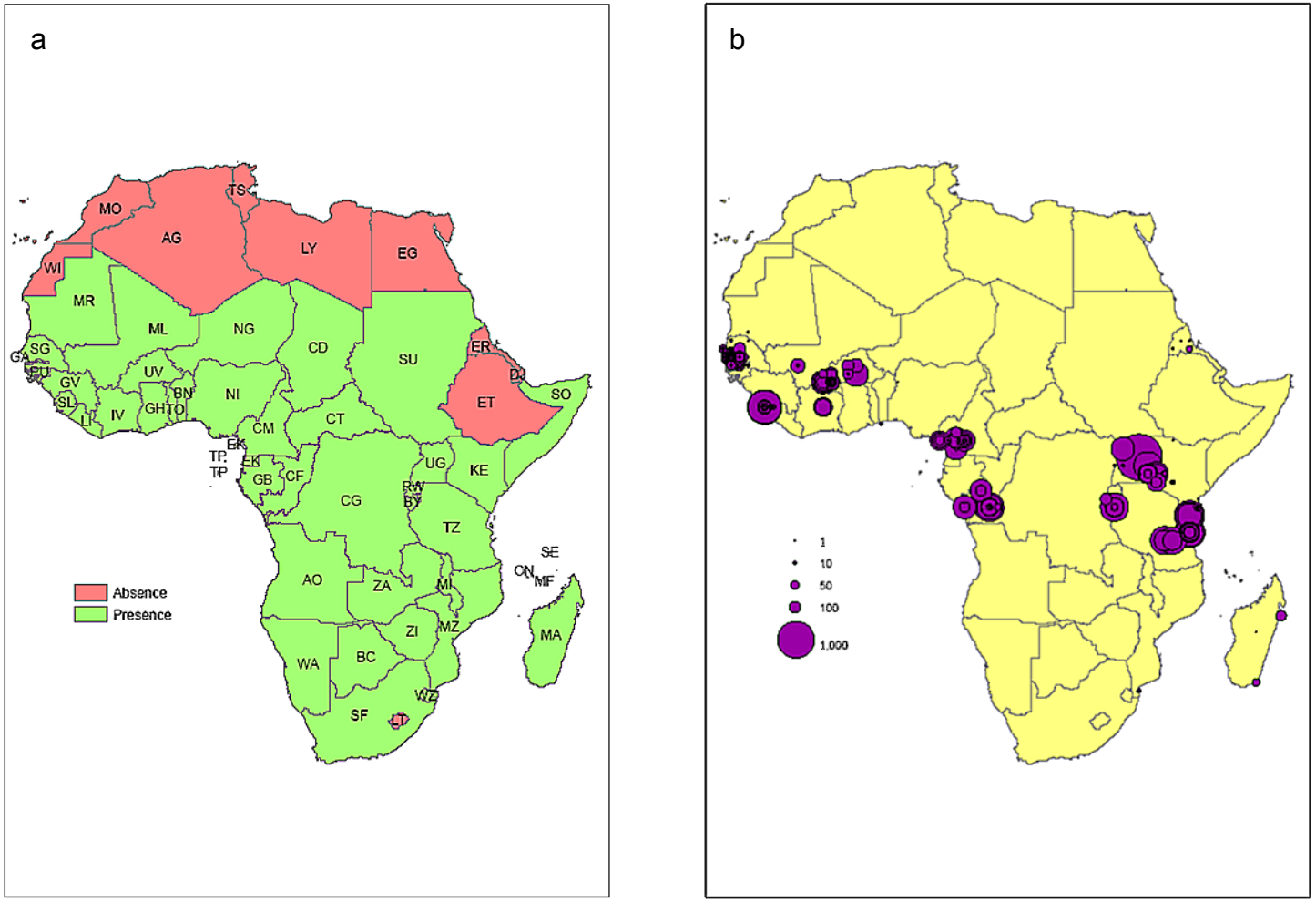


Figure 5.1 Reported (a) presence/absence for *Anopheles gambiae* s.s. by country versus (b) entomological inoculation rate (EIR) by region

Source: data compiled in 2009 by Quinlan, Leach, Carrasco and Mumford, unpublished

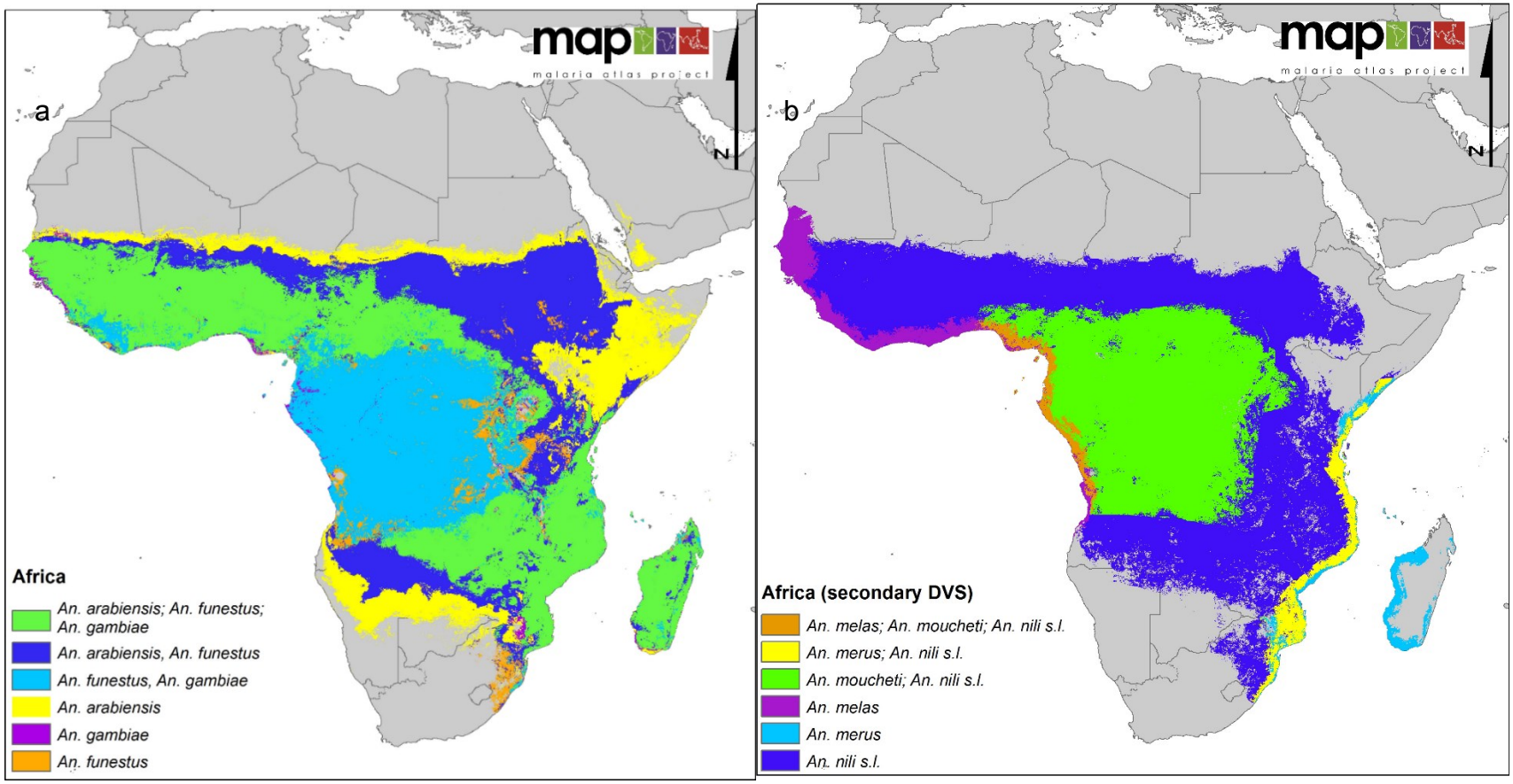


Figure 5.2 Distribution of (a) dominant and (b) secondary malaria vector species using predictive scoring and ranking by most significant vector when multiple species are present (not showing *An. coluzzii* as a separate species)

Source: Malaria Atlas Project, 2010

Uganda did not pass a comprehensive biosafety law until 2017 (Ligami, 2017), but had already submitted a plan for implementing the NBF by 2007 and approved confined field trials of GM crops, awaiting the bill before evaluating their move to commercial use. A moratorium could have indicated a national approach of banning use of GM organisms until the NBF was completed and implemented, rather than reflecting a final societal rejection of the technology. For example, Benin had declared a moratorium on GM crops in 2002 until a national legislative framework was in place (Nang'ayo, 2006), which ended in 2013 when at least a partial NBF was in place (2015, bch.cbd.int).

Birhanu (2010) describes the political landscape from 2001 when the African Union (AU) published a model law on biosafety. This document (promoting a harmonised approach but not an actual model law) encouraged a highly precautionary approach, extending beyond the terms of the Cartagena Protocol itself by including non living modified organisms (e.g. food products) and requiring, essentially, proof that harm could not be caused rather than demonstration of safety. This overly precautionary approach may not suit the development objectives of Africa (NEPAD, 2014).

African countries appeared to follow three different approaches, according to the review by Birhanu (2010), following either a biosafety approach using scientific risk assessment (which was considered more pro development of biotechnology), a precautionary approach closely following the Cartagena Protocol, or the more protectionist approach of the AU model law. The regional push towards harmonised NBF in line with the model law has dissipated since, however, as countries are moving towards less harmonised implementation (as discussed in section 6.1-2). The principal concerns of maintaining sovereignty in decision making and avoiding trade disputes would seem irrelevant for the use of genetic strategies against a vector species of mosquito.

Drawing on this experience, the researcher advised use of the following criteria as a minimum for NBF:

- Ratification of the Cartagena Protocol[57]

[57] A number of countries were signatories to the Protocol when it was opened, but the full process of national ratification is needed. This may take the form of the national legislature approving membership or similar procedures. The Protocol is a supplementary agreement not imposed on members of the Convention on Biological Diversity, but rather requiring additional adoption. This is not uncommon, but in contrast to some other sub agreements to treaties (such as the Agreement on the Application of Sanitary and Phytosanitary Measures, under the World Trade Organization). According to the official Biosafety Clearing-House, the Cartagena Protocol was adopted in 2000 and came into force (90 days after the 50th national ratification) in 2003 (https://bch.cbd.int/protocol/background/).

- Submission of the national framework for biosafety to the Biosafety Clearing-House at the time of review (e.g. in 2009 for this study)
- Submission of the implementation plan and routine national reports (e.g. the national report with a 2007 deadline for the figures shown)

These three indicators of possible preparedness for regulatory decision making (reviewed in 2010) are shown in Figure 5.3 maps a, b and c, making the differences among the factors clearly noticeable. The final map, d, shows countries positively prepared (NBF in place and operational), signatory to the Cartagena Protocol but without evidence of being prepared to effectively make decisions on applications for field studies, or with an official ban or moratorium on GM commercial use. The status shown for the African countries was not researched in depth, but rather based on easily gathered public information, primarily from the Biosafety Clearing-House website (https://bch.cbd.int/, accessed in 2009 for this compilation).

Figure 5.3 shows that if using a few general criteria in the context of the Cartagena Protocol, most of the continent would have had potential as hosts for research partners at that time. This clearly did not reflect the reality of the situation, which may be more accurately seen from a combination of all four maps. More recent evaluations and analysis of national capacities and NBFs have provided more useful information, such as the Black et al. (2011) review of example East and West African countries, which lists all of the initiatives working with GM in country at the time.

In addition to the NBF, the researcher considered national capacity by proxy of such indicators as participation (list of individual names not publicly available) in recent training described in WHO/TDR (2015) and membership in the International Centre of Genetic Engineering and Biotechnology (ICGEB), a research and training network first established under a programme of the United Nations Industrial Development Organization (UNIDO). These were not found to be directly linked to other factors.

The Convention on Biological Diversity website was the source on status of each country – https://www.cbd.int/biosafety/parties/list.shtml – accessed in 2009. At the time of the data compilation for this example, the following four states were not signatories/members of Cartagena Protocol, but had submitted an NBF: Guinea Bissau, Morocco, São Tomé and Sierra Leone. Côte d'Ivoire was not a Cartagena signatory/member but had submitted both an NBF and a 2007 Implementation report.

A list of countries and copies of their draft NBFs were found on the United Nations Environment Programme website: http://www.unep.org/biosafety/National%20Biosafety%20frameworks.aspx

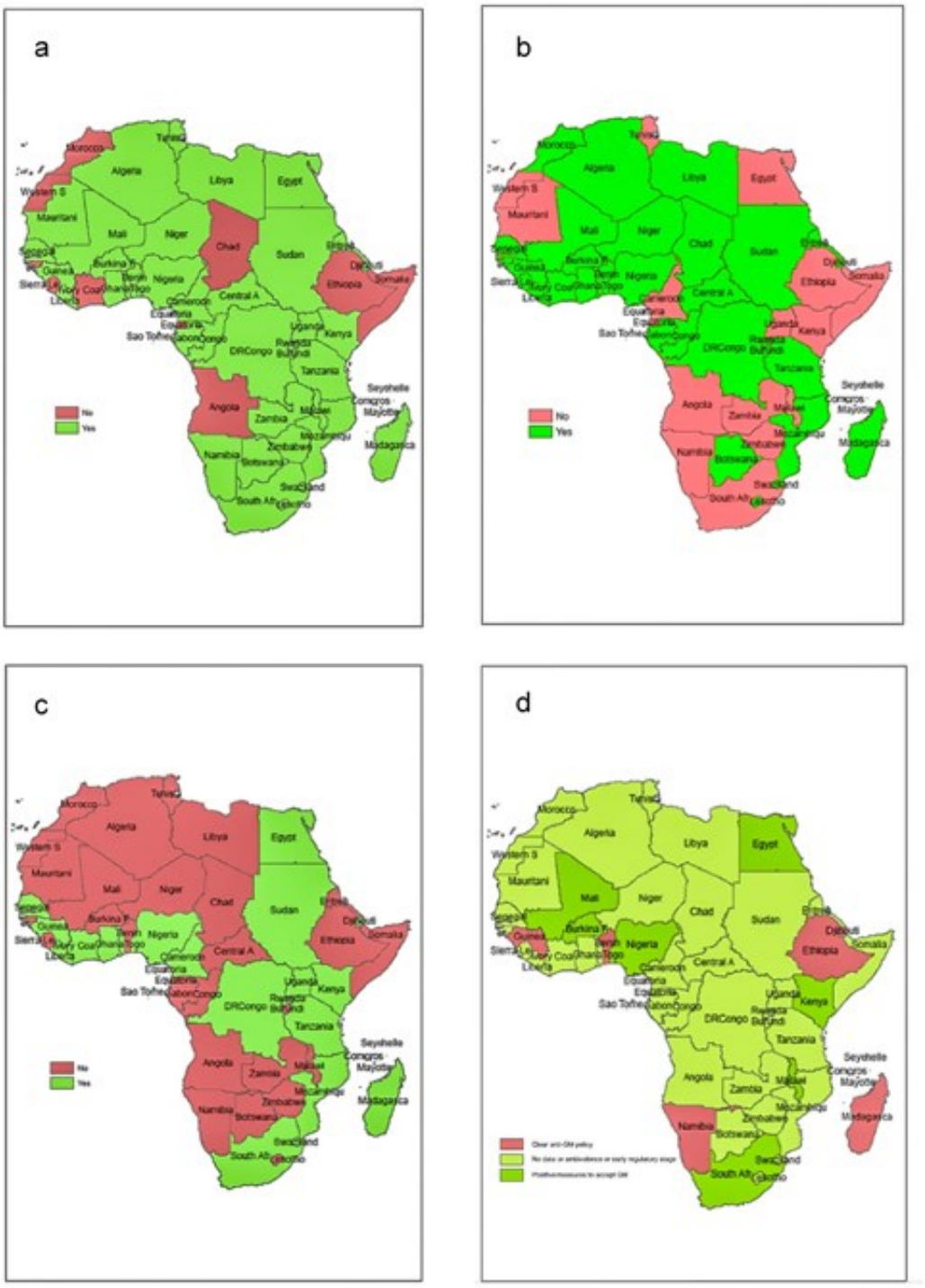


Figure 5.3 Approaches for identifying the status of a biosafety framework by country

Source: information compiled in 2009 by Quinlan & Leach

Legend: Yes green, red no for (a) Contracting party to the Cartagena Protocol; (b) Report submitted on the national framework and (c) Implementation Report submitted. For (d) Interpretation of level of preparedness ranging from moratorium or no data available on the Biosafety Clearing-House (red), to regulatory framework established (light green) or positive signs of acceptance according to posted decisions (darker green).

Records for total numbers of published articles on *An. gambiae* were considered by country, with individual researchers or institutions being evaluated in terms of number and quality of publications (see Section 5.6). Existing research links with preeminent researchers and universities in the UK and USA, for example, gave further evidence of experience of research groups in international projects or collaborations, in particular. Finally, Imperial College London colleagues working in vector or malaria projects in sub-Saharan Africa were interviewed to learn of their general experiences, which provided valuable insights often unpublished.

In summary, DEC in sub-Saharan Africa were considered as potential hosting partners for research on novel interventions in vector control. The review process was based on publicly available data regarding EIR and *An. gambiae* incidence, country policy and actions on biotechnology. (EIR was considered one of the best indicators of transmission at the time, although other approaches are now used in addition to that, e.g. Pothin et al., 2016.) These two criteria, along with any restrictions by the funding agency, were the key requirements to proceed in the screening. General security and infrastructure, related simply to the recommendations on travel by the British Government (https://www.gov.uk/foreign-travel-advice), comprised a further screening requirement.

As considered further in Section 5.6, the researcher found that many of the country level criteria available in published data at the time were not sufficient to give a true indication of suitability of a country to host such research[58]. Country level information was found to be coarse, although it provided an important general orientation. The initial review of country criteria gave a general context in which to search for specific institutions that could be a good match for the objectives of any particular research team or consortium. Primary among the sources of insight on the adequacy of these indicators was the Target Malaria experience.

Box 5.1 describes Target Malaria's process for finding potential candidates for a partnership for co-development of a novel intervention, for the first round in 2009-2012.

[58] It is feasible, with the right selection, that existing sources of data can be used to determine country characteristics which represent a functional NBF, for example. This type of analysis is done for other purposes, such as for receiving international aid (Hayes-Birchler & Staats, 2014). Many of the data sources for such an analysis are not freely available, however, and the researcher did not attempt to pursue that approach for partner selection.

Box 5.1 The first round of Target Malaria's approach to finding a research partner

The researcher participated in the initial DEC partner search process for the research consortium that became Target Malaria. The search began at the country level in sub-Saharan Africa. The decision to work where the impact from malaria was high, rather than along the edge of distribution of the vector, for example, immediately eliminated countries with good research infrastructure such as South Africa and Botswana. Funding restrictions in the case of the BMGF aligned with the US Government policy of the period[a].

As with most vector control initiatives, Target Malaria focused on entomological criteria. More subjective criteria arose, however, because of the aim to begin co-development of the proposed novel intervention using transgenic mosquitoes earlier than most documented research initiatives. Essentially, the research consortium needed the potential DEC research partners to choose Target Malaria, as much as the other way around. This implied a DEC research team with interest in genetic strategies, a self-assessed capacity to provide the staff and infrastructure needed, and the ability to manage a complex project.

To create this opportunity for 'finding each other' the Target Malaria team considered issuing a call for expressions of interest, announced through relevant networks and/or a news source such as to advertise in *The Economist*, where numerous contract and employment opportunities are published from UN and multilateral development groups. The subject was considered too specialised for that forum, however. Instead, it was decided to carry out an internal review of country criteria before contacting potential candidate institutes directly.

After the country level screening using publicly available information, the Principal Investigator of Target Malaria contacted all research institutions identified. This was done by emails to individuals associated with the institutions or the main institutional contact email. Not all institutions contacted in this manner chose to pursue the partnership. Each group was offered a remote meeting to hear about the plans and ask questions. Most of the factors considered at the country and institutional level had been enumerated in a then recently published discussion of gene drive (Benedict et al., 2008), although the initial proposal was for studies using non-driving strains of transgenic mosquito[b]. The list of main points and questions to orient the remote meetings appear in Table A2.1 (in Appendix 2).

In line with desired partnership style, potential DEC partner institutions were asked to support preparation of the next funding proposal, featuring containment studies using sterile males from a transgenic line as part of the stepwise approach towards evaluating other transgenic strains of the targeted vector species. The general contents of the proposals requested by Target Malaria are shown in Tables A2.2. The initial questions concern country level characteristics such as the status of the disease and vector species; governance, regulatory, and ethics review framework; and the societal context, to confirm or clarify what was found through public information.

The scientific capacity of the partner institution; physical and administrative infrastructure; and relative estimated costs completed the topics covered. After receiving proposals from the candidates remaining in the process, a template (Table A2.3) was used to organise the information across various sites. Results of the proposal submissions and this tabular summary of submissions are commercially confidential and have not been shared.

Although the comprehensive and detailed responses to Table A2.2 were to form the basis for the next application for funding, the responses were not elicited to a level that would allow full feasibility studies or in depth comparisons among countries[c]. Even so, this approach placed a burden on the potential partner institution to prepare a proposal using their own time and resources, and some candidates may have found this investment of time and resources prohibitive. On the other hand, a DEC research team willing and able to provide the responses requested by Target Malaria would appear to be capable and accustomed to the rigours of research partnerships and international funders.

The initial search, contact and remote interviews led to a shortlist of potential candidates in late 2010 and concluded with agreements with the first stage partners by early 2012. A major change in direction during this process was to include more than one partner. Many challenges arise that limit progress in DEC research settings. The decision to work with more than one research group at a time has been justified over the subsequent years.

Local area eradication of malaria could be much easier in other regions in the world that present a low population density of an individual species of malaria vector, and/or are locations easily accessible and with existing infrastructure. The choice was made to work in the region where malaria's impact on human health was the greatest, namely in sub-Saharan Africa, reflecting the values of the key funders, the BMGF and more recently Open Philanthropy, and the discovery researchers' desire to contribute the most to reduction of suffering from this disease.

[a] At the time of the search for a partner, this eliminated what was then Sudan from consideration. An eradication programme was already in the planning stage in Sudan (now North Sudan or the Republic of Sudan) using SIT and integrated measures.

[b] The use of gene drive has been considered a special case requiring additional scrutiny (James, 2005). The recommendation to use a sterile (male sterile) strain for initial releases to avoid persistence in the environment (Benedict & Robinson, 2003) was taken up by Target Malaria.

[c] The need for economic or costs-benefits studies has been acknowledged, with suggested approaches described since (Undurraga et al., 2015). Experience from SIT studies suggests that even the simplest cost-benefit and feasibility studies require a minimum of six months and cost from US$10,000 to US$50,000, depending on available information.

5.4.2 Institutional and individual researcher level criteria

Given the limited literature specific to DEC partners for research in innovative vector control, the researcher sought to evaluate if there is a best approach for finding appropriate DEC partners by learning from researchers themselves. The Target Malaria research consortium employed the country criteria laid out in the section above, as an initial screening for suitable partners. The country level process (described in Box 5.1) resulted in a short list of countries, but more importantly the beginning of a list of potential research institutions. Once the country review was complete, the next step was to identify experienced research teams with interest in working on development of a novel intervention for genetic strategies against mosquito vectors.

Over the period of this study, detailed baseline data on mosquito populations in the Target Malaria proposed field sites for confined studies were not available, although published studies provided insights into the potential density of mosquito populations for each country in general. The subsequent investment in collection of these baseline data has been high. Unfortunately, the researcher's experience has been that existing and even published field data may be unavailable in raw form, unreliable with insufficient descriptions of methodologies, or hard to interpret. Even in the field of SIT, which is well established, basic aspects of data on areawide programmes were found lacking in numerous publications (Quinlan & Larcher-Carvalho, 2007). This may give more weight to the criterion of having comprehensive data about the vector species in a country or area before selecting it for field studies, but only for the highest quality data.

Even with the experience of Target Malaria to learn from, there were insufficient example research projects or countries to serve as a control or for comparison in order to reach clear conclusions on how many of the researcher's proposed criteria stood the test of time. Therefore, the researcher employed additional methods to investigate and draw lessons from the typical process for identifying a DEC partner and possible best practices.

5.5 Online survey of innovators or discoverers about their partnerships

The researcher developed and implemented an online survey that ran from January through June 2017, as described in Chapter 4[59]. The full content of the survey introduction, consent, and questions as presented to participants is shown in Appendix 1. The survey aimed to learn how innovators in vectored disease research (covering vectors, vector control and similar) from the Americas, Europe and Asia identified their research partners in DEC, and what lessons learned could benefit others seeking the same. An online survey was considered the most effective way to reach a large range of researchers working on vector control or vectored disease with partners in DEC[60].

5.5.1 The respondents: researchers external to DEC

The survey was designed to explore the perspectives and experiences of researchers in discovery labs which had formed partnerships with DEC researchers or with institutions to conduct in-country lab and field testing. The targeted participants were intentionally representing those whose work originated in countries that are not disease endemic, sometimes referred to as 'the North', or more resource rich countries[61]. Responses confirmed

[59] J. Mumford and Z. Makuch were instrumental in progressing the related materials through the ethics review process for this survey and helpful in discussion of the results.

[60] A similar survey was trialled the previous year, but individual email contact was not effective, so it was changed to be a more anonymous online format with outreach through research networks. The response *rate* was actually quite low (50 out of an estimated 1200 individuals contacted, see Chapter 4 on that process); this was explained by the fact that a number of those contacted might be in roles that precluded participating in decisions regarding partnerships, such as technicians, administrators or students. Fifty responses was still considered to show a range of geographic locations and varying years of experience. Furthermore, the initial questions resulted in only 31 self-identifying as researching 'innovative vector control measures or vectored disease control' within the past 15 years (question 1, Q1, 50 response), whereas two-thirds of respondents (36) confirmed their involvement in vector research with partners in DEC within the past ten years (Q2, 48 total responses). The distinction between innovative lines of research versus other approaches to vector interventions was not sufficiently precise in the wording of the questions, perhaps, to apply consistent application of the distinction.

[61] In fact, only one respondent, out of the 50 who completed at least one question, stopped the survey after noting he or she was from a DEC and did not quality to proceed. There were also 5 individuals stating that they had not worked with DEC partners within the past ten years, Q2, at which point they were directed to stop the survey by the wording of the question. Therefore 44 of the original respondents qualified to complete the survey to the end. To a large degree this bias results from geographic and language limitations of the survey, since the method of targeting potential participants was biased itself towards the Americas based on number of solicitation emails sent, with only a few respondents expected to be from Europe or Asia and no anticipated responses from Australia, for example. As expected, no responses were collected from African Discovery Researchers, who were not targeted by the survey.

this was the perspective represented, because results showed that over 76% of the partnerships reported on had been initiated by the Discoverer group or individual, versus by some other mechanism (e.g. a third party) or by the DEC research group (question 5, or Q5, with a total of 42 responses). The identity of respondents as a group also was confirmed (Q7, 37 responses) by the statement that the individual completing the survey was either the main decision maker (33%) or a member of a team making the decision (57%). Very few felt they had not influenced the selection of a partner. Thinking from the point of view of a project structure, the distinction of project Work Packages was not so relevant (57% stated it was not applicable, and 3% that they had not decided who was in their group, in Q8, with 37 responses), but some did state that they chose the partners in their subgroup. Finally, less than 12% stated that additional partners in the research or project had been chosen in a different way than those discussed in their responses (Q9, 34 responses), leading the researcher to conclude that the answers provided have not been complicated by multiple approaches.

It also was confirmed that those participating were responding from a current experience and were generally not new to this type of work. For nearly 90% (32 of 36 responses, Q22) the partnership was ongoing at the time of the survey and over half (25 of 37, Q23) either did not have a given end date for the research, or planned to apply for an extension when that date arrived. Those who included the optional write in for number of years working in such partnerships, if not necessarily the one reported on, had experience ranging from four to over 30 years, with most reporting a range from 12 to 25 years.

Administrative arrangements to secure these partnerships included a range of approaches, shown in Figure 5.4. But respondents were asked to include any that applied, so one might have a contract and still use MTAs, for example (Q3, 41 total answers).

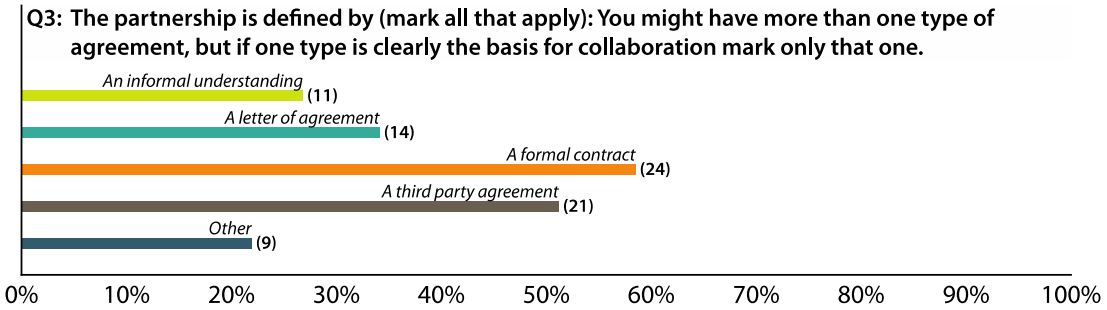


Figure 5.4 Method of formalising a partnership with DEC researcher on vector interventions

Q3: The responses offered were: informal understanding; letter of agreement or informal document; formal contract; agreements of both you and the DEC partner with a third party, such as the funding body; or other (e.g. Material Transfer Agreements).

Although the identity of respondents was anonymous, there was sufficient information to confirm that the survey represented experiences of researchers in the Americas, Europe and Asia.

5.5.2 Finding a research partner

As already mentioned, this survey aimed to represent the perspective of researchers external to DEC who would need a research partner where the proposed intervention for addressing a vectored disease could be developed and/or tested for future use or to improve delivery. The first findings of note were that these partnerships are based more on individual researchers and their institutions than the selection of a particular country within the target region or among DEC, as shown in Figure 5.5 (although presumably country criteria would need to be favourable as well, when choosing individual partners). More than 63% (Q4, out of 44 responses in total) indicated that their research partnership was related to an individual researcher in a DEC, and (as multiple answers were possible) half of the same respondents indicated they had partnered with particular departments or research groups, or work with particular universities or institutions. This was well above the 25% who indicated particular countries were chosen for their research.

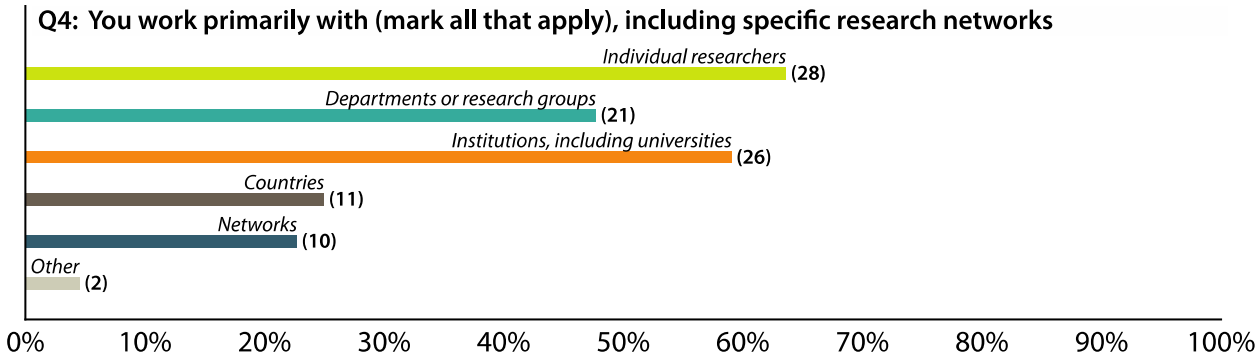


Figure 5.5 Research partners in DEC ranging from individuals to countries

Q4: The choices were presented as: individual researchers; departments or research groups; institutions, including universities; countries; through specific research networks; other.

The process for finding a partner was not as clearly skewed to one approach, although use of personal contacts was notable. This was reiterated with write in answers, which included: personal relationships formed during university studies, because of knowing the Director or others at an institute, through existing ties between the respondent's university and the DEC

institution, or in projects run by others prior to forming a direct partnership. Less than 23% (Q6, out of 41 responses) indicated that a particular research network provided candidates for partnership, whereas recommendations by colleagues was only slightly higher (24% of 41 responses) and by funders a mere 5%. The online survey (Q6) also revealed that Discovery or Novel Researchers would classify their process to find DEC partners as a 'deliberate and well considered' process (61% of 41 responses). (Only two responded that the selection process was fairly *ad hoc* in nature. Further distinctions in these concepts might have resulted in different answers.)

5.5.3 Ranked criteria

A series of criteria were evaluated under the groupings of: biological factors; human population and disease factors; capacity at the level of the researchers, institutional and national; national characteristics such international relations, language and culture; security; the potential for community engagement; and influence of funding source. Results for these categories are presented in question format (Q10-19) and were ranked on a scale of 1-5, with 1 being 'not considered or not very important', 3 being 'taken into account but no more important than other criteria', and 5 being 'most considered or very important'[62]. (0, 'not applicable', was never chosen in this series.) Figure 5.6 presents the responses to these questions on criteria, averaged and rounded to the nearest percentile.

The highest ranking criteria of all categories were: presence of the study organism (under Q10, with 35 respondents) and disease incidence at the site (under Q11, with 34 answers), which ranked an averaged 4.71 and 4.48 respectively out of a maximum of 5. The number of vector species at the site was ranked in importance at 3.30 average (Q11). Other interventions already in place ranked at 3.55 (Q11), but the impact of this would depend largely on the nature of the novel intervention.

[62] Ranking of one criterion under a group did not affect the outcome of other criteria, so that it would have been possible to indicate the same level of importance for more than one. The respondents were not asked to rank criteria against each other, absolute highest and lowest, but rather the questions were presented as clusters not directly comparable: biological; human population and disease; researcher's capacity; institutional capacity; national capacity; international relations; social and language factors; stability of the country; characteristics of the country that might affect capacity for community engagement; and the funder. With these options, therefore, some respondents marked everything, particularly in the biological category, as 5 and some skipped criteria entirely once the top one was chosen for that category. Because of these varying responses by question, the total number of responses for each subquestion or related criteria appears at the end of the corresponding bar graph.

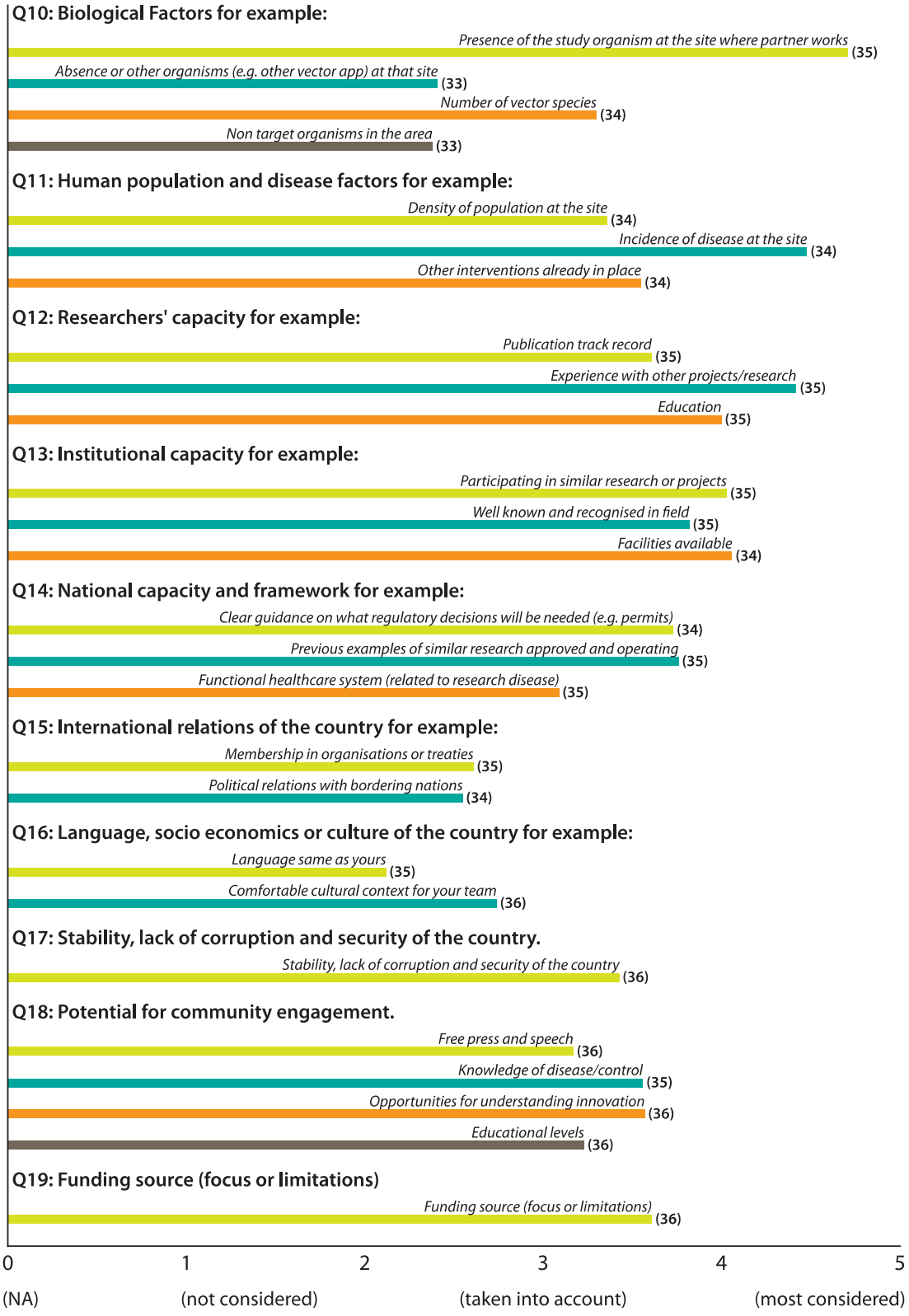


Figure 5.6 Averaged responses from an online survey of researchers external to DEC, in relation to various criteria for selection of research partners for vector interventions in DEC (total responses for each question shown at the end of each bar)

Density of the population at a site was also considered, according to the averaged response of 3.36 (Q11), whereas non target organisms at the site were hardly taken into account according to the average 2.38 (Q10). It is likely this is not an important criterion because presence of non target organisms at a favourable site cannot be avoided, rather than any lack of interest in protecting or avoiding harm to them.

The overwhelming importance of success building on success was shown by responses regarding researchers and institutional capacity (Q12, with 35 responses, and Q13, with 34), which indicated that the higher ranked factor of experience with other projects or research is key.

For individual researchers, this ranked 4.42 on a scale of 5 (Q12) and was followed by education and publications, at 4.0 and 3.61 respectively. Participation of the institution (Q13) in similar research or projects also ranked high, at 4.03, while availability of existing facilities was the other highly ranked institutional criteria, at 4.06. An institution that is recognised in the field (average 3.82) is more considered than 'taken into account' but scored less important than experience with projects. Keeping in mind that those surveyed work with a range of interventions, nothing else in Q10-19 ranked above 4 in terms of importance (as shown later in Table 5.5). The national level criteria of having clear guidance on what permits will be needed (3.73) and previous examples of approving similar research (3.76) were considered more important than a functional health system related to the disease being researched (3.09). Perhaps the difficulty in choosing accessible, accurate indicators for evaluating a health system is part of this ranking.

The survey put a shared language and culture (under Q16, with 35 respondents) as only 2.12 and 2.74 average, respectively, with a number of respondents ranking these at 1 ('not considered'). This suggests that much has changed in selection of DEC partners since the historical post-colonial period, when a shared cultural context was the basis for many partnerships. (The researcher found that consideration of language and culture could be different, however, if the Discovery Researcher is already embedded into an 'existing network', as discussed in Box 5.2.) This survey result may be down to many more science professionals in DEC being fluent in the language of the Discoverer (or in English as a shared second language, since the survey was limited to English speakers), although it was apparent that English was not the native language of many of those participating in survey.

Connections to individuals or research groups appeared to be long standing (and even expanding, insofar as over half had worked together on other issues or with other funding sources in addition to the example collaboration being reported (Q27, total of 36 responses).

Only seven cases of 37 respondents for that question (Q24) answered that they had moved, transferred or ended a partnership due to an individual leaving (five) or an institutional change of staff (two). In the majority of cases (over 60%, or 23 responses), respondents reported not facing the situation of key staff moving, although some (six responses) had faced the departure of staff without making any move away from the original partner research group themselves.

The researchers who participated in the survey indicated factors such as corruption were 'taken into account' but were not important as criteria (40% ranking this at 3 on the 5 point scale, averaged as 3.43 with 5 as most important). Only one respondent mentioned this issue in the write in question about challenges (Q30). Similarly, the perception of free press and speech, and potential for community engagement with the communities understanding the disease and its control or the opportunity to understand the innovation, ranked as criteria that were 'considered' but not of high importance. Again, this may be because of those targeted through the research networks to participate in the survey. Few, if any, appeared to be social scientists, for example, due to the organisation of the survey.

From write in responses, it was found that at least one good partnership had to be abandoned due to the reduced numbers of the vector spp. under study, after other vector control interventions (such as LLIN) had been implemented. Another researcher reported the drop in political will on the national level led to the end of that research partnership. Despite the challenges, over 88% indicated the relationship with their DEC research partner to be a satisfying or highly satisfying experience (Q28, 34 total responses). While 11.6% felt expectations were not entirely met, no respondents reported being disappointed with the research partnership.

The researchers who responded to the write in question (Q21), *describe in your own words what influenced partner selection,* included the following criteria:

- Personal recommendations and friendships
- Encounters at technical meetings
- Being part of the same research network
- Their previous experience in the field
- Their research publications and grants held
- Proof of previous successes in carrying out complex research

and, albeit more subjective,

- Honesty
- Curiosity, enthusiasm
- Passion; initiative
- Reliability; willingness to cooperate to make the project a success
- A good team player; [good] group dynamics
- Attention to detail
- Interest in the research more than the funding

It was considered important to find countries with the regulatory framework to take decisions on necessary approvals. Being supportive of capacity building as a means to support staff retention in country was noted.

Responses to this write in question (Q21) also suggested these courses of action: (i) Discussing specific objectives, seeking a match; (ii) visits to country site, face to face meetings there; and (iii) meetings with others from the institution, i.e. administrators, indication of sufficient institutional support. Fewer respondents had used competitive bidding (considered further under Section 5.4). One recommended starting with pilot projects to determine their success before committing to larger joint efforts.

Table 5.3 lists some responses to the write in question about what factors were most important for success of the partnership, and Table 5.4 lists responses regarding the greatest challenges. It was noted (Q31, write in) that research will be more successful in general with a local partner on board.

It is unsurprising that several of the factors noted as determining failure (Table 5.4) are the same as those influencing success. These might be considered generally more bureaucratic or institutional than those listed in Table 5.3, however, rather than relating to individual characteristics.

Several respondents highlighted issues with capacity, including management skills and administration. The researcher believes that personal attributes of potential partners and the depth of relationships are key factors for successful partnerships (Table 5.3), but that these have not been reported to the extent of their importance in other literature on innovative vector control research.

Table 5.3 Factors for success in research partnerships on vector control

Obtaining regulatory approval	Availability of partners to reach the goals
Infrastructure of DEC institution	Knowledge, education and expertise
Clearly defined objectives	Capacity building
Clear expectations; clear communication	Mutual respect; mutual benefit
Frequent communication; regular meetings	True sharing of planning, responsibilities and credit
Reasonable time frames including advance preparation of the experimental scheme	Respect of local culture [by researchers]
Respecting deadlines and milestones	Good working relationships with personnel
Product or outcome driven	Trust gained from prior collaborations
Flexibility regarding logistics and bureaucracy	Trust
Collaboration at the institutional level	Patience
Continuity over time; ongoing research projects; long term partnerships	Cooperation
Publications	Motivation and work ethic
Upfront agreement about data ownership and publications	Friendship with DEC researchers
Good data collection	Long term partnerships
	True academic exchange of ideas

Responses to Q29: What do you believe are the three most important factors for any successes from this relationship? (Not in order; paraphrased, and with similar responses combined).

It is interesting also to note, since publications were a recurring point, that over 75% of the 37 responding (Q25) indicated that publications or patents already had resulted from the collaboration they were describing. The optional write in (Q26) to list these publications did not receive sufficient responses across the pool to allow for analysis of who was first author or frequency for each individual author.

The final write in question (Q31) covers recommended approaches to finding a DEC partner for vector control research, some of which were already noted (duplications of response to other write in questions). A few additional comments were: to keep in touch by using Skype (or other Internet communication platforms); check there is sufficient institute support; visit the site; and when a partner is identified, meet with national government contacts (e.g. regulators) before committing to work in the country. The process and various options for finding a partner will be discussed further in Sections 5.6 and 5.8.

Table 5.4 Main challenges in research partnerships on vector control

Obtaining regulatory approval	Competing priorities
Governmental 'red tape' for ethics approval, import/export regulations, material transfer, etc.	Very time consuming to build the mentoring relationship
Unpredictable policy changes in host country	Education, especially of lower level staff
Lack of infrastructure; issues of reliability of equipment and facilities	Untrained personnel
Delivery of materials and equipment to perform experiments cause unforeseen problems	Logistical problems due to social instability
Unclear and slow process for ethics review and institutional research boards	Changes of personnel
Budget, funding constraints	Weak local management capacity
Delays, missed deadlines; logistical issues	Lack of cooperation
Lack of institutional interest	Uneven writing expertise
Administrative contracting and payment slow timelines	Issues with reporting
Lack of experimental design and replication of studies	Unclear communication
Poor data management or incomplete data collection	Cultural issues regarding meeting deadlines
Lack of data collection framework	English language requirements
	Obtaining a visa for DEC researchers to visit our country
	Difficulty in foreseeing all of the technical/logistical problems that will arise

Comments on (Q30) What have been the three major constraints or biggest challenges? (Not in order, paraphrased, with similar responses combined).

Based on their experiences, the feedback from these respondents suggests that a toolkit for Discoverers or Novel Researchers inexperienced in working in the DEC context would be a useful contribution to the field. Their participation in this survey provided the beginnings of just such guidance.

5.5.4 Summary of online survey findings

This survey was aimed at those working with novel interventions in vector control who were assumed to be external to DEC and therefore requiring some collaboration with a research partner where the vector and vectored disease are established. Therefore, the most obvious

approach to selecting a partner is (paraphrased, write in response for Q21): *identify sites with the relevant disease incidence and biological factors, then look for partners there*[63].

This would, in fact, correspond with much of the literature on transgenic mosquitoes, which has focused on site selection rather than partner selection. Indeed, presence of the study organism and the incidence of the related disease were the highest ranked criteria in the series of subquestions under Q10-19. This is not surprising and aligns with the researcher's proposed 'go/no go' criteria and the process developed within Target Malaria. The survey findings suggest, however, that there are a number of critical factors at the more personal and institutional level that are very important. While the questions were not designed to ask for a ranking of comparative importance among the various categories, and were retrospective from the point of view of often years of experience with the partner, the rankings shown in Table 5.5 and write in answers to other questions (Q21, 29, 30, and 31) would suggest that individual characteristics and accomplishments of the individual researcher and experience of the institution have had significant impact on the outcomes of the research pursued.

Table 5.5 Highest ranked criteria influencing partnerships, according to responses to an online survey of vector control or vectored disease researchers

Criterion (question number from survey)	Ranking (1-5)
Biological factors: presence of the study organism at the site where the partner works (Q10)	4.71
Human population and disease factors: incidence of the disease at the site (Q11)	4.48
Researchers' experience with other projects/research (Q12)	4.42
Institutional capacity: facilities available (Q13)	4.06
Institutional capacity: participating in similar research or projects (Q13)	4.03
Researchers' education (Q12)	4.00

Only those criteria with an average ranking of 4 or above are included. The rank shows the average of response on a 5 point scale, with 1 as not considered or not very important, 3 as taken into account, and 5 as most considered or very important.

[63] Similar responses included: [Find] appropriate location (in terms of epidemiology, entomology and vector control situation), [and review potential partner's] capacity, reputation, in-country relations with the government. Although one response suggested partner preference would be obvious (*They are the 'go to' site for collaboration.*), many researchers in novel vector control may not have that insight, particularly if coming to the research from other backgrounds or a previous focus on domestic research.

The survey might support the idea that the research agenda, on novel vector interventions at least, is set largely by the more developed country researcher. It was not designed to clarify that question, however, and the survey did not seek out DEC researchers working on novel interventions with domestic or intraregional teams.

The partnerships reported on were overwhelmingly successful, as defined through the majority of respondents feeling satisfied or very satisfied with the relationship and results. (It is possible that those with unsuccessful partnerships chose not to complete the survey.) Ultimately, although this survey was from the perspective of an external researcher seeking a DEC partner, a partnership is down to what one respondent wrote in (Q21): *We select partners that are willing to work with us*.

This survey provided insight to the search for a suitable partner. There are limitations to this method, as already noted in Chapter 4. Respondents were self selecting, but this is offset by the fact that many of the relevant researchers around the world would have received the invitation to participate, as part of the research networks that collaborated. The targeted participants were allowed to define their own qualifications to participate (i.e. working on novel research) and the survey was not specific to use of transgenic mosquitoes or living mosquitoes for delivery of the intervention. Similarly, such a limited survey may not be extrapolated to the entire sector of vector research. It does provide some insights into the importance of individual DEC institutional track records and even very personal attributes of researchers, rather than only the national characteristics as key criteria for selection. Another source of insights, considered in the next section, comes from study of some example institutions working with other types of innovations in health, environment and agriculture.

5.6 Other approaches to research partner selection

The researcher pursued other methods for learning about partner selection for development of innovative technologies, not necessarily related to vector research. This section draws on the results of interviews with research groups in France and some international organisations. France was chosen because, particularly in the context of francophone Africa, the researcher had detected a different approach in general by French organisations in comparison to the British institution (Imperial College London) where she works. Initially many African nations aligned more with European values and regulations than, for example, American ones in the development of an NBF (Adenle, 2011).

The researcher perceived partner selection in UK based initiatives as more fluid and based on individual researchers of interest. The major French institutes interviewed appeared to work overwhelmingly with partners in francophone countries with historical geopolitical relationships. Research leaders and institutional managers were interviewed about the criteria and process for selecting specific partners for field (in target countries, not necessarily outdoors) testing and further product development. Further, two European projects related to pest interventions or biological product development[64] informed the researcher on practices from those sectors.

5.6.1 Enabling innovation

An enabling environment for innovation refers to the general policy framework that encourages pursuit of novel research and results in technologies put into use. The Organisation for Economic Co-operation and Development (OECD, 2014) describes innovation that leads to economic growth as requiring both 'excellence' and 'relevance'. It goes on to say that for knowledge transfers there are various styles:

- Collaborative
- Via mobility of key individuals
- Through business creation
- Contractual
- Through transfer of IP

Transfer of systems of knowledge are achieved through sharing of standards or other means for benchmarking, SOPs and databases. One of the criticisms of the French context at the time of the OECD innovation review (OECD, 2014) was that administrative activities related to IP (i.e. filing patents) were confused with economic activities (i.e. exploiting patents). Other studies have indicated that numbers of patents is not a good indicator for innovation (NASEM, 2017a). Numerous metrics regarding excellence in research have only confused the field, when objectives and missions, and localised contexts, are critical to this evaluation (NASEM, 2017a; NASEM, 2016a; Hicks et al., 2015). Collection and evaluation of indicators of success

[64] This section was complemented by participation in two projects for novel products in plant protection (EMPHASIS – Effective Management of Pests and Harmful Alien Species – Integrated Solutions, and EUCLID – Europe China Level for IPM Demonstration) funded by the European Commission under the Horizon 2020 research and innovation programme. Horizon 2020 is described at: https://ec.europa.eu/programmes/horizon2020/en/what-horizon-2020. For more information on the two projects, visit their websites: http://www.euclidipm.org/ and http://www.emphasisproject.eu

are often not even attempted in complex situations in which various influences may be at play (Aizenman, 2017).

Private sector participants in innovative product development in particular note the need for a predictable regulatory framework in order to flourish. Cross ministerial or authorities coordinating mechanisms were identified as an important aspect to that predictability (NASEM, 2016a).

5.6.2 Supporting innovative products

Under the legal framework aimed at promoting innovation, it is a legal requirement in France to report annually on 'inventions' that may be appropriate for development to a commercial product using a form covering particular key points related to the framework (Le Tinevez, pers. comm., 2016). Working under the EUCLID project, Quinlan & Tourneur (2017), however, highlighted how the reliance of not only France, but several European countries on the Declaration of Invention form could miss opportunities for exploitation of ideas, tools and products that are more innovative and may be protected commercially in some fashion other than patenting.

The EMPHASIS project has worked with purpose made business plan templates (Alden et al., 2017) and other tools to support biologically based or otherwise plant health related products that did not fit the usual planning templates. Some of the distinctions requiring bespoke templates included that: (i) such work was not always aimed for profit, being supported by publicly funded or philanthropic sources; (ii) there were often mixed groups of developers, possibly sequentially over long periods of time; and (iii) sometimes the complexity or previous developments made use of IP protection options too onerous or difficult to obtain. The project also found that improvements might emerge as collateral enhancements to existing technologies already in the public domain (Alden et al., 2017).

In the case of drug discovery by WHO or WHO-supported initiatives (described by the researcher in FAO/IAEA, 2008) licensees would be chosen that will take the innovation into the commercialisation phase, generally after development through a technology readiness level (TRL) of perhaps 5, 6 or 7 (according to the researcher's perception). For LLIN or bed nets, WHO would oversee development of product specifications but not participate in the development and delivery phase. The OIE has procedures for recognising laboratories for diagnosis, for example, and a similar system for testing efficacy and production of animal vaccines (OIE, 2016).

5.6.3 Various styles of partnerships

Interviews with French institutions known for providing relevant innovative technologies or products revealed a variation in approaches to partnering or transferring these innovations. The simplified version of three approaches, described in Box 5.2, may be appropriate for different objectives or may be applied to the same product at different periods of development.

A fourth approach is to certify or otherwise recognise a laboratory or other type facility as conducting the research, studies or production to a pre-set and described level of quality. This form of accreditation or often times an official recognition then supports the resulting outputs, while not being actively involved in delivery of them.

Some of the responses to the online survey noted above (Q21 write in) would also align with these other styles of partnership. For example, what influences choosing a partner:

> *In country ability to conduct research and have facilities available to handle our samples and data*
>
> *We partner with experienced research firms or institutions that are selected through a competitive bidding process per our organization's procurement policies*

For research with innovative vector control interventions, the TRL system would require a review across a wide range of approaches and mechanisms to reach a useful description of these levels. In this study, the idea of ‘proof of concept’ might be what is demonstrated in the Discovery Lab whereas ‘proof of principle’ is the application of the innovation to a disease endemic setting, with proof consisting of demonstrated impact on either the vector or the vectored disease, depending on the context. A different definition would put TRL 3-4, Concept Validation, as some form of testing the application of the technology. It is important to agree on what terms mean and how, when and in what way DEC partner researchers will be involved in this type of progression. TRLs provide an additional tool to consider when communicating across international partnerships.

The researcher proposes some of the more frequent partnership patterns in terms of timing of entry in relation to the TRL in Figure 5.7. Under the EMPHASIS project and similar initiatives, The UK Food and Environment Research Agency (Fera Science Ltd, 2017) adapted the TRL approach first described by the US National Aeronautics and Space Administration (NASA) to better fit plant health and biologically based products. Some of the adjustments include adapted descriptions of each TRL.

Box 5.2 Cultural variation in approaches to working with DEC laboratories

Traditionally, scientific research partnerships have been determined by 'historical, geopolitical and linguistic conditions' (Gaillard, 1994). Over the course of this study, the researcher reviewed how different organisations identified and formed partnerships for other types of innovations. Guided interviews with members of three French institutions involved in innovations in science, health and agriculture (Institut Pasteur, CIRAD and INRA) revealed a deep cultural difference between their approaches, albeit different from each other, and other representative projects based at Imperial College London (observed in an ad hoc manner over time).

Generalising and simplifying, the study revealed three principal approaches to delivery of innovation:

1. Selection of partners from within a permanent, existing and fairly integrated network with training and leadership coming from the European headquarters but some decisions at the local level (Institut Pasteur, a private non-profit foundation)
2. Selection of partners from existing professional networks to conduct the delivery research on site of the target location, but with a long term secondment of staff from the European headquarters to initially oversee but eventually hand off leadership on the local level (Centre de Coopération Internationale en Recherche Agronomique pour le Développement – CIRAD, French government aid deliverer)
3. Selection of partners that will take the innovation from a Technology Readiness Level (TRL) of 5 or 6 when transfer is considered through to through a licensing type arrangement, with support from the Discovery lab (i.e. that involved from TRL 1-3) for initial work to support hand over, but increasingly leaving the licensee in charge past TRL 7 (Institut National de la Recherche Agronomique – INRA, French agricultural body for domestic outcomes)

The Institut Pasteur draws on both its own organisation's staff in centres throughout the world (https://research.pasteur.fr/en/ip-network), and the established network of recognised partners. A new technology then, in theory, could be developed, tested and distributed efficiently throughout this system. The subject expertise would not be as flexible in this type of system, however. Some staff would need additional training and/or additional staff would be hired if a new theme such as genetic strategies became an important research thread.

<table>
<tr><th>Technology Readiness Level</th><th>TRL Cluster</th><th>Environment</th><th colspan="7">Generalised types of partnerships</th></tr>
<tr><td>TRL 9</td><td>Deployment</td><td rowspan="3">Real / Operational</td><td rowspan="3"></td><td rowspan="3"></td><td rowspan="3"></td><td rowspan="3"></td><td>Mosquito control agency</td><td rowspan="10">Possible involvement of technology transfer entity that was also the initiator of the invention (in particular government development or innovation agencies or programmes)</td><td rowspan="2">Private licensee, commercialising entity</td></tr>
<tr><td>TRL 8</td><td>Operational Validation</td><td rowspan="3">Possible research in operational</td><td rowspan="4">DEC mosquito control research unit</td><td rowspan="3"></td></tr>
<tr><td>TRL 7</td><td rowspan="2">Technology Demonstration</td><td rowspan="4">Possible involvement in proof of principle</td><td rowspan="4">Collaborating DEC partner lab and field teams</td><td>Initial engagement</td></tr>
<tr><td>TRL 6</td><td rowspan="2">Relevant /simu-lated</td><td rowspan="4"></td><td rowspan="4"></td></tr>
<tr><td>TRL 5</td><td>Application development</td><td rowspan="4">Intermediary or innovation entities</td><td rowspan="4"></td></tr>
<tr><td>TRL 4</td><td rowspan="2">Concept validation</td><td rowspan="4">Laboratory</td><td rowspan="4">Discovery laboratory</td><td>Initial engagement</td><td rowspan="4"></td><td rowspan="4"></td><td rowspan="4"></td></tr>
<tr><td>TRL 3</td><td rowspan="3"></td></tr>
<tr><td>TRL 2</td><td rowspan="2">Invention</td><td rowspan="3"></td></tr>
<tr><td>TRL 1</td><td></td></tr>
</table>

Figure 5.7 Entry point for selection of DEC research partners in terms of technology readiness level (TRL)

Adapted by Fera Science Ltd (2017)

5.7 Published criteria for transgenic mosquito research site selection

As noted in Section 5.2, at the start of this study, there was little literature specific to the case of transgenic mosquito research. Here, the researcher revisits more recent studies to determine if additional criteria might relate to selection of research partners.

5.7.1 Country and field site – beginning with a meso level perspective

Country selection, when working with transgenic strains, depends on (i) political will to carry out the novel research and employ resulting technologies; (ii) a framework specific to evaluating these innovations; and (iii) mechanisms for engaging with stakeholders that goes far beyond the usual consent for areawide control programmes (e.g. Brown et al., 2014; Lavery et al., 2008; Macer, 2003). Most of the criteria for field sites would hold true for non-GM research strains, but at the national level, much is made of the fact that genetic modification is the basis for an intervention. Publications specifically aimed at evaluating transgenic mosquitoes for disease control agree on five key criteria for selecting a field site:

1. Established populations of (preferably a single) malaria vector species with a clear genetic identity, homogeneity (no or low population gene flow) and clear spatial boundaries (e.g. Marsden et al., 2013)[65]
2. Geographically isolated areas, even oceanic islands (e.g. Marsden et al., 2013; Benedict et al., 2008), which also prevents movement out of study mosquitoes
3. Presence of human communities at the proposed sites with sufficient numbers to attract sizeable mosquito populations, but without extensive human movement that could introduce and remove mosquitoes and change the disease status (e.g. Brown et al., 2014; Marsden et al., 2013)
4. Active transmission of the vectored disease at the site (e.g. Brown et al., 2014; James, 2005)

[65] Coetzee et al. (2013) re-evaluated the taxonomy of *An. gambiae* s.s., resulting in the molecular forms being separated into two species. This change alone caused changes in the distribution of the single species as a vector.

The ability of the local community and national regulatory system to engage with and make decisions about a novel intervention in vector control (e.g. Lavery et al., 2008; James, 2005). Perceived isolation from actual physical islands was mentioned and promoted in several forums as a way to avoid reinvasion and keep the study in confinement. Again, however, it was one criterion to be balanced with others, and what the parameters in terms of isolation should have been was not entirely defined in literature at that stage.

Even the obvious biological characteristics required for a site, such as 'presence of the target vector species', have been found to be more nuanced in case of differences in mating compatibility or insecticide resistance on a more localised scale. Abundance of target populations and relative species composition are known to shift with ongoing use of interventions such as bed nets. The impact of the number of species in an area that are able to vector malaria has been discussed in Chapter 2.

Brown et al. (2014) found that for the highly-anthropophilic species of *Ae. aegypti* a minimum number of people permanently residing in an area was linked to sufficient abundance of the vector species in order for studies to be statistically analysed.

The mechanism of action of a novel intervention can add further criteria (e.g. ideal vector density at larval stage), or affect the preferred sequence or inclusion of existing mosquito control measures (e.g. timing of insecticide use), which interacts with both country level decisions regarding national mosquito control and decisions at the level of potential field sites, such as districts, municipalities or villages. This aspect of selection criteria needs consideration on a case by case basis, until an agreed classification of mechanisms, or of ideal conditions for various mechanisms, has been published.

More detailed criteria, relating to country status and field sites, are compiled from some of these publications and presented in Appendix 2. These are presented against the most detailed criteria tables published, from the supplemental data files of Brown et al. (2014), which relate to transgenic *Aedes* but have some similarities with sites for studies of malaria vectors. The researcher complemented these publications with others on site selection for mosquito control using SIT (e.g. Iyaloo et al., 2014; Malcolm et al., 2009), although also focusing on site selection for field studies, which are cited in Tables A2.2-A2.4.

The researcher developed Figure 5.8 to show key criteria out of the literature for selecting sites for field studies or pilot implementation of malaria vector control interventions, from three different approaches: SIT, genetic strategies and chemical-based measures.

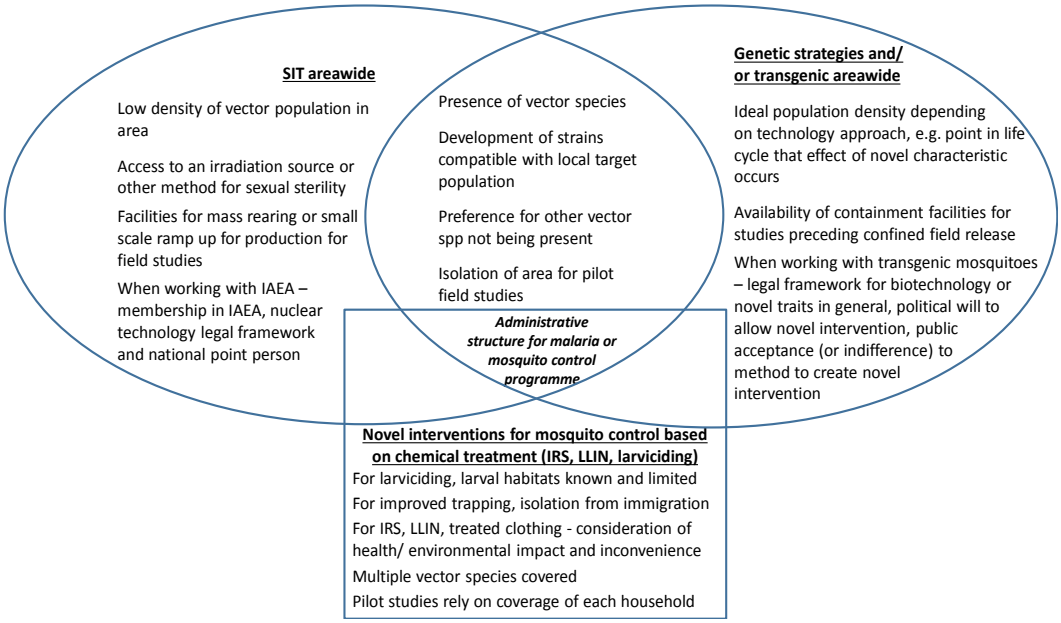


Figure 5.8 Published criteria for selecting a site for field studies for different approaches to large area mosquito control

5.7.2 Containment facility or confined cage sites – micro level

Decisions regarding the siting of a research or mass rearing facility refer to somewhat different criteria (FAO/IAEA, 2008), depending largely on the purpose of the facility. The siting of this type of facility will be influenced by whether the insect under study or production has a restricted or regulated status at the proposed site; the nearby infrastructure in terms of distribution to future field locations (e.g. road network or air infrastructure); if the plan is for eventual release of the reared insects along the edge of the species' occurrence in an area, or in zones with higher population and therefore more damage or impact; and so forth. At the same time, siting near areas of human habitation oriented towards vulnerable populations, such as schools or hospitals, might be avoided simply to avoid any appearance of risk (FAO/IAEA, 2008).

Some of the literature on field site selection presents practical points that hold true for facility siting:

- The proposed sites are accessible
- Ownership of the site is clear and those involved agree to the studies
- Existing infrastructure is available for use
- The location does not present risks to the project staff

Further discussion on quality control for mosquito research and overall capacity appears in Chapters 7, 8, 9 and 10, and various publications including Mumford et al. (2018).

Location of a facility should be considered when doing research on plant diseases, to site containment greenhouses away from areas where vulnerable crops are grown (Adair & Irwin, 2008). When planning studies on GM crops, consideration has been given to proximity to centres of origin for plants or the presence of potential non-target organisms that are considered threatened or endangered, so that special care would be needed to ensure no impacts occur (Keetch et al., 2014), e.g. through removal from containment or when studied in confined field situations. The centre of origin is less relevant to mosquito research, although one would not want to introduce a different strain to an area particularly if it displays greater insecticide resistance or other traits that affect potential control. The issue of potential impact on non-target organisms during a confined field study is an example of safety studies that ought to be pursued and might indicate the need for avoidance of certain areas. If the site is in or near a protected area or habitat, the reasons behind that status should be reviewed to avoid any impact, albeit unexpected, that could have more serious consequences. Such criteria are especially important in early stages of evaluation, when safety of the organism or biosafety of the facility may not yet be well established or officially recognised.

Physical factors (discussed further in Chapter 7) may be determined by whether it is best to have a new build or adapt an existing building, a single facility plan or a modular approach, and to what extent manual labour versus automated processes is preferred. Although the possibility of serious natural disasters such as earthquakes or flooding should influence the site selection, in fact several major facilities are sited in higher risk zones. In more than one case of Semi-Field Systems, the anticipation of flooding led to the structure being constructed on an elevated base (Facchinelli et al., 2011; Ferguson et al., 2008).

The Model Business Plan for Sterile Insect Production Facilities (FAO/IAEA, 2008), written by a team led by the researcher, provides a financial spreadsheet to compare affordability of sites in terms of capital investments and ongoing operation costs. Examples of facilities producing several different species in various parts of the world are included, with similar financial criteria.

Another step in delivery of novel interventions may be studies in outdoor cages, meant to imitate conditions in vector disease affected villages, in most cases, to evaluate possible environmental impacts on mosquitoes that have favourable traits in the lab (Mumford et al., 2018; Facchinelli et al., 2013; Knols et al., 2004). Ferguson et al. (2008) describe the design and use of a large outdoor cage, referred to as a Semi-Field System, in Tanzania. Ritchie et al. (2011) describe a level 2 containment outdoor cage complex developed for studies of *Wolbachia* infected *Ae. aegypti*. In both cases the criteria for site selection are not discussed and the research assumes that availability of land on campus is the highest criterion. Ferguson et al. (2008) lists other such facilities in Europe, India, Thailand and Australia as well as Kenya, Tanzania (Muheza) and Sudan. Of these, few would be considered containment facilities, for example those in Thailand were constructed of mesh and bamboo at the site of the field studies (Harrington et al., 2008).

The primary criteria for outdoor research cages discussed for Tanzania were (Ferguson et al., 2008):

- A site that is representative of environmental – and to the degree possible ecological – conditions normally experienced by the local mosquito species (although some conditions may be managed intentionally as part of study variables, e.g. cooling/heating or humidity).
- Ease of access and use by researchers, while facilitating restriction of access by others.
- Existing services (roads, electricity, water, security, etc.).
- Negligible risk to neighbouring communities in case of an escape of the research organism.

This final criterion led Benedict et al. (2008) to suggest locating cages (in this case for studying gene drive mosquitoes) as far away from communities as feasible taking into account ease of access for researchers, while also acknowledging that using existing infrastructure also is preferred. The same publication noted the need

for community agreement and ethics and regulatory approvals. Other criteria were related more to quality control of the study colonies, insofar as existing baseline data of the native populations of mosquitoes would allow comparative monitoring of the behaviour of mosquitoes in cages (Ferguson et al., 2008).

Ramsey et al. (2014) describe the most complicated process to date of engaging with and obtaining both regulatory and stakeholder permission for siting a facility (in this case a Semi-Field System in Mexico), while McNaughton (2012) has argued for enabling the public to participate more deeply in the scientific aspects of a similar scenario, albeit in a much more resourced country, heading towards field release.

In short, the criteria for siting a research or production facility overlap with those for field site selection, but some of the primary requirements vary considerably.

5.7.3 Other types of criteria emerging

The need for general laboratory capacity in a country to address significant diseases such as malaria has often focused on individual skill sets and sometimes institutional capacity (Njelesani et al., 2014), but there appears to be less detail on the specific skills needed for transgenic mosquito research, although the need for capacity is frequently mentioned.

Co-authorship has been used to identify networks in health research and was considered in the novel intervention project studied as well. Other measures of scientific collaboration are now employed, including analysis of social networks. Fonseca et al. (2016) considered the network of research institutions developing vaccines against chikungunya virus, which identified key countries and institutions working in this area. Relationships between research communities and industry or the technology sector can also be identified in this way. This is likely to be more useful for external evaluation and review, however, or social research on evolution of networks and degree or closeness of relationships (Fonseca et al., 2016), than for discovering a research team not already known to someone working in the same subject.

Country affiliation of authors of peer reviewed publications was considered by number of researchers, and reviewed quickly during development of the initial criteria in this study (discussed in Section 5.2). An example of publications in 2009 on *An. gambiae* is shown in Figure 5.9. Even co-authorship does not necessarily

represent knowledge co-development or sharing, although it assumes some active collaboration and exchange of information (Fonseca et al., 2016).

Previous understanding and awareness of the novel technology by the scientific community in the target country also has been recognised as important in more recent analyses, because regulatory and other decision makers will turn to that community for expert advice. Although some question the awareness of the DEC scientific community about novel vector control in general (Boëte et al., 2015), a study in Nigeria found that over 90% of the scientists interviewed were familiar with genetic modification as a methodology at least 'somewhat', five years ago even with intentionally surveying mixed fields of expertise (Okorie et al., 2014). In addition, conferences and publications were found to be key sources of information about novel vector control options, along with personal contacts (Boëte et al., 2015) and important conferences have included this topic in the past few years.

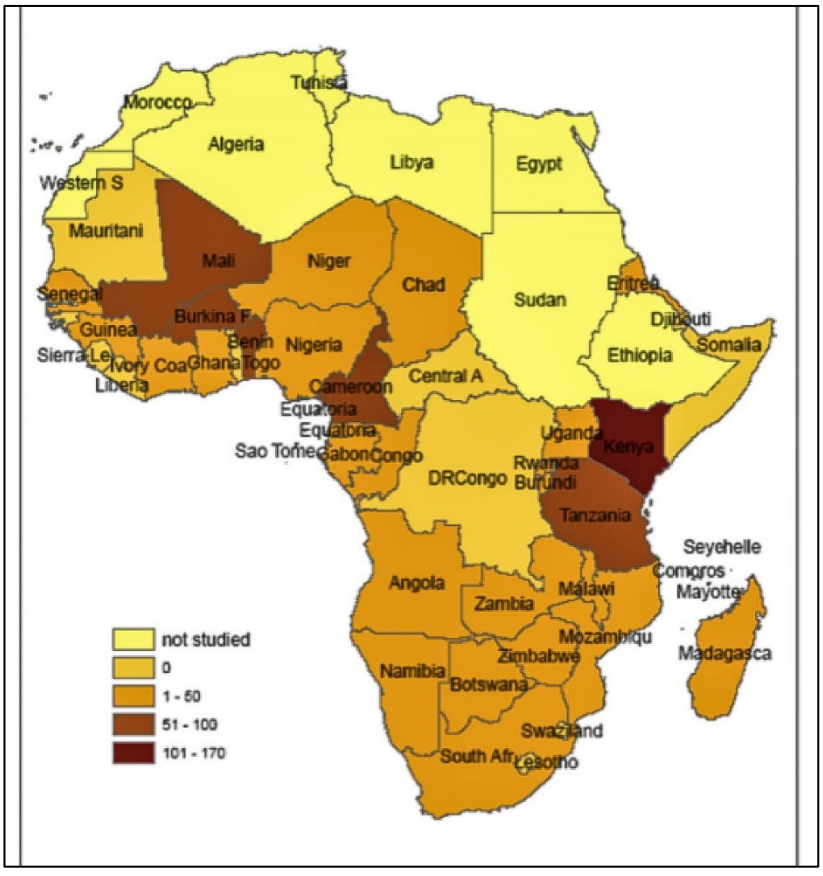


Figure 5.9 Bibliographic index of papers published on *Anopheles* in prominent journals

This was based on the combined number of papers with *Anopheles* or *An. gambiae* in the topic and the country name in the address of an author for the period of 08/2004-08/2009, using Web of Knowledge. Countries in Northern Africa were not included in the search.

It was concluded from the research, after this more recent literature review, that additional guidance on early stage selection of research partners in DEC is still needed. This could support decision makers involved in the delivery of a novel intervention in vector control, particularly when the person is lacking direct experience with the type of organism, or technology, or research context.

5.8 A learning framework for finding the right DEC partners

The researcher reviewed criteria suggested by publications, survey results, interviews, experiences external to the field of vector control and other sources. Significantly, the researcher noted throughout that criteria often were somewhat conflated among steps along the delivery pathway or objectives, thereby lowering their utility in supporting decision making. For instance, suggested factors included those that addressed the technology itself, specific biological traits of target mosquito populations, national ELSI characteristics, some aspects of international relations (e.g. participation in international conventions or protocols), and a range of characteristics of field sites. Although integration of criteria is needed in decision making, the researcher concludes that maintaining competing criteria by category will help to find the best balance among all of them.

One way to improve these groupings of criteria, therefore, seems to be to delineate among the various levels of criteria at the meso through to micro scales of: country criteria, field site criteria, institutional criteria, facility site criteria and individual researchers. This has been done naturally among publications focusing on only one step, e.g. field cages, but not as much for those considering the overall delivery pathway. An attempt by the researcher to present the main criteria by each step in a revised set of criteria appears in Table 5.6. This format allows for comparison and consideration across geo political levels. Furthermore, the impact of research on policy decisions (micro to meso level influence) may be as powerful as the reverse, so that influences across criteria for DEC partners run in both directions.

Another observation is that criteria are overwhelmingly presented in existing literature at a single level of priority, other than to note what are absolute requirements (‘go/no go’), which remain rather few. Further research would be needed to give comparative weight to each criterion, but a general categorisation of required, priority, desirable and when possible was attempted in Table 5.6, based almost entirely on findings from this study and experience of the researcher.

Table 5.6 Revised Meso and Micro criteria for potential DEC research partners to co-develop novel interventions in vector control

Significance of criteria	Country criteria	Field site criteria (for confined trials, not full release)	Institutional criteria	Containment facility site criteria	Individual criteria (lead researcher)
Required to proceed 'go/no go'	Officially recognised presence (established population) of targeted vector spp. Disease is endemic[a] and considered significant by society and government No restrictions imposed by funder or initiator's country on spending there (due to political sanctions, failure to meet set standards in financial reporting, or other factors)	Targeted vector spp. at the site in sufficient numbers (which may relate to human numbers) and clear enough identity to allow for monitoring and measure of impact at statistically valid numbers Safe access to site for researchers of both teams Conditions in place for carrying out community engagement	High reputation in related research Institutional level commitment to the research Administrative capacity and commitment to fulfil requirements of funder Involvement of at least one champion for the concept/project Available facilities, including ancillary labs outside containment; access to or ownership of field sites Existing institutional biosafety and ethics committees, linked to national systems Ability to identify multi-disciplinary support and additional expertise as required	The site does not present risks to the research and insectary staff Ownership is clear and transparent; site is available for at least medium term (e.g. 15-20 years)	True commitment to the proposed scientific enquiry Trustworthiness and integrity in research Collaborative, team player[b] Already working on similar or related research

[a] If the vector has established it may also be that the disease is not yet endemic, or even not present, but that the threat is sufficient to take action before this occurs. This should be a national decision, not restricted due to external values.

[b] The first three criteria in this section are the most subjective in the Table. While more difficult to determine in advance, measure or document with evidence, these characteristics will become known to those working with such an individual over time. Training in ethics, what is conflict of interest, biosafety, the dangers of dual use, financial rules, and so forth could contribute to these qualities.

Significance of criteria	Country criteria	Field site criteria (for confined trials, not full release)	Institutional criteria	Containment facility site criteria	Individual criteria (lead researcher)
Priority	Clear framework to review applications and grant permits, including for the specific technology; conditions in place for national stakeholder engagement Active participation in regional and international health and technical bodies; linkages for trans-boundary issues Politically neutral towards or supportive of solutions using biotechnology	Quality baseline data on target mosquito spp. population Reliable access (all weather) and links to communications Community understanding of and concern about the target vectored disease and the proposed research; mechanism to obtain consent – willingness to host research[c] Reliable information about current malaria and mosquito control interventions	Available facilities, including ancillary labs outside containment; access to or ownership of field sites Existing institutional biosafety and ethics committees, linked to national systems Ability to identify multi-disciplinary support and additional expertise as required	Basic existing infrastructure is available through the partner institution (i.e. partner holds contract, lease or owns the site), including access to electricity, water, incinerator, etc. Site is accessible to existing insectary staff or near urban area from which staff might be hired Activity is acceptable to near neighbours (although this is to be confirmed)	Reputation for excellence in related research (e.g. mosquito biology) Relevant post graduate education Publication track record, or other evidence of technical capacity Experience in managing teams, both in lab and field

[c] One of the pillars of ethics for health studies has been that the study population could benefit from the results of the research. The researcher does not consider those in a community where mosquito research is being conducted as 'human subjects' in the study. Therefore, while some put presence of the disease at the actual field site of studies as a requirement, e.g. malaria transmission at the village, the researcher challenges this as a long term paradigm. As long as vector impact is the indicator of success (possibly through initial phases), this would not be a requirement.

Significance of criteria	Country criteria	Field site criteria (for confined trials, not full release)	Institutional criteria	Containment facility site criteria	Individual criteria (lead researcher)
Desirable	National ethics process suitable to vector control proposals Positive policies for innovation and R&D Articulated health goal of malaria elimination; competent mosquito surveillance and control programme Clear IP protection (if relevant); feasible requirements for benefit sharing	Only one vector spp. of importance, or seasonal variation when one spp. is prevalent New vector control interventions not starting, or ending, in the area during the study period Away from international borders or areas of special vulnerability or protection (e.g. schools, centres of biodiversity)	Demonstrated capacity to support publications, deliver reporting Permanent research staff Existing certified containment facilities, already approved for studies Experienced institutional committees for biosafety, research and ethics	Single use option for entire separate containment area (which may be in the same building or lab, but with bio-safety features ensuring isolation) Site is in area zoned for research, but not designated medical or hazardous in terms of national waste regulations or by the Basel Convention (see Basel Secretariat, 2014)	Minimal demands from other research, teaching or administration Skills in research design, statistical analysis, reporting and writing for publication Known to be initiating researcher; or part of international network, or on editorial boards, or invited speaker at preeminent conferences

Significance of criteria	Country criteria	Field site criteria (for confined trials, not full release)	Institutional criteria	Containment facility site criteria	Individual criteria (lead researcher)
When possible	Previous experience in regulatory decision making on open field/commercial use of products of biotech-nology Framework to support public input to biosafety decisions, case by case Effective monitoring of the incidence of the vectored disease and accessible, effective treatment Corporate vs individual liability frameworks	Geographically isolated area with little or no movement of mosquitoes from or to site Similar site available for use a control Experience with documenting community support for research Quality baseline data on other spp. in the area, particularly mosquito predators or non target organisms that share larval habitats	Shared language across sites Experience with contracting and managing multi-disciplinary team, or in house expertise (e.g. social sciences, regulatory compliance) Possible co-funding or complementary funding to support long term commitment to research/ product	Near similar facilities or research labs that may share resources in terms of lab management, opportunities for training, possibly oversight or safety officer. Near international ports (airport) if import/export of strains will take place (or reliable courier service is recognised by NBA)	Long term commitment to remaining with the research project; no other work demands Excellent skills in research design, statistical analysis, reporting and writing for publication Established working relationship with initiating researcher prior to current research Good project management/ communication skills

These categorisations, or orders of priority, were not validated or tested during this study.

If this revised set of criteria, which is far more comprehensive (although lacking some detail still available from Table 5.2 and other sources), is accepted by decision makers, then a set of objectives, definitions, case stories, and indicators could be elaborated for each one as part of enhanced guidelines for choosing partners in future research aimed at delivery of novel interventions in vector control. This begins to coalesce into a resource for holding knowledge with clear rationale and harmonised objectives (in terms of decision making) in an accessible manner. New knowledge could then be supported by this simple system.

Even at this level presented, a learning framework could be prepared by making checklists and requesting periodic evaluation and updating of responses. The researcher considers that such a learning system would be most effective if taken up by a standing official body – at an international, regional or country level or by an association to both give authority and ownership, and to ensure administrative continuity. Possible entities include the IAEA, FAO, WHO, or AU, the NIH, NAMSE, or the Pan African Mosquito Control Association (PAMCA). (Carter & Friedman (2016) summarise an expert group's recommendation that WHO lead on guidance related to health uses, such as transgenic mosquitoes.)

This system should fit in and be coordinated with a possible initiative towards facility accreditation, under discussion in a process led by FNIH (O'Brochta et al., in press). Adelman et al. (2017a) call for further updating of WHO/TDR & FNIH (2014) guidelines, and a more coordinated international guidance on risk assessment has been recommended by Oxford University's Mathematical Ecology Group (2017). These complementary initiatives could also be coordinated by a single entity to strengthen the effectiveness and support accessibility.

This table can be converted into a graphic summary, so that decisions are documented in a quick view page for comparison and review. The value of defining a learning system for finding partners and forming partnerships is that decisions can be based on evidence, albeit sometimes expert opinion, which can be reviewed and revised for future use, or use by others in similar situations. When success is in doubt, a framework may clarify whether: (a) the criteria were correct but are not being met, (b) there are missing criteria, or perhaps (c) the balance

among the criteria is not ideal. Weighted criteria would offer a more sophisticated system that could show the nuances of choices.

Written criteria also can support the enculturation of new team members at either location (external or DEC), by providing evidence of the thoughtfulness and deliberation given to commonly held objectives and values at the time partnerships were formed. The graphic format of a pathway or Theory of Change communicates how activities and immediate short term outputs are expected to contribute to medium term outcomes and ultimate goals. When used for learning, this also can guide routine reviews of research activities and support planning and inform remediation when the pathway is not proving to be effective.

5.9 Summary of study on partnerships

Forming research partnerships currently appears to be overwhelmingly at the initiation of the Discoverer who is often external to DEC, rather than the DEC research team, at least for the collaborations in the novel vector interventions reviewed. Furthermore, the focus for virtually all initiatives reviewed relating to mosquito research was, first, on field sites for future confined studies and national characteristics relating to decision making for the eventual field studies and release of GM organisms. The location of containment or other insectary facilities is generally not even mentioned. Therefore, the best practice for DEC partner selection at the time this study began was to consider criteria for field study sites and progress through a general review of country status and compilation of (early) criteria for the most suitable conditions. While not always spelled out, this would then lead to eventual evaluation of institutions and possibly researchers in the appropriate countries for potential research partnering.

This study sought best practices for a research partnership linked to early phase studies. The researcher proposed additional, more detailed criteria relating more to ELSI factors and also delineated criteria into micro, meso and macro levels. Most of these criteria could be matched to specific indicators. When compared to the few detailed publications regarding selection of field sites, these criteria were either confirmed by being the same as published or were not matched to field objectives. This general approach of first filtering for country criteria still remains valid, although with not much experience one can effectively bypass a laborious country review because information on conditions is ‘in the news’ and much more obtainable than even a decade ago. Equally, for those researchers following a

more traditional approach of working in DEC that have cultural and language familiarity and historical ties, such a review is irrelevant because the information is already at hand. If an already existing research network exists, the focus would be on building or hiring additional capacity for these existing partners, thus highlighting the importance of choosing a point of entry for the DEC partner before considering best practices.

Interviews and an online survey reveal that in current research contexts, on the other hand, most researchers rely on personal relationships, connections at conferences and meetings, or familiarity through research networks to find qualified potential partners rather than historic national ties. Siting of a research or containment facility also is found to be critical, not least due to the need for proximity to staff and the proposed field site (e.g. for transgenic mosquito studies, consider Figure 2.1). It would therefore seem that one also can begin the search at this micro level, and then consider the characteristics of the country. It would appear naïve, however, to bypass consideration of field site criteria until transferability of study results permits the external researcher to separate these two stages in a stepwise approach towards delivery of the novel intervention[66]. When a mechanism is established to allow for transferability, research opportunities might be actually more equitably distributed among countries meeting some of the required criteria, but not all.

[66] The only time presence of the targeted vector spp. and the disease status of the country might change from being the lead 'go/no go' criteria is if results of studies in containment in a different country are allowed as evidence for evaluation elsewhere, for example if an application to carry out confined field studies are evaluated by one DEC using results from containment studies done in another country. Transferability of data might make the presence of the study organism in the area, or even in the country, irrelevant for studies conducted in containment, for example. Some publications (e.g. Benedict et al., 2008) recommend locating a containment facility away from the zone where any escapes could survive, even in different countries or regions; but this again raises questions about involving the DEC researchers as well as transferability of the results. Transferability could be used to accelerate an evaluation process for a new intervention, for example during an outbreak, using sound technical reasoning. It should be expected that after the first few countries are satisfied with results of the same initial studies, regarding safety in particular, regulators in other countries would allow applications for permits using transgenic strains of mosquitoes to be evaluated for field studies using results from other locations. This would be particularly valid when a country is similar in terms of risk acceptance, regulatory style, disease status and ecology. (Sterile insects are often shipped from one country's production facility to another country for field use. This is generally a government to government agreement and only done with species already having a strong track record as far as areawide control.)

Therefore, one could conclude that although the micro level individual characteristics and institutional qualifications are important, it is difficult to find indicators for many of these criteria[67] and therefore difficult to build a generic learning system. Some initial consideration will need to be given at least at a national (meso) level or even larger (macro) scale, before considering an individual's characteristics to effectively employ the system described in Table 5.10.

In summary, the initial criteria proposed by the researcher proved to be well founded and, for many, valid over the course of work in subsequent years. The study has revealed that a focus on field site criteria overlooks other important criteria for the overall success in delivery of the intervention. Consideration of criteria beyond the biological and regulatory has become well accepted, yet details on many of these are not well established and in no sense thoroughly validated.

This chapter considers the value of a systematic search and sound basis for forming partnerships to progress through the steps towards delivery of a novel intervention. Complementary building blocks for the pathway to authentic research partnerships – focusing on the micro level of individual researchers, research groups, labs or institutions – are shown in Figure 5.10, which will be added to the overall Theory of Change (Chapter 11). The expansion of concepts regarding capacity, discussed further in Chapter 10, should inform any approach or type of engagement with partners. For example, an open and accountable process for partnerships and development of a product is recommended, regardless of the approach or degree of involvement and transfer of power. DEC institutes sought out as service providers will need this clarity as much as those more deeply involved in co-development. A broad range of innovation capacity is needed for a partnership formed for collaborative research in the DEC delivery phase, but may also be critical for those selected to complete the product development or manage the final deployment and delivery phase, as much as a future licensee.

[67] Trying to identify indicators for the individual characteristics described is not dissimilar to the researcher's own dilemma of measuring trust and confidence in terms of readiness for proceeding with novel intervention evaluation or testing. This was not pursued in the current study, as explained in Chapter 4, Box 4.1 in particular, but remains an avenue of research for social or organisational scientists. This challenge also is raised again in relation to socio-economic factors in Chapter 6. Chapter 7 proposes some indicators related to facilities readiness.

The initial findings of this study suggest that collaboration towards a product or technology, when the private commercial sector is not (yet) a key player (and perhaps the technology is not patentable), can benefit from a pathway of partnering that is more equitable between the Discoverer and the DEC Researchers than is currently the norm, and perhaps more equally across the multiple disciplines involved. Funders and project planners must recognise, however, that this more equitable dialogue takes more time. At the same time, researchers must recognise that important research aimed at development of health solutions or products may legitimately take priority over national agendas and priorities when that is the objective of the project, research consortium or line of funding (Nuffield Council on Bioethics, 2002).

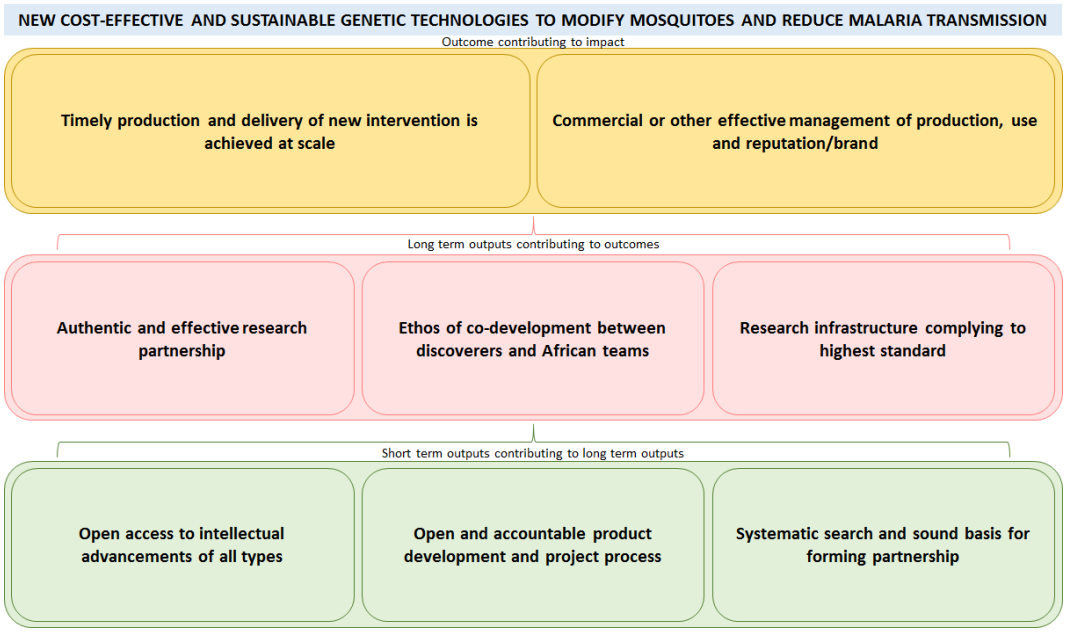


Figure 5.10 Short term outputs leading to authentic and effective research partnerships for delivery of novel interventions for vector control in DEC

In short, there is no single best practice for an external researcher to find a DEC research partner. Much depends on the point of entry of the DEC partner and style of partnership defined at that time. The qualities of individuals and research groups identified in the online survey will be harder to evaluate or assign metrics to than publicly available country level criteria.

It can easily take years to reach understandings and make headway on the inevitable capacity gap-filling activities, for both external and DEC individual researchers and their research groups or institutions. Ultimately, however, the partner selection discussed here is not about achieving capacity but rather

achieving a useable outcome, in this instance in the form of an innovation for malaria vector control. Novel interventions are sorely needed to achieve the next phase of reduction of malaria.

Chapter 6. Gaining Regulatory Approval

One of the critical decision points in delivery of a novel intervention for vector control is to gain regulatory approval for each of the steps, beginning with laboratory applications. Many researchers have identified this as a significant barrier in the stepwise delivery process for genetic strategies against mosquitoes (NASEM, 2016b; Costero-Saint Denis et al., 2016; James, 2011; Alphey et al., 2010). Others argue that existing frameworks are adequate, with proper application (Mumford, 2012; AHTEG, 2010). Despite the regulatory frameworks not being entirely suited to transgenic mosquitoes, regulators have found approaches that enable proper evaluation and decision making.

The subquestion addressed in this study was: **Will regulators be supported to make more effective decisions about import and use of novel interventions by using decision frameworks?** (Chapter 6)

The researcher used two methods, in addition to literature review, to explore the issues regarding regulatory approval for interventions employing transgenesis and the challenges regulators in East and West Africa face.

First, this was done through an informal focus group of regulators, industry experts and risk analysts (through Skype calls to talk through the questions supplied), which set the scope for a broader participatory symposium presented in 2013 during a broader conference on regulation of genetically modified organisms, documented in Quinlan et al. (2016a)[68]. The participants in the informal focus group leading up to the symposium were from the UK, USA, Australia and Philippines. The researcher spoke with other regulators at the conference to compare the symposium speakers' experiences with their own and used literature to expand on experiences in South Africa and other parts of Africa and the European Union, as reported in the published article.

[68] The researcher conceived of the symposium and applied to the program committee, then with Joe Smith, approximately 50/50, organised the informal focus group questions and discussions in advance and planned and led the symposium. She led the preparation of the article, created figures and tables, and wrote or extensively rewrote approximately 70% of it, as well as managing the final proofs.

Quinlan, M. M., Smith, J., Layton, R., Keese, P., Agbagala, M. L. U., Palacpac, M. B. & Ball, L. (2016a) Experiences in engaging the public on biotechnology advances and regulation. *Frontiers in Bioengineering and Biotechnology*. 4, 3.

Second, the findings and additional questions were considered against responses in individual guided interviews with representative regulators, focusing on transgenic organisms they had evaluated. The researcher interviewed four West African and one East African regulator in this period. (Other regulators spoke with the researcher on specific questions subsequent to formal interviews.) The regulator's names and countries will remain anonymous, as promised in the interview, since individuals spoke from their own opinion and experience, and were not representing any national policy. As noted in Chapter 4, the interviews were preceded by the researcher sharing the research introduction, seeking a signed consent statement and sharing the guided questions that appear in Appendix 1, if the person being interviewed wished to see the questions ahead of the interview. The guided interviews followed up some questions, but were designed to allow new topics and issues to arise during the course of the interview.

6.1 The overriding role and limitations of the Cartagena Protocol

As already noted in Chapter 2, the fact that many of the new genetic strategies for vector control employ transgenic strains of mosquitoes has brought national legislative and regulatory frameworks developed to implement the Cartagena Protocol to the forefront as the primary pathway of regulation for this type of innovative vector control[69]. As of October 2017, only four of the 54 countries that are members of the Africa Group of the United Nations are not adhering to the Protocol. All 54 countries are members of the Convention on Biological Diversity but Sierra Leone, South Sudan, and Equatorial Guinea were 'non parties' to the Cartagena Protocol at that time. Unusually, São Tomé and Principe had acceded to the Nagoya Protocol in 2017, but not yet the Cartagena Protocol itself. This is not so different from the status in 2009, shown in Figure 5.3 a. As noted in Chapter

[69] Oye et al. (2014) conclude that gene drive will be regulated in some countries (USA) as a veterinary medicine. This occurred with *Wolbachia* infected mosquitoes in Australia, but has proved to be challenging throughout the process because the usual quality control monitoring for that category is not appropriate for mosquito releases (Ryan, pers. comm., 2017). Mumford (2012) documents how Eliminate Dengue – using *Wolbachia* infection not genetic modification – needed to request clarification of the regulatory pathway from the Australian government at the time. A description of the process settled on is provided by Iturbe-Ormaetxe & O'Neill (2015) In other words, several genetic strategies will face this issue but only those with genetic modification as the production process will be covered under the national biosafety frameworks, in most countries.

5, being a party to the Cartagena Protocol is not a unique qualifying criterion for being qualified as a host country for a research partnership.

The Protocol is not prescriptive, but rather uses general principles and broad objectives so that interpretation and implementation can evolve and be adapted in each national context over time (Pereira, 2014). The implementation of the Protocol also includes a strategy for capacity building. The Protocol presents procedures for risk assessment (primarily in Annex III) and risk management of import and intentional releases of GM or living modified organisms (Articles 15 and 16). Guidance on risk assessment is fairly general, however, and has been developed into more focused, but still voluntary, guidance by an Ad Hoc Technical Expert Group (AHTEG, 2016; AHTEG, 2012) including for GM mosquitoes (AHTEG, 2010). Risk assessment was also found to be a valid organising tool for consideration of socio-economic impacts from use of a transgenic insect for pest management in Spain (Turner et al., 2018).

The Cartagena Protocol, the Nagoya Protocol and other future agreements officially negotiated and recognised comprise the main international legal framework for transboundary movement of GM organisms (Pereira, 2014). Unintentional transboundary movement is covered by other provisions of the Protocol and should be considered and, as a good practice, discussed with neighbouring countries before any field release, unless geographical confinement is judged to be entirely reliable. The scope of the Protocol is limited, however, as it does not cover GM organisms moving through a country in transit nor for import to a containment facility for research. This was confirmed in a multiyear process of review, described by the Executive Secretary in November 2018 and earlier that year by a report from the Compliance Committee (CBD, 2018).

In fact, Marshall (2011) suggests (Pereira, 2014, confirms) that the precepts of the Protocol can be avoided if the transgenic mosquito strains are imported for study in containment and then later moved to field studies from that domestic source. For example, there are obligations for Advanced Informed Consent, but these are for transboundary movement aimed at intentional release, analogous to those for hazardous materials or chemicals (Mackenzie et al., 2003).

The researcher provides a schematic of phases in assessment in Figure 6.1 (taken directly from Quinlan, 2014: Figure 18.2), showing how review of an application regarding transgenic insects would pass through similar steps, whether the

initiating event was the import of a strain or its creation domestically. The requirement for an import permit and measures for safe transport specifically support a similar level of assessment and evaluation as would occur if managed directly under the articles of the Cartagena Protocol.

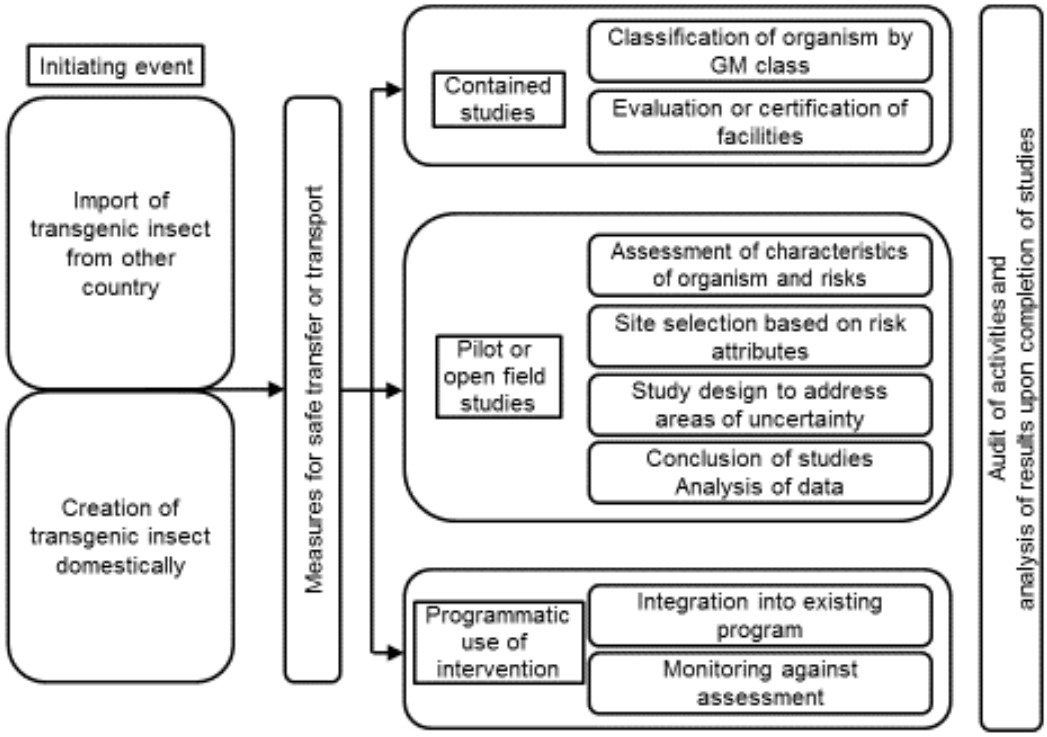


Figure 6.1 Phases in assessment, testing and approval of a transgenic insect for use in an on-going programmatic intervention for pest or vector control (Quinlan, 2014)

While this thesis focuses on transgenic mosquitoes as a novel intervention in vector control, there is much discussion of approaches using gene drive. Marshall (2011) expresses concern whether research using gene drive organisms within large field cages, for example, is truly contained or should be subjected to the requirements of the Protocol for open release. He later argued (Marshall, 2010; 2009) for research imports of gene drive mosquito strains for study under containment to be managed as field trials would be, specifically referring to the issues of transboundary movement and Advanced Informed Consent.

In this scenario, Akbari et al. (2015) propose some additional safeguards for work with gene drive in the lab. The US National Academies of Sciences, Engineering, and Medicine also led a review of the US system for regulating biotechnology in anticipation of the number and range of upcoming new products or systems that

already can be anticipated (NASEM, 2017b). Transgenic mosquitoes were one class of the many products considered in this review. The NASEM panel categorised mosquitoes incorporating gene drive as a new area of risk that has few comparators and therefore may not fit into existing frameworks as currently structured, although they concluded that risk-based decision making could be adapted.

If a NBA chooses to add requirements for import into containment, one critical issue remaining is who would pay for a risk assessment of import into containment (Marshall, 2011). This aspect of funding also can be regulated by the national framework. Many countries charge significant fees for receiving an application in order to finance evaluations.

The researcher would support the idea that not only containment research but even field release evaluation should be in line with that for other similar scenarios posing similar risks and taking into account the surrounding context in terms of potential for survival, relative fitness, presence of a breeding population near a facility, season and immediate weather conditions, life stage and feeding status of the released mosquitoes and so forth. A fairly robust, but simple example framework from the researcher is shown in Table 6.1. This could be supplemented with other characteristics depending on the mode of action of future novel interventions, or the application planned.

A recent expert discussion (Mathematical Ecology Research Group, 2017) further supported the use of risk-based decision making but recommended measures to support the appropriate application of risk assessment to gene drive scenarios. This specifically included a call for: ‘collaboration between international bodies (such as WHO/TDR, UN – FAO, World Bank – Hazard Management Unit) to develop high-level ecological risk assessment principles for developing, testing and implementing gene drive technologies, and create a framework to enable development of supporting guidance relevant to particular fields in human health, animal health, agriculture and conservation’ (Mathematical Ecology Research Group, 2017: p.4). Until this coordination is underway, however, potential measures for disease control may be delayed or lose investment.

Table 6.1 Examples of introduced traits and their anticipated relationship to risk (Quinlan, 2014: Table 18.3)

Example characteristics	**Expected to have increasing risk** →			
Fecundity	Fully sterile	High percentage sterile	Same as target population	Greater than average reproduction rate
Mating competitiveness	Not compatible with native population	Mating compatibility less than native population	Same as target population	Preferred mate and/or able to mate with other species or molecular forms
Dispersal	Non-flying and not transported through other pathways	Disperses in immediate area (e.g. field or house)	Disperses in local area (e.g. village, river basin)	Wide ranging naturally or through other pathways
Life span	Lethal trait arises, larval or pupal phase	Early adult mortality	Same as target population	Extended beyond average
Genetic insertion	Demonstrated to be stable over multiple generations in laboratory conditions	Apparently stable over multiple generations in small confined space	Able to transfer to other species under forced laboratory conditions but not in studies mimicking natural conditions	Able to insert into other species in confined conditions, or after open release
Transfer mechanism	Novel genetic material not transferable	Novel genetic material may be transferred in small percentage of cases	Novel genetic material will transfer to approx. half the population through mating	Novel genetic material will transfer in greater than Mendelian percentage (gene drive)
Relation to control programme	Integrates with other control measures without changing their application and without loss of efficacy	Integrates with other control measures if they are stopped for periods of time (e.g. pesticide spraying)	Displaces some control measures but integrates with the main control measures	Displaces other control measures or reduces efficacy of integrated programme
Post-release monitoring	Trapping or detection feasible and identification routine, part of permanent monitoring programme	Trapping or detection feasible and identification routine, but relies on specific project funding	Difficult to trap but easily identified as a GMO	Difficult to trap or to identify as a GMO if caught (e.g. life form caught by trapping is not easily identifiable)
Ecosystem effects	Introduced species not closely linked with native ecosystem (e.g. anthrophilic or recently introduced)	Introduced species which occupies niche formerly associated with a native species	Important role of predator, prey or competitor in relation to other species	Highly significant predator, prey or competitor of importance to ecosystems; or released species is native to area of release

Public consultation, discussed further below, is also important in the regulatory process for field studies or open release[70]. It is required in most national frameworks for field studies, because of the marked increase in potential to impact on people and the environment. In some cases, it will be allowed, recommended or even required through the regulatory framework for containment studies, although this is much less common and relates more to confidence in the biosafety of the facility. Others (Quinlan, 2014; Andrade et al., 2012; Mumford, 2012) believe that requiring additional regulatory steps for imports into containment facilities for research would be out of line with the intentions of the Cartagena Protocol and a distortion of its scope.

From her initial literature review, informal focus group and guided interviews with regulators, the researcher concluded that appropriate guidance and decision frameworks could support regulators to make more effective decisions about import and use of novel interventions. Additions or changes to the Protocol would be time consuming and face the same issues of becoming obsolete if too specific to current technologies. Additional guidance and decision frameworks would also support the applicants insofar as the regulatory pathway becomes clearer in a case where the existing materials (e.g. application forms) may not be entirely appropriate.

Interviews with regulators revealed more about effective decision making (Box 2.2), which included the ability to make a decision within the timeframe and resources available. Experiences in Malaysia indicated that additional training for hazard identification and a deeper understanding of risk was needed by those making decisions about novel mosquito strains (Beech et al., 2009b), which included a range of decision makers.

Adelman et al. (2017a) discuss the use of self and soft governance to ensure considered, informed decisions are made by the researchers and funders, in the absence of international guidance specific to the case of GM insects. The regulators interviewed confirmed that peer reviewed and published guidance of this nature supported their own deliberations, as did extensive literature reviews and provision of the publications for ease of access. National decision makers may benefit from referring to this guidance to supplement the existing biosafety framework when GM insects are involved.

[70] Public consultation in this context is a formalised process taking place within specific parameters and under a government authority, described in regulatory frameworks and not to be confused with stakeholder engagement or community empowerment to use the consultation mechanism.

6.2 National biosafety frameworks

Additional regulations or requirements are allowed under the principle of sovereignty that underpins all relevant international agreements. While the international instrument lays out principles, terms, responsibilities and obligations as agreed during the process of negotiating the Cartagena Protocol, it is the national framework that implements these[71]. The relationship between international agreements (both binding and non-binding) and national frameworks is explained in FAO (2011), recognising that influences run in both directions (French, 2010).

There was no requirement for new legislation to be developed to implement this convention after it came into force (Koch, 2014), but that is the option that most countries took. The researcher (who was involved in national legislative reviews at the time, to determine how existing frameworks might accommodate the additional responsibilities) believes that this was due to the availability of funding and a general unease at the time regarding novel technologies, rather than a careful analysis of the issues or a legislative gap analysis.

National frameworks developed under the Cartagena Protocol perspective for the evaluation of living modified organisms will have a risk-based decision component. As already noted, the vast majority of national frameworks in sub-Saharan Africa are based on interpretation and implementation of the Cartagena Protocol, and often more strictly than the Protocol states (Gupta & Falkner, 2006). In addition to safety and risk assessments, Glowka (2002) identifies the other two oversight mechanisms in the overarching biosafety framework as decision making and institutional oversight (discussed in Section 6.6). Ultimately, there is no universal decision on how to categorise transgenic mosquitoes, so that import and research of transgenic strains are likely to remain under biosafety legislation. This puts decision making and institutional oversight as key mechanisms for safeguarding national interests when evaluating the early phase delivery questions of import of the research organism and containment studies.

Early on in the implementation of the Cartagena Protocol, Glowka (2002) and others (Jaffe, 2005) identified the primary gaps in guidance as (a) how to incorporate socio-economic factors and (b) appropriate public participation. African countries that followed the AU model biosafety

[71] In reality, the vast majority of national systems are based on implementation of the Cartagena Protocol. Yet, Gupta & Falkner (2006) discovered that this did not lead to harmonised domestic regulatory policies. Rather, each country sought to balance national priorities in regard to agricultural trade with domestic political tensions from varying opinion groups.

framework (African Union, 2002) or set up a framework through the United Nations Environment Programme Global Environmental Fund likely will require socio-economic studies for all types of applications and have a provision for public consultation for research, for example, although not required by the Protocol. It should be noted, however, that the copy of the model law and revised model law was removed from the African Union website, possibly in light of varying views on some of these issues.

The permit application presents the NBA with an opportunity to address socio-economic factors and consider public input, if designed to accommodate these. The review of an application for research is the opportunity to ask questions that relate to facilities readiness, but also reach beyond the immediate activities to eventual aims and desired outcomes for later research. The review process allows for requests for additional information. Adenle et al. (2018) recommend that socio-economic factors are only considered when there is some indication of impact in this area.

Institutional oversight is another aspect to consider. The lack of a fully functional biosafety framework through to the institutional level (discussed in Section 6.6) is equally challenging. Koch (2014) emphasises the need to consider additional factors that go far beyond a legislative framework for an effective biosafety system. This includes coordination among authorities, structured decision making based on evidence, and use of risk management that is commensurate with the estimated risk. Effective risk communication with stakeholders is also essential.

Koch (2014) expressed the opinion that national committees can be comprised of only three to six individuals, who can call on outside expertise, in order to remain functional decision makers. Institutional preparations often lag behind the national ones.

Box 6.1 considers whether the national biosafety frameworks developed to implement the Cartagena Protocol are sufficiently robust to address applications for use of transgenic strains that will persist in the environment (in contrast to sterile male release, for example, or strains designed to not persist through other mechanisms).

Box 6.1 Are national biosafety frameworks drawing on the Cartagena Protocol sufficiently robust to guide decisions on import of transgenic mosquitoes or traits that persist in the environment?

Some experts question whether the current approach to evaluation of products of biotechnology, which was established in nearly all sub-Saharan African countries to implement the Cartagena Protocol, is adequate for new products coming through the research pipeline (Kenya NBA & ISAAA-AfriCenter, 2019; Wambugu, 2014). For genetic strategies in mosquito control, research is underway under containment conditions to establish the feasibility and safety of modified organisms that will persist in the environment, or will spread the desired trait for control objectives into the environment.

Persisting traits present a different mechanism and different potential hazards. Therefore, there are few precedents to consider, although there are potential comparators working from the same principles (EFSA, 2013). In many published opinions and earlier training, persistence has been considered a hazard in and of itself. More recently this has been clarified with improved problem formulation and guidance on establishing a pathway to harm, rather than simply persistence as a threat (Quinlan, 2014).

If regulators are able to take advantage of the growing literature presenting varying opinion, they may also compile several useful checklists, proposed models, and approaches to EIA and so forth to accommodate this novelty. The researcher was introduced to new templates developed by DEC regulators and contracted consultants to organise and guide consideration of socio-economic or other societal ramifications.

These decision makers, like other around the world, may never become experts in all of the emerging technologies *per se.* External financial resources will be needed to facilitate learning from each other amongst regulators, as much as from topic experts. However, the principles and general risk based approach would appear to be firmly established in the countries where the researcher interviewed regulators. Furthermore, there is increasing transparency that the applicant is a provider of information, while at the same time greater opportunity for public engagement to increase understanding and ability to participate meaningfully in public consultation and to hold both the applicant and regulator to account (Gupta & Falkner, 2006).

Based on these developments, the researcher is submits that despite the imperfections of the biosafety frameworks as designed a decade or more ago, that the national biosafety frameworks are proving to be capable and operational in those African countries that have chosen to consider biotechnology solutions to pressing priorities.

If successful, and judged appropriate for release, persisting approaches to vector control would significantly shift the cost-benefit towards something feasible for large areawide programmatic control (which could be determined more precisely with an adaptation of the cost-effectiveness approach in Alphey et al., 2011). This change could make elimination of malaria more attainable (as suggested by Burt, 2014).

Another challenge is that existing regulatory frameworks created specifically for international transport of genetically modified organisms were largely based on GM crops, and not written to fit the decisions surrounding import and release of mosquitoes or other organisms. Despite this, transgenic mosquitoes and other insects generally have been accommodated using the same authorities and principles (Quemada, 2015; Beech & Miller, 2014).

There is some frustration in sub-Saharan Africa that the resources committed towards implementation of the Cartagena Protocol are inefficiently limited to GM organisms, rather than all forms of novel traits in living organisms (Wambugu, 2014). Okoree (pers comm, 2018) confirmed that this is under consideration in Ghana, for example.

If an additional or supplemented framework is needed for analysing categories of modified mosquitoes, this would further decrease the benefit of a following guidance under international agreements developed for GM crops. It could require changes in national legislation and regulations, as well as adjustments to the mandate of the NBA, if tasked with evaluation of these other technologies.

For this reason, and due to the novelty and complexity of the science, additional training and capacity to evaluate GM insects is also required, either within the regulatory bodies or as an accessible resource to those decision makers. The initiatives for training by TDR were already described (Chapter 2) and sessions on GM insects have been held at the ISBGMO conferences (see each programme: http://isbr.info/ISBGMO14; ISBGMO13; ISBGMO12; etc.). More recently, a number of conferences or association meetings have provided training for regulators and/or researchers on emerging issues in genetic strategies for mosquito control, in particular on the use of gene drive (e.g. Roberts et al., 2017).

The researcher discusses good practices for co-learning in Chapter 5 and capacity development in Chapter 10.

While formal training is welcomed, several regulators commented that the most effective way to learn is through engaging in an actual case (application submission) and that learning from sister country NBAs was also highly effective.

6.3 Public consultation versus public engagement

Finding the best approach for obtaining public input to regulatory decisions on novel biotechnology products was identified as a key issue in meetings (e.g. ISBGMO, held in 2012) and conversations leading up to this study. Figure 6.2 illustrates a possible continuum between what a regulator may consider under a typical biosafety framework, through to what might be

termed stakeholder engagement, which is the responsibility of the developer of the technology or applicant for a permit, in particular for providing sufficient information on what may be commercial confidential data and responding to legitimate questions from the public. (Indeed substantial consultation must take place between the applicant and the regulators, according to some interviewed, to clarify with precision attributes of the technology and what fundamental questions, therefore, are being asked of the regulators.)

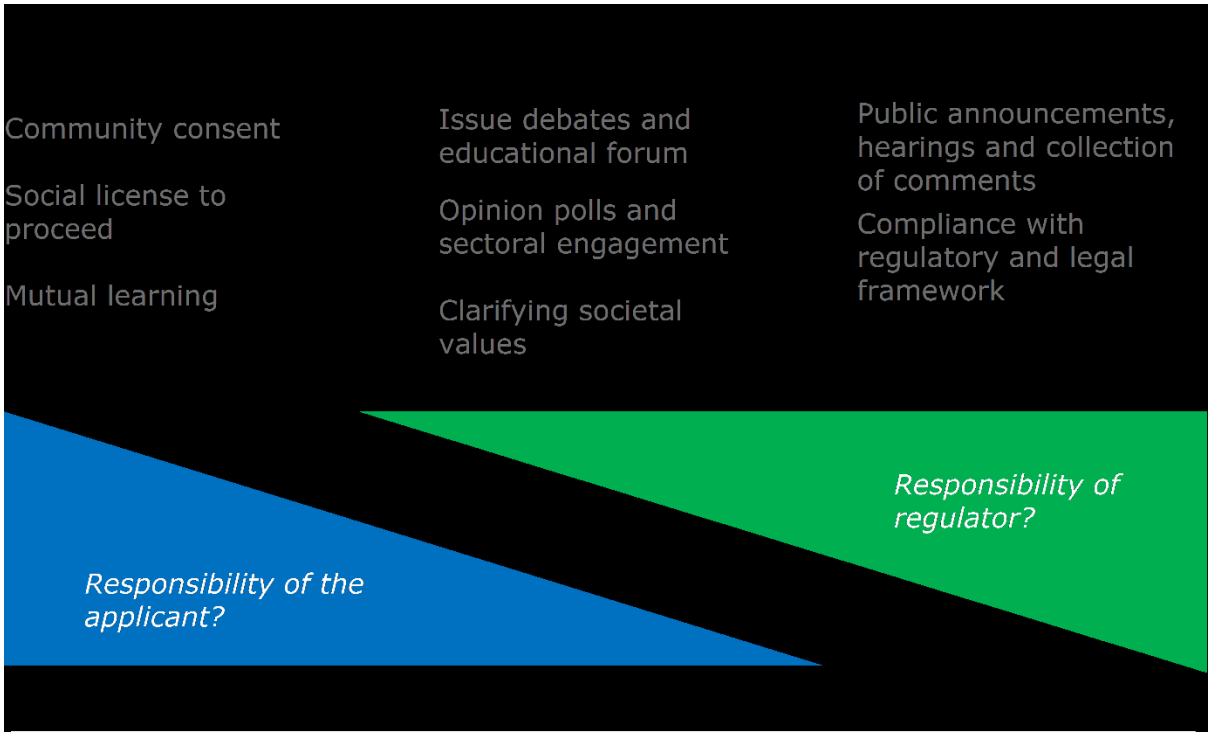


Figure 6.2 The continuum of public involvement in biosafety decisions (Quinlan et al., 2016a: Box 1)

There are often statutory requirements for public consultation that, in general terms, require information and notification, an opportunity for comment, and a process of incorporation or consideration of public comment. Various policy researchers have found that a structured approach is important for public consultation and even inter-ministerial or institutional collaboration on decisions regarding innovative and complex technologies, or any case by case decisions that require review and understanding by the public (Baldwin & Black, 2016; Quinlan et al., 2016a, Ochanda, 2010). Table 6.2 presents key attributes for best practice regarding public input to regulatory decisions proposed by Quinlan et al. (2016a). These suggestions are to support systematic methods to 'gather, acknowledge, respond to, and even incorporate public input', so that the process of public consultation within the regulatory context will have increased transparency and value.

Experiences from the USA, UK, Australia, and various African regional and national contexts were shared in more detail, with 'lessons learned' (Quinlan et al., 2016a). The participants in

preparations for the symposium were asked about the objective of seeking public input in their country or region. Having an entirely open consultation with no guidance is counter-productive since comments often are submitted that do not relate to the scope of what regulators are addressing or that express personal values that are difficult to translate into proposals relevant to the case at hand. For example, criticism of the overall decision framework cannot be considered in deliberations regarding a single case (Quinlan et al., 2016a). Reeves et al. (2012) argue full documentation for applications for permits, including all data provided, should be published for technical review by interested stakeholders. A more practical process might be for the deliberations of expert groups on the quality of information provided to be shared, as part of the rationale for a decision. Opening the full process to broad debate allows those opposed to use of a technology, *per se*, to turn consultation into a delay tactic as much as to contribute to improving a process.

Table 6.2 Best practices for effective engagement with the public on regulatory decisions, based on practical experiences (adapted from Quinlan et al., 2016a)

1. Use a range of resources to facilitate public education and opportunities for understanding complex technologies, acknowledging that governments do not have the resources to do this but making clear the motives and positions of each party providing resources
2. Define in advance the goal of seeking input, then limit the consultation to that scope
3. Identify and communicate with the critical public groups from which input is needed, consider limiting input from those not within the community involved
4. Use a clearly defined approach to gathering and assessing what will be used in making the biosafety decision, such as templates, guidance for input or online forms
5. Communicate using clear and simple language, and let those who provide input know what happened

Another key question, therefore, is who should be included in the consultation. Does the public include foreign entities, non resident in the country, with no investment or community at the local level? When should consultation be with those in the immediate community, versus the entire national public? Such questions have reached the level of the national High Court of the Philippines and are best determined in advance of setting guidance for public consultation (Quinlan et al., 2016a).

Another issue reported by those sharing experiences at the symposium and some of the regulators interviewed was the difficulty of defining socio-economic impact for individual cases. This is particularly unclear for studies in containment, which are not intending to provide benefits beyond the possibility of building on the outcomes of the research.

While there are some good practices to consider, the researcher recognises that this is an area that remains challenging for meaningful implementation.

6.4 Approaches to socio-economic aspects of regulation

During face to face interviews by the researcher, several regulators highlighted the challenge of covering socio-economic factors during the review of an application for import or release, when end points or thresholds were not already established. These include benefit sharing, impact on agriculture and food security, conservation and livelihoods linked to biodiversity and other aspects of employment, with particular focus on impacts on indigenous communities

Box 6.2 Indicators and thresholds – a missing element in effective decision making

The challenge of either inappropriate application of regulations (e.g. requirements for Environmental Impact Assessment or studies beyond the scope of the potential impact) or the lack of acceptable end points for studies (e.g. what level or type of socio-economic impact is acceptable, especially if considered against benefits) has been identified by regulators and researchers alike. Selection of indicators, or even the best metrics to use, has far reaching impacts and should not be approached lightly. On the other hand, harmonising a process for decision making whil allowing countries to set their own limits of acceptance would facilitate the application and permitting process, market analysis by developers, and potential transferability of data, which could go a long way towards increased efficiency for national systems.

Jaffe (2005) noted the lack of applicable safety standards as one of the key gaps in the Cartagena Protocol and a serious challenge to development of harmonised regulatory systems to implement the Protocol. He states that: 'safety standards set forth what level of safety must be satisfied to approve an application and what factors a government will consider before making a decision', and summarises some countries' efforts towards reaching a definition of these (Jaffe, 2005: p.303). Although the procedures for risk assessment, decision making and notification are described in the Protocol, much like the ISPM 3 on release of biocontrol agents (Chapter 3), or even the ISPM 24 on determining equivalence (Quinlan, 2016; IPPC, 2005b), there is far less on the content.

The idea of 'Limits of Concern' is being debated in the European context (Dolezel et al., 2017). This same principle has led to years of debate for the implementation of the Agreement on the Application of Sanitary and Phytosanitary Measures under the World Trade Organization. It refers to an Appropriate Level of Protection (or Acceptable Level of Risk) to be set by the national process, while not indicating what that level should be nor exactly how to determine it (Quinlan, 2016).

The researcher concluded that, in order to respect sovereignty and differences in cultural and socio-economic contexts, guidance on *methods for determining a threshold or indicators* would best support progress on this aspect of biosafety frameworks, rather than any attempt to impose or harmonise what the threshold should be.

(Mackenzie et al., 2003). A lack of defined indicators or metrics leaves regulators to debate the conclusions even when experts are commissioned to prepare socio-economic assessments, as discussed further in Box 6.2. It was also not clear at times when a categorical exclusion or the reduced requirements for containment remained appropriate and when the novelty of a technology should provoke additional questions and considerations.

A lack of socio-economic experts, who also are familiar with the technologies and technical aspects they may raise, was noted as another challenge for arriving at decisions on field release or use of a GM organism. This limitation could lead to erroneous conclusions by these external experts, with no scientific basis or direct causal pathways; such outcomes are difficult since ignoring commissioned reports may be questioned. (This was also reported to the researcher in relation to Vietnamese training of best methods to review *Wolbachia*-infected mosquitoes, prior to those experts being expected to review any applications, in an interview not part of this study that took place in 2014.)

At the time of writing, the AHTEG on Socio-Economic Considerations (AHTEG, 2017) had agreed on concepts for supporting socio-economic considerations and presented Draft Guidance (AHTEG, 2017: Annex), which includes principles and an outline of the assessment process. Based on this committee's operational definition, socio-economic considerations discussed in Article 26 *may* be taken into account, 'if they are not already covered by risk assessment procedures under Article 15 of the Protocol'. Socio-economic considerations were defined to cover: 'economic, social, cultural/traditional/religious/ethical aspects, as well as ecological and health-related aspects'. The AHTEG called for further work on methodologies in particular. No further updates appear in the Biosafety Clearing House as of February 2019.

Countries, including those where regulators were interviewed, have begun to adapt their risk assessment templates and forms to better manage these issues within that existing process. For example, the NBA in Kenya uses their own form that describes various categories of potential socio-economic impacts (Kenya NBA, 2013). This helps to define the scope for literature review, review of resources on the Biosafety Clearing-House, discussion and additional expert studies. It still requires a summation by the NBA of any application into 'support', 'neutral' or 'does not support' for each application, with documentation of the reasons. Burkina Faso has recently introduced new forms that incorporate socio-economic factors as a series of questions with explanations or descriptions, in a longer format (though not yet publicly available at the time of this writing). Regulators from other countries were interested at the time of the interviews (2016) in learning from and taking advantage of other countries' processes and forms, to better manage these aspects. (Other areas for improvement in effective decision making that arose during interviews are noted elsewhere.)

The interviews and literature support a conclusion that one of the best ways to facilitate effective decisions, while allowing for different conclusions to be reached, is to develop harmonised systems for consideration of the various factors, including socio-economic considerations but to encourage a national participatory process of setting the thresholds for acceptance, using indicators employed by international entities or other relevant bodies to the degree possible. This would increase predictability for the applicants, even where variations occur on a national basis, and has potential to harmonise the data requirements for applications, as well.

6.5 Laws, regulations and requirements additional to the biosafety framework

Although the Cartagena Protocol has an overwhelming role for evaluation and decision making in regard to a GM organism, numerous fields of law and regulation may affect research in transgenic mosquitoes and use of genetic strategies for areawide control of a vector species. The researcher was asked to advise on a good practice for researchers, referred to as Discoverers, by various projects over the years, in terms of identifying and complying with possible legal or regulatory requirements. Towards this end, she developed Table 6.2 as list of topics to orient review of these requirements, on a case by case basis.

As noted by Quinlan et al. (2018b), the NBA may be able to provide direction to additional requirements outside the biosafety framework because its membership would cover the most likely Ministries posing such requirements. Her experience has suggested, however, that those on such a committee may not necessarily know all the requirements arising through their Ministry, Agency or Division. She and her co-authors concluded, therefore, it is good practice as a Discoverer hoping to work with partners in a DEC – or even as a DEC researcher not familiar with all the requirements – to contract a legal review of the nature scoped out in Table 6.3.

It should be emphasised that the list in Table 6.3 is for non-commercial, research activities. In fact, the majority of such initiatives are from academic, non-profit or charitable research institutions. It also has not included review of the implementation of the Nagoya Protocol (discussed in Chapter 3) or the Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety. The latter is yet to be implemented in most countries, despite entering into force in March 2018 (Biosafety Clearing House, https://bch.cbd.int/protocol/supplementary/about/).

Table 6.3 Topics for a legal review extending beyond the biosafety framework, for studies of transgenic mosquitoes in containment and anticipating field studies

Topics identified by the researcher
Directly related to certification of facilities, import of research organism, and/or approval of study
Biosafety legislation and related regulations, including on institutional arrangements to implement legislation and delegated authorities (for genetically modified organisms)
Containment regulations (biocontainment) additional to the above
Public health law regarding transport of and disposal of waste classified as biohazard; regulations that explain the classification of regulated waste versus medical, hazardous or biohazardous waste (see Quinlan et al., 2018b for discussion on this point).
Zoning laws regarding types of activities allowed in particular locations; Laws regarding public nuisance (e.g. for the insectary or containment facilities; this is more relevant to a larger facility for mass rearing)
General environmental impact law requiring assessment of new activities (possibly for facility and field studies; law should state a threshold for negligible activities)
Related to research on mosquitoes, whether transgenic or not
Environmental or public health law regarding use of insecticides; regulations on registration of pesticides (pesticides are used for monitoring mosquitoes inside houses or ending a field study)
Public health law regarding capture, release and rearing mosquitoes due to their vector status
Public health law or Science, innovation and research law regarding uptake of innovations, new interventions or practices, registering and permitting to do research – including the testing phase
Laws regarding access to private property (for purposes of public health, research or agricultural health)
Related to responsibilities of each party
Civil and criminal liability for damage; contract and tort law remedies (if there is an environmental consequence, especially due to negligence or withholding of research information; to protect IP of the technology and contracted service agreements; to respond to grievances if the grievance process breaks down, etc. May be more relevant when reaching programmatic use)
Libel, slander and fraudulent claims (about promising too much from a study, but also regarding false statements about the research or researchers that could damage the reputation of the innovation)
Public health laws or regulations and those regarding emergency measures, which allow the government to carry out health interventions without consultation and/or individual consent, for example in an emergency or when the intervention is approved and considered of importance for the wider community health
Laws, regulations or protocols regarding informed consent to participate in research
Related to eventual field studies involving confined or open release
An Environmental Management and/or Conservation Act, and related biodiversity laws
Environmental law regarding release of any organism into the environment
Environmental law regarding import, study or release of an exotic species
Agricultural law in relation to biological control agents (may also include containment facility regulations, e.g. as quarantine facilities)

The requirement of an Environmental Impact Assessment (EIA) or Statement for construction of a containment facility, mentioned above, has been reported in Quinlan et al. (2018b) for two East African countries. Based on experience for other buildings on the campus of research institutions, it is not clear that this requirement would be imposed for small laboratories or research facilities not aimed at research on transgenics (although this was not stated in either case). On the other hand, El Sayed et al. (2009) comment on the need to obtain permits for simple weather stations and similar requirements in Sudan for a non-transgenic control strategy, so the requirement for an EIA may also be routine.

The impact of legislation outside the biosafety framework is not limited to applicants. At least one regulator interviewed commented on the impact of environmental legislation being applied to field studies in situations that would normally not be scrutinised for impact, except for the presence of genetically modified organisms. This has led to duplication, at times, in terms of requirements from the national environmental authority and the NBA.

The researcher had observed this over the course of her thirty-five year career, including leading EIA teams (Ukraine, Russia, Peru and for multilateral donors), in terms of application of environmental impact frameworks not designed to consider biodiversity issues. This led to inclusion of categories of impacts or specific questions that were irrelevant. Conversely, applying terms of reference not fit for purpose also may have missed some potential biodiversity impacts of more importance. A similar requirement for an EIA perhaps beyond the necessary parameters arose at the national level for use of SIT as part of a control programme in one African country.

On the other hand, when an EIA is required, Reeves et al. (2012) argue for better quality EIA by public provision of scientific evidence underpinning decisions and less reliance on what may be lesser quality precedents. Their table, *Checklist for assessing the scientific quality of approvals for un-caged field trials, based on the examination of documents made publically available by regulators prior to the start of releases*, lays out clear guidance for a regulator, or other interested party, to evaluate the quality of the information used in the EIA, and therefore its validity. While Reeves et al. (2012) criticize generic materials, the researcher has found that basic materials can provide the foundation for a review, before determining what additional or more in depth issues should be addressed.

On the other hand, on a larger scale, consideration of potential harm from the escape of transgenic organisms from a large research or a production facility, or during transport, or outside a confined study area may invoke the legitimate requirement of an EIA, if this is considered to be a transboundary threat to biodiversity (Republic of Nicaragua, 2014: p.281).

This is true even if the risk is judged to be low, because of the transboundary aspect of the threat. Some of the other international agreements that may guide or influence decisions on genetic strategies are considered by Pereira (2014) and FAO (2011).

6.6 The role of institutional committees for delivery of novel research

Functional institutional committees to interface with the research team are an important component of a national biosafety framework. These may include an institutional ethics committee, institutional biosafety committee (IBC), and an institutional research board or committee, if other mechanisms are not used to cover each of these roles[72]. Supporting these institutional bodies contributes to more effective decision making by regulators, as well, as does national ethics capacity, already noted in Section 5.1.

An early initiative in supporting ethics committees, although with focus on national level, was undertaken through the African Malaria Network Trust (AMANET), which was founded in 2002 and began with a focus on vaccine trials (Kilama et al., 2007). AMANET led needs assessment, analysis of challenges, and capacity building of national and institutional ethics committees facing applications for clinical trials (Nyika et al., 2009a; Nyika et al., 2009b; Effa et al., 2007). Much of the Trust's efforts would relate to capacity for institutional ethics committees facing novel technologies in vector control. Indeed, Kilama (2005) anticipated capacity for analysing ethics of GM mosquito trials as an area needing enhancement.

A valuable analysis of the success of this initiative identified the participation of individuals in training and professional meetings, who potentially were not representing the main bodies needing training. Their participation was based more on opportunity and ties with the network, which were important to the national pool of experts but not necessarily contributing directly to decision making (Ndebele et al., 2014). It has also been noted that while the chairs or leads for ethics committees have been offered training, the administrators of these bodies had not been included in most opportunities (Kasule et al., 2016).

[72] A data monitoring group is proposed for research in which real time analysis and oversight could prevent otherwise undetected harm from occurring among human research participants (Resnik, 2014; Kimmelman & London, 2011), but studies in genetic strategies for vector control are not working with human subjects, but rather interfacing with communities around a containment facility or living in a village or site where a field trial will take place. Data management and overall M&E has been the topic of training over several years (Garley et al., 2016). In regard to potential biting by released mosquitoes, see Box 1.1.

While a number of institutions in sub-Saharan Africa are qualified for malaria or mosquito research in terms of technical capacity, many have only recently begun operating ethics committees. An exception appears among some Kenyan institutions. The preparation for biotechnology began with the agricultural sector, so that the Kenya Agricultural Research Institute (KARI) was one of the first to develop institutional guidelines and set up an IBC (as reported by Wafula, 1995). The KARI drew on existing guidelines formulated by the International Potato Centre (CIP) and the Inter-American Institute for Cooperation on Agriculture (IICA) and was supported by an advisory group of biosafety experts, including government representatives. The KARI anticipated national guidelines would be forthcoming on experimental release, so therefore directed guidance towards establishment of an IBC, self regulating lower level risks, worker safety, risk assessment and categorisation of containment.

More recently, another institution based in Kenya, the International Livestock Research Institute (ILRI), has explained to the researcher the use of its own IBC by other parties, such as small business, when those are not able to maintain a separate IBC (Birungi, pers. comm., 2016). This approach increases the effectiveness of those on the IBC, because of the increased exposure to different cases and the opportunity to apply training in a broader context than might arise from the single institution.

One regulator interviewed noted that an opportunity for novel research had passed by because the institutional structure did not exist in the potential host research institution. An institutional biosafety committee (IBC) is required as liaison with the NBA in that country. Despite the existence of a science and an ethics committee in the institution, an IBC did not exist. It was considered to be too onerous on resources to create one in that time frame.

High containment laboratory oversight requires additional training of the IBC members as well as additional monitoring of compliance, based on failings observed in the US system (Race & Hammond, 2008).

What may prove even more of a challenge than a fully functional institutional ethics committee and IBC is support for the role of a research review by an institutional research board or similar entity. It has been suggested that while considerations of risk to the participants and informed consent are critical, clinical trials aimed at public health should be judged more stringently than is current practice on the study design and the probability that the study will result in learning and data that can answer important research questions related to delivery of the intervention, such as clear causal chains even when mechanisms of cause are not entirely understood (Kimmelman & London, 2011).

For vector control, the criteria of a community involved in a study having direct benefit from the research may be misplaced. It will take some years before novel interventions are ready for use in a control campaign. Other forms of malaria or vector control may be introduced, for example as part of a health campaign by the government, and conditions will change.

6.7 Summary on regulatory decision frameworks

Regulatory approval poses a significant challenge for all those involved in delivery of novel interventions, owing to several issues: the lack of knowledge of researchers about the regulatory process; the lack of experience of regulators with truly novel technologies; and a regulatory framework often not suited to purpose, particularly for transgenic mosquitoes. Currently biosafety frameworks throughout the world are overwhelmingly based on interpretations of the Cartagena Protocol, therefore limited to definitions within that document. Much of sub-Saharan Africa would have based legislation on the AU model law and popular belief that socio-economic factors must be studied as part of each decision.

The Cartagena Protocol itself includes an annex of the proposed components of a risk based analysis. Additional guidance specifically on transgenic mosquitoes has supported this approach. There have been recent proposals to have a different approach to decision making about transgenic mosquitoes, in particular when gene drive is incorporated as a mechanism for delivering the desired characteristics (e.g. sterility to a population). The researcher suggests that building additional criteria into a risk assessment would result in a better decision process rather than abandoning the framework of probability and consequences altogether, given the deeply embedded model of following the Cartagena Protocol or the African model law for biosafety.

Despite the varying views published, the researcher believes that the risk-based approach is suitable to nearly all scenarios, simply by adding additional sources or parameters of risk into the system that is already working on a case by case basis. The Cartagena Protocol process has also proposed guidance on inclusion of socio-economic factors for decisions regarding field release. Currently that forum is collecting materials relating to containment, as resources for member countries.

There is an emerging trend towards creating biosafety national systems based more on potential and feasible risks of any type of novel characteristics. This would be more robust than one based on a single method of creation or production of a novel product, which is out of sync with scientific advances. This shift may require the same legislative overhaul that other proposals would evoke, however, and therefore may not come to fruition.

Regulatory evaluation sometimes includes review of input from the public as a mandatory (or statutory, meaning controlled or required by law) requirement. Best practice for soliciting and organising public input for regulatory purposes is discussed. Engagement for this purpose will necessarily be limited in scope to what the regulators may take into account. The development of forms, templates and systems for receiving and holding input can greatly enhance the value of public input. The researcher proposes some good practices on this based on a symposium that addressed the topic.

Apart from such requirements, many applicants are aware of an engagement paradigm which aims for two-way communication rather than input limited by regulations. The researcher supports this more open approach, and research into improved methods to encourage it (Bartumeus et al., 2019), which are now the expected good practice for applicants and funders. This study does not address decisions regarding timing, approaches or other aspects of stakeholder engagement beyond recognising its critical importance for gaining a social licence to conduct research in a novel intervention for a particular place and time.

The researcher also established from interviews that the use of transparent, well documented procedures for lab safety and biosafety, quality assurance, and study design and reporting goes a long way in supporting regulatory decision makers. The key factor in supporting regulatory approvals for this stage of research, however, is that the studies are in a containment facility. The concept of when a research consortium believe they are ready to apply for the containment study permit is the topic of Chapter 7. The use of internal audits that precede regulatory inspections is discussed in Chapter 8.

The move to field studies is a much larger challenge, which has been debated more in literature than the decision to proceed with a contained study. That said, for studies in containment some experts have called for greater scrutiny, particularly in the scenario of importing novel organisms for study and then bypassing some requirements of the Cartagena Protocol when moving to field work using the domestic lab as a source. National frameworks can easily address this without any change to the Cartagena Protocol itself, and applicants also may insist on the same process of review whether shipping from external facilities or going to the field using colonies established domestically by that time.

Furthermore, there is still an important role for institutional bodies to review ethics and biosafety in particular. Ethics committees have been strengthened through recent initiatives but are more familiar with the paradigms of development of vaccines, pharmaceuticals or other types of products. Research into mosquitoes and malaria poses some unique challenges. Where creating, training and maintaining committees of this nature is either too resource

demanding for an institution or small business, or when the limited number of staff implies conflict of interest, use of external or shared committees appears successful in more than one country included in interviews.

As laid out in Figure 6.3, these various factors are believed to provide the short term outputs for supporting regulatory review and, when appropriate, approvals for the various steps in delivery of a novel vector control intervention. Credible regulatory decisions are imperative if later decisions for open or commercial release are to be respected. The regulatory decision process is the place for integration of monitoring of safety and efficacy features. These will further support decisions by the Ministry of Health or other policy makers in uptake and funding of novel interventions (discussed further by Cisnetto, 2017).

In conclusion, regulators face challenging questions during the review and evaluation of cases of truly novel interventions, such as the case of using transgenic mosquitoes to fight malaria. The researcher confirmed through an informal focus group and interactive symposium, described in Quinlan et al. (2016a), the value of structured frameworks to receive and organise input from the public on case by case decisions. For regulators with limited mandates, public comment is only useful if the input provided is (a) allowed consideration within the legal framework and (b) is organised and coherent and related to the case at hand.

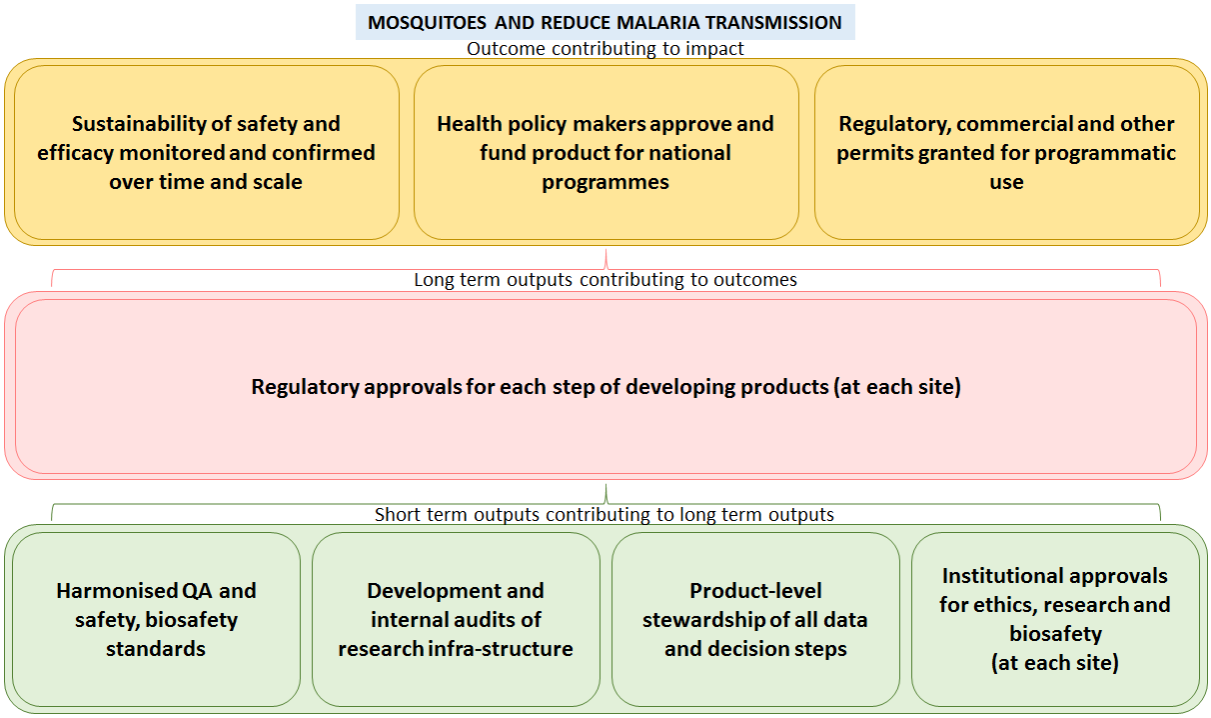


Figure 6.3 Short term outputs leading to regulatory approvals for each step of delivery of novel interventions for vector control in DEC

Independent from this study, regulators themselves have demonstrated the value of decision support tools such as templates to articulate the scope of what can be considered on a case by case basis in terms of risk assessment, socio-economic issues and similar, as reported to the researcher in interviews (though most example templates are not publicly available).

What is less apparent is whether any systems are in use that provide feedback to the broader decision process or add data and evidence that lead to learnings. No doubt, these learnings are occurring within the NBAs and similar bodies, but perhaps they are not documented or shared at this time.

Finally, despite the value of training opportunities, templates and other materials, regulators who had already made significant decisions about GM organisms in the past still stated that individual contacts and learning from experiences of sister country regulators was valuable to gaining confidence for one's own regulatory decisions, according to interviews conducted by the researcher.

Chapter 7. Facilities Readiness

In the delivery of a novel intervention for vector control, particularly the release of a novel organism, much discussion has surrounded the question of when to move from the laboratory to a field setting for testing and eventually to a planned open release (e.g. Facchinelli et al., 2013; Lacroix et al., 2012; Vreysen et al., 2007; Knols & Louis, 2006). A critical decision point in the stepwise approach that comes much earlier, however, is to determine at what point the source research team (Discoverer) is ready to physically share the novel intervention, in the study case a transgenic mosquito line, and the DEC research team is ready to receive it into their containment facilities to begin studies. (Questions surrounding sharing the concept, IP rights, data ownership, and other aspects of working with partner researchers or a research consortium are discussed in Chapter 5.) Transfer of the research strain is one of the key steps, and decision points, in early phase of delivery, as defined in Chapter 1.

This chapter considers what type of learning system could support this decision from the perspective of the research teams or research consortium, apart from regulatory approvals. The research subquestion addressed here, and in Chapter 8, is therefore: **How does benchmarking a point of readiness for use of containment facilities support effectiveness of this first step in the delivery of the intervention?** (Chapters 7, 8)

The researcher employed action research methods, beginning with observation of the issues involved surrounding the decision point of facilities readiness. As a result of this interaction, the researcher further deconstructed this subquestion into components and ways of expressing the issues from literature and discussions with experts, presented below. The beginning of a framework of key questions and concepts was developed leading up to meetings with relevant participants for Target Malaria[73], and clarified in response to discussions at these meetings. The framework was confirmed (by the same participants in those project discussions) subsequently, during interactions for documenting that process (reported in Quinlan et al., 2018a[74]).

[73] Many of the initial ideas and presentations offered at these meetings were developed in conjunction with Peter Raymond, of the Donald Danforth Plant Science Center.

[74] The content of this Chapter draws heavily on the researcher's role as facilitator during action research. She wrote and prepared at least 85% of Quinlan et al. (2018a), on which other co-authors provided comments. The publication was based on work carried out by the research consortium represented by all of the co-authors.

Quinlan, M. M., Birungi, J., Coulibaly, M. B., Diabaté, A., Facchinelli, L., Mukabana, W. R., Mutunga, J. M., Nolan, T., Raymond, P. & Traoré, S. F. (2018a) Containment studies of transgenic mosquitoes in

Quinlan et al.[75] (2018b) further documents the details of preparations of containment facilities, including aspects of design, construction and equipping that are specific to contained culturing and studies of mosquitoes.

While the ideas were tested in only one research consortium, all of the participants had worked with mosquito research in various institutions, initiatives or projects over time and, as in other types of action research, the approach grew out of that community and their experiences. After the concepts and approaches had been taken up, the researcher followed up with interviews of country PIs from Target Malaria and one former country management level participant, for a final evaluation of the process.

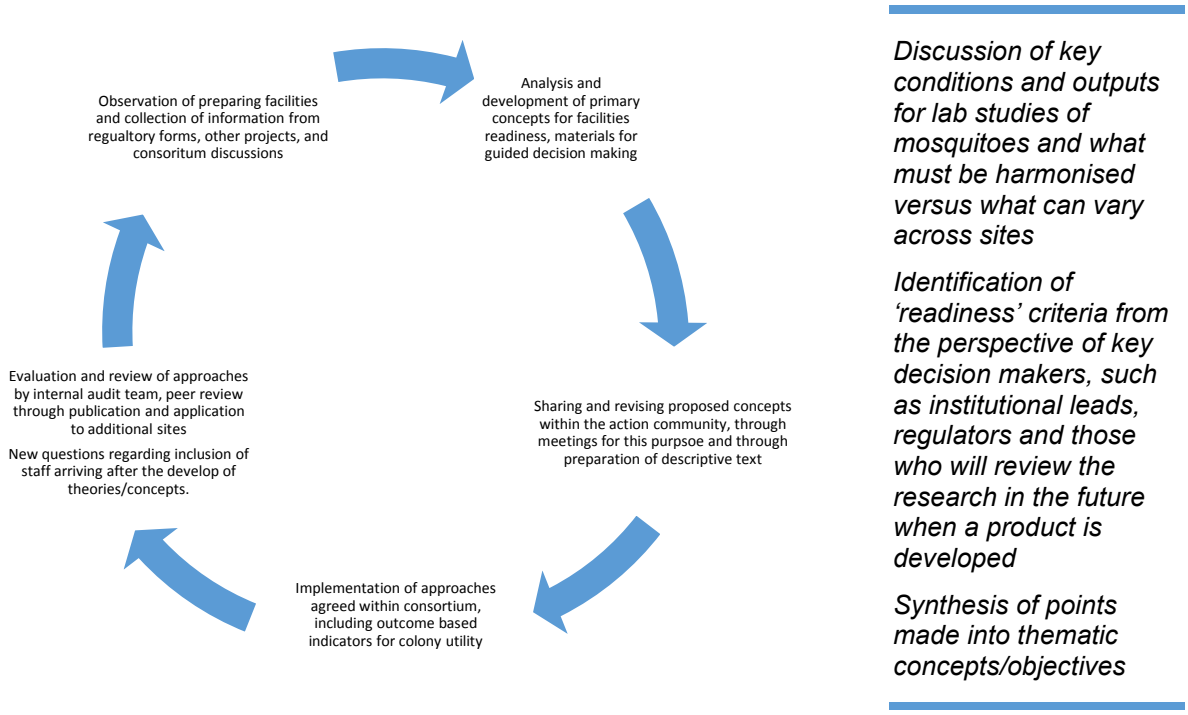


Figure 7.1 Action research cycle as applied to facilities readiness concepts

disease endemic countries: the broad concept of facilities readiness. *Vector-Borne and Zoonotic Diseases*. 18 (1), 14–20.

[75] A more detailed description of preparations has been reported in Quinlan et al. (2018b). The researcher wrote at least 65% of the publication, with J. H. Mutunga contributing most of the remaining writing. Clark and other co-authors provided comments. The publication was based on work carried out by the entire research community represented by all of the co-authors.

Quinlan, M. M., Mutunga, J. M., Diabaté, A., Namountouqou, M., Coulibaly, M. B., Sylla, L., Kayondo, J., Balyesima, V., Clark, L., Benedict, M. Q. & Raymond, P. (2018b) Studies of transgenic mosquitoes in disease endemic countries: preparation of containment facilities. *Vector-Borne and Zoonotic Diseases*. 18 (1), 21–30.

A mechanism to identify, classify and communicate disruptions to the status of readiness of a facility was developed primarily from literature review. Additional components of a learning system are described in the summary, to complement the overall framework. Description and diagrams of key components of a framework for determining the point of readiness of a containment facility are elaborated below.

7.1 The point of readiness

The concept defined in this current study as 'the point at which studies in containment may proceed' with novel research in a containment facility, from the perspective of the researchers, is multifaceted and also case specific. This is largely due to variations in the nature and objectives of the anticipated studies (Quinlan et al., 2018a). Different decision makers may have different criteria that determine that point in the delivery of a novel intervention. Defining 'facilities readiness' as that point, therefore, requires consideration by the decision makers, or by each group of decision makers involved, as to what should be the defining criteria and, where possible, the indicator and trigger or threshold for each. This chapter addresses decisions by the Discoverer and DEC Research teams, notwithstanding the process that may occur through a regulatory pathway. In other words, the researchers maintain responsibility to determine readiness above and beyond obtaining a permit. No one will know the level of readiness to the degree of accuracy or level of knowledge that a PI and his or her research team should know. Obviously, official approval through a regulatory process is also a prerequisite to proceeding.

The sense of readiness from the researcher's perspective is closely linked with official procedures to inspect and certify, evaluate and approve permits for import or studies, and so forth (and are therefore included in Figure 7.2 below). Researcher, research team or project decisions about readiness will vary, according to their own perspective and advance planning of criteria and thresholds. Despite this acknowledged lack of consistency, use of a framework to organise and present evidence for taking the decision is expected to benefit any research team facing this decision (discussed further in the chapter summary)[76].

As with any ongoing activities, there are choices about when and how to determine a state of readiness of a research facility, or the degree of acceptability of that readiness, against some

[76] The role of an insectary risk assessment and risk management plan is explained further in the section on disruption to readiness (Chapter 10), although the issues illuminated in such a plan may also provide details to the conceptual foundation, and elucidate the case specific aspects, for an evaluation of facilities readiness. The use of an audit to benchmark 'facilities readiness' is discussed further in Chapter 8.

standard or criteria. Figure 7.2 shows several approaches for assessing readiness to receive a novel organism, in this case a transgenic mosquito into an insectary. These could include various triggers, actions or stages in the ongoing operations of a containment facility when such assessments could take place. The researcher provides more details in Table 7.1 on the attributes of approaches to assessment and benchmarking for this step.

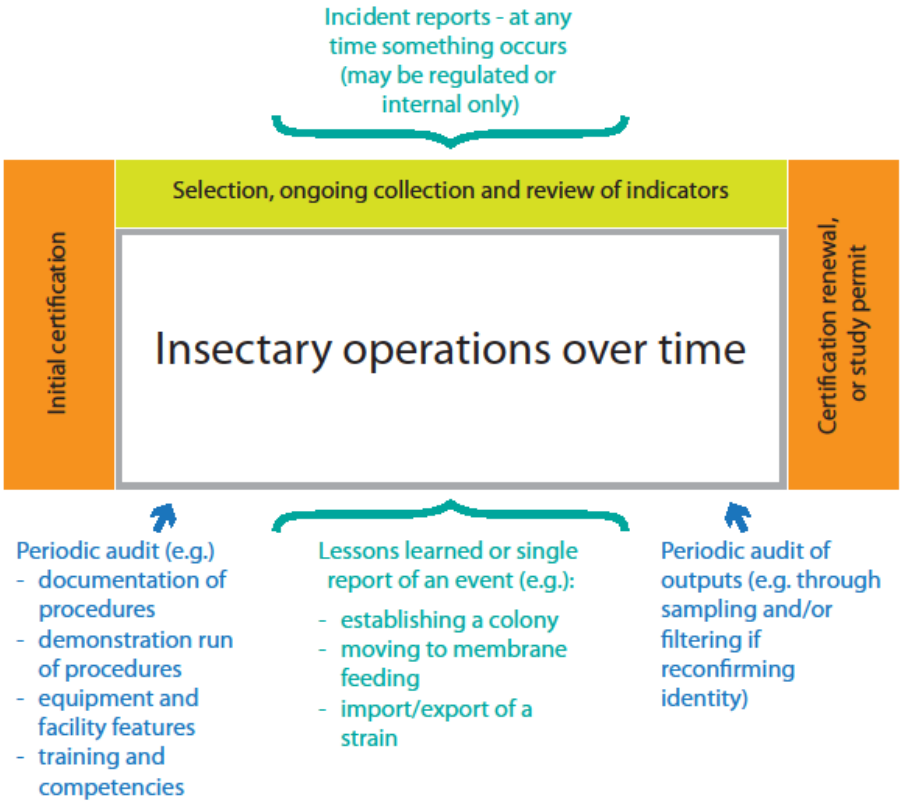


Figure 7.2 Approaches for assessing the 'facilities readiness', including at various stages of the ongoing operations of a containment facility

To make this evaluation more accessible, consistent and transparent, indicators of various aspects need to be considered, even if they are qualitative or hard to link with evidence. Criteria for various aspects of operations should have predefined indicators or proxies and time periods (e.g. an audit over two days, identity check every 5th generation), since relying on an absolute measurement of readiness – a multifaceted status – is often impossible; the status of everything that comprises readiness is never static. This poses the question of whether the concept of a decision point to determine 'readiness' is an artificial one. Indeed, it is an artificial concept (versus a biological one) required for an operational decision. It is the type of decision that has been made in numerous projects or initiatives, but often without documented criteria beyond that of a regulatory permit.

Table 7.1 Aspects of the approaches for assessing readiness of a containment facility

Approach or method	Parameters or criteria	Use of information
Certification	Characteristics of a containment facility benchmarked against regulations or referenced international guidance on containment facilities. Some aspects of the staffing and procedures may be covered.	National authorities will use this to establish the acceptable status of specific facilities at the time of commissioning or when inspection occurs.
Permit for import of a transgenic strain and/or studies	Evaluation of a specific proposed activity by a named entity, against the risk management or study plans described in the application, and any relevant regulations.	National authorities will use this to approve or deny, or to set specific additional terms and conditions (T&C) possibly beyond regulations in place, to ensure safety of the activities. Some authorities may also evaluate the quality of the study design and potential benefits of learning the study results; and may require ethics or IBC approvals.
Periodic audit (internal)	A review of evidence of compliance with specific conditions, standards, and policies set and shared in advance to ensure an acceptable level of readiness. This may include demonstration of procedures, but generally is a review occurring over a short point in time focusing on indicators rather than observation by the auditors of actual operations.	This is proposed as a key method for researchers to establish 'facilities readiness', in a manner and timing useful for decision makers, in anticipation of import or initiation of studies with regulated novel organisms. It should reveal any gaps in known requirements for regulatory inspections as well. (See Chapter 8.)
Ongoing monitoring of indicators: environmental conditions and inputs	A range of appropriate conditions for mosquito culturing are established in literature including: temperature, humidity, light regimes, density in trays/cages, diet components and other inputs.	Facility managers will use this information to ensure that conditions for best quality are maintained. Data may also be reviewed retrospectively if quality changes, to establish possible causes.
Ongoing monitoring of indicators, or a periodic audit of samples: mosquito identity, quality and outputs	A range of indicators of quality of the output, including any changes in factors and indicators of the identity (genetic or phenotypic) for individual sampled mosquitoes and as a colony or lab population.	Facility managers will use this information to ensure that study results will be valid (colony utility) and that appropriate conditions are maintained. Regulators may query outputs, particularly in terms of identity maintenance, as part of meeting T&C.
Incident reports	Description of some type of disruption, when this occurs.	Facility managers will use this information to ensure the disruption has been resolved, improve risk management and planning, and prevent future incidents.
Lessons learned reports	Description of particular activities, possibly supplemental to the usual operations of the facility. The lessons may be positive or negative but record useful details.	Facility or project managers will use this information to improve specific activities or components of routine operations.

Despite the options of legitimate methods or approaches used to determine the status of operations, or degree of readiness, choosing a point at which to declare readiness becomes more of an art. The sense of mosquito colonies being in a good state, for example, may rely on various quality indicators, but there is also the judgement of the researcher that they are 'happy' and ready to proceed (Kelly & Lezaun, 2017).

The first approaches noted in Table 7.1 are essentially regulatory assessments that should have clear objectives and procedures established in the regulation, legislation or other guidance employed by the government (although many countries will not have experience with inspection of mosquito facilities). Official inspection, certification or official periodic review of the facilities will be against the benchmark of national regulations, if these exist and are framed in a way that allows assessment of compliance. Quinlan et al. (2018b) detail some of the preparations leading up to the point of requesting an inspection or certification from the relevant authorities (or possibly a final inspection, if the NBA has been involved throughout the design phase). In Figure 7.3, the steps show that it is critical to assess proper design, construction, installation and other physical features, and many times these steps are regulated by an authority not specific to containment laboratories. Advice on specifics unique to containment facilities for insect studies, in particular mosquito culturing, are also noted (Figure 7.3, steps 9-15). These physical features, which are part of what must be in place in preparation for import or study permits, may or may not be evaluated by an official inspection. Determining whether each particular step is covered by an official inspection is an important step towards defining what the researcher needs to consider separately, beyond regulatory criteria.

Unless it is a certification strictly of a physical structure, such as a new build or renovation of a laboratory for containment at the point when preparations are complete, however, an official assessment is likely to also include documentation of the qualifications of the lead researcher (i.e. the PI), if not all of the research team. Figure 7.4 summarises more operational type preparations, including the actual official inspection and applications themselves (steps 5, 15, 16, 18). The addition of a legal review for requirements outside of the national biosafety framework of the country (step 3) was detailed in Chapter 6 (Table 6.2). Although activities such as internal considerations of work flow, hiring staff, procurement, training and practice or trial runs, selection of quality indicators, creation of data templates, and writing then subsequent review of use of protocols generally are not evaluated during an official inspection, the inspectors may include review of the evidence or outcomes of these types of activities. In particular, inspectors for the NBA are likely to review the Biosafety Manual, SOPs and training records.

1. Construction site selection
2. Review of land ownership, zoning, permits

3. Proposal for funding or finalization of budget
4. Formulation of institutional or project committee to oversee development process
5. Final design and request for bids
6. Cooperation agreement with external funder, laying out any expectations, ownership, etc.

7. Hiring of contractor for construction
8. Detailed drawings for final discussions
9. Specifications for containment related aspects
10. Environmental Impact Assessment if required

11. Monitoring of construction including added containment measures
12. Choosing right materials for detecting free fliers and to withstand humidity
13. Setup of insectary environmental monitors, sources of humidity and temperature control
14. Installation of filters, screens, and autoclave, verification of containment measures
15. Verification of readiness of final stage of waste stream (e.g. incinerator, septic tank) in terms of planned containment measures; readiness of animal house if required for blood

16. Installation and testing of minor equipment, including controlled access equipment (swipe entry, keypad, surveillance camera or other methods)
17. Portable Appliance Testing and/or setup of surge protection and electricity backup devices
18. Filing of owner's manuals and installation certificates for all equipment
19. Development of a maintenance plan or service agreement

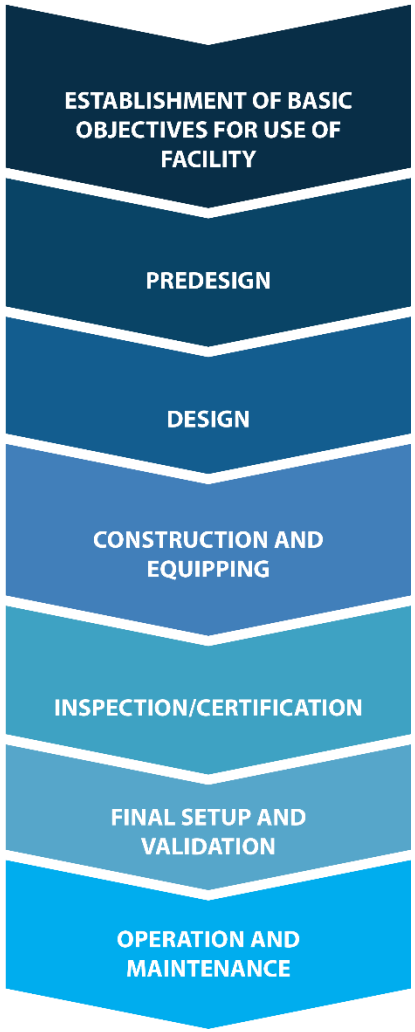


Figure 7.3 Summary of the construction and equipping steps performed in preparation for an arthropod containment facility for studies of transgenic mosquitoes in example disease endemic countries (Quinlan, et al., 2018b: Figure 1)



1. Initial risk assessment and determination of ACL-2
2. Understanding of workflow for colony maintenance and studies (consideration of whether same facility will be used to ramp up mosquito numbers for later field studies)
3. Review of all regulatory and legal context, beyond what NBA will address
4. Discussions on need for harmonized environmental conditions or other approaches to colony utility and quality assurance, which may require consideration in design
5. Initial discussions with NBA on anticipated application(s)
6. Safety and access addressed

7. Hiring full complement of staff
8. Equipment procurement, setup, documentation
9. Drafting of Biosafety Manual, SOPs, and other QA documentation
10. Contingency and emergency planning
11. Training in Biosafety Manual and SOPs - document all training
12. Practice shipments of mosquito eggs to test chain of custody, handling, customs processes, and practice handling training strains if available
13. Project audit by institutional colleagues or external experts

14. Completed preparation of databases, templates, and study protocols
15. Submission of regulatory application to NBA
16. Review of application including inspection by NBA
17. Training in protocols or SOPs specific for studies
18. Approval of application and importation permit received

19. Ongoing monitoring of compliance to regulatory requirements, T&Cs of contained use approval, any ethical approval received (for example, for use of animals for blood meals)
20. Regular review of documentation, i.e. SOPs and training records

ACL, Arthropod Containment Level; NBA, national biosafety authority (generic term); QA, quality assurance; SOP, standard operating procedure; T&C, terms and conditions.

Figure 7.4 Summary of the operational steps performed in preparation for an arthropod containment facility for studies of transgenic mosquitoes in example disease endemic countries (Quinlan et al., 2018b: Figure 3)

7.2 Defining facilities readiness

Based on the initial literature review and early discussions with experts, the researcher prepared a possible description of 'facilities readiness', for the Target Malaria preparation process.

This was clarified, as the concept evolved, over the course of meetings among new partner institutions in the Target Malaria project to take decisions regarding preparations for import of transgenic mosquitoes. For example, one key decision of those in the meetings was to aim towards comparable outputs (mosquitoes) rather than attempt to maintain all of the conditions of an insectary as an exact match to the other sites. Although environmental conditions such as humidity, temperature, exposure to light (natural or artificial), and culturing methods may be standardised in theory, the reality was that it was considered too onerous to harmonise and calibrate these and to avoid minor variations.

A diagram of the components of facilities readiness for work with transgenic mosquitoes is shown in Figure 7.5, reflecting, in general terms, the relative time and resources involved for preparing each. While showing components of facilities readiness, this does not yet reveal the details of each step. Preparation can take many person months of effort and this may be supported by working guided by themes or objectives. It was found that most activities were aimed towards one of three intentions, or audiences, referred to as the underlying concepts (Quinlan et al., 2018a).

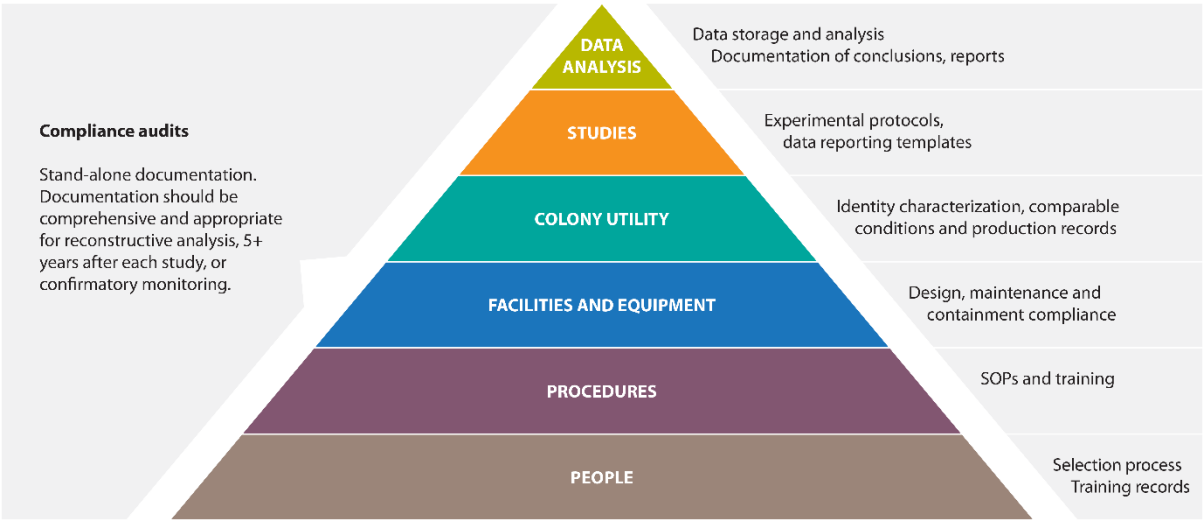


Figure 7.5 Components of facilities readiness preparations leading to reliable study results and defensible science (Quinlan et al., 2018a: Figure 2)

7.3 Underlying concepts

For this research on mosquitoes, there is a substantial history of referencing the Arthropod Containment Guidelines (American Committee of Medical Entomology, 2003) as guidance to set the level of containment, referred to as the ACL and to provide details on what features ought to be considered for each level. Figure 7.6 shows the key measures for ACL-2 from that guidance. The publication of guidelines allowed many parties to systematically develop a harmonised set of measures, which were more easily benchmarked across the sector (Tabachnick, 2006; Scott, 2005).

In addition to the initial design, construction and equipping of a containment facility, the three themes observed in preparing for facilities readiness were described by Quinlan et al. (2018a) as:

- Compliance
- Colony utility
- Defensible science

Compliance involves ensuring that the requirements of existing regulations are met, but may also entail aligning with the intent of regulations which may not be specifically fit for purpose for the research in question. For example, one intention of lab biosafety regulation is to prevent exposure of people and the environment to infectious agents. While a requirement to isolate a novel organism during the initial research phases, due to lack of knowledge, is widely applied, some specific measures related to infectious agents may be irrelevant. On the other hand, new technologies are being applied that may not fit within a country's biosafety framework but that still merit evaluation in terms of the resulting traits or product, or risks from that particular case (see NASEM, 2017b for examples). Working within the existing national framework, researchers can identify and explain to regulators, such as the NBA, which requirements may be irrelevant when working with transgenic insects, while at the same time proposing other measures to maintain flying insects within primary containment. International guidance may be referenced, either by the regulators themselves or by the researchers, where some aspect of this 'compliance with the underlying intentions', described by Quinlan et al. (2018a: p15-17), or the objective is not covered by regulations.



Figure 7.6 Key components of ACL-2 containment and example measures relevant to transgenic mosquitoes (Quinlan et al., 2018a: Figure 1)

Colony utility was defined by those represented by the co-authors of Quinlan et al. (2018a) as achieving particular characteristics and quality control so that studies using mosquitoes from the lab colony can be compared across generations, sites and strains. This generally implies a minimum fitness, although quality may be defined in terms other than ecological fitness due to the desired or priority characteristics as ultimately defined by the necessary level of performance in the field (Mumford et al., 2018).

Defensible science relates to the documentation and evidence trail that can withstand inquiry regarding: all methods used, ability to replicate study results, maintenance of the identity of the colony and its characteristics (e.g. maintenance of a trait), demonstration of key biosafety features, and other factors that could affect study outcomes and support product development. A central aspect to this concept is that the appropriate 'paper trail' can defend conclusions and decisions over many years, which is necessary given the time line for development of a novel intervention and the likely range of stakeholders. Peer review publications of study results often have not been held to that same standard.

The experiences of those working in the Target Malaria project, and based on their other experiences at the time, have shown the value of organising and planning preparations using these three themes. The concepts were reconsidered when preparing the related publication (Quinlan et al., 2018a) and continued to appear valid. While some activities and indicators will cross over more than one underlying concept, the three concepts of compliance, colony utility and defensible science may support planning and preparations, as well as retrospective evaluation of readiness of a containment facility.

7.4 Metrics for the state of readiness

After establishing the general definition of 'facilities readiness', its underlying concepts and some of the approaches to determining the status of a facility in terms of its readiness (or for each component of those themes), the next question is to select measurable indicators or other forms of harmonised, comparable evidence. This is often where existing literature appears weak.

Although the use of pre-prepared lists of points to consider or questions can prove valuable without quantification (see comments on checklists in Chapter 4), this relies on the user having significant knowledge and experience to properly apply them. Simple yes/no type questions are the most common style of checklist, such as Appendix III *Biotechnology facility inspection worksheet for plant containment facilities* (Adair & Irwin, 2008). A similar approach towards choosing the best indicators and metrics could be employed for the components of facilities

readiness. These simplified assessments require some standard or benchmark against which to compare, however. Valerio et al. (2016) describe, for example, benchmarking of mosquito colonies, which could facilitate comparisons of study results across sites. Consensus documents on technical and operational issues for sterile insect technique, for various target species, have been coordinated by the FAO/IAEA since the beginning of that Joint Programme[77]. The OECD has produced consensus documents based on expert group deliberations; the series on the biology of an organism are aimed at use in national risk or safety assessment (OECD, 2005). The aim is to harmonise the information used, in this case about the biology, not necessarily to harmonise the conclusions and outcomes. This saves the time and resources of the national authorities at the time of decision making regarding a biotech product. A process is underway to prepare such a report on the biology of *Ae. aegypti*, for example, due to the use of transgenic mosquitoes for dengue control in Brazil (OECD, 2016).

International Organization for Standardization (ISO) laboratory standards are widely recognised. It is possible to be inspected and certified for running clinical trials, for example. The Association for Assessment and Accreditation of Laboratory Animal Care International (or AAALAC International) is a private non-profit organisation that offers accreditation of research using lab animals (https://www.aaalac.org/). The Innovative Vector Control Consortium (IVCC) is supporting development of a network of Good Laboratory Practice (GLP) certified facilities for testing vector control products, such as LLIN, which previously had been conducted outside sub-Saharan Africa. The first certification was achieved in April 2017 in Tanzania (IVCC, 2017). The NIAID has been supporting interdisciplinary research into malaria, working from and among US funded International Centers of Excellence in Malaria Research (ICEMR). The ICEMR network, which was recently expanded (NIH, 2017), is moving towards employing the same methods, protocols and technologies, which can provide a quality control benchmark for the studies they conduct (Moss et al., 2015; Rao, 2012). While standardising study designs, the ICEMR sought heterogeneous field sites associated with each ICEMR (Rao, 2012), thereby providing a range of conditions across several countries for comparative research. Although focusing largely on epidemiological research, the ICEMR network reported research in vector control includes studies in LLIN and IRS.

The European Union, through its EC Framework Programme 7 (FP7), has a programme to better utilise and harmonise major research infrastructure, including enabling resources beyond simply physical infrastructure. This programme has developed a framework and

[77] Current versions of this resource appear here: http://www-naweb.iaea.org/nafa/ipc/public/manuals-ipc.html

roadmap, along with other specific tools for the European area research infrastructure, in order to coordinate its use and promote innovation, and to 'define common evaluation principles, impact-assessment criteria and monitoring tools' (ESFRI, 2016: p.4). It is also developing metrics that could be adapted to smaller scale or regional infrastructure hubs. A complementary framework for global research infrastructure is underway (GSO, 2017), which has harmonised ideas about categories of research infrastructure as follows:

- Single-sited global facilities: major research infrastructure funded and managed as international entities
- Globally distributed research infrastructure: national or institutional sites that are part of an international network, with international governance
- National facilities of global interest: existing national facilities of potential interest globally, but under national management

A research infrastructure originally sponsored by one country may be identified as of global interest, or may be identified as a regional hub. Strategic aspects of this programme may be useful for other examples in other regions. For example, one of the challenges identified in Europe has been the coordination of the resourcing by various stakeholders in order to provide continuity in the level of funding between various projects (ESFRI, 2016: p.10). This issue has been highlighted by the researcher and her colleagues in other European projects working with plant health or integrated pest management (e.g. Mannino et al., 2019). Not only is infrastructure maintenance and staffing potentially lost, but also models, tools, and at times reports and records of decision making processes are lost (as also outlined in Quinlan et al., 2018c). This issue of funding gaps could be anticipated and addressed early if sub-Saharan African networks for genetic strategies in mosquito control are formalised.

The Infravec project provides mosquito research infrastructure in Europe, for use by a host of researchers (Crisanti, 2013) and its successor project (Vernick, 2017) also provides research products to any qualified research institution (Infravec 2: https://infravec2.eu/).

A framework to review a multifaceted state of readiness is bound to require a range of standards, references or resources to provide the detail required for a meaningful evaluation. There has been increasing interest in establishing a more formalised certification programme for mosquito research facilities, drawing on a more international community of expertise. Most recently, this has been spurred on with the rise in funding for Zika research in the Americas and interest in novel strategies for control of its vector (von Seidlein et al., 2017), as well as in more efficient ways to identify and compare facilities in sub-Saharan Africa. Funders, for one, must rely on the researchers to self-govern to a large degree in terms of maintaining practices

in line with stated policy and procedures, observing biosafety commitments and producing reliable data. Furthermore, variety in methods and study designs hampers the ability to replicate and compare studies and results.

The PAMCA (2017) has identified the lack of compiled data on 'the number, level and geographical location of entomological personnel or institutions in Africa' and their home institutions, as a barrier to progress towards control of mosquito vectored diseases. Their initiative to compile that information is to encourage further capacity enhancement of existing experts and encourage future experts. This commissioned consultation also aims to 'assess the practical competencies in the execution and management of vector borne disease', which will establish an important benchmark against which to assess competencies.

The Arthropod Containment Guidelines have played a role similar to ISPM 3 for biocontrol agents (discussed in Chapter 3; Kairo et al., 2003). The Guidelines have provided a consensus, albeit originating from one region, on what is appropriate for arthropod research, as an important supplement to the extensive literature on biosafety levels and associated requirements, which often are not relevant. The ISPM 3 has been taken up by countries that either do not have separate regulations or rely on the international standard for details on the roles of each party in import and export of biocontrol agents (Kairo et al., 2005).

Although the classification system of ACLs (American Committee of Medical Entomology, 2003) has stood the test of time, the description of categories may require updating. For example, some novel technologies are not mentioned and the process to establish levels through risk assessment is not detailed. The Arthropod Containment Guidelines are also limited in detail relating to mosquitoes, due to the broader taxonomic coverage. Furthermore, these Guidelines were not designed as the basis for a harmonised certification scheme, although they have been applied in that manner. For one thing, the guidance is fairly dichotomous, without the opportunity to see the degree of adjustment needed[78] or increasing capacity and compliance. Areas requiring additional detail or updates (in the researcher's opinion alone), if taken up for a global certification system, are noted in Table 7.2.

[78] The use of descriptive steps towards the ideal state has been compared with other approaches for assessment of capacity in plant health (Day et al., 2006). The same approach was developed for benchmarking animal health national capacity, the OIE Evaluation of Performance of Veterinary Services tool (http://www.oie.int/en/support-to-oie-members/pvs-evaluations/oie-pvs-tool/), which was based on an earlier tool created by IICA (undated).

Table 7.2 Suggested revisions to the Arthropod Containment Guidelines (American Committee of Medical Entomology, 2003) to adapt them to an internationally agreed certification system for mosquito research or colony maintenance facilities

Section of ACG	Current approach	Proposed revision
General – throughout	Checklist of highest standard measures	More detailed checklists with descriptions of progressive steps towards the highest standard, this allows the facility to map and plan progress but also to evaluate if 'good enough' versus highest standard is appropriate to the case
General – throughout	Combines all measures and criteria by ACL level	A modular approach of stand-alone documentation, either by the key objectives (isolation, risk reduction) or by category of activity (e.g. shipping, culturing, waste) – or both if clearly delineated
General – throughout	Applies to all arthropods, although with some notes on exceptions	A general framework across taxa could be complemented with annexes specific to species, guilds (flying insects) or traits (e.g. blood feeding)
General – throughout	Classification of uninfected genetically modified arthropods (ACL-2)	Discussion of the reasons and characteristics that affect the classification, more guidance on classifying novel strains or constructs
Risk Assessment for Arthropod Vectors	Guidance for recombinant DNA technologies	Analyse and describe other technologies, classes of production processes
Transportation and Transfer	References US regulations	Insert a range of materials as examples, but leave current regulations to be included in regional annexes that may be easily updated
References	Current references are in each section	An online version would allow for regular updates of relevant publications, with some vetting process prior to adding
Add additional modules as agreed by participating experts	Modules may be designed to be by theme or procedure (e.g. maintaining equipment, or preventing strain contamination), by species (e.g. *Aedes*, *Anopheles* or other mosquitoes), by region (focusing on any unique legal, cultural and ecological characteristics)	Modules may also be added that apply to members of international conventions or parties to treaties, to explain and support specific requirements (e.g. Nagoya Protocol)
Add tools, templates and other resources	Could be online for interactive use or downloading	If the guidelines become linked to an accreditation, resources should be clearly indicated as optional

The OIE standard for biological risk in veterinary labs and animal facilities (OIE, 2015) shows a risk-based approach to laboratory biosafety and biosecurity. That standard is summarised (OIE, 2015: Appendix 1.1.4.2) to match considerations for assessing risk, determining the level of risk, and possible risk management measures. Further to these steps, risk communication and verification of the measures with continual improvement are necessary steps towards achieving appropriate management of the risks. This emphasis on using risk assessments to plan for facility preparations reflects the OIE World Membership's concerns

that a biosafety level and classification of an organism has taken away from more case specific review. This standard states that: 'It is the individual biosafety and laboratory biosecurity measure or composite of measures, rather than a designated biosafety level, that guides a laboratory in the safe and secure handling of any individual biological agent or toxin.'[79] (OIE, 2015: Chap. 1.1.4, Section A).

The 'social and institutional' aspects of containment have already been noted (Chapter 5) and are well elaborated by Marris & Jefferson (2013) for a European context. These could be clearly identified and better elucidated in any future certification system for transgenic mosquito facilities, or revision of the Arthropod Containment Guidelines, or handled as a separate topic.

7.5 Summary of facilities readiness as a framework to support decisions

The researcher found few examples of published literature providing guidance on these preparatory steps that are not regulated, but that underpin the results. Quality control of mass reared insects (e.g. for fruit flies, FAO/IAEA/USDA, 2014) and mosquitoes more specifically are reviewed in Mumford et al. (2018) as well as other reviews (e.g. Ekechukwu et al., 2015, specific to *An. coluzzii*). Preparing for the point of import or studies in containment also encompasses preparations of this nature. Performance check of outputs (mentioned in Figure 7.2 either as ongoing or periodic) could be measured in large cage or confined field studies, against desired traits for field use.

In some sectors, there is a clear benchmark or standard against which a facility, its equipment and supplies, the research team and research procedures may be measured, with the intention being that a particular level must be achieved before proceeding. In some sectors, a level of readiness or recognition of achievement of the necessary standard may be measured and recognised through a certification or annual audit. This type of pre-existing standard is not available for containment facilities aimed at study of arthropods, although various forms of guidance (generally unpublished literature) are developed by most research institutions, often referencing the Arthropod Containment Guidelines. Adelman et al. (2017a) present a table of what that group considered to be the most important reference documents for work with mosquitoes employing gene drive, which is considered to be of higher risk and therefore

[79] See Quinlan et al. (2016b) for a discussion on the meaning of biosecurity in relation to biosafety.

requiring additional management compared to transgenic arthropods without this mechanism. Benedict et al. (2018) describe possible enhancements of ACL-2 for working with gene drive.

It is possible to achieve a more international set of guidelines regarding mosquito research. In this instance, a modular approach with progressive steps was found to be the preferred style. Critical to this process is a recognised entity that can serve the function of coordinating the implementation and/or certification of the guidance and support further development and eventual revision.

Finally, there is an aspect of overarching accountability implied by declaring facilities to be ready to begin studies of novel organisms. By this point in time, individual responsibilities should be clearly understood and any gaps in staffing or training identified by the PI on site (or equivalent, as well as institutional leadership). For similar scenarios (such as a vaccine manufacturing facility), procedures should be validated already and a self-inspection or audit would occur at this point in time (OIE, 2016). (Facilities operating under Good Manufacturing Practice would have other requirements, such as a process for managing recalls or complaints about the product (OIE, 2016), but this was not considered necessary for mosquito production during the study phase.)

Current literature uses a similar concept of ‘readiness’ based on multiple factors, for example readiness for malaria elimination or health system readiness (malERA Refresh Consultative Group on Health Systems and Policy Research, 2017). Determining ‘readiness’ is largely an operational decision, specific to the nature of what is evaluated and the location, but that can lead to more strategic decisions affecting implementation of the research through to delivery of innovative interventions in a vector control programme. It also is possible to identify more general criteria for readiness (e.g. for capacity assessment) for early stage assessments whereas criteria and indicators may become more sophisticated and detailed as the project or initiative develops (Bates et al., 2011). Readiness for a containment facility may indicate one thing for a lower risk mosquito strain, such as a sterile male construct, but require a different standard for higher risk scenarios. This suggests that a framework that allows variation is most appropriate. Similarly, in reference to their framework for capacity building, Bates et al. (2011: p.8, Conclusions) stated: ‘The use of overly complex systems [for monitoring and evaluation] too early in a project may lead to resistance and collapse of the monitoring process.’

Figure 7.7 proposes a pathway of influence from these early preparations towards the longer term status of a research infrastructure complying with the highest international standards. This infrastructure in turn is an important ingredient for eventual production and delivery of such an intervention (one that relies on release of living organisms) at the scale and quality

needed for delivery where required. The preparations towards an established, and ongoing, level of readiness for a research facility can also provide a foundation for future R&D during the programmatic use of a novel intervention. Sustainable provision of operational R&D demonstrates a commitment to the safety and efficacy of the product over time, not simply its delivery to the user.

This entire study was conducted based on an assumption that a potential product or novel intervention exists and passes through the scrutiny of proof of concept, to demonstrate the required safety and efficacy in a lab setting. It is also presented from the perspective of an innovation arising externally to countries with the targeted disease, thus requiring some form of technology transfer or partnership. The framework for considering 'facilities readiness' highlights a critical decision point for delivery of this novel intervention. Depending on the nature of research partnership and the funder, this may be a decision primarily by the research lead in the institution under consideration, or it may be for a final sign off by external parties. Ideally, this is a joint process and exploration.

For transgenic mosquitoes as the technology, the researcher has created diagrams, lists and suggestions to support critical judgement of 'facilities readiness', focused on a series of preparations organised under the themes of compliance, colony utility and defensible science that were developed in the context of action research within a project. This guidance is to support decisions – not to make them. Although such a framework would be inadequate for anyone not already well trained in the type of research under consideration, it should prove useful at the very least as an aide memoire, even for the most experienced.

This chapter cannot suggest specific trigger or threshold points in regard to preparations that would apply to all containment facilities, due to variation in the context and purposes of this research infrastructure. A 'good enough' point, however, must be defined and recognised by researchers of sufficient experience and commitment to 'know it when they see it'. The aim for defining facilities readiness is to make that decision more transparent and replicable by choosing best criteria and documenting more experiences from that step, to support the creation of a related learning system for other individual cases.

The process of clarifying and describing this decision may provide a record suitable for stakeholder examination and a road map towards continual improvement, or be an exercise in 'ticking boxes' without thinking beyond the questions on the page. Issues of competency and vocation go far beyond records of qualifications and training, and are discussed in Chapters 5 and 10. The type and level of documentation and product stewardship required for

the novel interventions emerging over the past few years is discussed in more detail in Chapter 9.

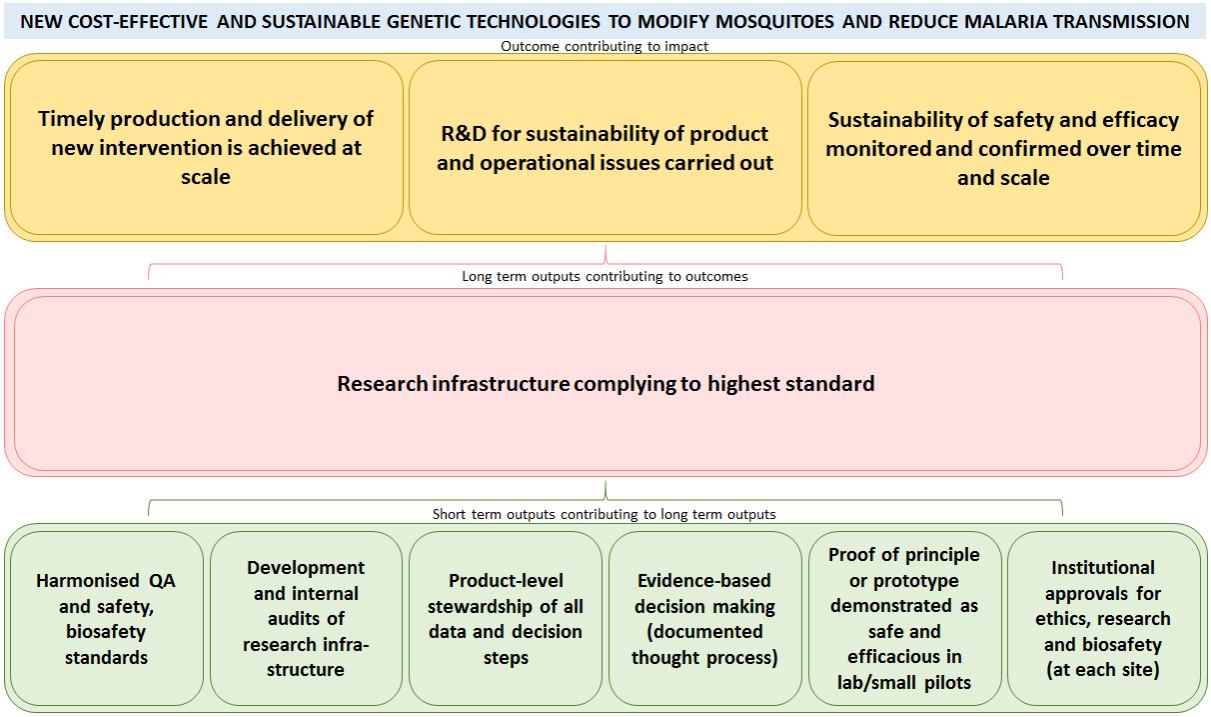


Figure 7.7 Short term outputs leading to research infrastructure complying with the highest standard for delivery of novel interventions for vector control in DEC

In each instance, there is a balance between requirements of evidence of 'readiness' and progressing the very studies that will provide evidence. Facilities readiness provides a framework for 'checking in' with a research team, across a consortium, or even with external experts and peers, prior to taking the step of beginning the containment studies. The next chapter describes the method of a periodic audit for determining the level of readiness.

Chapter 8. Internal Audits of Facilities Readiness

An audit of various factors relating to readiness of a containment facility and team is one of the approaches identified in Chapter 7 (Figure 7.2). The research subquestion addressed here, and in Chapter 7, is: **How does benchmarking a point of readiness for use of containment facilities support effectiveness of this first step in the delivery of the intervention?**

Chapter 7 summarised results of an action research process, complemented by literature, relating to preparations for import of a transgenic strain as an important decision point in the delivery of a novel intervention for vector control. Quinlan et al. (2018a) presents the underlying concepts used to organise activities towards achieving facilities readiness. Preparations described in Quinlan et al. (2018b) were focused on the physical infrastructure and preparation of procedures. These articles refer to internal audits, without going into detail.

In this chapter, the researcher considers the use of audits in some other settings through a literature review and the possible objectives of an internal audit such as prior to seeking regulatory approval. She describes her own experiences in leading the teams that conducted audits of two containment facilities, following the process she developed and using the materials she prepared. In this context, the audit is aimed at identifying conformity or gaps in relation to a set of established criteria to support planning and decision making. The audits described are not for the purpose of any certification or accreditation.

8.1 Establishing the basis for an audit of facilities readiness

Chapter 7 presents a concept of 'facilities readiness' that aims to be a more holistic view of the status of the lab. Many research labs, however, will be working towards specific certification. The researcher reviewed literature relating to these types of experiences, before designing her own approach to facility audits.

Health research labs in Kenya, Ghana, Malawi and Sri Lanka, for example, worked against an ISO 15189 checklist[80] (current version ISO, 2012), to identify gaps in good practice before attempting to achieve accreditation (Njelesani et al., 2014). The purpose of that initiative,

[80] The Target Malaria consortium did not consider ISO or similar certification as relevant to the containment labs, because of the type of work conducted on research of uninfected mosquitoes. On the other hand, if a system for evaluation, accreditation or similar did exist, that project would likely employ the recognised standards and processes.

described in more detail in Njelesani et al. (2014), was to scale up, broaden the user base and find cost savings Indicators were selected to evaluate the phases. While the objectives are not entirely appropriate for a dedicated use mosquito facility, the researcher found publications of this type of experience extremely valuable operational guides.

Guindo et al. (2012) describe some of the challenges to resource limited contexts for achieving good laboratory practices appropriate to the research, in this case for a malaria research lab in Mali which is part of the Malaria Research and Training Center (MRTC). They found overlap among relevant portions of harmonised standards for US-funded trials and international guidance and selected those most appropriate to their setting. This included use of over 100 document templates from ISO 15189 (ISO, 2012) for proper documentation of the clinical trials. Guindo et al. (2012) describe a collaborative process between NIAID and the MRTC to plan, assess and improve the facilities, to the level of accreditation by American Pathologies inspectors. Their own assessment benchmarked their compliance as moving from 65% to 100% over a two year period (Guindo et al., 2012: Figure 4). This process was referred to as a Quality Management System, following guidance from various international Good Clinical Laboratory Practices guidelines while adapting these to the local conditions and the specific facility.

The overall capacity for health research at an institution in Ghana was examined using an evidence-based tool, after initial awareness of the need for this support and literature review on options for approaches to evaluation (Bates et al., 2006). This initial review resulted in an agreed definition of health research capacity and identification of the key principles of the best practices found. The key principles can be summarised as: (i) a phased approach including early and sequential involvement of stakeholders in the process, (ii) integration and strengthening of the existing procedures or processes, and (iii) building partnerships around similar ideas and objectives aimed at problem solving (Bates et al., 2006). (The organisation of the actual evaluation tool prepared for the Ghana institution is considered in Chapter 7 of this study, see also Bates et al., 2011. Like other good learning systems, it allows different outcomes because the priorities and gaps are identified by the institution itself.)

The literature reviewed for Chapters 6, 7, 9 and 10 was informative in regard to topics covered in the facilities audit. Useful questions for an audit of an aseptic production facility are laid out in a recent revision of the *Design Requirements Manual* (NIH Division of Technical Resources, 2018: Exhibit 13.1, p.1027-1031), many of which are sufficiently general to apply to other restricted lab settings. Some aspects of *The management, design and operation of microbiological containment laboratories* (HSE, 2001) or *The Genetically Modified Organisms (Contained Use) Regulations 2014* guidance (HSE, 2014) were useful in developing audit

questions. Possibly the most relevant resources have not been found publicly originally, but rather were shared by colleagues: *The CDC Import Permit Inspection Checklist for Arthropod Containment Level 2 (ACL-2)* (CDC, 2014) is the primary example. More closely focused documents added to the review, such as the Kenyan *Guidelines and checklists for the risk assessment and certification of facilities dealing with genetically modified organisms* (Kenya NBA, 2013). More recently, a revision of the NIH Division of Technical Resources (2018: Appendix 1, p.1191) *Design Requirements Manual* outlined the requirements for insect facilities, beginning with a definition of purpose, recognising that this sets the more specific guidelines for a facility. It does not enter into detail on certification of such a facility, however (NIH Division of Technical Resources, 2018: p.1195). Clearly, any guidance for certification should inform an audit in any country that conducts such a procedure.

Despite these examples from literature, much of the set of questions were prepared in relation to the Target Malaria work plan, policies and facilities readiness concepts developed within that consortium context. Specific questions would vary within a different research setting. All of these experiences and literature demonstrated to the researcher the need to (a) identify the purpose of evaluation as a starting point and (b) agree on critical definitions prior to an onsite assessment.

8.2 What is a facilities readiness audit?

In the context of this study, the researcher has defined a facilities readiness audit[81] (in contrast to an official certification audit) as a project-internal review of various aspects of the containment facility and team at each site, to ensure at least the minimal compliance level of design and operations are in place, or to support planning for reaching that level on all fronts. To achieve this, she designed a series of questions regarding general lab practice, specific project policies or SOPs, national requirements on containment facilities to the degree these are known, or international practices when other guidance is not available. Such an audit focuses on the containment facility internal operations but could be expanded to address other themes such as engagement with stakeholders nearby the facility.

[81] Relationships to the institution, the national network of researchers (formal or informal), regulators and other stakeholders might require a different type of audit, such as a review of political will and a national strategy described in FAO (2007). If there is a national framework for certifying the facility, this type of audit will complement the internal process which must include project specific requirements. However, if there is no national system, this form of facilities audit simply provides some reassurance to the project management and funders that an appropriate containment level has been met, despite having no authority outside the project.

The researcher determined that observing operations and procedures in progress may be difficult in many research settings. She realised, in discussions with research teams, that some tasks for mosquito rearing may occur once a generation; work may be disrupted by an audit, and loose utility due to distractions; and human nature would lead someone being observed to perform a task with more attention and strict adherence to SOPs when in routine practice this might not be so. Much of the evidence she designed into an audit framework, therefore, relies on observation by the auditor of the existing structure, equipment, work flow layout and so forth, without necessarily seeing the procedures in action.

Documentation also is critical for a successful audit because of the limited time for an audit visit, in contrast to ongoing supervision or monitoring indicators for ongoing operations. A range of types of documentation, by purpose, are noted in Table 8.1.

Some of these may overlap, but in general the focus of an audit of the facility will be:

- To ensure the informative records are properly managed (in place, sufficiently descriptive, timely and accessible);
- To check documentation and observe operations, to the degree possible, against what is in standardising documents;
- To review confirmatory documentation, as part of ensuring that procedures are followed.

Informative documents record something that might be checked but do not necessarily provide evidence and are often taken at face value. For example, competencies and skills can be summarised and recorded in training files which include job descriptions, curriculum vitae, record of relevant training received (diplomas, certificates) meetings or conferences attended. All training received must be recorded, including non-certified training and short term training on specific tasks or skills, such as performing polymerase chain reaction (PCR) or handling blood safely. The NBA is likely to review the training files as part of the inspection of a facility. These records do not necessarily demonstrate the competencies or skills in the way that a supervisor might through observation, however. Review and signature of records by a supervisor or trainer adds greater evidence of achievement.

Formative documentation, which is designed to provide feedback for learning (Table 8.1), might be evaluated as part of an audit, to ensure that improvements are ongoing and systematic. This is often not included in example audit checklists, however, because some additional aspect is needed as part of the facility routine operations to support learning. For example, data on generation length may be recorded but a graph of trends will facilitate

recognition of a change over the course of time. Predictive and conclusive documentation is more likely to be considered in a review of the research by the national or institutional authorities, than during an audit of a facility.

Table 8.1 Types of documentation, by purpose, used in mosquito containment facilities and as possible sources for review of operations

Purpose	**Nature of the documentation**	**Example from mosquito labs**
Informative	Record or report of what happened, without further evidence	An organisational chart Training records Method used in a study Equipment maintenance records
Standardising	Documentation to support consistency, for example harmonised procedures, protocols and policies	SOPs and study protocols Data reporting template Orientation for visitors
Confirmatory	Evidence to demonstrate that the procedures, study protocol or policies were followed (evidence requires collection of some indicators, not simply statement of compliance)	Autoclave sensor showing temperature reached Swipe card access records PCR gels attached to identification records
Predictive	Description of anticipated outcomes, such as expected data or thresholds, which may be based on prior experiences, scenario analysis or modelling (useful to indicate if action should be taken if this is not what happens)	Sex ratio of a batch of mosquitoes in lab Likelihood of survival and persistence if a research mosquito escaped from the lab (age and status of feed if female, weather conditions outside, presence of potential mating population, area covered by remediation measures, etc.)
Formative	Facilitated interpretation or new presentation of information that will add knowledge and feed back into decision making, to support learning and possibly corrective actions	Trends in production numbers for a GM strain of mosquito, over several generations Threshold for free flying adult mosquitoes, a point that provokes additional action
Conclusive	Documentation of analysis, with supporting facts, leading to a conclusion	Average generation days in one site compared to that in other sites, analysed against differences in practices Data on temperature and humidity fluctuation in the insectary over time, contributing to analysis about any link to change in mosquito production observed

The evidence for an audit will be either documentation of practices or observation of practices. In the context of this study, this is not the same as ongoing supervision or an audit of the outputs (e.g. quality assurance indicators), as shown in Figure 7.1.

Table 8.2 shows the general topics and subtopics included in the researcher's checklist. The results of the actual audits conducted are confidential and not shared here, nor publicly available.

Table 8.2 Topics covered by initial checklist for facility readiness audit for Target Malaria.

Facility design and construction	**Equipment**	**General biosafety**	**Organization, training and competencies**	**Emergency preparedness and worker safety**	**Mosquitoes**	**Data and documentation**
Containment Biosafety Containment or biosafety Construction Emergency recovery Local exhaust ventilation (LEV) Air filters General lab environment Monitoring of any adult flying mosquitoes outside cages	Confirmation of receipt Equipment records and maintenance in general Centrifuges Microscopes Heating blocks PCR equipment Autoclave Sink filters Mosquito traps Consumables (supplies)	Facility access and security Preventing mosquito escapes Preventing unauthorised removal Colony management Containment compliance Chain of custody of imported mosquito eggs Identity declaration and confirmation Regulated waste General lab environment	Organizational Existing competencies Required competencies Project orientation Training Mentoring and evaluation Required authority Summary	Awareness Emergency recovery Health Fire First aid General personal protective equipment General safety Electrics Chemicals Hazardous chemicals Sharps General lab environment Reporting	Set up Simulation Identity SOPs Collecting eggs Bleaching larvae Separating larvae Sexing larvae Counting larvae Larval diet Sugar diet Blood meals Preventing escape or cross contamination Preventing escapes Supporting risk management	Security and usefulness of files Internet Incident reports Training records Authorised access Facility management documentation Research-specific documentation Process on publishing results Process on publishing results and Stakeholder engagement

The researcher chose to rely on a checklist approach to a facilities audit. Other approaches could be used, depending on the stage of the research and the objectives. For example, an audit of an existing certified containment facility could focus specifically on transfer of a new research organism into or out of the facility. Similarly, an audit could be organised from the perspective of the life cycle of any given mosquito, offering a chain of custody with biosafety measures along its path.

Food safety and quality systems often rely on a hazard analysis and critical control point (HACCP) review as a planning tool for maintaining safety of the food product. Supply chain analysis may also be relevant, but in both cases aspects may be taken up in a review of ongoing operations by using specific points that may reflect activities before or after the one being monitored. The concept of systems approach and critical control points as used in plant health (Quinlan et al., 2016c), or other fields (e.g. in aquaculture, Palić et al., 2015) is a useful one to adapt. The researcher did not approach this audit in terms of critical points, but it is another option.

Another tool to support an audit could be a roles and responsibilities table showing who carries out each task and who checks it. This was done for the construction phase, showing who would contract the service and inspect or validate the work done in another type of lab (NIH Division of Technical Resources, 2018: p.1040).

8.3 Experiences with internal facilities audits

The researcher led development of an internal facilities audit process from literature review and approaches identified through her action research role. The facilities audit covered a range of attributes of readiness (Table 8.2), as the concept was explained in Chapter 7. The researcher then led a team to test the audit process in two West African partner facilities of Target Malaria. The composition of the audit team was the same for these two audits, reducing the influence of individual auditors on a review of the outcome. The Figures 7.3, 7.4 and 7.5 show timing of internal audits in relation to other activities, according to the researcher and Target Malaria colleagues who participated in developing the concepts.

These audits took place April 20-22, 2015, in Burkina Faso and September 2-4, 2015 in Mali. The objective of these audits was to determine 'readiness' for import of the research organism, prior to submitting an application for the relevant import permit[82].

Alternative objectives of an internal audit of containment facilities could include:

- Benchmarking the level of preparations and competencies at the beginning of a research project, possibly to inform a training plan
- Preparation for an external inspection by government authorities or some other accreditation body
- Periodic review of progress against some established criteria for each component of readiness
- Confirmation of compliance for a particular area of readiness that was not sufficient in previous audits or that has been added or supplemented

In both cases in follow up meetings and in the final interviews with the country PIs of Target Malaria, it was confirmed that such a structured audit serves to reassure the researchers themselves, the research consortium management and, to some degree, the funders, of a level of readiness prior to submitting a regulatory application.

It is not always possible to demonstrate proficiency in all aspects of capacity until the moment the actual research implementation begins. (See also the discussion of interruption to readiness levels, Chapter 10.) The PI on site will ultimately determine the capacity of his or her team through previous collaborations, observation and supervision. In this aspect of planning, in particular, the current events in the area, other demands on staff (if not employed full time), and personality and behaviour of team members will also be taken into account as part of the 'other' or unstated factors that influence the state of 'readiness'.

Although the facilities audit was tested with only two West African sites, the researcher discussed the outcomes and lessons learned with the other auditors and concluded some good practices to offer for future internal audits of mosquito facilities.

[82] Separate audits were undertaken by the Target Malaria partner labs to assess community engagement activities in the neighbourhoods near insectaries or, for future studies, in villages where confined field studies may take place. One key objective for that project is to gain and maintain a 'social licence to operate' starting with community acceptance in villages where baseline entomological surveys will be needed for field studies and more generally in the country.

A field readiness audit relating to future confined field studies was also developed. Collins & Quinlan (in press) report on this process, which is separate from the facilities audit described as part of this study.

8.4 Good practices for conducting an internal audit of a transgenic containment facility

8.4.1 Preparation of the auditors and the facility to be audited

The researcher held a series of calls with the auditors (see below on selection) to discuss the objectives, the topics to be covered and their roles and responsibilities. The researcher designed a facilities audit to follow a checklist of all the selected criteria, which may be developed as a series of questions or simply stated in simple terms as an aide memoire. The auditors then commented on the final checklist prior to it being shared.

The researcher shared this checklist, or an abbreviated version similar to a terms of reference, with the facility manager and country PI well in advance of the audit, to guide preparations and reassure staff of the intention and possible outcomes of the audit. The researcher also prepared a frequently asked questions (FAQ) style paper to address any unease regarding the purpose of possible outcomes of the internal audit. She then held calls in advance to answer any specific questions. A good insectary manager will use the preparations to review factors independent of the checklist and not be limited by it.

The travel schedule for the auditors was arranged to allow discussions in the country, the evening before the audit. In this instance the researcher reiterated the agreed objectives and the auditors divided up the checklists to cover their own areas of expertise, with only some overlap. An important point emerged when the researcher explained that the main criteria in this particular process was to determine if the facility readiness level was sufficient for submitting an application for import of the research organism. This eliminated confusion as to the level of compliance needed. For this purpose, the categories of reporting were defined as things that had to be done immediately for compliance, and those that should be done prior to an import. As noted already, some items in a checklist may be premature, for example when it regards SOPs for rearing and labelling transgenic strains but there is no such strain in the lab at the time of the audit. Proxies from field caught strains or other indications of understanding of the principles and purposes of the SOPs may be sufficient to give confidence regarding compliance.

8.4.2 The experience of the auditors during the tests

The audits were carried out by visiting the facilities for several hours, asking questions and making observations. (In line with Target Malaria policy, the auditors received a visitor orientation prior to entering the containment facilities.) The audit team then returned to their

hotel for discussion of the findings. The next day, the auditors returned to finalise any points that were left unclear. That afternoon, preliminary results were presented by the research, as the audit team lead, to give an overview and allow for any obvious corrections (e.g. auditor did not see a record of something, but it was shown to be on site). In these two instances, there were no corrections. The researcher collected the hand written notes on the audit checklists from the auditors, and continued preparing the report. On the third day, the auditors reviewed the report. Further review of the report was made by email after departure.

As already noted in Chapter 7, having dichotomous (yes/no) answer options reduces the information for follow up, especially when the assessment of a question is not a fully compliant 'yes'. The two experiences of the researcher in testing her proposed materials showed that ambiguity can reduce the value of the tool when the criterion:

- Is only partially met
- Appears to not apply
- Is premature in terms of timing, for the preparations of the facility
- The evidence required to demonstrate a conformity is not clearly stated, or is unavailable even if the criterion appears to be met.

To remediate this, the researcher added a comment column and instructed the other audit team members to note in writing their reasoning for a choice of yes/no for those points less obvious or lacking evidence. For the second audit, the checklist was adapted to have 'yes/no/not applicable' answers.

Auditors should agree in advance what it means to be 'not applicable'. This may be elaborated on in the comments section, for example if it is because the facility has not reached a step in operations yet, then the criterion will become applicable later and should be noted in the report for follow up. If the point appears irrelevant due to the location or setting of the facility, for example, then the criterion will never be applicable and may be either a variance or simply something to be explained. This reiterates the importance of a column for comments to capture those type of observations and notes for consideration when preparing a report. In general, those points not meeting the criteria for a 'yes' should be noted in the report and carried over for follow up. Some of the observations may be mandatory and immediate action, some may be recommendations for improvement but not requirements, in which case this may be given more time to fulfil. Further enhancements to what is observed during an audit may be noted, but not required, to give direction to medium term improvements in the facility or capacity of the team. This could include options for achieving the same outcome, to give greater choice to the facility manager, or other observations drawing on the experience of the auditors.

The researcher used additional notes, photos, documents, etc. from the audit team to complement the resulting checklist and final report. The audit team should be allowed to make general observations about the set up, operations, documentation or overall risk at the site, which may not be tied to a specific question. Any findings of this nature should be written up as soon as possible during the audit visit, to capture this type of commentary that may fall outside the listed criteria.

8.4.3 The outcome of the facilities audit designed by the researcher

The researcher's approach to a facilities audit therefore will result in a report on the status of the facility at the moment of the visit. The benchmark of this status is set against a set of criteria, some of which are minimum requirements to proceed to import. The country PI will have time to comment on the audit report and prepare a follow up plan which will form part of the original audit report. This will be updated when all points are addressed.

The researcher envisioned the audit report as a confidential document for use internally. If it may be distributed, or shared with regulators for example, the process could take on a different atmosphere and the questions related to internal policy but not related to compliance may become inappropriate. In any case, the policy on distribution should be decided prior to the audit and any changes should be approved in writing. Drawing on these two tests of the framework and process she designed, the researcher concluded some good practices for documentation of an internal audit, shown in Table 8.3.

8.5 Choosing the audit team

Adams (2000) explains the value of working with a team, rather than individually, when conducting an audit of field activities or environmental sampling. The researcher agreed that this was an important practice for the context of the study, as well.

The choice of auditors depends heavily on the topics covered in the audit (see Table 8.2). The researcher worked with a mosquito research expert, a biosafety containment expert and a laboratory safety expert. Each was familiar with the Target Malaria policies, but the researcher was in charge of questions that were more project-specific than a typical audit might include. These comprised questions regarding the employment structure, use of internal platforms for document and data storage, project internal training and similar.

The researcher found through interviews with US and European labs that few experts have been subject to an audit of this nature, and even fewer will have carried out such an audit.

Guidance from other sectors may provide insights (ISO/IEC, 2015). Auditors will need to be oriented in terms of their role and responsibilities.

Table 8.3 Good practices identified by the researcher for documenting an internal audit of a containment facility for transgenic mosquito research

Ensure the objective of the facility is agreed and understood. This may include decisions such as whether it is a single use, or multi user facility. The latter implies a greater chance of strain contamination and also potential variation in lab standards. This may require additional coordination and criteria to add to the checklist.

- Establish the objective of the audit (include a clear statement in advance communications and the report)
    - To inform decisions by the funder, research consortium, or supplier of the strain to be sent
    - For internal planning and/or to show when to proceed to requesting official certification, submitting an import application, or other steps for external review
    - Other
- Include details on the auditors, at the least contact information and main qualifications (in advance communications and possibly the report)
- Determine the scope of what is to be audited – which site, which actual rooms or level of activities (e.g. only door locking system or security at the level of the campus), which staff (e.g. only those working inside a facility or those interacting with it for management oversight, estates, stakeholder engagement, etc.)
    - document this in the introduction of the report
    - document which staff at the site are to be involved
- Agree categories of what will be audited (e.g. Table 8.2) and whether any processes/work operations will be observed or the auditors will rely on evidence provided – this could affect the timing of the audit
- Prepare a checklist of criteria and related evidence, including simply observation by the auditor, if no hard evidence is relevant or feasible
    - Consider providing at least three categories of response: yes, no and not applicable
    - Provide a space for comments
    - Consider if the checklist should be peer reviewed by other independent researchers, or if comments back from the facility being audited would be useful prior to finalising the checklist
- Determine the categories of findings (e.g. significant, observation) – are traditional categories appropriate and how do they relate to a response?
- Provide the completed checklist to the facility being audited well in advance
- Present a summary of findings before ending the audit
- Write up the findings as soon as possible, preferably before ending the audit visit
- Include in the report positive findings as well as any gaps identified
- Allow a response from those audited, to ensure findings are accurate before closing the report
- Determine in advance if the auditors are involved in any capacity during follow up, i.e. do they check the evidence for remediating a negative finding or is that left for internal management?
- Treat the findings and report as confidential, unless a broader distribution is determined in advance or express permission is obtained afterwards
- Provide a sign off letter and possibly a certificate of completion for the facility to acknowledge the efforts involved in participating in an audit

An audit of a quality system or learning system is a frequently used method in other fields. Gordon & Kennedy (2016) describe implementation of a system for food products, focusing on developing country settings, starting with establishment of clear objectives. Of the 30 step process for implementation they describe, the use of internal audits to monitor conformance and effectiveness of the system (steps 20, 22, 24) and external audits for obtaining and retaining certification (steps 25, 26, 27) are key elements of the process that could be most relevant to the audit of containment facilities. Following a gap analysis for the initial plan, their advice was to develop capacity of an internal audit team, drawing on multidepartmental or cross-functional teams. An audit lead may require formal training in quality assurance (QA) or audits, but all audit team members should be exposed to theory and practice to prepare for this role. The output of an audit is a report on findings, which should include not only the basic note of conformity with all policies, procedures, instructions etc. but also some comment on the effectiveness of the same. Management then develops a corrective action plan and monitors progress, during regularly scheduled safety and quality meetings (Gordon & Kennedy, 2016). This case represents the situation of a larger business, and might not be emulated precisely in a smaller facility setting. Inclusion of a multidisciplinary team was found to be important. The need for multiple steps and recognition that the internal audit is a learned skill are the key messages to apply to other cases.

Following good practice, all auditors should be introduced to the facility they will audit, with some basic information about qualifications and expertise. If an internal team member is asked to serve as an auditor, it should not be assumed that colleagues know the qualifications of this person. He or she should be introduced in the same way as external experts.

8.6 What is included in a facilities readiness audit?

When considering the scope of the audit, the most important question is the objective of the audit at that time. If only a single activity is under review, e.g. blood supply or shipping and transfer of mosquito eggs, it may be organised as a lessons learned study or report rather than in the format of an audit. This depends on the stage of research, whether any activities have already taken place and if a more narrative approach would be useful for the activity in question. For example, if a team is not functioning well together, more exploratory questions could provide useful feedback instead of pre-prepared audit questions, even when related to the topic.

In general, anything important for success of the planned studies should be considered in an audit. For example, policies and practices regarding data entry and management should not

be overlooked. While the audit will focus on what is under the control of the project or initiative, general laboratory good practice and worker safety, which is likely under the broader institutional authority, may be audited (e.g. signs posted, fire equipment, sharps container). Requirements for complying with all policies relating to a research and/or import application should be considered during an audit, such as SOPs, a site specific Biosafety Manual, protocols for studies. Any national regulatory requirements should be included, although the internal audit has no legal status in that regard. Compliance with national regulations can only be determined to the degree that the research team can interpret them prior to receiving a permit; additional requirements may come as T&C of such a permit.

The researcher did not include a series of basic operational factors which are the responsibility of the institution in the audit checklist. These might include proper employment practices and reporting, any necessary permits or fees paid for conducting business in the country, financial accounting, provision of security for the general campus, and oversight of equipment provided by the institution including vehicles, aircraft or boats, an incinerator for autoclaved waste, and other services. The audit team may inquire about some of these, however, in the course of the visit, but this does not imply change in responsibility for these factors.

Any remaining lack of clarity on what is the responsibility of a project versus an institution should be addressed during the presentation of initial results. A letter from the institution acknowledging the list of responsibilities may be useful to avoid misunderstandings and cover these types of issues.

8.7 Outcome of an internal audit

Because the objective is to highlight any gaps in conformity with the set criteria, an internal audit is not a ‘pass/fail’ tool as much as support for strategic planning in research facilities. On the other hand, if minimum requirements are not met, the researchers involved may choose to not proceed with an import application for contained studies, for example. (Other factors outside this audit, such as funding flow and staffing issues, may also affect a decision to proceed or not with an application; the audit is focused only on the documented criteria.)

Any area requiring follow up will be discussed with the research lead, such as a country PI, to plan for how best to fill the gap in the short term and achieve sustainable compliance over time. A decision will be made, possibly by the auditors or by the research lead, as to whether a follow up, formal audit visit would be useful to review progress against any gaps identified. Another option is to document progress against the plan, which the research lead and/or

auditors may review to confirm that progress meets their satisfaction based on technical expertise.

Eventually this type of audit could be applied entirely within a research team, as a self audit, and/or similar audits may be organised of sister facilities. To maintain some independence, the auditor should never review a role or activities that he himself fills. Conflict of interest also dictates that auditors should avoid reviewing someone above him in the chain of command or work oversight. The audit itself should not require much of the local staff's time, although preparation of everything for the audit might.

8.8 Summary on the use of audits

A periodic audit is one method for benchmarking facilities readiness across a range of factors. Audits have been useful in other fields, and for laboratory certification. Some possible contents of an audit are proposed by the researcher, while recognising these should be case specific and tightly aligned with the objectives of the audit and the facility.

Any progress towards an international standard, or series of modules setting a standard, for mosquito research facilities, would make results of such an audit comparable and more meaningful for funders or researchers seeking partners. Figure 8.1 indicates how this step of internal audits combines with the use of harmonised indicators or standards and the pursuit of defensible science, through careful documentation and traceability of evidence, will lead to a high standard of research infrastructure.

The demonstrated capacity and competencies will support regulatory approvals for each step in the development of novel interventions, beginning with the import permit. This approach towards product stewardship is necessary as a foundation for the eventual regulatory review and decisions regarding incorporation of a novel intervention into vector control programmes.

The researcher has prepared a list of best practices for an internal audit of a containment facility based on experiences of auditing two West African facilities. Ultimately, in the context of this study, the purpose of such an audit is to inform an internal process to support decision making regarding the start of containment studies.

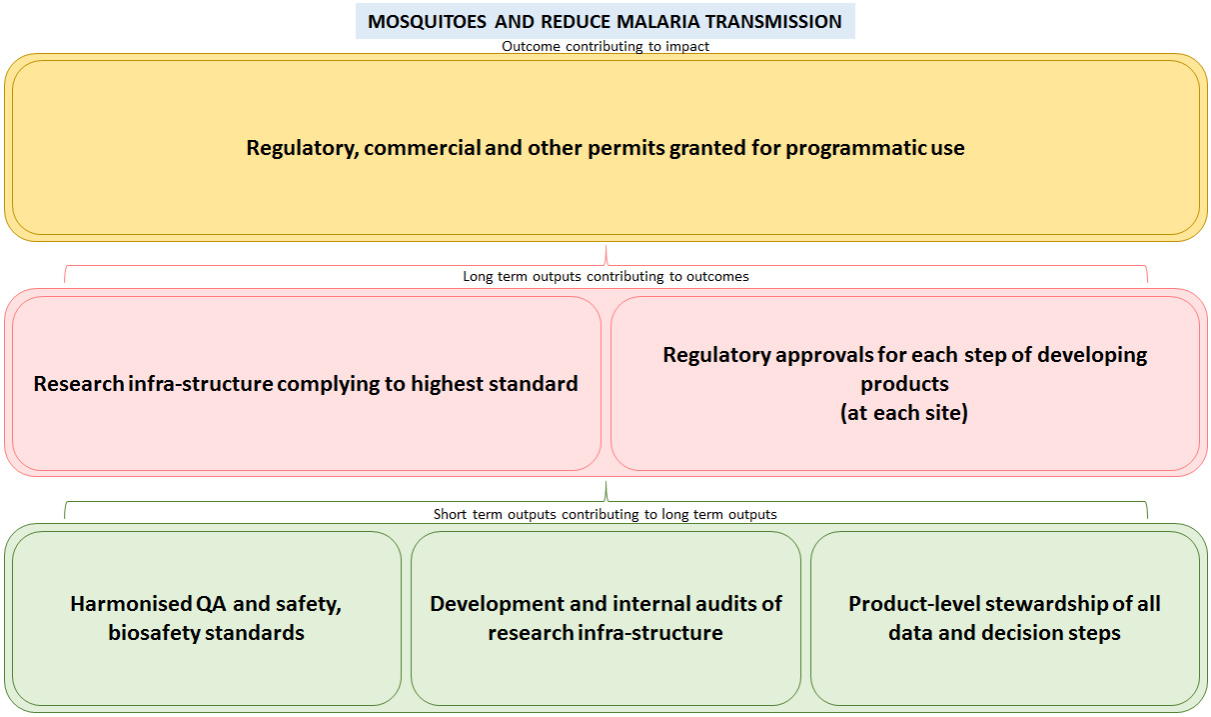


Figure 8.1 Short and long term outputs leading to regulatory, commercial and other permits being granted for programmatic use as part of delivery of novel interventions for vector control in DEC

Chapter 9. Building Product Stewardship

Laboratory research for proof of concept, safety and efficacy of measures using living organisms has rarely included record keeping in the detail and/or under the management needed for the objective of long term product development. Product development includes practices that are embedded in vaccine or pharmaceutical development, for example, but are as yet very unevenly applied in research on novel genetic strategies with mosquitoes.

Here, the researcher uses the term 'identity maintenance' to mean a systematic, reliable and replicable process of initial and ongoing (routine periodic) confirmation of the identity of representative individuals from a population (in this case, a lab colony), including genetic and phenotypic characteristics, to the highest level[83] of reasonable interest to future reviewers using readily available methodologies accepted at the time of the activity. Stability of these characteristics remains an integral part of identity.

The research subquestion for this chapter was: **Is a product stewardship approach to identity maintenance and data management necessary to support decisions about safety and efficacy in containment studies, moving towards field studies?**

This of course begs the question regarding what information or data are necessary to demonstrate identity maintenance, let alone to contribute to the interpretation of study results.

Decisions regarding data selection generally have been by individual site or project, rather than harmonised across the sector. At times, data collected are not even harmonised within the same institutions. Even definitions of the objectives of the data, such as fitness indicators, are not harmonised (Mumford et al., 2018). Benedict et al. (2008) considered that mosquito colonisation and competition studies would need to be conducted on a larger scale than previously done, if they were to compensate for the lack of laboratory indicators of field performance.

Box 9.1 discusses this 'gold standard' of product stewardship, which arises in various fields of study and commerce.

[83] The idea of highest level of interest (see section 4 *Taxonomy versus identity* mentioned in EFSA, 2005), for this purpose, may generally be to the level of species. Notwithstanding, additional aspects are often required for mosquito populations, including phenotypic ones such as insecticide resistance. The more complex the nature and history of the strain, however, the more data that may be needed and these requirements in fact often influence the design of the strain in the first place (Marshall & Akbari, 2018).

Box 9.1 The concept of product stewardship

The idea of managing a discovery or concept from research through to delivery is not uniform across sectors, but has some common elements. When referring to product stewardship in this study, the researcher is employing an idea closer to 'identity preserved production and marketing', by the terms defined in Smyth & Phillips (2002), for novel products in agriculture.

Others are conceptualising a more forward aimed intention of management, for example of all wastes or impacts resulting from a product, which is more in line with life cycle stewardship. Significant losses have resulted in agricultural trade when seeds or grain for market were found to include GM material, if labelled as not modified, or containing material from a different genetic insertion than that approved and declared. For example, Louisiana State University was charged with having contamination in its seed rice that was distributed to US growers (Delta Farm Press, 2006). This purportedly came from a GM strain of rice under testing by the institution, which had not been approved by the US Department of Agriculture (USDA) and Food and Drug Administration (FDA), although all seed stock was shown to be free of contamination in later testing (Delta Farm Press, 2007a, 2007b). A US$750 million pay out was made by Bayer when a number of US long grain rice growers were found to have shipped rice to Europe that was contaminated with GM material (Delta Farm Press, 2011a). This incident was said to have a long term effect on the price and market due to loss of trust (Delta Farm Press, 2011b).

When considering maintaining identity during the research through to product stage, one only has to consider the history of cell biology research before contamination by HeLa cells was discovered to realise the potential impact of contamination (Skloot, 2010). Horbach & Halffman (2017) describe the 'contamination' of scientific literature with publications based on inaccurate identification of these cell lines. They propose that in order for misleading published articles to be identified later, articles could be linked to cell lines listed in existing databases. Subsequently as misidentification or contamination is discovered, it is easier to see the research that may have relied on those results. They also propose posting 'notification of concern' where any such publication is online so that those reading it can review the conclusions in the context of this new information.

No similar analysis has been made of vector mosquito research, although Vernick (2017) notes the possibility of false conclusions. Inconsistency in taxonomic distinctions has introduced some confusion in the literature on malaria vectors already (Coetzee et al., 2013).

Therefore, while the term product stewardship initially suggests the type of data management necessary for regulatory approval and product integrity, excellence and integrity of the scientific conclusions (NASEM, 2017c; Mårtensonn et al., 2016) is another vital part of the concept for the current study.

9.1 Existing context on documentation for related interventions and vector research

Data management to the level of what could be called product stewardship is a recurring issue across various interventions. The researcher's experience in searching historical data for preparation of the *Model Business Plan* (FAO/IAEA, 2008) showed that published information about insects used in areawide control from earlier field programmes sometimes lacked even the most basic information, such as whether it was a single sex or both that were released. In response, Quinlan & Larcher-Carvalho (2007) proposed a harmonised set of appropriate data to collect for sterile insect technique transport and distribution, to serve as a source for general 'market' demand and strategic planning in production sectors.

Sometimes data is not timely or not managed in a useful format. An analysis of vaccine delivery in Nigeria (Sarley et al., 2017), aiming to address challenges throughout the supply chain, began with analysis, assessment of capacity and review of lessons learned from other countries. Before working on structural realignment, a performance management step was implemented to address urgent failures in supply and provide visual status of the supply chain. This visual 'information dashboard', showing stock levels as a 'live' display (updated weekly), gave critical support to other improvements (Sarley et al., 2017). In other cases, the data is inadequate because the methodologies need improvement. Gutierrez et al. (2015) enumerate the limitations of data from the current methods for surveillance of mosquito populations, and need for improved data in order to benefit from better informed modelling of probable outcomes for disease control.

A repository of nanoparticles was created to provide representative materials to researchers so that the identity of these is maintained and assured, and studies following the same methods may be more reliably compared (Totaro et al., 2016). This implies homogeneity within a batch and stability of identity of the material, which is something that does not apply so easily to lab reared mosquito colonies. Furthermore, it may be impossible to recover identity information for the material used in various mosquito studies to date due to lack of this detail in many studies, even if the named strain could be considered consistent. As Vernick (2017: p.217) notes, 'Many current mosquito colonies are old and poorly characterised, and have likely diverged genetically and phenotypically in different laboratories.'

Higgs (2018) argues that defining a 'standard strain' from lab colonies currently in use may not have the value to science that the effort would require (particularly given the additional variations, such as introduced from the various blood sources). He is speaking about

replicating scientific studies, however, not creating products based on studies. The move to product development and stewardship argues a more rigorous approach.

The researcher concluded, therefore, that establishment of new colonies is a good practice for research in genetic strategies that may lead to a product for the field and that improved documentation should complement this task. Although time consuming, establishment of new field collected colonies allows for better record keeping from the start. The researcher collated what information is included for mosquito stock suppliers at the time of the study, and proposed what future users may seek to prepare for a new wave of colony establishment and ensure the accessibility and quality of information. Table 9.1 summarises the information already considered to be important for exchange of research materials.

While these forms for existing or now closed suppliers of mosquitoes for research give the impression of some traceability and record keeping, historically much material has been shared and transferred without this level of information. In recent years, the US Government has required more rigorous permitting for even domestic transfer of mosquitoes that vector disease, but there is no international standard for managing these exchanges. In 2018, there was a call for coordination on a new standard for documentation regarding strains, albeit in relation to infection studies (Minimum information for reporting arthropod infection studies project, found at https://gtr.ukri.org/projects?ref=BB%2FR021198%2F1), in part to comply with expectations of funders (Lauer, 2016). It is not yet clear if this initiative will be successful in setting more harmonised expectations for this type of documentation across mosquito research undertaken in the US, and if so whether this trend will spread or there are in fact similar initiatives in other regions.

Other factors arise when the mosquito is transgenic or modified in other ways, such as by infection of a gut symbiont. For example, the strain of *Wolbachia* used for infected or inoculated *Ae. aegpyti* releases is of increasing concern due to varying approaches (Booth, 2017), with some incompatibility, particularly in Southeast Asia, but a single open database of this information does not exist. Looking to the future, information on the mosquito microbiome is recognised as an important part of a colony description when considering comparability of study results (Vernick, 2017). There are specific genes now recognised as linked with particular characteristics, so that one might test for the gene rather than repeatedly establishing the trait in each colony (e.g. Lawniczak, 2015). Furthermore, requirements for identity maintenance may dictate preferences at the point of creation of new mosquito strains. For example, Gantz et al. (2015) propose restricting CRISPR transformation to the germ line, to ensure maintenance of the nuclease activity and target-site specificity for gene drive lines, across multiple generations.

Table 9.1 Information in frequently used forms regarding shared mosquito colonies

Information fields	
Unique identifier	Each group may have a system for unique identifiers to match the traits of the mosquito or simply a file number
Infection status	For example, infected with *Plasmodium* If not noted, it is assumed that the mosquitoes are produced under monitored conditions as free from vectored disease
Taxonomy	Classification/Genus
	Species
	Strain or subtype
	Genotype[a] (molecular form, population; or – transgenic composition and insertion or driving mechanism)
	Common name and/or synonym
	Karyotype
Phenotype	Infection susceptibility or resistance
	Transmission competence
	Insecticide resistance (noted for each chemical tested)
	Particular trend in a characteristic in life tables*
	Visible characteristic relating to a mutation (e.g. colour variant)
Genotyping	Presence of specific genes of interest (e.g. presence of alleles that have been established to relate to particular behaviour or appearance, such as insecticide resistance)
Geographic location (where material was collected)	Country of field collection
	District, Province, County or similar
	Village
	Latitude & Longitude
-or- **Lab colony source**	Existing colony or collection
Origin of colony	Date that the colony was established using either field collected mosquitoes, or date of transfer for subsequent colonies in labs in different locations. Person or institution establishing the colony.
Contributor	Person, project or institution who has made the collection; donor who presents sample (e.g. from their lab colony)
Shipping terms, life stage	Life stage at time of shipping; shipping container, labelling or other requirements

Recommended biosafety level or special measures	Use or sharing restrictions; recommended level of containment if needed – this is most relevant for those carrying novel traits or infected mosquitoes
Required permit, forms or MTA terms	This may be the form itself, a licence for use, a bespoke MTA, or other requirements by country of export/import
Growth conditions or special handling	SOP or other details of culturing conditions Required outcrossing or backcrossing (e.g. for a sterile strain to continue)
Requested acknowledgement or citation	Contributor, Institution, Country
Published references	Anything that describes the strain, studies on it or the host population, genes of interest, etc.
IP or information on benefit sharing*	IP on patented material or technologies; Nagoya Protocol requirements or other national terms

[a] If modified, additional information may include the donor organism for any genetic material; method of modification; homing rate for homing endonuclease genes; paratransgenic organism; cytoplasmic incompatible organism such as gut bacteria; strains of these and so forth.

Sources (* denotes a field not included in any example forms reviewed at the time of the study):

CDC (Centers for Disease Control and Prevention). (undated) BEI Resources, Product Information Sheet template (https://www.beiresources.org)

MR4, Production Information Sheet MRA template © 2012 American Type Culture Collection (ATCC).

Infravec (2016a) Infravec Deposit Form v. 10 Oct 2016. Infravec Virtual Insectary. (Inactive website available at http://archive.is/0hw0H)

Infravec (2016b) Infravec Stock list Form v. 10 Oct 2016. Infravec Virtual Insectary. (Inactive website available at http://archive.is/0hw0H)

Gutierrez et al. (2015) propose electronic records to be kept in databases for other types of research on malaria, based on experiences with ICEMR network. This could include consent records, personal details to link to human samples (e.g. blood) and disease status, or geographic locations. Research on malaria per se is not the focus of the researcher in this study but may supply ideas for mosquito-based data management.

Other tools relevant to mass rearing mosquitoes also are important, but not the focus of this chapter. For example, the Joint FAO/IAEA Programme has a website hosting manuals, forms and other tools for managing data in the use of mass reared insects for release, including mosquitoes (http://www-naweb.iaea.org/nafa/ipc/public/manuals-ipc.html), including detailed record templates for data on blood, in this case for use in feeding tsetse (http://www-naweb.iaea.org/nafa/ipc/blood-processing-database.html). There is also a template nearing completion for planning the design of a small mosquito insectary, prepared by IAEA (Cáceres, pers. comm., 2018).

Collecting and managing this level of detail, with perhaps even additional information, may appear onerous for research labs that are not set up as suppliers for other colonies. As already noted in this study, such changes in data collection and record keeping are cultural and organisational changes and require buy in by the entire insectary team – if not the entire institution, a strategic plan, resources and time. The value of these data go beyond informing the interpretation of study results, because of the level of regulation of areawide use of mosquitoes, particularly when the strain is transgenic or otherwise modified.

9.2 Setting identity maintenance requirements

The researcher refers to identity maintenance as a systematic, reliable and replicable process of initial and ongoing confirmation of the identity of representative individuals from a population, including genetic and phenotypic characteristics. The details of appropriate requirements for identity maintenance of mosquitoes, which are will be used themselves as vector control, remain unclear. The limits of these requirements often are defined with a 'self-policing system' within the research sector, via the peer review system of journals to establish the minimal requirements for authentication of mosquito strains used in research (Higgs, 2018: p.187).

When thinking of future products based on mosquitoes, however, the objectives of identity maintenance are multifold:

- To ensure that what is used later is going to have comparable results as what was in a study, for example be as effective and safe.
- To ensure that conclusions about safety and efficacy are based on accurate identity in relation to the later product.
- To ensure that good lab practices in the process are followed, which builds trust and reliability of results.
- To ensure that studies can be replicated in the future.
- To ensure that if something performs differently in the field, there is adequate information about each factor to support investigation into the possible causes and rectification of this change.
- To satisfy regulatory requirements.

In terms of mosquitoes, it is important to know if the local genetic context is a factor in results of any studies. However, in the case of back crossed strains, most of the genetic composition of the product will be from the pre-existing background population used for introgression until a few generations have passed. If there is any variation such as in phenotypic, behavioural or

insecticide resistance in the background population, this should be established in advance of studies so as not to be attributed as unique to the modified strain.

For these reasons, identity maintenance and integrity are part of the evaluation of risks in various guidelines.

9.2.1 Confirming identity

Clear identity of the wild type[84] colony is critical to interpretation of early phase study results with mosquitoes. This information also facilitates insight into eventual control efficacy. Therefore, first and foremost, the identity must be verified before documentation makes a difference. Quinlan et al. (2018b) describe a two step process used by Target Malaria to ensure that the gravid females collected and a sample of progeny are identified satisfactorily, avoiding hybrids or individuals not showing clear species identity. Methods in such a process must always be included.

To ensure that this has been done according to best practice and defensible conclusions, evidence should be saved along the process, rather than noting only the outcome. For example, scanned protected (e.g. pdf) copies of field notes, lab notes and PCR gels and notes are requested within the procedures proposed here by the research, as part of the foundation of the record. These records of direct evidence can be attached to the identity record, or simply filed in the same folder depending on the users' access. The value of attaching files to the record is that there is no chance of separation. The disadvantage is it makes the files very large for working with later.

9.2.2 Regulatory requirements or guidelines

Correct taxonomic identification of the target population and research organism is critical for effective control of insects (Sharma, 2008). This is even more the case for areawide control using the species itself as the weapon against its own populations. Therefore, part of the evaluation of an application for field release is to describe in detail the strain of insect being mass reared and that will be released. This presumes a robust procedure for validating the research organism's identity in the first place.

[84] In this study, wild type refers to populations in the wild, so a wild type colony is always one that is established from field caught gravid females. (Many others refer to non-transgenic lines as wild type, even if they have been in the lab for many years and the origins are unknown.)

Consistency in testing is promoted for achieving comparable materials when using transgenic mosquitoes (WHO/TDR & FNIH, 2014). The guidance regarding evaluation of transgenic insects resulting from a European Food Safety Authority (EFSA) expert committee (EFSA, 2013: p.88) notes the importance of 'management processes that affect the consistency and efficacy of the mass-reared GM insects and the release systems'; one part of that consistency obviously will be the taxonomic identity of the research organism. EFSA (2013) also discusses the stability of traits, but in reference to inserted transgenes in this instance. This guidance document raises the need to consider this over time (EFSA, 2013: p.89), 'The stability of the GM insect trait in mass-released insects and/or the efficacy of the intended effects in suppressing the target population should be assessed.' There also are recommendations for monitoring genetic stability post release in areawide programmes.

The researcher concluded that a harmonised set of data and consistent record keeping regarding mosquito colonies could support decision makers along the entire pathway towards delivery of a novel intervention in vector control.

9.2.3 Operational events worth documenting in the life of a colony

For the objectives noted above and in the next section, a colony record should be a fairly stable document, although certain events in the life of the colony should be recorded. Such a record is not meant to replace ongoing records, such as for quality assurance, study results or other frequently changing or short term activities.

The main 'events' in the life of the colony that have been identified in this study are:

- Establishment and the requisite identity check
- Replenishing (adding to the original colony)
- Split/merger when the same colony is divided and managed separately and then if it is merged back again (not merging with a colony of different origins)
- Filtering a sample through an identity check, for example annually
- Transfer – this study refers to export but it could be to a different facility even on the same campus
- Receipt – import so that one will start a colony in a new location but with material from this originating colony
- Termination – this could be intentional or accidental but should be recorded with the cause, if known

The value of having this information is twofold: first, while those on site at the time know what has happened, for a large international consortium it is useful to always know the state of any colony at any site at any time; second, if a colony does die out or requires replenishment, it may be more efficient to return individuals from a colony that was formed from it rather than introducing new genetic material through a replenishment with field caught gravid females.

9.3 Establishing mosquito colony founder records

Better documentation of identity for newly established colonies will address some of the objectives of better data collection and management.

9.3.1 Objective and specification of a record

The original purpose of the record was to allow one to trace any wild type colony back to its founders, where they came from, when they were collected and when and how their identity was verified. Over the course of validation, additional purposes were considered useful and easy to accommodate in this record, including:

- Adding a basic description of the location of collection, from field records or experience (e.g. latitude and longitude)
- Method and approach to identity confirmation, and
- Tracking location of subcolonies in case of need to quickly recover

Other possible purposes were not taken up, such as use as a shipping document or for recording the use of the colony over time (i.e. stock maintenance, studies, etc.). On the other hand, the opposite was found useful – the colony identity was recorded in the records of studies so that it was clear which strain was used for each study.

A comprehensive and standardised method to document the local colony pedigree was designed for the proper stewardship of the ultimate field technology. Discussions among experts, primarily in the Target Malaria research consortium, on what features affect the identity of a new colony, and the realities of capturing mosquitoes and establishing lab colonies led to an outline of events (Section 9.2.3) and characteristics important to document.

The first versions of this tool were simple Word templates with a list of questions to answer. This grew to be several pages of questions, and was not so easy to view. A Microsoft Excel™-based Wild Type Colony Record (WTCR) was designed to document the most relevant details of each field caught colony. The preference for Excel is that it is widely available, does not

require significant space or capacity on the computer hosting the files, and can support simple macros.

Figure 9.1 shows the sections as they appear in the Excel template[85].

9.3.2 Codes for initial naming

In the WTCR tool, the information entered on country of collection/species identity/date of first collection automatically creates a unique identifier for each colony. A unique identifier has been used by various systems. This is to be used at the original site, used in other databases and transferred with any material sent to other labs.

The abbreviations have been proposed as[86]:

CC = Country code, using the ISO and UN two letter country code
Gs = Genus species initials
TTT = Strain code
P = Split letter (if necessary), for example A, B, C
YYYYMMDD = Date identified families first transferred to cage

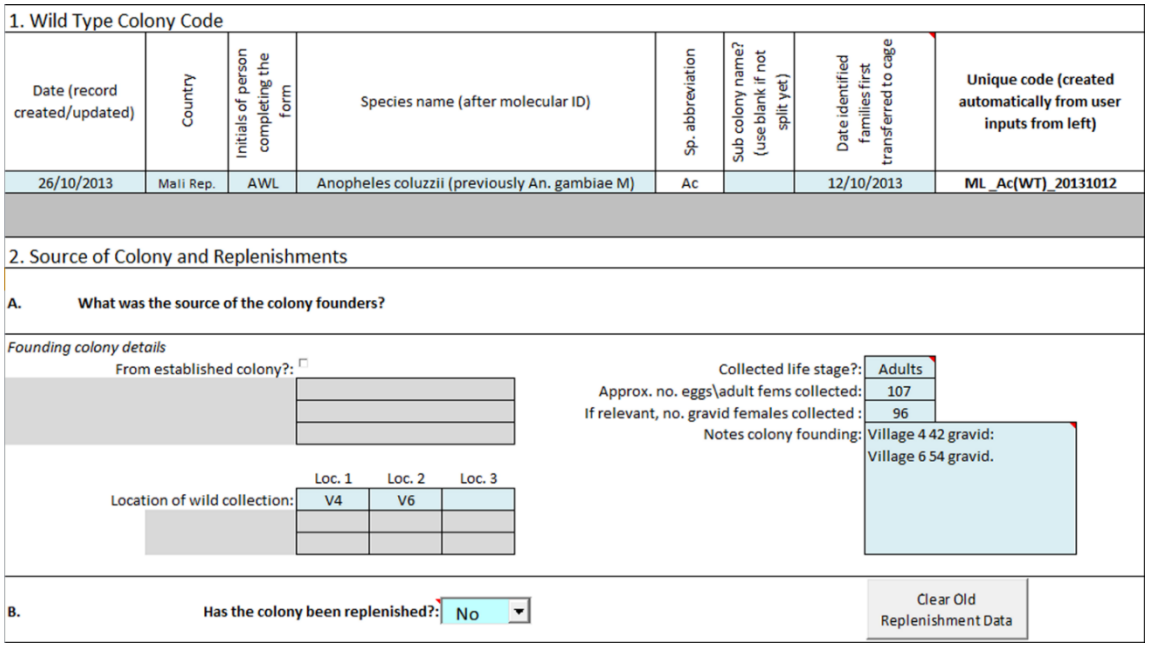
This would result in a unique identifier something like this: CC_Gs(TTT)P_YYYYMMDD.

[85] Taken from Quinlan et al. (2016d). Adrian Leach created the Excel version of this form, which is derived from a similar one that was bespoke for Target Malaria. The specific villages or site names have been removed, but would be added back according to the project, for use by others.

[86] The only exception for two letter country codes adopted by British users has been to use UK for the United Kingdom, rather than GB for Great Britain because of the potential for confusion with Gabon (GA). Needless to say, this is not so relevant in terms of field caught mosquitoes, but could arise for laboratory sourced colonies, with no record going back to origin. Also, if more than one lab in a country uses this system, something more specific than the country should be employed and the system should be agreed by all labs working with it.

The two letter mosquito genus potential conflicts were resolved by assigning Ag to *An. gambiae* s.s., not the complex. Decisions should be made based on the relevant species in the area. For example, *An. coluzzii* is Ac, then *An. coustani* could be Au. If a sample is identified only to the level of the *An. gambiae* s.l. (complex) it is not as useful for identity records, but could be called Ax.

The strain code as a this three letter code was developed specifically for the Target Malaria project based on characteristics exhibited, such as sterility, and should be substituted for other projects by their pre-determined choice. Some may choose to use the type of insertion or other information, but the traits exhibited might be of more interest to a regulator visiting an insectary. In all cases, aliases or shorter names are often used in labs and these should be noted against the unique identifier code.



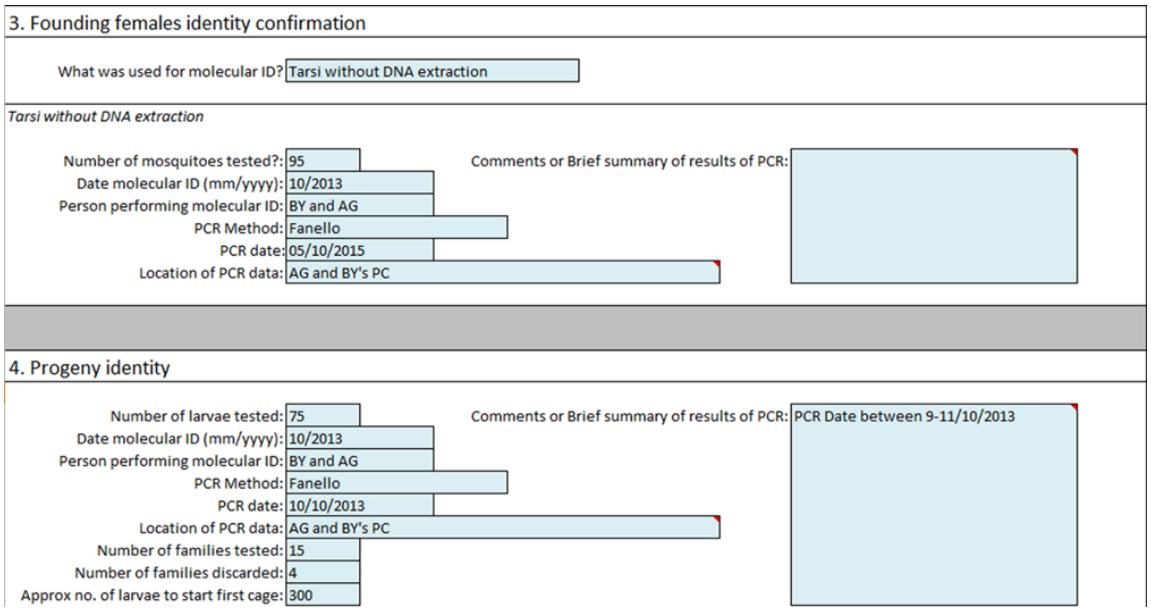


Figure 9.1 Screen shots of a generic Wild Type Colony Record template

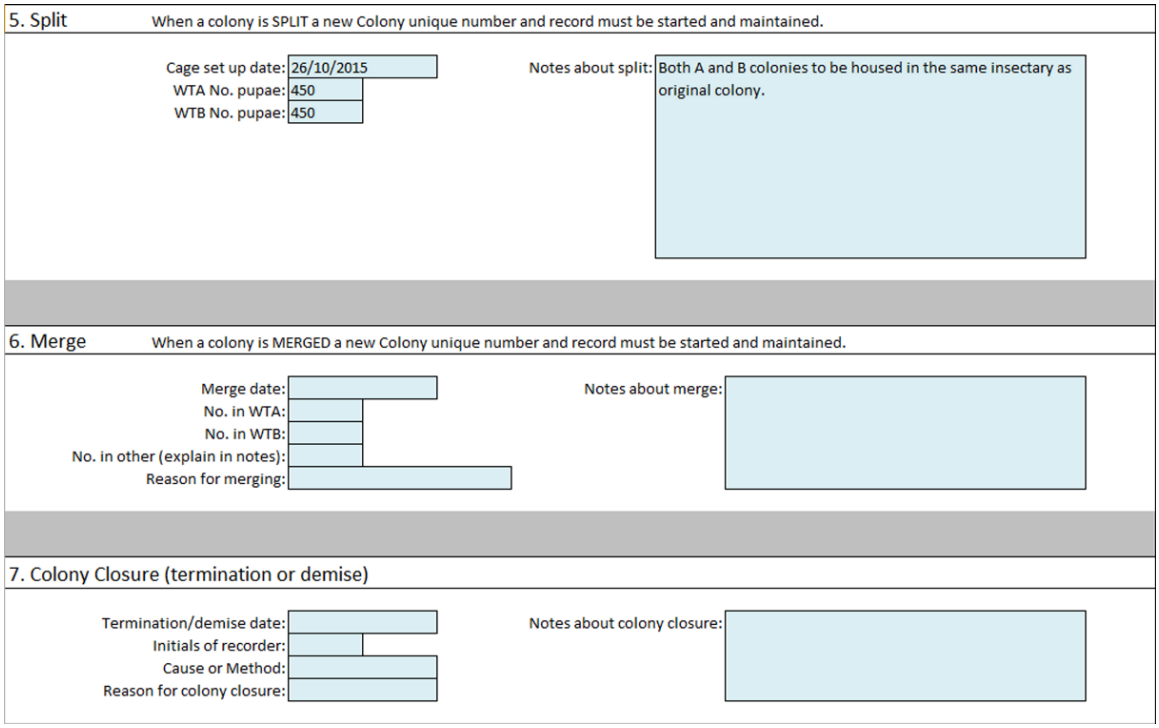


Figure 9.1 Screen shots of a generic Wild Type Colony Record template (continued)

The unique identifier generated by the WTCR should be recorded on all documentation from that point forward, to link each note to the colony identity. For example, that identifier is what is used in the initial registration of colonies in the Target Malaria ongoing Insectary Database. This registry list could be posted on the door of a facility or in the entry, for verification by regulators or institutional safety officers, for example, of the colonies in the facility. If colour tags are used in colony identities (e.g. for marking cages), the legend of registered colonies also could be colour coded. This is especially beneficial when nicknames or aliases are used on a daily basis by the staff, in place of the unique identifier or the full name of the strain. All of this information appears in the first section in Figure 9.1.

Dropdown menus can be employed in Excel based templates, to avoid mistakes in writing. More options can be added over time to these, and changes do not affect the cover page of the WTCR. These menus are shown, for a generic case, as Figure 9.2. A new user would enter the actual names of Villages or other land areas if making several collections, or manually enter the information each time. Additional methodologies for identity confirmation, such as by creating assays to use with a loop mediated isothermal amplification (LAMP), would be added or replace what is on these dropdown menus, as would the details of the sites (under point 2 in Figure 9.2).

Sections 5 and 6 of the WTCR shown in Figure 9.1 show a split and merger. When the population of this colony reaches an agreed level, for example approximately 2000 male and female adult mosquitoes, some labs will split the colony into two separate sub colonies to allow for expansion and different uses of the colonies. This should be done at the pupal stage and the split is recorded in the WTCR. Equally, if numbers fall or a study period is ended, the colonies originating from the same field caught individuals could be reunited and that would be recorded as a merge. (This is not the same as replenishing from a different collection time and place.)

After the identity of the colony is established, the completed record should be saved as a file named using the Unique Colony Identifier generated from the data entered, with the date the file is saved (yyyymmdd) as numbers at the end of the file name. This would make the first file name the same as the identifier: CC_Gs(TTT)P_YYYYMMDD. If any changes are made to the record, however, the date changes in the file name according to additions to the record, although the unique identifier date does not (unless an entirely new colony is set up at a different location). Although this date format could be confusing for some national practices, it is hoped by putting the year first it will call the attention and avoid transcription errors.

The creation of a new file (or same file, but with a new date) for the WTCR at the time of each significant event should not result in numerous changes. To ensure continuity and clarity, each new record could be added as a new sheet on top of the existing Excel file, with the new information added and a file name reflecting the latest date of changes. Therefore, only one record is saved because the previous sheets could be labelled (at the sheet tab, bottom of the Excel file) with their associated date for change, even though not appearing in the file name.

The addition of a sheet on the Excel file to list exported and imported material for establishing colonies is another proposed enhancement. The content for this sheet is proposed as:

Export

- Date of export:
- Export to: (both person and location)
- Colony code:
- Approximate numbers, volume or weight (with life stage written out, e.g. 2 grams of eggs)

1. Wild Type Colony Code

Country	Abbreviation
Angola	AO
Benin	BJ
Botswana	BW
Burkina Faso	BF
Burundi	BI
Cameroon	CM

Species name	Abbreviation
Anopheles arabiensis	Aa
Anopheles coluzzii (previously An. gambiae	Ac
Anopheles gambiae ss (previously An. gaml	Ag

Sub-colony
A
B

2. Source of Colony and Replenishments

Founding colony details

Still in existence?
Yes
No

Collection life stage
Adults
Eggs
Larvae

Colony been replenished?
Yes
No

Replenished from where?
Established colony
Field collected
Both

Village	Village. ID
Village 1	V1
Village 2	V2
Village 3	V3
Village 4	V4
Village 5	V5
Village 6	V6
Village 7	V7
Village 8	V8
Village 9	V9
Village 10	V10
Village 11	V11
Village 12	V12
Other	LATLONG

3. Founding females identity confirmation & 4. Progeny identity

How?
Tarsi without DNA extraction
DNA extraction

PCR method
Fanello
Wilkins (IMP)
Santolamazza (SINE)
Fanello & SINE
Wilkins & SINE

5. Split

No Dropdown

6. Merge

Reason for merge
Low numbers
Other (explain in notes)

7. Colony Closure (termination or demise)

Method
Alcohol spray
Boiling water
Desiccation
Freezing
Pesticide
Starvation
Drop in numbers (add notes)

Reason
Biosafety incident
Contamination/mislabelling
End of study
Genetic drift

Figure 9.2 Screen shots of dropdown menus for a generic Wild Type Colony Record template

[a] Taken from Quinlan et al. (2016d). Adrian Leach created the Excel version of this form, which is derived from a similar one that was bespoke for Target Malaria. The specific villages or site names have been removed, but would be added back according to the project, for use by others.

Import

Date of import:

Import from:

Colony code:

Numbers (volume or weight):

Quality (e.g. survival):

These and other details of the terms of a MTA may be added easily with the format of an Excel template. Other possible details could include the name of the courier or other method of transport; use of temperature loggers or other monitoring of conditions; and reports of the outcome of transfer as far as successful establishment of a daughter colony or, if not, the reasons that prevented it.

Such a format will vary if used in a version of Excel for French or other languages, and might best be left in an English version with supporting notes in the local language rather than trying to make a new template for each.

9.4 Accommodating variations

Over the course of validation, a number of scenarios arose or were anticipated regarding management of wild type (field collected) colonies. One variation already encountered in the sites where the tool was validated is when the lab is using non-transgenic strains which are not local wild type (not collected in the field in the same country). As the coding system applied for the wild type colonies was already established, the same approach was applied to strains imported from other labs.

In this instance, the following was proposed:

1. The country code should refer to where the colony was exported from (not where it was imported to) even when not a field caught strain, thereby potentially allowing for strains with country codes of Europe, for example, and
2. The date would refer to the date of first transfer to a colony maintenance cage in the founding country (not the date of shipping nor reestablishment in the new location).
3. The file name with its date would show the new event of establishment in a different location but the WTCR would continue to include the previous records on the life of the colony.

In this way, as long as the genetic composition is similar the colony is shown as a daughter colony of the originating field caught colony. If altered through transgenesis or other means,

the WTCR is no longer applicable. This example shows the utility of the framework, however the meaning of some parts of the code then differs. A table similar to Table 9.2 should be maintained by any lab using the tool and system, so that variations are recorded and followed to the same degree that an SOP would be documented. It should also be recognised when the colony is so far removed from the initial establishment that the WTCR is no longer relevant. Therefore, the WTCR was left as only documenting the pedigree of a new wild type colony at the point of field capture onwards, when the information can realistically be expected to be forthcoming.

The tool can only provide useful information when the data is available, however. Many labs are maintaining stock not originally well documented in terms of field capture and establishment, as already noted, and with only vague references to original colony establishment. For example, Mopti strains are presumably all from the Mopti area in Mali but this does not indicate which collection initiated colonies for a lab-reared strain and for how long it has been in a lab setting, which may affect genetics and quality. G3 strain has origins from collections in Gambia in the 1970s, at a time when *An. gambiae* s.s. and *An. coluzzii* were not distinguished and both molecular forms M and S were included in the collection. In such cases, it is difficult to even name the species of this lab strain. Despite these limitations, the WTCR is a superior system to most in use.

Decisions on how to accommodate these in the tool are recorded as a series of questions in Table 9.2.

Although such variations tested the limits of the tool's use and resulted in it being not entirely consistent, there do not seem to be problems that cannot be overcome with minor resources for revision. The general premise suggested by this experience is that, with each new use of the tool, such assumptions or variations are documented in the instruction booklet and/or shared with the creating group (the researcher of this thesis, in this instance) for consideration of any 'knock on' effect of additions or changes. It is hoped that asking for this type of collaboration would not discourage the tool's revision and use.

9.5 Ongoing data requirements

The researcher also took part in developing specifications for an ongoing Insectary Database that addresses the following objectives:

- A current list of colonies and strains at any given location, and a record of past colonies (if backed up)

- An additional record of who is carrying out key activities at any given time, that is more accessible than reviewing hand written lab notebooks
- Quality control of the colonies, using indicators of each generation to highlight any changes in the general health of the colony
- Stability of the genetic trait, for example in this instance by monitoring the ratio of positive and negative trait individuals and male/female ratio
- Traceability for identity and any key characteristics of the strain for any studies, portions of the colony transferred or over time at the same site

The Target Malaria database also includes data showing the effectiveness of containment measures, in this instance by noting any adult flying mosquitoes, which suggests either these mosquitoes are getting out from the primary containment of mesh cages or some other poor practice, such as not entirely devitalising surplus pupae that have been disposed of inside the lab. Finally, because this database can provide an estimate of the number of mosquitoes in the insectary at any given time, their life stage, approximate number of adult females and whether recently fed or not, it supplies data for risk models and can inform fairly precisely what might occur if a catastrophic event led to escape of research mosquitoes.

Results of periodic and routine tests, such as for insecticide resistance, may also be managed in such a database. It is only those 'one off' events about the life of the colony that may be lost in this type of ongoing data management and should be added instead to the WTCR.

Such databases can also provide a reminder (e.g. an automatically delivered email), or visual gap, of data that has not yet been entered or stored and may be past due, of data that are outliers and worth checking, of trends in the data that might otherwise be missed, and over time the basis for setting thresholds, i.e. at which point the data shows an unacceptable situation, for example, if the size of mosquitoes becomes too small.

The choice of what should be included in the database is covered to a large degree by Mumford et al. (2018), although some additional information fields are included. There is also an 'information dashboard' to show a graphic representation of certain indicators and support rapid comprehension and response. The bespoke database was created by EarthCape (https://earthcape.com/) based on specifications from discussions among researchers (primarily M.Q. Benedict, A.W. Leach, J.D. Mumford and C.M. Collins) and the researcher of this current study, and was commissioned by and is implemented by Target Malaria.

Table 9.2 Decisions related to contents, role and coverage of a Wild Type Colony Record

Question or problem	**Answer or comment**
We moved our long standing colony into the new lab for research. Does that comprise a new colony?	Yes. If a WTCR did not exist for the original colony, and there is information about the source of the original lab colony, there is a place to record that the new colony is from that originating source. This would hold true for import of a colony from another site (although see below on naming that colony). It would be best to start with full information by beginning with establishment from the field, but if a colony is started from a strain transferred from an existing lab one, it is useful to secure as many details as possible for the record.
We collected in more than one place to have enough mosquitoes as founders for this colony, is that more than one WTCR?	It is not ideal to have multiple places of collection, but if within a very short time frame this may be done to establish a single colony. Therefore, it would have one WTCR, but both locations should be noted as source locations. If there are more than a few days or a few miles separation between collections, this might best be considered a replenishment.
The colony was not large enough after a few generations so we added some more. Is that a new colony, with a new WTCR?	Replenishment of the colony will change the genetic identity. However, this may be represented by using that tab instead of starting over as if it were an entirely new colony. The key question is whether the added mosquitoes are similar to those already in the colony. Details regarding the collection site should be recorded, and the step process for confirmation that progeny are limited to only the species of interest, should be followed.
We split the colony for the purpose of introgressing it with a modified strain. Does that make it a new colony?	No. The colony split should be recorded, but the existing and surviving wild type colonies are from the same field collection despite divergence of use. It might be noted that best practice would be to alternate using each split of a colony (i.e. A and B) if introgression or back crossing is the purpose, to ensure no genetic deviation occurs.
After splitting, we found we had to merge the colonies back to the original single one. Is that a new WTCR or is one needed?	There is a place to record merges of colonies that had previously been split from the same one. It is a new version but the same colony record (same unique identifier).
A portion of the colony is removed to conduct a study. Is this considered a colony split?	No. This portion will not be recovered and does not affect the future or identity of the surviving colony. It was, however, representative of the colony at the time of the study. For example, removing some for an insecticide resistance study does not alter the colony identity, but could provide information to add to the remaining colony's WTCR in terms of that factor.

Question or problem	Answer or comment
We carry out a confirmatory genotyping of the colony every year to ensure no contamination has occurred. Is it considered a new colony after that confirmation is done?	No, if the identity is as expected it is not a new colony and the same WTCR will continue on. This is following the filtering process, but with only a few individuals; the rest of the colony carries on with the assumption that the sample checked is representative. The WTCR has a place to indicate that the confirmation was done, however, and one should always note the method too. [If the testing shows the identity is NOT what was expected, the entire colony and all study results should be re-evaluated.
Wild type material is transferred to a new location. Does this newly established colony require a new WTCR?	No. The WTCR will ONLY be completed in the country where the wild type material was field collected (and presumably first colonised). The unique identifier code for that strain, which is generated by completing the WTCR, will be used in all subsequent colony and cage records, no matter where the colony is held. Therefore any imported wild type strain (originally collected in other country) will maintain the country of origin as part of its unique code. For projects or initiatives sharing data from more than one site, using the same wild type colony, the location code should clarify which sub colony is being discussed. One could add a split letter code if desired, but this is not suggested.
Wild type material is transferred to a new location. Does this newly established colony require confirmation of identity?	This would depend on two factors. No, if the identity from the exporting lab has been confirmed over time. The receiving lab may wish to have the results of the last verification in the WTCR sent and on file and then continue with an annual filter screen. Yes, if there is mixed use by various projects or PIs in the exporting facility, or there is reason to fear that some mixing might possibly have happened at the time of colony establishment in the new location. This is more likely to be through mislabelling of egg dishes, larval trays, etc., than from free flying mosquitoes mating to cause strain contamination, but both failures of systems are a possibility.
Transgenic mosquitoes that originated from the colony described in the WTCR will be shared. Do we use the WTCR for shipping and informing the new site?	Once transgenic traits are introgressed to a strain, even though it was collected in the field as WT, it no longer is recorded in the WTCR as it was originally structured. A colony unique identifier is generated in the ongoing insectary database, in the registration section. Actions taken with that colony are recorded in a Certificate of Analysis for shipping and the ongoing database of insectary indicators. The WTCR was found to be a useful record format for some strains such as the colour variant (natural mutation) used for training.

9.6 Conclusions on using the WTCR for product stewardship

The WTCR was trialled by two West African and one East African labs and proved to be an effective addition to the best practices for confirming appropriate establishment of colonies and documenting the events in the life of the colony to the level of product stewardship. The issues encountered resulted in the question/decision process documented in Table 9.2. It was only through attempted use of the tool in real lab situations that some of these issues arose.

The tool was presented at the 3rd Annual Meeting of PAMCA (Quinlan et al., 2016d) under the theme of *Control of Mosquito Vectors: Opportunities & Challenges in the 21st Century*. This was presented as a poster (shown in Appendix 3) with the opportunity of follow up to request an electronic version of the template. The same approach of sharing the Excel based file with the template will be used until there is an appropriate website or other organising mechanism to share such tools more broadly.

Broader use of this tool for record keeping over the coming years can feed back to enhance the tool, and provide a pedigree for genetic background starting with field records, to support later review of research and eventual uptake of novel control strains. A harmonised tool now will make future evaluations and exchanges of material much easier.

The WTCR was validated over the course of approximately two years, from the initial Word based form through to the Excel based template presented in generic form in Figures 9.1 and 9.2. The range of decisions related to the contents, and the purpose, of this record is captured in Table 9.2, from the perspective of the users. The WTCR template belongs to Target Malaria and can be obtained from the research consortium.

9.7 Summary on maintaining identity of mosquito strains for product stewardship

Historically, insufficient documentation has been kept for mosquito colonies used for studies or shared among laboratories, and ambiguity regarding the strains is the result. In the future, when living mosquitoes are the product to be used for field campaigns, but especially when it is a transgenic strain, additional identity checks and related documentation will be needed to support the evaluation of studies leading up to deployment. Identity maintenance also is generally a requirement under regulations or the terms of import and study permits.

The researcher worked with colleagues to propose a more detailed system for documenting colonies founded with field caught mosquitoes. This template has been revised to

accommodate a number of situations encountered during mosquito production and has been tested to be fit for purpose and generally user friendly. In addition, the researcher contributed to development of a bespoke system for recording factors indicative of quality and identity maintenance for laboratory mosquito rearing and studies.

These data support what has been defined in Chapter 7 as colony utility, but also contribute to defensible science. The output of such databases may directly supply data for regulatory applications and reports, research publications and product stewardship during the process leading to inclusion of an intervention in a regular mosquito control programme.

In response to the subquestion, **Is a product stewardship approach to identity maintenance and data management necessary to support decisions about safety and efficacy in containment studies, moving towards field studies?** it appears that various initiatives have reached the same conclusion. Additional details on colonies *are* needed in order to achieve reputable, repeatable and reliable results of studies. The concept of product stewardship remains to be defined more fully, however, in light of what that entails for the novel interventions discussed in this study. The aim will be to agree what data are critical without burdening lab workers with unnecessary data collection.

In the meantime, study results are the foundation of significant decisions regarding not only the progression of particular strains to field use, but also of accepting particular types of genetic strategies overall. Therefore, decisions to progress along the stepwise approach should be properly supported by adequate data and subject to third party or peer review. The link between using harmonised standards within an insectary and product-level stewardship of all data and decisions leading to progression to the next step is suggested by Figure 9.3, as part of a larger Theory of Change developed by the researcher. These good practices and data then support the longer term outputs of having an established freedom to operate when using potentially patentable material or other forms of IP protection, providing details for regulatory applications and as part of publishing under peer review.

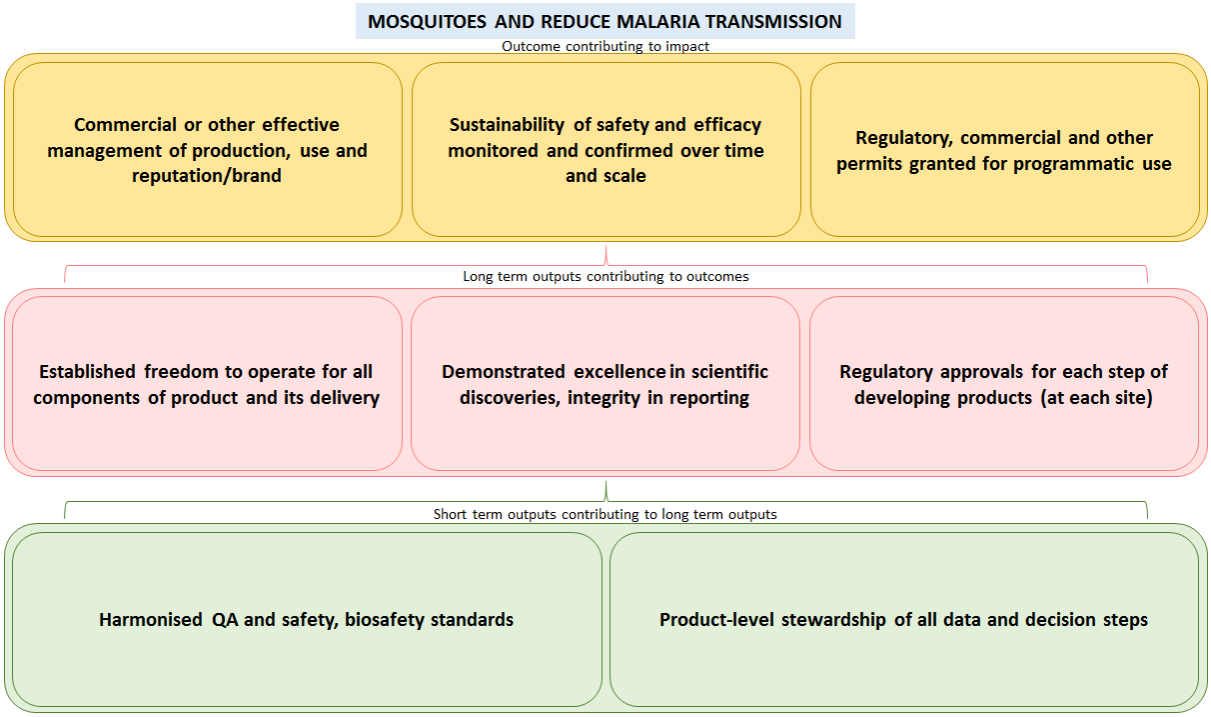


Figure 9.3 Short term outputs leading to freedom to operate and supporting excellence in reporting, and regulatory approvals for delivery of novel interventions for vector control in DEC

The aspects of integrity and excellence in research rely on documented evidence as the basis for all decisions. The outcomes of obtaining permits and having a commercial product that can be registered, for example, are supported down the line. Particularly in the case of required monitoring for safety and efficacy, these background data are important as benchmarks for comparisons over time. Data choice and selection of indicators should be reviewed routinely, however, to ensure that the resources going into their collection and management are efficiently employed and that the data has proven effective in the objective (Hicks et al., 2015), such as for maintaining identity of the study organisms over time through to the point of deployment.

Chapter 10. Maintaining Readiness and Biosafety

10.1 Reviewing the context

Chapters 1 and 2 explored some of the challenges involved in delivering novel interventions for vector control and in conducting research in DEC contexts, in particular. The importance of individual researchers in attracting partnerships has been noted, and was confirmed in an online survey by the researcher (reported in Chapter 5). Capacity building and assessment often focus on individuals, building their skill set and credentials over time to ensure their ability to carry out assigned work. In Chapter 5, however, the researcher presented a range of materials and experiences to put the individual researcher into a broader context of the DEC research team and international partnerships.

The research subquestion addressed in this chapter is: **Can biosafety objectives and quality assurance in the containment phase be achieved more effectively if using harmonised procedures and tools for research in DEC settings?**

The response to this question was based largely on analysis of earlier chapters and literature review. The researcher and others (Quinlan et al, 2016a) gave evidence that regulators are supported in carrying out their specific mandate by using more structured approaches to public input and for socio-economic considerations, in particular. One could ask, therefore, how consistent frameworks would support the researchers in managing a variety of information sources.

It is well established that harmonised procedures are critical to maintain safety and what the author calls ‘colony ulity’ (Quinlan et al., 2018a) of mosquitoes in a lab setting. That initiative worked through joint discussions to agree on the basis for the SOPs and the performance outcomes. Imposing harmonised procedures and tools from external sources (from outside of a particular research team, not necessarily from outside of their country), however, can lead to lack of engagement with them. Adelman et al. (2018b) have observed as well that relying on SOPs that are perceived to be too onerous can be counter-productive to the biosafety objectives sought, since deviations will emerge that are not recorded leading to a gap in practice. Instead, with each new biosafety challenge or entry of new personnel, SOPs should be revisited; the outcome of adoption of a new SOP should be monitored against the objectives as well (Adelman et al., 2017b: e.g. Fig 1, Box 6, p.445-446).

This chapter provides further discussion of capacity of the research teams and the process of transferring ownership of novel technologies – either literally through transfer of IP rights or

through increased decision making and leadership while maintaining regulatory compliance, biosafety and excellence in science. To support discussion of these concepts, the researcher selected definitions of capacity, competency and culture from literature, as reported in Box 10.1.

Box 10.1 Defining capacity, competency and culture

There are many definitions of these terms with valid perspectives. The researcher has chosen to use them in this way:

> **Capacity** – the ability of an individual or a group to carry out their professional role effectively (adapted from OECD DAC, 2006).
>
> **Competencies** – Measurable or observable knowledge, skills, abilities and behaviours that are critical to the successful job performance (FAO, 2010).
>
> **Culture** – Everyday practices, norms, values and beliefs that permeate behaviour in professional relationships, teams and organisations (adapted from Drago-Severson & Blum-DeStefano, 2018a).

It is interesting to note that all of these definitions relate to both individuals and teams. Individuals 'think, feel and act' differently in different groups or settings (Drago-Severson & Blum-DeStefano, 2018a: n.p.) making the culture of the organisation, laboratory or other team of particular importance when planning for capacity enhancement.

A continuing challenge noted in international partnerships is to make the capacity gained a legacy of the collaboration, rather than a short term contribution, somehow owned and owed to the initial lead partner. An even further reaching objective is to instill a culture of biosafety and quality assurance in a containment facility. The researcher started from an assumption, however, that establishing a work culture remotely is even more challenging than to do so from within the work environment. The researcher drew on studies in the use of feedback to adults in educational systems, as well as biosafety literature to explore these issues.

10.2 Capacity, competencies and culture

10.2.1 Research and biosafety capacity

One of the key factors for delivering facilities readiness for studying novel technology is the capacity of the research team that will be conducting the safety and efficacy studies in containment. In short, there is a need for capacity of an entire group, beyond the individual level.

The Target Malaria insectary teams worked with the researcher to adapt existing risk assessment methodologies (e.g. OIE, 2015) to insectaries in containment. They used visiting experts to review the risk mitigation measures, and cross-site discussion of these risks and the appropriate measures for each locale. Consortium or project-wide policies, SOPs and databases were also developed across the consortium, with broad participation to support delivery of consistent administrative controls. After discussion of common factors, each team drew up site specific emergency preparedness plans, including for rapid termination of the colonies. The focus of the contingency planning included highly likely scenarios, such as electricity outages, as well as the highly unlikely but of potential significant impact scenario of an accidental release of the research organisms into the area surrounding the facilities. Plans were made by each local team for notification of an incident or emerging crisis, and how and when to secure assistance in facing challenges (discussed further in Section 10.4).

Visits to similar labs allowed training in specific techniques, but also laid foundations of trust among researchers throughout the consortium. Follow up visits by those experienced with the technology and techniques and routine group calls to discuss particular issues contributed to the atmosphere of shared learning. Although technical contingencies were important, this particular international research consortium found that training in communications was equally valuable to instil new skills for insectary staff.

Capacity is made up of relevant and proficient competencies not only for compliance with biosafety requirements, but also to achieve reliable study results and preserve a record of activities and findings that will endure over time, as discussed by Quinlan et al. (2018a). Competencies may be in technical areas, such as the ability to design and interpret results from studies, but also comprise skills, abilities and behaviours relating to, for example, performing necessary tasks reliably when under pressure. Those working in capacity development have long since understood that technical capacity is only one aspect of the ability to carry out successful work (FAO, 2010; OECD DAC, 2006).

Capacity also is needed at the various levels or contexts influencing a research team (referring back to those challenges shown in Table 2.1). Many analysts of health related research argue for a more holistic and system-wide approach to finding partners and transferring technologies, particularly when working with institutions in more resource limited settings. For example, Njelesani et al. (2014) propose that capacity of lab systems is based on simultaneous preparedness of individual, organisational, national, regional and international aspects and influencers, much as the current study considers issues at the micro, meso and macro levels.

Araya-Quesada et al. (2010) lay out some of the ways that individuals, groups and institutions may be trained in biosafety. Keeping the focus within the lab, the Centers for Disease Control and Prevention (CDC) and the Association of Public Health Laboratories in the USA prepared an analysis of the required capacity for biosafety laboratories at increasing biosafety levels, and for increasing levels of responsibility according to roles (Delany et al., 2011). They identified four domains needing training, review and monitoring: identification of potential hazards, hazard controls, administrative controls, and emergency preparedness and response.

Recent benchmarking of a safety culture (CDC, 2011) has indicated that those who are supervised on safety measures by the PI or insectary manager are less likely to have incidents (Schroder et al., 2016). This culture 'by example' applies to collaborating laboratories in the North as well. Catino (2008) describes the cultural differences between seeking to assign individual blame versus looking to identify weak points in organisational function in response to an incident. Reflection on the organisation and possible learning is the opposite of the instinct to blame, which 'is the instinct to find a clear, simple reason for why something bad has happened' (Rosling et al., 2018:p.206).

The role of a team or organisation in creating a culture of biosafety is harder to define. Biosafety compliance should be on equal footing with workplace safety and shared among those authorised to handle GM mosquitoes directly. It should be acceptable for any member of the team to call into question any activity or task – planned or observed – that could lead to non-compliance. Creating a 'blame-free' environment and safety culture are critical components of capacity for facilities readiness.

Researchers from discovery or development labs outside DEC require awareness raising of the operational issues and working conditions of the institutions in the DEC, which requires a shift from provider of information to respectful discussion. Cultural differences may include avoidance of pointing out individual errors or perceived faults in front of colleagues, something the researcher has observed as particularly unacceptable in developing country contexts. This ties in with research establishing trust and respect, or indeed a perception of 'safety' and 'dignity', as critical preconditions for capacity enhancement (Drago-Severson & Blum-DeStefano, 2018a), particulary in situations of perceived power imbalance.

Box 10.2 outlines findings from the education sector regarding the relationship of groups of professionals working together with feedback as a learning method. The researcher considered if further lessons could be drawn from outside of the laboratory research sector.

Box 10.2 Learning from mistakes

A comprehensive study of professionals in education systems identified a series of practices that encourages receiving and learning from feedback (Drago-Severson & Blum-DeStefano, 2018b). These include the simple act of regularly scheduled meetings to create opportunities for feedback rather than waiting for an incident to require interaction. Feedback is offered in a manner consistent with the personality type that the person in question demonstrates, always seeking to make it a learning experience and to offer ideas for how to achieve improvement. Another practice was to clarify expectations. The research was aimed at educators and highlighted the need to train them to play this role for others. An 'infrastructure of collaboration' is described and considered another pathway to resilience in the work place.

Without the preconditions of trust and openness in a work team, that acknowledges each person's inherent value, it is difficult to establish a culture that promotes learning over blaming (Drago-Severson & Blum-DeStefano, 2018a). Cox & Cheyne (2000) identified the impact of subcultures in gaining broad participation in safety initiatives. Their assessment tools showed how organisational objective indicators, such as a safety policy, are only one part of the culture, with perceptions of the organisation and individual perceptions of those impacted being other critical components of the overall culture.

The importance of group interaction has been further demonstrated by results that show individual intelligence of group members is less of a predictor of lab and field problem solving outcomes than is social perceptiveness, or understanding the others' perspectives (Williams Woolery et al., 2015). They identified both bottom up (composition of the group) and top down (processes such as ensuring all members speak and are involved in discussions) ways to improve collective intelligence. Such simple practices as regular group meetings and allowing time for discussion create a context that is essential to benefit from mistakes or incidents.

Psychological safety was one of the key indicators of higher performance among multi-cultural and globally disperse groups that worked together in another study (Glikson et al., 2016), The collective intelligence of such a group was only allowed to achieve higher performance in an atmosphere of safe communication.

10.2.2 Organisational policy compliance

Analysis of errors in the aviation industry has shown that beyond faults in individual performance, which only increase under the stress of externally caused incidents, it is the deficiency in team interaction that most frequently leads to serious events (Műller, 2004). One review of organisations requiring high reliability (Provera et al., 2010) points to a culture of considering the entire system rather than assigning all responsibility to individuals. Appropriate reporting mechanisms, debriefing opportunities and dissemination of corrective actions

demonstrate a commitment to learning from incidents and improving work place practices. This study describes the continual, incremental process of learning by explaining that: 'The no blame approach is about 'nurturing' small errors and near-miss incidents…to eliminate the need for radical and traumatic learning' (Provera et al., 2010: pg 1059).

Methods for embedding general policy compliance at Imperial College London include new staff induction, use of and training in risk assessments, review and certification of specific skills, and periodic lab inspections against an institutional framework based on national legislation and regulation. A DEC research partner may have their own approach to lab procedures, emergency preparedness, stakeholder engagement, data collection and management, sharing of IP and materials.

In general, the funding agency imposes a particular set of expectations, or even contractual terms, on project activities. Other types of policies imposed by projects or institutions on research partners may include: use of branding, particular acknowledgement for funding, publication review prior to submission, and information embargoes based on the project's communication plan. The tension of competing objectives that this may cause is already noted.

Organisational structures to encourage accountability always intermesh with the individual's experiences, capacities and perceptions of the culture. The researcher sought to link these findings of others to the concepts relating to determining a point when one can proceed with the next step, for example facilities readiness as developed under her study.

10.3 Disruption to the state of readiness

Maintaining biosafety and facilities readiness implies working through any disruptions to these states. Because 'facilities readiness' is multifaceted and determined based on the nexus of several aspects at a particular point in time when a decision is taken, any change or disruption could potentially revoke the status. When these factors no longer conform with the concept of 'readiness', this may call for action on the part of the research teams to declare a disruption and take remedial actions. Depending on the significance and impact of the disruption, realignment might be achieved through corrective actions or additional aspects being factored into a redefined, new state of readiness. For this chapter, existing literature was used to develop a learning system using disruptions to readiness as a source of potential improvement of the system, beginning with reporting of disruptions.

10.3.1 Defining an incident

In many laboratories, incident reporting is used as the mechanism to report, describe and begin to address any disruption to the state of readiness of a facility and will need to be in place. The term 'incident', however, should be clarified as to whether it is uniquely a hazard or something negative that *has* happened, or if it will include what some call a 'near miss'[87] or something negative nearly happening. To break this down in terms of risk, using the more extreme examples:

Risk = the estimate of the probability of a hazard occurring ×
the consequences of it occurring

Incident =

1. The hazard occurred (100% probability), and the predicted consequence occurred
2. The hazard occurred (100% probability), but the predicted consequence did not occur or was prevented
3. The probability of the hazard occurring increased markedly, but it did not occur and therefore consequences were avoided
4. The magnitude of the predicted consequences increased markedly, but the hazard did not occur or some other mitigation prevented the higher consequences

Hypothetical examples of the above include: (1) the hazard of variable water quality in the lab was identified, the water was contaminated and the colony died – or (2) the hazard occurred and the colony quality dropped but it survived as a whole. Or, (2) untreated waste was removed from the facility accidentally but there was no living material so the mistake could be corrected upon discovery, with no consequences (other than possible regulatory ones). (3) key pad failure meant that someone could have entered the containment facility, but no one did during that fault. Or, number of free flying adults was observed to rise precipitously in the lab, but there was no strain contamination found after testing and no one contracted malaria, as shown by tests. Along the same vein, (4) outdoor traps found a population of *An. gambiae* now surviving around the insectary, so that any escape of a lab mosquito carrying some inheritable trait would likely lead to mating and persistence in the environment, but there was no escape or release due to the ongoing containment measures. Since the likelihood of

[87] The Health and Safety Executive (HSE) of the UK classes 'near miss' as 'an event not causing harm, but has the potential to cause injury or ill health', including 'dangerous occurrences'; and 'undesired circumstance' as 'a set of conditions or circumstances that have the potential to cause injury or ill health' (http://www.hse.gov.uk/toolbox/managing/accidents.htm). 'Dangerous occurrences', in this context, is a term based on reportable adverse events defined in regulations. These together could be another guide to classifying what to include in an incident report for a specific facility.

something happening could be all the way up to 99% and still not occur, due to that 1% probability of it not happening, there is always some ‘luck’ involved.

In reality, it is more likely that the changes in risk are along a continuum (e.g. the predicted consequence occurred but at a lower magnitude than predicted), rather than not occurring or occurring at the worst case level of impact.

Most cases of non-conformity with procedures in a lab will not result in the outcome of concern over a short period, until brought back into conformity, but it will increase risk when considered over longer time periods. Not using proper personal protective equipment (PPE) is an example where some researchers gain a sense of false security that the consequences will not occur because of the number of times they do not comply yet are not infected or injured. For scenario (4), if a lab worker is unknowingly working while infected with a resistant form of malaria, the consequences of in-lab transmission may increase from that predicted but by following management procedures the pathway to that harm does not occur. This highlights an important point that risk management measures should buffer the outcome of many types of incidents and may have an effect on risks for which they were not designed or implemented.

It should be noted that an increase in the estimated probability of a hazard occurring or of the predicted magnitude of the consequences implies an increase in risk, unless additional management has been employed. It is possible, however, that the incident in question has raised these only during a short term situation (what the Health and Safety Executive (HSE) might call the ‘undesired circumstance’) that does not alter the original predictions. For example, if an unauthorised person enters the premises (which has been identified as a possible pathway to harm, rather than a hazard in itself), the probability of a number of hazards would increase but only during the period this situation goes unrecognised. If new measures are introduced to prevent future similar incidents, what could be a ‘near miss’ will become a lesson learned leading to improvement. This analysis of potential disruption highlights conceptually complicated, but in general common sense parameters around the state of readiness and when it is threatened or lost. Research teams should consider their own national regulations regarding worker safety, for example, to find appropriate definitions and categories to describe or categorise incidents. When a common understanding of the term ‘incident’ is achieved and when all of the above types of scenarios are covered, a useful incident report template may be developed or adopted for a facility working towards the ‘readiness’ point.

To elaborate an advance plan for responding to disruptions, the researcher proposes a set of objectives (Table 10.1) for creating a mechanism that facilitates learning rather than only

reporting from such instances. Again, starting with their own objectives will allow a research team to adapt the proposed frameworks to their own situation, keeping in mind that this remains a new practice as yet under development. (As Kimman et al. (2008) stated, there is no consensus on how best to evaluate effectiveness of biosafety measures and many regulations are not clear on what level of protection is sought by the measures imposed.)

Table 10.1 Objectives for a learning system based on incident or lesson learned reports

1. To clearly identify what happened and to state what immediate actions were taken
2. To gauge the severity of the incident
3. To evaluate the potential impact of the incident, and its relevance to the overall readiness of the facility
4. To determine if the incident was anticipated during risk assessment: if so, was the management appropriate? If not, what steps are needed to better anticipate a similar incident (e.g. additional types of experts)? Or is there risk management that could cover the type of incident without being able to foresee the specifics?
5. To analyse the cause of incidents and 'near misses'
6. To document process problems for internal correction
7. To document for regulators if non-conformance with T&C of a permit occurred
8. To develop, communicate and plan for implementation of corrective actions
9. To correct the underlying cause(s) of problems
10. To document why the same thing will not go wrong again (such as possible enhanced risk management)
11. To evaluate the effectiveness of the corrective action(s), including understanding the remaining or residual risk in terms of both its nature and its magnitude
12. To report on completion of the implementation of the corrective action(s)
13. To prevent future problems in other locations for research consortiums operating in multiple sites

An Incident Report is not a risk assessment of the incident occurring again nor of its potential knock on effects, as such, but instead asks for evaluation of severity and impact for a single event. (Feedback into a risk assessment and management process would benefit from a separate form organised by risk topic and handled by risk experts.) For lab settings, a Corrective Action Preventive Action, or CAPA, report plays a similar purpose.

10.3.2 A system for ranking an incident

In regard to the three aspects of 'facilities readiness' in particular (covered in Chapter 7), the following ranking is proposed by the researcher using a descriptive approach to risks, such as a consequence assessment criteria matrix (Quinlan, 2014: Table 18.4). In the example proposed in Table 10.2, the risk is judged by the highest (high, medium or low) checked category (e.g. at least one box ticked), until each aspect of that category is resolved. In other words, a higher risk for a single aspect continues to put the activities at that level of risk, even if other aspects are managed or never disrupted.

Of course, alternative distributions of the descriptions may be chosen by a team, depending on their own context, priorities or sensitivities. The proposed matrix is to guide discussions within research teams in order to define these levels as part of the advance preparations so that any disruption to the readiness of a facility may be immediately identified, communicated and acted upon.

Any incident report should also invoke a review of whether all the aspects of it were already considered in a risk assessment or something was not identified as a hazard or predicted. For example, some incidents may be anticipated and therefore the incident form supports a review of the management in place. Other incidents perhaps are not anticipated, so this would lead to a repetition of the risk analysis and additional planning to prevent future occurrences, possibly by adding further management. In other instances, something may have been anticipated but the management or response was not adequate.

Finally, there are other things that cannot be anticipated and may have no direct relation to the activities but may cause impact. Some avenues for learning about hazards in the broader national context include news services, an alert system provided by insurance companies, an agenda point in routine meetings or calls or some other reporting service. This general information of what is occurring external to a facility may also be incorporated into the case specific management system. Management measures may impact risks that they were not designed for, due to similar pathways or mechanisms of impact. In these instances, a generally robust system including rapid notification and well trained response mechanism will make the most difference to avert or reduce consequences.

Table 10.2 Example matrix of disruptions to the state of ‘readiness’ of a containment facility.

Level of disruption/ description of incident	Impact	Response
Low Incident or near miss	□ Does not significantly disrupt the colony/ies □ Interrupts lab work for only for a short period of time □ Does not affect external stakeholders □ No impact on the health of the staff □ Damage is limited to delays and is easily remedied	Would require a response at the level of the facility staff
Medium Significant incident	□ Significantly disrupts the colony □ Interrupts the lab work for several days, but is not critical for the project □ Limited significance for a large number of stakeholders, or significant impact on a few stakeholders □ Damage is reversible but requires additional actions or resources	Would require a response at the level of the research lead (PI), and possibly the institution
High Emerging crisis or serious incident	□ The colony needs to be terminated □ Interrupts lab work for a significant amount of time and activities relying on the facility for supply (e.g. field studies underway that are supplied from the facility – see Figure 2.1) □ Could require reporting to regulatory/ethical authorities to report failure to comply □ Has moderate impact on the health of the staff □ Poses a threat to the immediate environment around the insectary □ Damage is not easily reversible	Would require a response at the level of the research lead (PI), institution and possibly the entire consortium and national authorities
Extreme Crisis	□ Threatens continuation of the research □ Requires disinfection, refurbishment or other significant changes to the containment area or facility □ Could lead to the loss of 'social licence' □ Could lead to loss of regulatory/ethical approval or permits □ Poses a threat to worker health and safety □ Poses a threat to the immediate environment around the insectary and any area where studies were supplied from this facility □ Damage (of any nature) is not feasibly reversible	Would require a response at the level of the entire consortium, national authorities and funder

10.4 Access to excellence

The concept of capacity appears to vary by research theme, with some subjects appearing to be more collaborative than others[88]. Capacity to publish has been noted as an indicator of capacity but also has been challenged as an appropriate indicator due to the barriers to DEC researchers in this regard. Developments such as Open Access of publications have had significant impact on availability of the latest research results for those outside academic settings in the 'North'. Eisenstein (2017) considers this to have altered the research context for the 'South'.

In translational research, however, the requirements for excellence extend beyond the laboratory. Biotechnology research is a case in point. Partners are needed that have non-scientific expertise in areas such as institutional procedures and operations, strategic planning and setting of priorities, ethics, communicating knowledge, linkages to policy and policy makers, public-private relations, the ability to create new partnerships or seek new expertise, etc. – in short the ability to use the knowledge generated effectively as well as generate it. This has been referred to as innovation capacity (Hall, 2005). Capacity building of individuals alone is not adequate (Waiswa, 2015).

The OIE (2015) standard for managing biological risk in laboratories, although technically oriented guidance, recognises that biological or related regulatory risks are closely linked with funding, communication, and M&E systems. The standard goes on to state that the investment and financial outlay should be commensurate with, or proportionate to, the level of risk identified. The human factor, such as project management and oversight, is in actuality more commonly posing risks in many research configurations than the research organism or new technology. The risk of harm to the reputation of an individual project, institution or facility, therefore, may warrant some investment beyond the estimated risk based on more biological principles. In such an instance, methods for establishing and demonstrating a reliable reputation should be considered as a means to reduce this cost over time. This may also relate to effective risk communication, which would extend beyond those parties noted by OIE (2015: section 4) to a wider base of stakeholders and potential critics.

From the literature on use of transgenic mosquitoes, WHO/TDR & FNIH (2014) came closest to elaborating some of the skills required by partners to participate in a meaningful and

[88] There is variation of collaboration among research fields as well, with biological research emerging as one with more international co-authors in analyses of literature over four decades, but from analysis including only those countries found in the original studies reviewing research from 1970s forwards (Coccia & Wang, 2016).

competent manner. Studies of national innovation systems do not necessarily capture the innovation capacity of individual research institutions, or individual researchers. The former is influenced heavily by innovation policies in the host country; the latter may be down to individual mentors, institutional leaders and personality.

In addition to varying approaches to partner selection, other differences were noted when comparing British and French approaches to biosafety compliance, as a relevant albeit European example. Despite France and the UK both working under the same European Directives, national interpretations are often distinct. The researcher considered what biosafety measures are universal and strictly enforced and what may have more culturally based distinctions. The oversight of research under permits, for example in containment or confinement, provided evidence for two distinct approaches. While British research on transgenic exotic mosquitoes is still under inspection and review from the government, with an important role for internal systems, French researchers are put into a position of more self governance but with strong consequences for any failures in the containment system.

Figure 10.1 lays out the potential relationship among various practices and documents, and how they relate to the key concepts of facilities readiness discussed in Chapter 7: compliance, colony utility and defensible science (Quinlan et al., 2018a). In this way, a learning system is created for continual improvement so that any minor failures may lead to enhancements in hazard identification, risk management and communication.

The learning system takes advantage of feedback to:

- Use information to improve the facility operational practices and processes in the future
- Check whether the risk assessment or register of hazards had identified the hazard and prepared for it, or to provoke further risk assessment and management planning – or how to respond to the unforeseeable by building in early warning systems, redundancy of management where advisable, or resilience
- Employ intelligence about what is going on in the immediate surroundings or context of the facility that could affect the operations of the facility – including what is beyond the control of the researchers or institution

If feedback is built into a learning system, then incidents provide a positive opportunity for learning and gaining experience and knowledge, where previously there may have been only uncertainty. Figure 10.1, however, shows the range of different sources that might provide different types of information. Some cohesive overview is needed to benefit from the wide picture. After preparation for disruption of the status of readiness, researchers or other

decision makers should proceed more confidently to the point of declaring readiness when set criteria have been met.

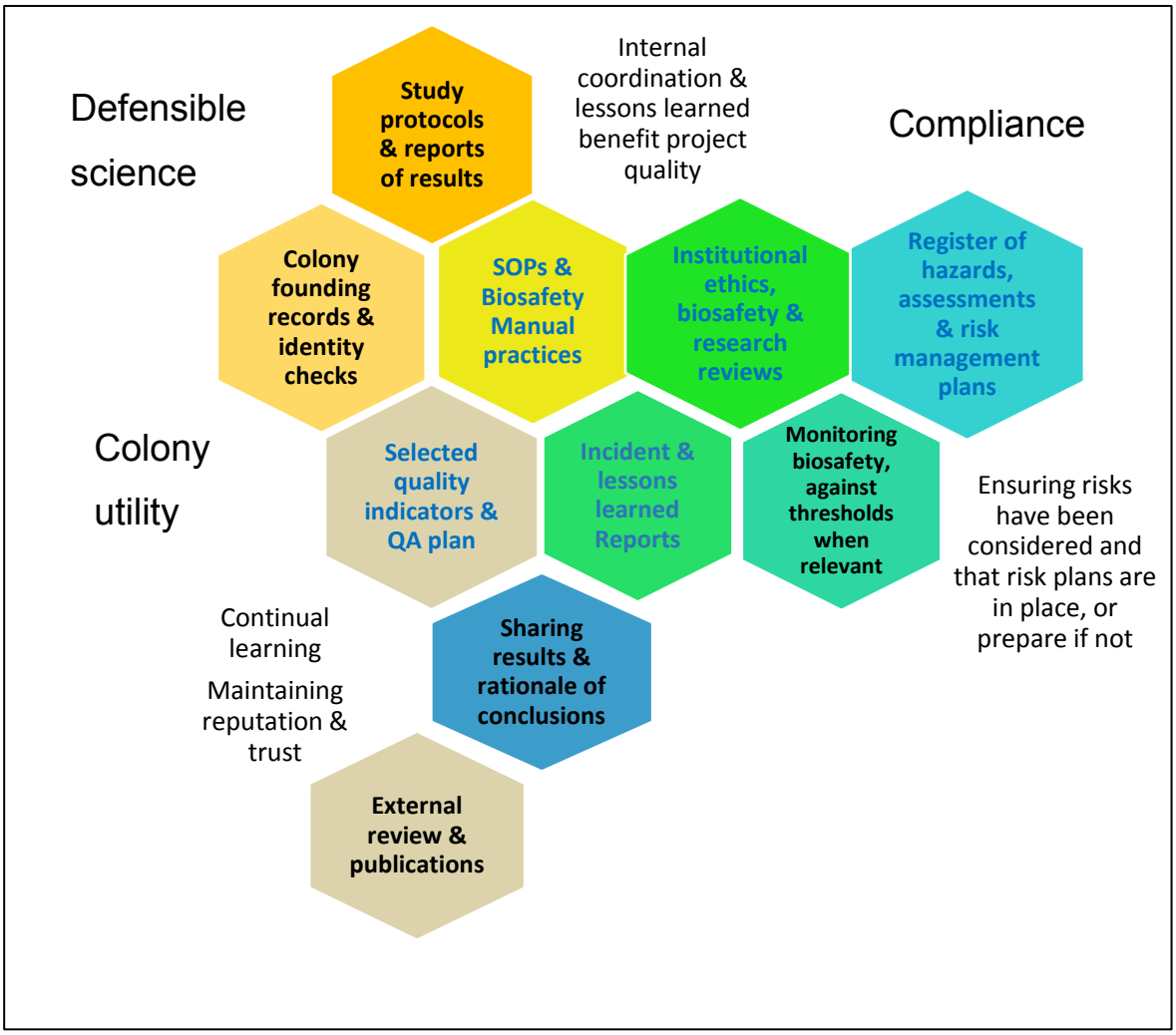


Figure 10.1 Components of the three themes in facilities readiness to maintain biosafety over time

10.5 Summary on maintaining readiness and biosafety

This study came from the perspective of a research partnership or consortium initiating studies in an external lab, but involving joint work with a DEC research team to develop the novel intervention beyond initial concept. A range of approaches to partnerships was discussed in Chapter 5 leading to the consideration in this chapter whether there is an ideal partnership model for maintaining the facilities readiness and product stewardship as designed, while delivering a novel intervention in vector control. The researcher concluded that no single type

or style of partnership is superior to any other but rather good decisions relate to a number of factors including culture. After considering a history of how partnerships have run in the past, however, some basic best practices emerge from perspectives of both external and DEC researchers. Underlying this is the understanding that the best avenue towards biosafety compliance is the ownership of achieving it, based on an understanding of the objectives of each measure and a sense of personal responsibility amidst an enabling group culture.

The study has considered the need for enhanced capacity of research teams and institutions, as well as individuals. A well embedded research or product development process in country, with an ethos of co-development with external Discoverers or Funders, continually addresses the third question of the WHO evaluation process, **Does it work for me?** This in turn leads to more confidence on the part of health policy makers in country who decide on expenditures and what to include in national health campaigns.

While the capacity and understanding is needed, some structures and frameworks were found to support compliance, self reporting and the necessary record keeping. Some of these were discussed in Chapters 7, 8 and 9. Suggestions on further supporting processes and documents are added in this chapter.

Figure 10.2 illustrates a pathway of influence from short term outputs involving access and participation of all teams in research and product development, through to sustainable monitoring of safety and efficacy of a novel intervention. Some of the short term outputs on the bottom level of Figure 10.2 have been covered in previous chapters, including internal audits (Chapter 8) and Product-level stewardship of data (Chapter 9). They are made up of procedural frameworks and systems supportive of capacity and engagement of research teams. In Chapter 10, the need for involving partners in the scientific research with open and accountable processes is also acknowledged. In addition to working towards an ethos of co-development, the aim of fostering personal responsibility and integrity in the scientific research is part of the transfer of ownership that will build the local experience and address the question of suitability to the location that underpin sustainable monitoring and effective procedural and policy decisions.

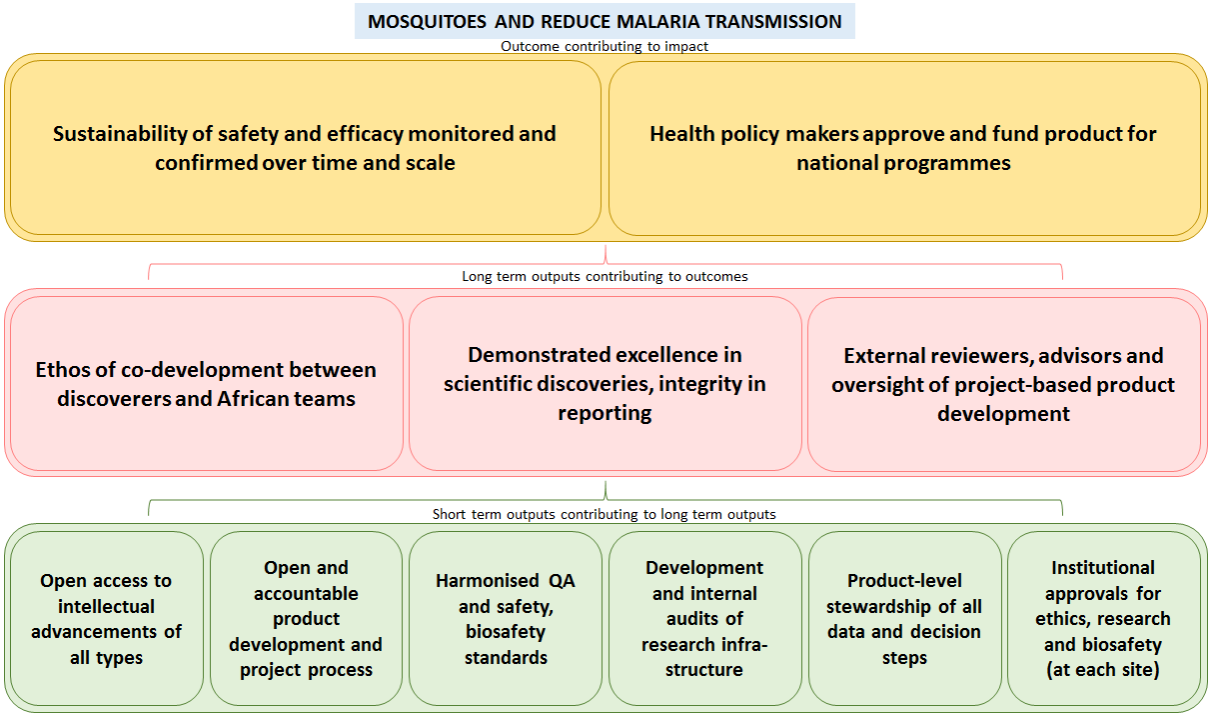


Figure 10.2 Short term outputs leading to an ethos of co-development and sustainability of monitoring safety and efficacy for the delivery of novel interventions for vector control in DEC

Although reviewers who are external to a research group (i.e. for peer review of journal articles) lend legitimacy to research conclusions, it is the internal commitment within a project, research initiative or team to integrity and excellence that will support stepwise delivery of novel interventions.

As with the other similar figures, this will be merged to form an overall Theory of Change moving towards reduction of malaria transmission, keeping in mind the requirements to achieve this goal (shown in Figure 1.1).

The researcher returns to the concept of effectiveness when considering the subquestion, **Can biosafety objectives and quality assurance in the containment phase be achieved more effectively if using harmonised procedures and tools for research in DEC settings?** The effectiveness of DEC research teams and institutions will depend not only on capacity nor even resources, but is largely dependent on the general culture of a research group or institution and that team's ability to manage the ongoing challenges of the research context.

Some observations on instilling a culture favourable to biosafety and quality assurance from a range of sectors were analysed for their value in the context of insect research in

containment. Use of structures of support for biosafety and quality assurance also may build robustness in this effort to excel in the face of challenges. Greater freedom from these routine barriers can enable a shift in attention from individual desires for capacity and advancement towards excellence in research, development of effective products or tools against malaria, and the possibility of true contribution to one's field. This is what inspires researchers everywhere.

CONCLUSIONS

Chapter 11. Discussion of Research Question and Conclusions

11.1 The problem

Significant progress has been made against malaria, primarily by using small area or individually applied measures such as IRS or LLIN. This progress is not expected to continue, however, because of alarming rates of insecticide resistance and the general inequities of limited access to sound health systems or vector interventions. Indeed, a rise in cases of malaria was documented from 2015 to 2016 (Maxmen, 2017; WHO, 2017a). As discussed in Chapters 1 and 2, improvements in malaria vector species control is considered one of the key means towards elimination of the disease. Many believe this will require novel interventions, used in combination with existing measures.

The study has focused on the early stages of the stepwise delivery of transgenic mosquitoes as an important case of new genetic strategies, from initial discovery of a potential concept to the point when field testing begins. Effectiveness was related to three components: efficacy, performance and efficiency (Box 2.2). All of these aspects to effectiveness may be hindered by complexity but the concepts remain true whether for a technology or a decision process.

Management of any vectored disease is complex. Although the ultimate indicator of success is a reduction in the incidence of the disease, it is difficult to show proof of principle in terms of health impacts in early stages of studies, even once the proof of a concept is established in the lab[89]. Ultimately, the intervention is not proven until impact on disease incidence can be validated, but the WHO VCAG has now developed a clearer pathway towards this using midpoint indicators such as entomolical impact (WHO, 2017c).

The same countries facing high incidence of malaria often are confronted with weak health systems, in which fever diseases are often undiagnosed or treated without proper diagnosis. Rather than analysing barriers to achieving meaningful health indicators, this study was positioned almost entirely in the sphere of vector control and its entomological indicators.

[89] If proof of concept, in this case that a mosquito strain can lead to crash of its target population through mating (e.g. Kyrou et al., 2018), may be demonstrated in the lab of a Discoverer outside DEC, then the proof of principle phase might be considered as demonstration that the method can be delivered to the field and cause entomological impact in a defined area (e.g. Harris et al., 2012).

In this context, the researcher considered the key bottlenecks to be sufficient confidence to take decisions regarding a novel intervention and the effectiveness of this decision process. Attempts to monitor trust and confidence were rejected early in the study, due to the lack of adequate metrics. The focus, therefore, was on effectiveness, which in itself should be considered to include confidence as a component of efficient decision making. Political will to alleviate suffering of one's compatriots can overcome many bureaucratic barriers related to regulatory or institutional frameworks. Confidence to take decisions on novel issues, however, can demand true courage and even personal sacrifice by the individuals entrusted with this task.

11.2 The research questions

After analysing the problem and research context, the overarching question posed in this study was: **How can learning systems improve the process of decision making around the delivery of a novel vector control intervention?**

This question was broken down into the following subquestions (with chapter numbers that address each), to facilitate the study:

- Is there a best practice for external innovators or discoverers of a novel intervention to find appropriate research partners in DEC? (Chapters 5, 10)
- Will regulators be supported to make more effective decisions about import and use of novel interventions by using decision frameworks? (Chapter 6)
- How does benchmarking a point of readiness for use of containment facilities support effectiveness of this first step in the delivery of the intervention? (Chapters 7, 8)
- Is a product stewardship approach to identity maintenance and data management necessary to support decisions about safety and efficacy in containment studies, moving towards field studies? (Chapter 9)
- Can biosafety objectives and quality assurance in the containment phase be achieved more effectively if using harmonised procedures and tools for research in disease endemic country settings? (Chapter 10)

The research approaches and methodologies for considering these subquestions were described in Chapter 4. Each of the subquestions was discussed by topic, but the overarching question will be revisited below.

11.3 Key findings of the study

11.3.1 The DEC research setting still faces numerous challenges

It may appear obvious that many of the locations burdened with endemic malaria are those with fewer resources in the research sector, as well. On the other hand, today's digital context may give the impression that research settings are similar globally. First, this study identified a number of challenges to decision makers in countries where such a novel intervention could be used. This includes the everyday challenges of research in DEC contexts, as described in Table 5.1. Other challenges were catalogued in Table 2.1 by decision maker, but many are attributed to the novelty of proposed interventions themselves. These barriers are not insurmountable but should be taken into account.

Tensions between capacity enhancement objectives and focusing on technical advancement, and project or product outcomes certainly persist. The competing objectives for limited resources (discussed mainly in Chapters 5, 6 and 10) are ubiquitous: for the country in terms of health care priorities; the regulators between caution and safety and benefits of progressing promising disease reducing interventions; the institution in terms of best use of facilities and staff time; and the individual in terms of meeting demands from various sectors while also progressing one's individual career. The need to deliver studies in a timely manner can appear to compete with the biosafety objectives. Many research teams have more than one project going simultaneously, which can also lead to time conflicts at busy periods.

Funders can create a better environment for managing these tensions by supporting early stage funding and partnership negotiations, for example with small grants for preparing proposals. At the same time, DEC research institutions need to explore ways to capture resources to cover gaps between project funding streams. Capacity building should remain on the agenda, but with clear links to the product outcome for product development initiatives.

Decision makers face additional barriers due to the complexity of evaluating both novel approaches, such as areawide vector control, and the range of aspects for any introduction of a living organism or for vectored disease interventions.

11.3.2 External researchers, termed Discoverers, should consider their objectives, resources, time frame and other commitments to determine the best timing and style of partnerships with DEC Researchers, and vice versa

Simplistic criteria, described in Chapter 5, such as national adherence to the Cartagena Protocol, was found to be inadequate to indicate the functioning of a NBF. Initial 'go/no go' criteria were limited but useful for quick orientation and generally based on publicly available (easy access) information.

Tools such as an adapted TRL or business plans oriented towards biological products can support decisions for finding DEC partners. Figure 5.7 shows possible points for partnership using the TRL system. The materials provided in Appendix 2 that lay out criteria for identifying appropriate partners are also adaptable to other initiatives. Table 5.6 proposes a better framework of criteria. It separates country, field site, institutional, containment facility site and individual attributes and organises these by 'go/no go', priority, desirable and when possible to make the weighting of each clear.

Depending on the objectives, it may be more effective in terms of cost and time to develop a product through to field application and find either service providers or late phase partners who can take the intervention into the programmatic stage, including commercialisation if appropriate. The co-development approach may be less effective in the initial stage but reap benefits over time in terms of reality checks for feasibility and relationships within the countries targeted for application of the new tools. These points should be considered carefully by Discovers so as to progress towards delivery with a consciously selected approach.

11.3.3 Despite a range of partnership styles, there are some good practices in finding DEC research partners that could guide any inexperienced external Discoverer

This study took place within the scope of considering external Discoverers and the early steps towards delivery of vector control innovations. The various styles of partnership may work best in different settings. The action research and interviews revealed over time that those not already working with DEC research teams might have had little insight into the best timing and terms for transferring the technology for further development (discussed further, below).

The value of early phase delivery partnerships, however, lies in these less quantifiable returns of greater local ownership of the technology and the chance to integrate local concerns into risk management and product design. Discovers may not recognise the importance of these qualities if starting from limited experience with DEC researchers or in the countries where interventions will be employed. Many of these barriers to novel research noted above can be

overcome through the opportunities accompanying long term equitable research partnerships. The online survey respondents suggested that longer term relationships do pay off. Other good practices included clarity of communication and expectations, advance agreements on data use and routine check in.

Many projects or initiatives are motivated primarily by the desire to contribute to alleviation or poverty and disease (Bradley, 2007); even product development is not always aimed at patenting or a profit motive (Quinlan et al., 2018c). The nature of vector control can be heavily influenced by either the business model or government programme support from development assistance[90]. Investment from private business or foundations, as already noted, will follow its own agenda aimed at the priorities of these organisations. The research consortium studied, Target Malaria, was not under a development assistance programme *per se* but rather primarily funded by the private foundation sector with the aim of finding solutions to the world's most pressing problems[91]. The funding foundation's evaluation of what those problems are, and to some degree how best to address them, has determined the long term funding for what was initially a discovery of a potential mechanism to achieve innovation.

Therefore, the trajectory of the first decade of research on the innovation considered in this study, transgenic mosquitoes, was aimed always towards a real world health challenge. Such cases render the concept 'technology push' simplistic in terms of predicting and mapping an impact pathway (discussed further in Chapter 4). A more complex reality than 'North-South' has arisen in authentic partnerships in this area of research, in which some observations made in decades past still sadly ring true, yet some principles of engagement are undergoing rapid change. Successful collaborations rely on a multitude of factors, such as outlined in Table 5.3. Many of these are supported by frequent and ongoing exchanges between research groups, which requires additional time and funding.

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90 https://www.technologyreview.com/s/602720/are-altered-mosquitoes-a-public-health-project-or-a-business/

91 The BMGF (https://www.gatesfoundation.org/) states that, 'Guided by the belief that every life has equal value, the Bill & Melinda Gates Foundation works to help all people lead healthy, productive lives.' The Open Philanthropy Project (http://www.openphilanthropy.org/about/vision-and-values) expresses one of the shared values of its participants with the statement: 'We believe that people have equal intrinsic value regardless of the circumstances of their birth, and that animals' lives have value, too. We believe economic development and technological innovation have greatly increased human well-being. We're optimistic that this trend will continue, and we hope to play a part in accelerating it. We're motivated by our vision of a day when every person's needs are met and each of us is empowered to shape our own life.'

11.3.4 Regulators can be supported by decision frameworks, some of which they have already developed

Quinlan (2014) considered risk assessment of transgenic insects and decisions relating to a risk-based method of evaluation. She joins others to argue that this well established and broadly applied methodology for evaluation of planned introductions to the environment can be adapted to a range of new technologies.

Quinlan et al. (2016a) and Chapter 6 of this thesis identified specific challenges in the regulatory decision making process when considering individual cases. Areas benefitting from better frameworks included: socio-economic considerations, assessing the scale of environmental impact to determine what further study is needed, and organising of public input so that it can be taken into account most effectively. The materials and symposium presented by the researcher may have contributed to this internal discussion, but most likely progress towards more robust systesms is a process driven by the regulators themselves.

Barriers to regulatory and uptake decisions can be lessened through use of learning systems, but this relies on opportunities for learning across similar national contexts. Regulators and others in decision roles learn much from each other.

11.3.5 Benchmarking a point of readiness for use of containment studies supports effectiveness of the Discoverer and DEC Researcher teams and institutions, and laid the groundwork for regulatory review

In the current study, examples of historical work on genetic strategies in DEC Africa are noted (Chapter 2), albeit largely for agricultural and livestock pests with sterile insects. The motivation of work on transgenic mosquitoes studied in this thesis is squarely in line with interests to address a serious tropical disease. As already stated, novel interventions against vectored disease can only be tested for their ultimate effectiveness in the context of DEC.

Chapters 2 and 5 discuss why this testing phase is best done in partnership with local collaborators. One reason is that a legal entity will be needed to host the field studies and, in most cases, to act as an institutional host for the containment facilities and studies as well. Access to field sites for establishing baselines for the target mosquito population and being an employer for staff are other good reasons. There are ethical reasons as well, however. For example, financing research infrastructure is one way to provide benefit to the DEC, but a more concrete way could be to create increasing capacity for research by supporting team members to share developments from the research initiative and train colleagues.

Management skills are also critical for science teams to develop. Given this context, one key decision point is when to transfer research organisms to the partner DEC lab.

Over the recent decades, best practice for conducting research on novel interventions has been established as following a stepwise approach to testing and development. This has been supported by numerous expert groups (as mentioned in Chapters 1 and 2, in particular section 2.2), despite the additional resources required and long time frames for moving towards disease impact[92]. The emphasis on a stepwise approach has probably been as much to allow for building confidence of those decision makers, as for increasing knowledge about the novel organisms or technologies themselves. Those following this pathway to delivery, however, will have found that little guidance was available regarding the early stages.

Decisions surrounding transfer of a research organism, or similar technologies, for testing in DEC conditions involve a choice in research partnership style. Regardless of transfer of ownwership/IP or timing of transfer, every researcher working with a living vector colony will need to decide when to transfer to a research facility. Most likely this will be a containment facility, as discussed in Chapter 7, given the novelty of the interventions under development. The conceptual framework for benchmarking facilities readiness, created and reported on by Quinlan et al. (2018a), provides a framework for organising activities that can become a learning system is the experiences are shared, such as through published papers. The framework reminds participants of the balancing act needed (see Figures 7.3 and 7.4) and the hierarchy of components (Figure 7.5) for successful research in containment in a DEC. The report on details of the process of preparations (Quinlan et al., 2018b) for West and East African cases should be supplemented with other cases, as they occur.

The options of methods for benchmarking are shown in Figure 7.2, including one off certification or periodic audits, described more fully in Chapter 8. Ongoing approaches, such as lessons learned exercises and incident reporting, are discussed further in Chapter 10. Recent discussions suggest that a formal certification process by a third party, external auditing entity may be useful for those with less internal evaluation capacity or those preferring an international level of recognition as part of facilities preparations. This was noted as of particular interest for organisms with gene drive incorporated into modifications (O'Brochta et al., in press).

[92] A Theory of Change would provide structure to the enquiry as to whether the objectives of the stepwise approach are being met. While a stepwise approach to development of novel interventions has been promoted, there is little structured monitoring of its effectiveness. Further research on the level of effectiveness and impact of various practices or tools would add greater rigour to the conclusions.

Another outcome of all these approaches to delivery of interventions is a new awareness of areawide mosquito control as a viable alternative to indoor spraying, fogging or individual protection from biting.

11.3.6 A product stewardship approach for novel interventions in vector control will become increasingly important

Few examples exist of a product stewardship approach for novel interventions in vector control, but this level of documentation is becoming more important. There are example data requirements for MTAs that are likely to be required in more cases. The biological identity of research organisms has come under greater scrutiny, which will be a burden in cases where this is not well documented from the start (Higgs, 2018).

In Chapter 9, the researcher proposes a system for documenting establishment of a colony in the lab using wild, field caught mosquitoes (the WTCR) and describes other drivers for product stewardship level documentation. Such requirements are even more likely to be needed in view of requirements for recognition and recommendation of novel vector interventions (WHO VCAG, 2014).

11.3.7 Biosafety and quality assurance in the research facility will always benefit from harmonised procedures and tools

Biosafety guidance is often aimed at working with infectious diseases, rather than uninfected but modified insects. The literature that has been published regarding transgenic or otherwise modified mosquitoes has mixed criteria across categories and stages, so that most included guidance at the macro, meso and micro level and even about aspects of the modification grouped together. Better precision in such guidance will enhance the growing collection of useful guides, tools and accepted standards (albeit not generally formal standards) being taken up in vector research communities.

This issue is not unique to African DEC settings. The conflicting priorities are strong in all research settings. Chapter 10 enters into the necessary ingredients for a blame free culture, where researchers learn from mistakes. Figure 10.1 shows a possible suite of reports and practices that support maintenance of what was defined as facilities readiness, returning to the organising concepts of Colony Utility, Defensible Science and Compliance.

11.4 Challenges and limitations to the research in this field

The researcher chose to study the current dynamics and potential support for a series of complex decisions involving several areas of expertise outside her experience and training. She did this as a facilitator, however, using the precepts of action research and drawing on years of experience with international development projects and biologically based product support.

The rate of change in the research topic has been remarkable, while the researcher's own interruption of studies has delayed outputs on this particular study. Verily, a life sciences branch in the same group as Google, announced a weekly release of 1 million *Ae. aegypti* mosquitoes modified with the *Wolbachia* gut symbiont last year, to begin testing control of the vector species in Fresno, California[93]. In 2016, the BMGF, the Wellcome Trust, and programmes under the governments of the UK, USA, Brazil and Colombia funded a US$18 million initiative using similar technology to combat the same species in South America where a Zika outbreak had occurred. While the non persisting sterile mosquitoes developed by Oxitec Ltd. are in use in Brazil, Colombia, India, the USA and Grand Cayman. Future supplies of the resilient eggs can come from a new production facility in Oxfordshire, UK[94].

That said, there were actually very few cases to review of uptake of this type of novel intervention for malaria-vectoring mosquito control past the point of a Discovery lab. Most of the emerging concepts are still under study or relate to other vector species with interesting counterpoints but insufficient similarities to form the main basis of decision support. Therefore, many of the conclusions are resting on experiences with a single project, albeit with both West and East African partners. This limits the breadth of the research geographically and for stages of research. On the other hand, the topic is cross cutting and some limitations are necessary to achieve meaningful research.

As well as being spread over several years at part time effort, the study also suffers from the fact that finding partners and simply preparing facilities took years to accomplish. In general, the proposed frameworks were under development when needed by the first partners, rather than in advance. There was an important milestone within Target Malaria, however, of the first transgenic mosquito strain imported to an African containment lab for research[95], according to

[93] https://techcrunch.com/2017/07/14/googles-life-sciences-unit-is-releasing-20-million-bacteria-infected-mosquitoes-in-fresno/

[94] http://www.oxitec.com/oxitec-build-state-art-mosquito-egg-production-unit/

[95] https://targetmalaria.org/dr-abdoulaye-diabate-give-us-an-insight-into-target-malarias-team-work-in-burkina-faso/

available documentation and news. This event occurred in late 2016, so that one may consider the parts of this study completed in the context of that project as part of the overall success of the preparations and an indication of effectiveness of the same.

More recently, the researcher has been limited in travel due to security concerns of her host institution (Imperial College London). This prevented follow up observations and interviews and her participation at larger forums of importance, such as the PAMCA annual meetings. The methods of validation for each proposed framework were found to be applicable (shown in Table 4.4) and might have been improved on if the restrictions to travel had been anticipated.

Thoughts on the specific research methods used are discussed in more detail in Chapter 4. Despite limitations to the research methods, the researcher was satisfied that her study brought conscious enquiry to a new partnership during a significant period in the development of a novel intervention that, if successfully delivered, could contribute to the elimination of malaria from the planet. The unique opportunity of her involvement would seem to outshine the constraints on the research methods and approach.

11.5 Lessons learned

Some of the best practices arose from other fields or research by others, which is a particularly efficient way to provide frameworks. For example, using the approach to compliance with the Nagoya Protocol that is suggested in Mason et al. (2018) would be a feasible starting point when country requirements are vague but where the opportunity for benefit sharing exists. The FAO/IAEA *Model Business Plan* (2008) provides financial planning templates, while the Joint Division is developing a mosquito facility design tool. The questions used by Target Malaria to summarise the characteristics of various research teams (Appendix 2) or other published criteria could provide the basis for partner search for others. Several of these resources are applicable to any novel intervention that requires an exchange of living materials, for example BCAs, the emerging industry in insects as pet food, or biologically based products for plant health or veterinary care. One lesson learned by the researcher is that even for the most novel technology, an extensive literature review and discussions with others at a very early phase of developing an idea about facilitating tools (e.g. Quinlan & Tourneur, 2017) can lead to time saved in preparing supporting frameworks in the new field.

11.6 Use of learning systems

In Chapter 1, the researcher defined learning systems in the context of other analytical tools and frameworks, with the objective of increasing effectiveness of delivery of a novel intervention for vector control. Not all frameworks are learning systems, but many of those introduced in this study can be employed that way by sharing results across different initiatives, vectored diseases, vector species or innovations in general.

The choice of developing learning systems or frameworks was to allow different conclusions based on differing criteria. While the study counted decisions made by the participants in the delivery pathway as a success, it was not the intention to advocate genetic strategies using transgenic mosquitoes. Instead, the aim has been to create evidence based systems that are able to adapt to new data, but reflect the values or criteria imposed by the decision maker. For example, if reduction of pesticide use is a national priority that may lead to one choice, whereas aiming for more equitable access to malaria prevention would relate to this distinct objective.

Dellinger & Leech (2007) look at validity of mixed methods research from the perspectives of fidelity in transferring the result, the use of the result, and the consequences from its use. Learning systems can contribute to decision making for early phase delivery of a novel vector control intervention and this has been demonstrated by the Target Malaria consortium.

Learning systems provide a structure for information as well as some mechanism for feedback or representation that supports learning, if employed by those who have a role in decisions and actions. The organising principles for facilities readiness arose through action research and proved effective for embedding a more comprehensive preparation for import of the research organism, while balancing potentially competing objectives. This becomes a more effective learning system if used in multiple cases (e.g. for new strains or technologies) by the same decision makers, or if the experiences are shared with others facing similar cases. The approach to audits described in Chapter 8 also may provide learning opportunities if results are builit up and shared over time. Other frameworks, such as the Wild Type Colony Record or the list of what type of information is worth considering for MTAs, are not so much learning systems as useful templates to support operations. Together, however, such templates can support a more pro-active approach to management of mosquito colonies that are going to be used in product development studies.

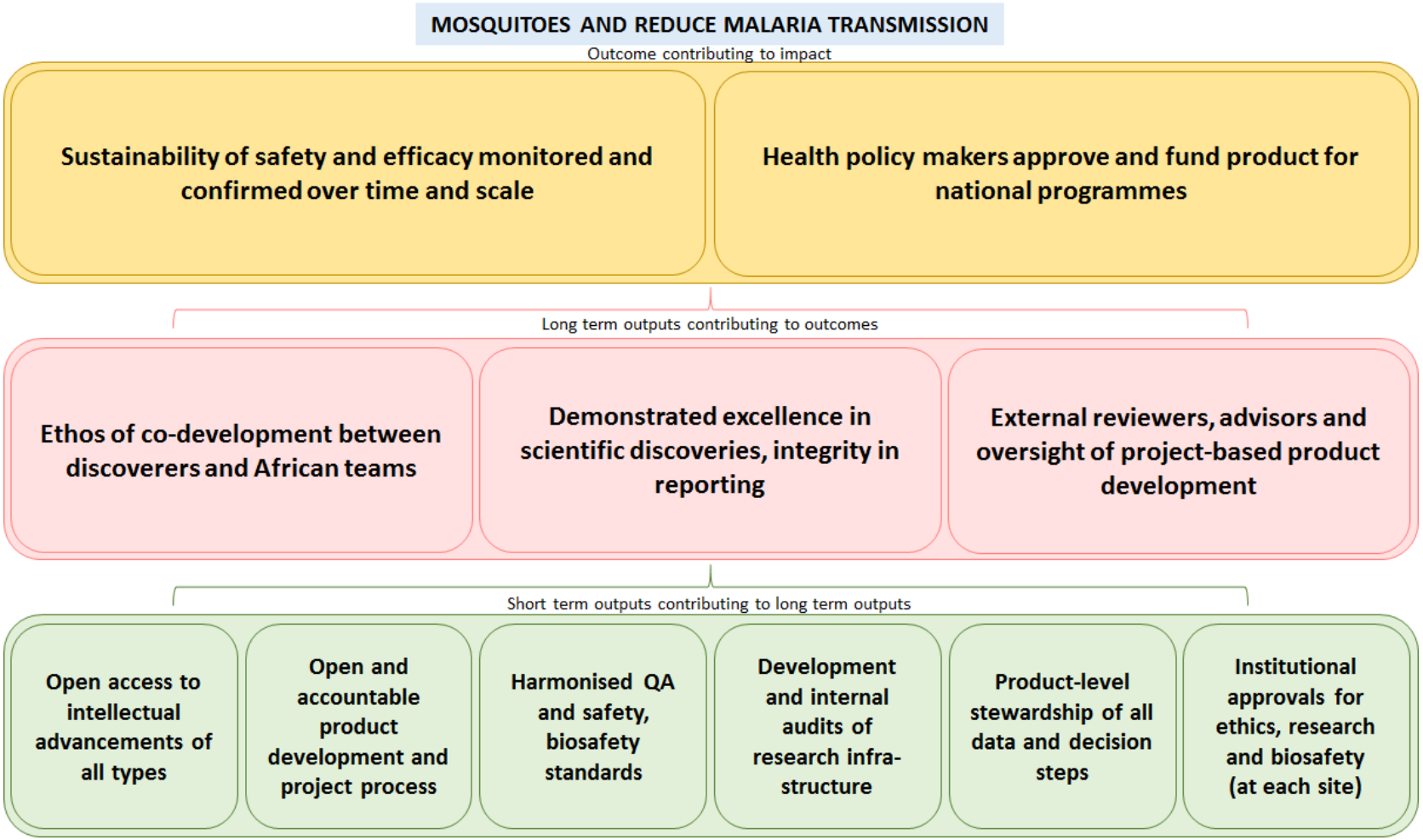


Figure 11.1 Short term and long term outputs leading to the key outcomes necessary for delivery of novel interventions for vector control in DEC and impacts on malaria transmission

Regulators have created their own frameworks such as templates to organise input on socio-economic factors. The frameworks reported on in Quinaln et al. (2016a) meet the definition of learning systems. Certainlly approaches created by regulators or designed at their request are embedded more effectively than something proposed by external observers.

Regardless of the particular objective supported, reviewing the decisions, choice of data and indicators on a regular basis may be supported by use of a Theory of Change. Figure 11.1 shows the full map developed by the researcher with the activities, values and mission of Target Malaria in mind. When managing complex activities towards a difficult objective, this is one of the methods recommended as a result of the researcher's experience during the study. Direct cause and effect claims and traditional logframes with assumptions play other roles, but may be less appropriate to the field of vector disease control. Figure 1.1 gives an overview of the changes needed to achieve elimination of malaria through new, sustainable, cost-effective interventions reducing malaria transmission. Mapping these concepts into a Theory of Change allows for review and monitoring of diverse activities.

11.7 Key contributions of this study

The researcher provided a clear analysis of the current dynamics in which decisions must be made. Challenges were identified that are typical of less resourced research settings, but also several that are unique to research with mosquitoes or on novel interventions of any kind. The findings from engaging with regulators (Chapter 6) to explore their experience resulted in a publication on best practices for organising public input (Quinlan et al., 2016a). The colony record (Chapter 9) was inspired by emerging regulatory requirements in Europe, and was the most specific output of the study. One of the key contributions of this study was to establish some organising principles for preparing for containment studies (Quinlan et al., 2018a) and the details for these steps (Quinlan et al., 2018b). This contribution can directly support decision makers to either proceed or continue preparations for an import or introduction of a transgenic organism for study. Additional materials for auditing a containment facility (Chapter 8) will be shared in a future publication, but the guidance on biosafety, incident reporting (Chapter 10) and a broader legal review (Chapter 5) can be used immediately by anyone conducting research with mosquitoes. The researcher showed how tools associated with project management could be applied in the study case. Theories of change provide a structure to evaluate and adjust practices in complex situations where other initiatives or activities may be affecting outcomes as well.

Chapter 10 lays out practices that could comprise learning systems individually, or an overaching learning system as a suite (Figure 10.1) to better embed biosafety and product development practices, providing continual learning and improvement. These various tools, frameworks and practices support a conclusion that learning conclusions can contribute to decision making for the early phase of the delivery of the novel vector control that was the focus of research, transgenic mosquitoes.

Perhaps the greatest contribution of this study is a comprehensive review of the different styles of partnerships, however, with some conclusions on what approaches are best in relation to product development. The online survey provided valuable food for thought regarding experiences of vector and vectored disease researchers already in partnership. Table 5.6 could be an important guide to selection of partners and sites. It presents a series of criteria by category of importance and at each step along the pathway to delivery in one of the more comprehensive but also well categorised contributions on the partner identification process. Appendix 5 is an abbreviated road map of these contributions for the potential user of the same. Key messages are also presented.

There is a daunting complexity of issues, considerations and criteria for making decisions about research and delivery of novel interventions for vector control, particularly when originating from external sources. Learning systems can contribute to decision making for the earliest phase of this process and support a co-development approach, if that is the style of partnership chosen. The research presented in this thesis confirms that harmonised procedures and tools will support implementation of biosafety and quality assurance, and that designing these with feedback and learning in mind enhances their value further. Some championing and/or ownership of the learning system and the capacity and time to employ them cannot be taken for granted.

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Appendix 1. Survey and questionnaires

List of documents
Table A1.1
Online Survey Recruitment Email
Online Survey Consent Form
Online Survey Questions
Participant Information Sheet
Novel Researcher Recruitment Email
Novel Researcher Consent Form
Novel Researcher Guided Interview Questions
DEC Lab Recruitment Email
DEC Lab Consent Form
DEC Lab Guided Interview Questions
DEC Regulator Recruitment Email
DEC Regulator Consent Form
DEC Regulator Guided Interview Questions

NOTE: At the time of these interviews and survey, the working title for this thesis was: *Deployment of GM mosquitoes for public health: a complex decision in risk management.*

The final title chosen was: *Delivery of a novel intervention for vector control: Learning frameworks to support complex decisions.* It was changed to distinguish the delivery component from overall deployment (see Box 1.2) and reflect the researcher's a shift to learning frameworks from a specifically risk-based approach (see Chap 3). There also has been a clear move towards use of the term "transgenic" rather than "genetically modified" in the related literature, and the researcher considered the novelty aspect as the most relevant characteristic by the end of the study.

Table A1.1 Documentation used for interviews and survey with each target group.

Target participant	Initial recruitment	Understanding and consent		Questions asked
Discoverers and introducers of novel vector control	Contacted by email to do on line survey **GM Mosquitoes – Online survey recruitment email**	**Online survey consent form** appears as a pop up that precedes the survey and offers contact for questions. Participants cannot respond to the survey without marking consent.		**On line survey questions** are found linking to the survey, but are the same as in this document, in a more user friendly format
Discoverers and introducers of novel vector control	Contacted in person, for example at meetings, to request participation in guided interview	All participants are given the **Information Sheet**	**Novel researcher consent form**	**Novel researcher guided interview questions**
DEC lab researchers	Contacted by email following the **DEC Lab recruitment email** and from Target Malaria project		**DEC Lab consent form**	**DEC Lab guided interview questions**
DEC lab researchers – not in Target Malaria	Contacted by email **DEC Lab recruitment email**		**DEC Lab consent form**	**DEC Lab guided interview questions** (with some being not relevant/not asked)
DEC regulators	Contacted by email, or in person after personal introduction by other colleague at meeting **DEC Regulator recruitment email**		**DEC Regulator consent form**	**DEC Regulator guided interview questions**

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Recruitment email for online survey regarding research partner selection

Dear Colleague,
You have been selected to participate in an online survey on innovative vector control research. This is a study about selecting research partners in disease endemic countries for further development of novel approaches. Your involvement in new technologies or approaches to prevent or combat mosquito vectored disease makes your participation very valuable for this study, which is conducted by a team from the Centre for Environmental Policy of Imperial College London.

The survey is located at: https://www.surveymonkey.co.uk/r/3PD6WKY.

The survey takes around 15 minutes to complete. It is taking place globally and is open over the next 4 months. The results will not be attributed to particular individuals, and will only be related to countries or regions if sufficient responses make this relationship anonymous. The results will be held confidentiality for up to two years before deletion, to be interpreted and analyzed for publication in a PhD thesis and possibly journal publication. Please let us know directly if you have any questions or concerns.

Thank you very much for your time!

Best regards

Megan

Megan Quinlan
Senior Research Fellow
Centre for Environmental Policy
Imperial College London
Silwood Park Campus
Ascot, Berkshire, SL5 7PY
United Kingdom
Tel.: +44 (0)20 7594 2496
Email: m.quinlan@imperial.ac.uk

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Selection of Partner Researchers in Disease Endemic Countries

1. Welcome & Consent.

Thank you for participating in our survey. Your feedback and participation is a great support to my research on implementation of complex novel mosquito control strategies.

If you have any questions at any point, please email me at m.quinlan@imperial.ac.uk.

If you would like to receive details of the outcome of this survey then please send me an email to that effect.

You may save the survey at any point to return to it, or submit it without answering all the questions.

The results will be shared, including possibly published, only if sufficient responses make them fairly anonymous.

By continuing with this survey you accept these terms.

1 / 7 14%

Next

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Online Survey Attachment

PhD research: Deployment of GM mosquitoes for public health: a complex decision in risk management

Prof Mumford, j.mumford@imperial.ac.uk
Ms Quinlan, m.quinlan@imperial.ac.uk

Description of the process of including participant and gaining consent appears in the protocol and consent attachments.

Online Survey regarding research partner selection

The final version of this survey, structured as fill in and tick options, appears at https://www.surveymonkey.co.uk/r/3PD6WKY.

Questions to project leaders on selection of partner researchers in disease endemic countries

If you work with more than one partner in a disease endemic country or on more than one project on innovative vectored disease issues, please complete a separate form for each one.

If you are answering for a group of people, such as your lab, consider whether this merits more than one answer form or the group aligns on most points.

I. Details about the context of your collaboration		
Question	**Answer**	**Comments on question**
You have been in charge of or involved in research on innovative vector control measures or innovative vectored disease control in the past 15 years?	_ yes _ no _ unsure Optional: Approx number of years _____	If unsure, explain the research briefly at the bottom of this form or an email, and I can come back to you. Most research of new approaches to vector or disease control would be considered innovative, at least at the time the research began.
You are working on research with partners in disease endemic countries (DEC), or have done so within the past 10 years.	_ yes, currently _ yes, collaboration ended in year: _ I have not worked with DEC research partners in the past 10 years	If your answer is yes (even if the collaboration is ended now, continue). If your answer is no, do not continue with the questionnaire but please do return it.
The partnership is defined by (mark all that apply):	_ an informal understanding _ a letter of agreement or informal document _ a formal contract	You might have more than one type of agreement, but if one type is clearly the basis for

	_ agreements of both you and the DEC partner with a third party, such as the funding body _ other (e.g. Materials Transfer Agreement)	collaboration mark only that one.
You work primarily with (mark all that apply):	_ individual researchers _ departments or research groups _ institutions, including universities _ countries _ through specific research networks __ other	
The research collaboration was initiated and/or proposed by:	_ you and your group _ the DEC research group _ other	
II. **Details about your role in partner selection**		
Question	**Answer**	**Comments on question**
How would you describe the partner selection process?	_ deliberate and well considered _ ad hoc and relying on chance encounters _ based on colleague recommendations _ based on funder recommendations _ other	Mark the one statement that best describes what happened.
How would you class your involvement in choosing a research partner?	_ sole decision maker _ member of decision team _ advisor to decision maker _ informed of decision but not influencing it _ other, please explain	If you had some influence in the decision, proceed to section III. If not proceed to section V.
If there are subgroups, such as Work Packages for a project, did you decide in whom to invite to your group? (explain if possible)	_ yes _ no _ not applicable	
If there is more than one partner in the research or project, was each chosen in a similar manner?	_ yes _ no _ not sure/do not know	

III. Criteria for choosing site (country, region or area)

Rank the importance of each of these typical criteria for selection of the research partner *at the time the decision was made** with 1 being not considered or not very important, 3 indicating taken into account but no more important than other criteria, and 5 being most considered or very important (0 is for not applicable):

1. Biological factors e.g.	0-NA	1	2	3	4	5

- Presence of the study organism at the site where partner works - Absence or other organisms (e.g. other vector species) at that site - Number of vector species - Non target organisms in the area						
2. Human population and disease factors e.g. - Density of population at the site - Incidence of disease at the site - Other interventions already in place	0-NA	1	2	3	4	5
3. Researchers' capacity e.g. - Publication track record - Experience with other projects/research - Education	0-NA	1	2	3	4	5
4. Institutional capacity e.g. - Participating in similar research or projects - Well known and recognised in field - Facilities available	0-NA	1	2	3	4	5
5. National capacity and framework e.g. - Clear guidance on what regulatory decisions will be needed (e.g. permits) - Previous examples of similar research approved and operating - Functional healthcare system (related to research disease)	0-NA	1	2	3	4	5
6. International relations of the country e.g. - membership in organisations or treaties - political relations with bordering nations	0-NA	1	2	3	4	5
7. Language, socio economics or culture of the country e.g. - Language same as yours - Comfortable cultural context for your team	0-NA	1	2	3	4	5
8. Stability, lack of corruption and security of the country	0-NA	1	2	3	4	5
9. Potential for community engagement - Free press and speech - Knowledge of disease/control - Opportunities for understanding innovation	0-NA	1	2	3	4	5

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- Educational levels	
10. Funding source (focus or limitations) 11.	0-NA 1 2 3 4 5
If any of these factors changed over the course of the partnership, please note the number of the factor a *current* ranking here: 12.	

IV. Describe in your own words what most influenced partner selection

V. Outcomes to date from this partnership

Question	Answer	Comments on question
Is your collaboration ongoing?	_ yes, currently operating _ no, ended previously (year research ended _____) _ no, faded out	
Is there an end date for this research?	_ yes (year _____) _ no _ yes, but we hope to obtain an extension	
Has your collaboration ever moved, transferred or ended due primarily to change in staff in your partner's research group or institution?	_ no, I have not experienced such a change _ no, the change did not cause us to transfer _ yes, due to individuals moving _ yes, due to institutional staff changes _ other (describe in general terms)	
Has this collaboration resulted in any publications, patents etc.?	_ yes _ no (or not yet) _ not sure (explain, e.g. there are publications but not directly from this collaboration)	

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If yes, please list by position (or name if you prefer) the number of articles and the lead author – your research group or the partner research group:		If it is easier, please append the publications for me to answer this question.
Has the research partnership resulted in work together on other issues or with other funding sources?	_ yes, with the same teams _ yes, with other parts of the institutions _ no _ not applicable	
If you had to rate the relationship with your DEC research partner, how would you rank it? 1 being a disappointing experience, 3 indicating that expectations were met, and 5 being a highly satisfying experience (0 is for not applicable or prefer not to say):		
What do you believe are the three most important factors for any successes from this partnership?		
What have been three major constraints or biggest challenges?		
How would you recommend other researchers select a research partner in DEC for innovative vector control or vectored disease control research?		

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PhD research: Deployment of GM mosquitoes for public health: a complex decision in risk management

Centre for Environmental Policy

Information Sheet for Interviews

Introduction
You have been selected to take part in a qualitative research study about decision making for use of genetically modified mosquitoes for public health purposes. The study focuses on the discoverer researcher selecting a partner in disease endemic countries; experiences of the DEC researcher in preparing for the early phases of research; researchers and regulators views on the progression from laboratory to field. Each group will be asked about preparations of containment facilities and early stage research capacity. Those relevant to decisions to proceed on to field studies or programmatic health interventions will be asked about that step.

Before you agree to participate, please read this summary and ask any questions or clarifications about the research that you may have. After that, you will be asked to read and sign a consent form to indicate your understanding and agreement to participate in the research. You may also ask questions during the interview, or at a subsequent date.

Your specific responses will be confidential, but will form the basis of general conclusions and interpretations by the researchers. The material may be included in a PhD thesis or shared during internal project discussions, in broader conferences or meetings, or prepared for publication.

Purpose of the research
Researchers at the Centre for Environmental Policy (CEP) at Imperial College London (ICL) are studying the value and impact of new, purpose made frameworks for supporting decisions of various groups involved in use of complex innovations, with a focus on the example of genetic strategies for mosquito vector control. The primary decision making groups are: the discoverers or developers of technology, who often are outside the target disease endemic countries (DEC); the researchers testing the technology within DEC research institutes; and the regulators in DEC countries asked to evaluate and approve the research. The purpose of the study covered by this ethics application is to learn about experiences in employing new frameworks developed by the researcher and others in the Target Malaria project, to validate or refine them for use by any new partners in the project, or to share more broadly with those facing similar situations in other research institutions, countries or regions.

Frameworks can provide a harmonised methodology and criteria, an accessible and transparent record of the decision, and a context for repetition of decisions to achieve similar outcomes for similar conditions and data. Frameworks also allow decision makers to recognise and emphasis any particular criteria of importance to his or her own institution, country or region in relation to the targeted disease vector. For example, a country may have the policy of achieving equity in coverage of a disease prevention or elimination method across the national population or wish to focus on more vulnerable and underserved populations. Using a risk-based approach allows decision makers to propose management and caution in proportion to the risks involved. This also allows for the reduction of uncertainty over time by organising data from various studies in a consistent and understandable framework. Such decision support tools should allow for consistent and robust decisions about various products, technologies or techniques. The framework should allow for different conclusions to emerge depending on priorities and risk acceptance of different decision makers.

Any tools or frameworks developed through this study, or indeed as part of the Target Malaria project, will be shared at no cost, when considered to be validated and reliable.

Procedures for the interview
You will be asked about your opinions and experiences. You may choose to skip a question or return to it, if you wish more time or are not comfortable with a topic. The time and place will be prearranged

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for your convenience. The interview time (depending on the topic) should take no more than an hour, but this timing is flexible and the interview may be broken down to shorter sessions. The interview will take place in English. If you are not comfortable holding the interview in English, it is best not to proceed.

The interview may be digitally recorded, but only as an aide memoire for preparing reports. The information recorded or written is confidential, it will be held on a password protected computer at Imperial College London and access will be limited to the research team. When the research is complete and all related publications are in final version, the recordings or hand written individual surveys will be deleted or destroyed.

Participation in the interview
There is no compensation or personal gain to participating in the research. The benefits are for a larger community of researchers working to reduce or eliminate malaria, and other mosquito vectored diseases, or regulators asked to evaluate this novel approaches.

Refusing to participate or withdrawing (entirely or partially) from this study will have absolutely no effect on your standing at your work or professional community.

Dissemination of conclusions
The researchers aim to draw conclusions and recommendations from the content of your, and others', answers to interview questions. The specific content of your interview or exact quotes, however, are confidential. The researchers will draw conclusions and make interpretations from the responses you provide to the guided interview questions.

Ethical Approval
This study has been reviewed by the head of department of CEP and by the Joint Research Compliance Office (JRCO). You can find more about the general criteria for ethics approval online: http://www3.imperial.ac.uk/researchethicscommittee

Who to Contact
Should you have any question later, after the interview, you may contact the following either with your question in writing or to schedule a follow up conversation to address your questions or concerns in person or by telephone:

M. Megan Quinlan
PhD student and Senior Research Fellow

Imperial College London
Centre for Environmental Policy
Silwood Park
Ascot, Berkshire, SL5 7PY
United Kingdom

Mobile: +44 7590 250436
Email: m.quinlan@imperial.ac.uk

Prof. John Mumford

Imperial College London
Centre for Environmental Policy
Silwood Park
Ascot, Berkshire, SL5 7PY
United Kingdom

Mobile: +44 7590 250407
Email: j.mumford@imperial.ac.uk

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Recruitment for Novel Researcher guided interview

The guided interview questions will be posed to people identified as colleagues from various projects, during meetings and conferences.

Therefore the recruitment will not be by email but rather in person.

The same information sheet and the related consent form will be used.

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Record of Consent to be interviewed

This interview is part of a policy research study on decisions surrounding innovative vector control. You have been selected as a researcher preparing to work with genetically modified mosquitoes or other novel interventions for public health.

Some interpretation and conclusions from this research may be published in a university PhD thesis, a publicly available report or a research journal. Questions relate to personal experience and opinions, reflecting a particular period in time and in the phase and progress of the laboratory research. Results will be anonymized.

Before beginning, the below statements are to indicate consent to be interviewed.

Statement by participant: **If you agree, please initial each box**

1. I confirm that I understand the nature and purpose of the research and have been allowed to review the study information sheet. ☐
2. I confirm that I have had the opportunity to ask questions about the interview and the research, and that those have been answered to my satisfaction. ☐
3. I confirm that I am sufficiently comfortable being asked questions and responding in English as to not require translation to another language. ☐
4. I understand that my participation is voluntary and that I am free to stop the interview or skip over particular questions, at any point, without giving any reason, or retrospectively before the formal end of the interview I may ask for my response to be disregarded or I may change a response. ☐
5. I understand that my interview may be recorded, but that the specific information I provide is confidential. My responses will contribute to a more general interpretation or conclusions regarding the topic. ☐
6. I agree to take part in this interview for the purpose of the study. ☐

_____	_____	_____
Name of Participant	Signature	Date (day/month/year)
_____	_____	_____
Name of Researcher conducting the interview	Signature	Date (day/month/year)

Location of this interview:

Imperial College London

Novel Researcher Guided Interview Questions Attachment

PhD research: Deployment of GM mosquitoes for public health: a complex decision in risk management

Prof Mumford, j.mumford@imperial.ac.uk
Ms Quinlan, m.quinlan@imperial.ac.uk

Research institution methods for enhancing capacity and ensuring biosafety compliance by partner institutions as part of technology transfer

Below are the guided interview questions for this aspect of the study.

The questions relate to three distinct components of novel technology research:

(a) How does your institution interpret, embed and achieve biosafety compliance in your own research on novel technologies or products?

The researcher will ask for a description of the approach taken in relation to national, regional, or local (e.g. institutional or by membership body) regulations and guidance. The researcher will ask for what guidance is followed and how it is interpreted with some specific examples.

Questions will vary by situation, but will be aimed at understanding what biosafety measures are universal and strictly enforced and what may have more culturally based distinctions. There will be a focus on research under permits, for example in containment or confinement but only at Level 2, to the degree possible. (Practices for Level 3 biological hazards are already well documented.)

(b) How have you selected research partners for field testing (with a focus on Africa)?

This section will closely follow the online survey questions, but with more qualitative responses requested rather than numerical ranking.

(c) What mechanisms do you use for ensuring those partners comply with relevant regulations on biosafety features or with international guidance in the absence of national ones?

The objective of this aspect is to learn about approaches to these situations and consider if the approach has been institutionalized in some way, is ad hoc, or follows some external guidance.

Methods for embedding compliance may include new staff induction, use of risk assessments, review and certification of specific skills and periodic lab inspections against an institutional framework based on national legislation and regulation. The researcher will ask an open ended question but follow up by questions about these practices, if the overall mechanism is not clear.

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Recruitment email for DEC Lab

Dear Colleague,

I am contacting you as a leading researcher in mosquito biology or control, in a country facing the challenge of malaria. I understand that you are conducting or preparing for research in novel approaches to vector control. Within the Centre for Environmental Policy at Imperial College London I am carrying out research for my PhD about decision making in the process of moving from lab research to deployment of genetic approaches to malaria vector control, and therefore includes the regulatory component.

My career experience has ranged from regulation and governance for prevention of transboundary pests moving with trade, to institutional structures and regulation of area wide control of insect pests of agricultural and vectors affecting human health. Our research group has much experience with decision support systems and I hope that my study will result in some useful tools, which will be freely available.

This is to ask if you would participate in an interview about your experiences and opinions in the process you have been going through. [information about time and place]. Before we start, I will provide you with details about the research and you will maintain the option of not answering any question as you prefer. You will be asked to sign a consent form before the interview begins.

The interview will take about 60 minutes to complete. An additional hour should be allowed for, however, to respond to any questions you may have. Please let me know if this time is convenient.

Best regards,

Megan

Megan Quinlan
Senior Research Fellow
Centre for Environmental Policy
Imperial College London
Silwood Park Campus
Ascot, Berkshire, SL5 7PY
United Kingdom
Tel.: +44 (0)20 7594 2496
Email: m.quinlan@imperial.ac.uk

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Consent form for DEC Regulators guided interviews

Record of Consent to be interviewed

This interview is part of a policy research study on decisions surrounding innovative vector control. You have been selected as a regulator in a country facing the challenges of malaria. Questions relate to personal experience and opinions, and will not be taken as official commentary.

Some interpretation and conclusions from this research may be published in a university PhD thesis, a publicly available report or a research journal. Responses will be anonymized.

Before beginning, the below statements are to indicate consent to be interviewed.

Statement by participant: **If you agree, please initial each box**

7. I confirm that I understand the nature and purpose of the research and have been allowed to review the study information sheet. ☐
8. I confirm that I have had the opportunity to ask questions about the interview, and that those have been answered to my satisfaction. ☐
9. I confirm that I am sufficiently comfortable being asked questions and responding in English as to not require translation to another language. ☐
10. I understand that my participation is voluntary and that I am free to stop the interview or skip over particular questions, at any point, without giving any reason, or retrospectively before the formal end of the interview I may ask for my response to be disregarded or I may change a response. ☐

13.

11. I understand that my interview may be recorded, but that the specific information I provide is confidential. My responses will contribute to a more general interpretation or conclusions regarding the topic. ☐
12. I agree to take part in this interview for the purpose of the study. ☐

_____	_____	_____
Name of Participant	Signature	Date (day/month/year)
_____	_____	_____
Name of Researcher conducting the interview	Signature	Date (day/month/year)

Location of this interview:

PhD research: Deployment of GM mosquitoes for public health: a complex decision in risk management

Prof Mumford, j.mumford@imperial.ac.uk
Ms Quinlan, m.quinlan@imperial.ac.uk

Questions for DEC partner PIs or others in the DEC research labs

Introduction by interviewer

(This sheet is for the interviewer to follow as a guided interview. It is not designed for handing out to participants for written responses.)

As a partner in research on a novel intervention for mosquito control, your opinion and experience on the following issues is valuable. There are no correct or incorrect answers. I suggest you respond with your first instinct for most questions.

Reponses will be used to inform my PhD research. Although I will not attribute specific comments, the limited number of participants may make it possible to identify your country and institution. The questions have been approved through the Imperial College London ethics process. If you believe your institution needs to review these, e.g. through your own ethics committee, please let me know at any point during the interview and we will stop and await that step. (Information sheet has already been shared at this point and consent is given. Information sheet with contacts in Imperial College London will be left with each participant.)

Understanding this phase of the project

It is recommended for research with novel technologies, such as genetically modified organisms, to proceed in phases.

Do you/your team understand the role of the containment laboratory studies in preparation for field studies? If so, please explain it.

What are the next steps or phases in the progression of the project after the sterile male studies in containment are complete?

What specific steps and studies would you recommend to move from the containment studies to a field study?

Do you/your team understand the phase of working with a sterile male strain before other technologies, even though this is not viable for field programs? If so, please explain it.

Could you explain what the term “facilities readiness” means for our project?

How would you describe the components of colony utility to someone outside the project? Do you think your team understands this concept?

What do you consider to be the main project-level policies that affect your laboratory based activities and studies, which were not already in place from your own institution?

Do you have the team you need in place and trained to import and carry out studies on a GM strain of mosquitoes?

- If not, what additional team preparation or team members would you like to have?

Options for preparing and supporting capacity

Consider these options for preparing and supporting your team. Comment on the value and effectiveness of each. Did you find this change over time? Do you think there is a good progression of approaches, or one is enough when considering cost and time delays?

For colony maintenance:

- Written instructions and documents are adequate to achieve this
- Monthly calls with the insectary working group provide all needed
- Members of our team being trained at other labs (e.g. in Italy) is effective
- Short term (less than a week) training at our lab is an effective way to increase capacity
- In general, individual visits from project partners has provided us with what we need to maintain colonies
- Meeting and visits to sister labs in the project, doing similar activities should be arranged
- Someone more experienced should be working with our team over several months

For documentation and data:

- Written instructions and documents are adequate to achieve this
- Monthly calls with the insectary working group or project management provide all needed
- Members of our team being trained at meetings such as the annual project meeting is sufficient
- Training at our lab is an effective way to increase capacity
- In general, individual visits from project partners has provided us with what we need to follow the SOPs on lab notebooks, create records and employ the insectary database and other record keeping
- A routine audit or review of our documents and data from others in the project is needed
- Someone more experienced should be working with our team over several months on this area

For regulatory compliance:

- Written instructions and documents are adequate to achieve this
- Monthly calls with the insectary working group, project management or the regulatory advisor has provided all needed

- Members of our team visiting other labs with similar containment levels has been most useful
- Training in biosafety at our lab was an effective way to increase capacity
- External training in biosafety and compliance mechanisms in other countries is needed to be able to do this in our setting

What other areas of training have you or your team completed because of the project?

What other areas of training are you or your team engaged in or actively seeking to organize within the near future (e.g. six months)?

Are you able to carry out procurement for any additional equipment or supplies needed?

Are you/your team confident in managing supplies, routine tasks and periodic tasks that make up the general work flow over the course of a month, for example?

Are you/your team prepared to ramp up production to twice the current numbers without additional training or staff? If not, what would be required?

Do you believe that five years from now the equipment and supplies introduced by the project will still be operational and maintained (if not, what will prevent that?)

Do you believe that you will have the same team members working with you in five years, if the project continues at the current or a higher budgeted level?

Standard operating procedures and biosafety manual

How involved were you in preparing the project-wide SOPs?

How involved were you in preparing site specific SOPs?

What went well and what would you suggest doing differently for a new site getting set up? (Regarding employing project SOPs or site specific SOPs or plans)

Are you (is your site) in compliance with all of the existing SOPs and biosafety manual to date?

If not, do you believe the SOPs need revision, or the team needs to comply more closely?

In terms of the insectary compliance and set up, are you are ready to import as soon as the permit is issued? If not, what remains to be done?

Documentation and records

Do you have a record for all mosquito colonies housed in the lab (Wild Type Colony Record, CoA for imported strains, or other)?

Is your team is recording laboratory activities performed using lab notebooks according to the approved SOP?

Is your team scanning and sharing lab notebooks routinely by saving to the correct location in a timely manner?

Are you using the correct template to record monitoring of free flier mosquitoes in the insectary and saving them to the database, in a timely manner?

Are you using the insectary database successfully?

How do you expect the data you are recording will be used?

Who do you feel owns the data and research outcomes?

Are you staffed and trained to do a full analysis and publish results of your work?

Role of insectary/facilities audits and visits from project partners

How was the time/work load required to prepare for the facilities audit in advance considered by you and your team (at the time)?

How was the time required for the audit to take place and the follow up response considered by you and your team (at the time)?

Did the report style of the audit made sense to you and your team; was it easy to use for follow up actions? What it too broad or repetitive? Would you suggest a different version, or a different approach?

Did you think the composition of the audit checklist covered all factors of concern to you in preparation for importation of a GM mosquito and the associated studies to be performed? If not, what would you add?

Did you consider the composition of the audit team to be adequate to the task? If not, what expertise would you add?

Could you or one of your team participate effectively in an insectary/facilities audit of another facility, within the next 12 months?

Could a self-audit carried out by your own team replace the type of audit you participated in, within the next two years? If not, five years?

Role and responsibilities

Where you believe the responsibility rests between the country PI as an individual researcher and your institution (including individuals above you in the institutional structure) in terms of ensuring facilities readiness, biosafety management and the reliability of study results?

Could you be held accountable for all lab biosafety requirements without external support at this stage?

If not, when might you and what would that require to achieve? What support would make the most difference to you to succeed?

In what time scale could this happen? e.g. 0-3 months, 3-6 months, 6-18 months, Unknown

Can you be held accountable for compliance within the insectary with any conditions that may be added to the permit for import?

- If you are uncertain or answer no, what support would make the most difference to you to succeed?
- In what time scale could this happen?
  14. 0-3 months 3-6 months 6-18 months Unknown

What is your greatest concern at this time about proceeding with the import and study of a sterile male strain of mosquito?

What is your greatest concern at this time about proceeding to lab studies with the next strains, which are classed as gene drive?

What is your biggest sense of accomplishment in terms of improvement in facilities readiness, biosafety assurance and preparedness for import and studies, from start of the partnership until now?

Is there any area of responsibility where you feel you/your team are ready but it has not yet been passed from the central advisors and management team?

What does it mean to you to be accountable for your facility and insectary research team? Other comments on transfer of responsibilities to the local PI or institution?

Thinking of these three themes, where do you think your facility and research group would appear in terms of preparation?

Colony utility

1. Identity of wild type colony is not clear or not properly documented
   15.
2. Identity of the WT colony is clear, but there is some question on identity maintenance for the imported strain(s)

3. Identity clear but variation amongst generations is too much (e.g. size of mosquitoes, fecundity) or the outcomes are not as expected (e.g. sex ratio)

4. Identity clear and generations are similar over time, indicators as expected

5. Identity clear, and generations are similar, and benchmarking has allowed us to estimate the relationship of our colonies to mosquito colonies in other locations of the project

Compliance

1. There is some doubt that all of the law and regulations that might apply are identified

2. All of the laws and regs that apply to both all of our activities have been identified

3. We know all of the laws and regs that apply and are in compliance with most of them
   16.
4. We know all of the laws and regs that apply and are in compliance with all relevant national requirements
   17.
5. We are in compliance with national requirements and project policies and requirements

Defensible science

1. The concept of defensible science and/or the burden of work to provide all of the records and evidence requested by the project remains new to us

2. The concept of defensible science to support longer term technology development is understood but not yet followed
   18.

3. Defensible science practices are understood and followed to the degree they are laid out in SOPs or the biosafety manual

4. Defensible science practices are understood and followed as laid out in SOPs or the biosafety manual, as well as from our own understanding and initiatives to ensure long term record keeping
   19.
5. We are confident that all of our work can be reviewed, evaluated and repeated some years later based on the records kept and the team's commitment to defensible science

Imperial College London

Recruitment email for DEC regulators

Dear Colleague,

I am contacting you as a key decision maker in a country facing the challenges of malaria. Within the Centre for Environmental Policy at Imperial College London I am carrying out research for my PhD about decision making in the process of moving from lab research to deployment of genetic approaches to malaria vector control, and therefore includes the regulatory component.

My career experience has ranged from regulation and governance for prevention of transboundary pests moving with trade, to institutional structures and regulation of area wide control of insect pests of agricultural and vectors affecting human health. Our research group has much experience with decision support systems and I hope that my study will result in some useful tools.

This is to ask if you would participate in an interview about your experiences and opinions in the process you have been going through. [information about time and place]. Before we start, I will provide you with details about the research and you will maintain the option of not answering any question as you prefer. You will be asked to sign a consent form before the interview begins.

The interview will take about 45 minutes to complete. An additional half hour should be allowed for any questions you may have. Please let me know if this time is convenient.

Best regards,

Megan

Megan Quinlan
Senior Research Fellow
Centre for Environmental Policy
Imperial College London
Silwood Park Campus
Ascot, Berkshire, SL5 7PY
United Kingdom
Tel.: +44 (0)20 7594 2496
Email: m.quinlan@imperial.ac.uk

Imperial College London

Consent form for DEC Regulators guided interviews

Record of Consent to be interviewed

This interview is part of a policy research study on decisions surrounding innovative vector control. You have been selected as a regulator in a country facing the challenges of malaria. Questions relate to personal experience and opinions, and will not be taken as official commentary.

Some interpretation and conclusions from this research may be published in a university PhD thesis, a publicly available report or a research journal. Responses will be anonymized.

Before beginning, the below statements are to indicate consent to be interviewed.

Statement by participant: **If you agree, please initial each box**

13. I confirm that I understand the nature and purpose of the research and have been allowed to review the study information sheet. ☐
14. I confirm that I have had the opportunity to ask questions about the interview, and that those have been answered to my satisfaction. ☐
15. I confirm that I am sufficiently comfortable being asked questions and responding in English as to not require translation to another language. ☐
16. I understand that my participation is voluntary and that I am free to stop the interview or skip over particular questions, at any point, without giving any reason, or retrospectively before the formal end of the interview I may ask for my response to be disregarded or I may change a response. ☐
    20.
17. I understand that my interview may be recorded, but that the specific information I provide is confidential. My responses will contribute to a more general interpretation or conclusions regarding the topic. ☐
18. I agree to take part in this interview for the purpose of the study. ☐

_____	_____	_____
Name of Participant	Signature	Date (day/month/year)
_____	_____	_____
Name of Researcher conducting the interview	Signature	Date (day/month/year)

Location of this interview:

PhD research: Deployment of GM mosquitoes for public health: a complex decision in risk management

Prof Mumford, j.mumford@imperial.ac.uk
Ms Quinlan, m.quinlan@imperial.ac.uk

DEC Regulators experience with decision making

Below are the guided interview questions for this aspect of the study.

The questions relate to experiences in making regulatory decisions about novel interventions (in any sector):

(a) Have you faced decisions about complex or novel products, technologies or techniques in your capacity as regulator?

The researcher will ask what made the proposed intervention complex or novel and if the regulator could evaluate it:

- Based on his or her own existing knowledge and experience
- Within the existing regulatory framework
- If not, how was this gap addressed

(b) Was this a research phase requiring containment (physical facilities) or confinement (physical, ecological or biological restrictions)?

The researcher will ask about:

- What was the nature of the containment/confinement
- How was this type and level of restriction chosen
- If the study is complete, did it move to the next phase

Questions will vary by situation, but will be aimed at understanding what biosafety measures are universal and strictly enforced and what may have more culturally based distinctions. There will be a focus on research under permits, for example in containment or confinement but only at level 2, to the degree possible. (Practices for Level 3 biological hazards are already well documented.)

(c) What specific decisions in this process proved challenging? How were they made?

The objective of this aspect is to learn about approaches to these situations and consider if the approach has been institutionalized in some way, is ad hoc, or follows some external guidance. The researcher will ask an open ended question but follow up by questions about these practices, if the overall mechanism is not clear.

The possibility for a decision support tool, framework or guidance will be discussed to see for which decisions and circumstances the regulator would be supported by this addition.

Appendix 2. Comprehensive criteria for site and partner selection

Table A2.1 Informal Questionnaire to guide conversation during initial Teleconferences

This is not a script but rather a list of important points to cover, that may also facilitate taking notes.
Questions in parentheses are more in depth and optional.
It may be worth agreeing in advance who will be taking notes, and who will cover each point.
Is it acceptable to record the call? Before starting, fill in the below basic information.

Name:_____
Title/Job:_____
Institution:_____
City:_____Country:_____
Department or project:_____
Known affiliation with our institution already?

Introductions of everyone on the call, and his or her role.

Explanation of the technology (no more than 10 minutes)

Comments on phased testing

(Comments on what role you see our institution taking, versus what is needed in the field, e.g. support for design, biosafety dossier, etc but management and reporting from field partner)

Explanation of the purpose of the call: to inform and to receive general information

(Have you or do you have any other affiliation with our institution?)

Explain status of funding – some support exists to prepare a proposal to seek funding

Be sure it is clear that final site selection is not yet taking place

Describe concept of a group moving forward with one or two field sites, but other partners remaining included for the next phase of field studies.

> Would that work for them? (Do they have any experience with similar groups working this way? Have they already forged any relationship with the other candidates previously?)
>
> *NB: Decide ahead of time if you are willing to share the short list.*

This research will require a multiyear process to move to the next phase.

> Ask if the person and institution are in a position to participate in a multiyear proposal process and multiyear research. (Encourage a clear answer: yes or no.)
>
> (Ask if they believe they would be prepared to provide a field site, or would prefer to participate as second phase. See final questions.)

What Anopheline vector species and other Anophelines are common in your potential field sites? Is the population similar from year to year? Seasonal? Significantly affected by current vector control measures?

Describe the relevant expertise of yourself and others at your institution(s) as reflected by previous activities in (a) entomological field activities in collecting and e.g. mark-release recapture, (b) culturing mosquitoes on a continuing basis, (c) analyses performed by PCR (d) other relevant experience.

Describe in general terms the existing facilities, equipment and personnel currently employed that might be used for this project. Briefly describe the projects in which these have been involved. Include approximate numbers of technical staff, outdoor and indoor cages, molecular laboratory etc.

Are there any plans for enhancement of the facilities? Do you believe the current facilities would be adequate for work with a GMO? (i.e. what is the security level, what about the location in relation to other activities, any perceived problems?) How booked up are these facilities?

What experience (if any) does your institution have importing and testing living organisms, including plants, or other organisms requiring containment? Or have you had other research requiring regulatory approval? (Construction of large cages? Use of infected mosquitoes in lab? Collecting native species for export?)

Do you have experience obtaining ethical approvals for research? (National ethical review board, institutional review board – although this is unlikely for insects unless GM, they may have interacted on some study of malaria incidence)

Briefly describe past projects working in local communities and the ethical and regulatory oversight that applied.

Does your institution have social science research, for example surveys of population on health interventions, behavior, and knowledge of disease? Or if not, do you work with some other organization on this front?

Has your institution any experience with public consultation, community education or other forms of engagement?

What is the general reaction to introduction of new technologies in your society? Is there a general trust in science and the government?

Does your institution have any formal ties or advisory role with government bodies or programmes? For example, vector control programmes? Describe the role or relationship.

Are these ties at the local, regional or national level (or all)?

What is your institution's main source of funding?

Has your institution much experience with proposal preparation and/or do you often bid with other partners?

> What do you believe would be the biggest obstacle to carrying out the field testing of a GM mosquito?
>
> Do you believe your country would be prepared to provide a field site, or would prefer to participate as second phase?

Do you have any particular concerns or questions?

Final comments from them?

> If someone asks a question, after you answer ask again if they have any further questions until none are given.

Explain what will happen next and the approximate time frame for that.

> Any questions on what will happen next?

Comments from the interviewers after the call ends.

Were any important points left hanging?

What follow up was promised? (Who will do it, by when?)

What is your general feeling about this partner? (The individual and the institution)

What most concerned you about their responses?

What did you find most encouraging?

From this initial contact, do you recommend that they become part of the team?

Objectives as stated in information about teleconferences:

1. Convey information to them.
- Explain the technology and general plan for phased testing
- Be sure that they know the status for the field project (i.e. that funding will be sought)
- Confirm that they realize that final selection of a field site is upcoming
- Introduce idea of more than one country/institution working together in this phase, and probably for the next phase as well
- Provide details on funding of this phase in terms of expenses for proposal preparation (only if asked? I would be discouraged if this came up at this stage)
- At this stage, you can confirm their interest and capacity in working on a proposal for funding over a multiyear time frame

2. Obtain or confirm general information about them.
- Hear about their work with An. gambiae in general (e.g. population based, malaria research, etc)
- Clarify the status of their current facilities and any planned enhancements
- Determine the extent of their knowledge of their country's regulatory procedures, especially concerning biosafety and ethics approval
- Find out any of their immediate concerns
- Get a feel for the person (people)

3. Obtain specific information on their institutes
    - Hear their ideas for potential field sites
- Find out about their staffing and current capacity– their current research, projects that are ongoing or other sources of funding, likelihood the same people will remain
    - Ask about their experience seeking funding and successful funding sources (do they generally partner with another group/country; Northern institution, etc)
    - Get any specific information they can provide on the national regulatory system for biosafety, find out if other GMOs have been introduced
    - Find out if they have ever imported mosquitoes or other insects (non GM) from other countries or know how this could be done
    - What level of security are their own facilities?

4. Obtain specific information on their national context.
    - Ask about the country's culture of community involvement in decisions regarding new technology (i.e. stakeholder consultation or trust in government processes?)
    - Their view of the public's general knowledge of vector control
    - Their own organisational capacity on social issues, community engagement or surveys that relates to these issues or similar
    - Their relationship with local and national governmental bodies

Table A2.2 Early questionnaire towards developing a proposal as expressions of interest from potential DEC research partners

(used with permission of Target Malaria).[a]

1. Identification of field site(s). Describe the sites for experimental releases of sterile males and sites to be used as experimental controls. Include descriptions of the following (with citations to published work as appropriate). If you have more than one location that you would like to consider further, then give the information for each one.

a) Geography (name; latitude and longitude; approximate area (ha or km^2); nature and extent of isolation from other populations; link to view on GoogleMaps).
b) Entomology (what vectors are there; seasonal abundance; what other mosquitoes are there).
c) Human population (how many people live there; what is the housing like).
d) Epidemiology (what is the current burden of malaria; what are the current control measures and who is responsible for these; are they likely to change in the next 3 years?).
e) Logistics of working there (including transport details from main institution and site of mosquito production facility).
f) History of working there (describe any previous studies you have conducted at this location).
g) Does the location include any protected or significant biotypes/ecotypes, such as nature reserves, or threatened or endangered species?
h) Describe the proposed locations in terms of risk of adverse natural conditions (e.g., hurricanes, floods, mudslides, earthquakes, volcanoes). This should include locations containing laboratory facilities, access routes, etc., as well as the proposed release sites themselves.
i) Describe the relevant similarities and differences between the proposed release and control sites.
j) Are there any studies you wish to do to confirm your choice of study site? If so, include description of these studies, timeline and budget.

2. Pre-release lab studies. These are the proposed lab studies to be done prior to release. Briefly describe how you would do each one (from a single sentence to a paragraph).

a) Establish insectary containment to suitable level (include description of current facilities and refurbishments or construction required, if any).
b) Import and establish transgenic mosquitoes.
c) Transfer transgene into local genetic background; confirm male sterility in crosses to local mosquitoes; and confirm phenotypic integrity of fluorescent marker.
d) Determine competitiveness against local mosquitoes.
e) Determine life history characteristics of transgenic mosquitoes.
f) Evaluate methods that will be used to monitor transgene frequency in the field (markers, species ID, PCR).
g) Describe other lab studies you think are worthwhile, explain why and what you would do
h) The proposed timeline is that the lab studies could be done in 2 years, once the facilities were built. Is this realistic at your institution? Describe the order in which you would do things. If construction is required, how long will this extend the timeline?
i) What regulatory approvals are needed for these lab studies?
j) What resources are needed for these lab studies (personnel, budget, other)?

3. Pre-release field studies. The following baseline information would be necessary or useful. Please describe how you would do each one.

a) Monitoring to determine seasonal abundance.
b) Monitoring natural sterility levels of wild-caught females.
c) Population modeling (this would be done in conjunction with the Imperial and Oxford groups).
d) Locating mating swarms (if possible).
e) Develop release methods.
f) Determine what methods of mosquito control are in use and if any changes are foreseen for the duration of the trial.
g) Describe other field studies you think are worthwhile doing, explain why they are worthwhile, and explain what you would do. Possibilities include studies of density-dependence; monitoring insecticide resistance; capture-mark-release-recapture studies, and other you may think of.
h) Could all this be done in the same 2 year period as the lab studies? Describe the order in which you would do things.
i) What resources are needed for these pre-release field studies (personnel, budget, other)?

4. Sterile male production facility. Describe the facilities currently available for the production facility and the upgrading required. Include construction budget and time required.

Personnel requirements will vary according to whether the sorting is done manually or by an automated sorter. What is the total cost of a technician at your institution, and how many hours per week would they typically work?

5. Field activities during and after the release period. Please describe how you would do each of the following activities.

a) Dispersal monitoring of transgenic males.
b) Continued monitoring to determine seasonal abundance of mosquitoes.
c) Monitoring sterility levels and mates of wild-caught females.
d) Determine whether HEG males [see footnote previous page] participate in mating swarms (useful but not essential).
e) Continued assurance measures of phenotypic stability (i.e., correlation between fluorescence and marker).
f) Describe other field studies you think are worthwhile doing during the trial, explain why they are worthwhile, and explain what you would do.
g) How long you would want to continue monitoring after releases stop?
h) What resources are needed for these field studies (personnel, budget, other)?

6. Capabilities. The following capabilities are necessary for the lab and field studies; please comment on your current capabilities and where resources are needed to fill gap(s). Please also describe any other capabilities you see as relevant.

a) **Lab studies:** Insectary support for genetic crossing; Fluorescence microscopy; Medium-scale mosquito production (~40,000 per day); Outdoor cages for preliminary trials of HEG males? [see footnote, this step was not mandatory]; PCR capability; Insecticide resistance bioassay/biochemistry; Stable and secure insectaries; Competent technical staff; Senior staff available for close supervision.
b) **Field studies:** Ease of reaching field sites from laboratory/insectary; Isolated field sites (islands, villages); Vehicles & drivers; Adult and larval entomological surveillance equipment and skill; Experienced supervisory field staff.

7. Social and community engagement; communications.

a) How is community engagement for vector control normally conducted in the country/location?
b) Describe (i) any surveys of attitudes and beliefs in the community, and (ii) communications or educational programmes you would carry out. Include names of collaborators, if appropriate.
c) What resources will be necessary for these programmes (personnel, budget, other)?

8. Risk assessment. Describe any risk assessment you think will need to be carried out, and who might do it. Will risk assessments be funded by applicants or by the regulatory authorities?

What are the requirements for mitigating adverse outcomes? Who is responsible? What kinds of insurance are needed? Who pays for the mitigation and insurance?

9. Project management. Describe how you would manage the project, including names of individuals involved and the proportion of time to be spent on the project.
10. Co-funding. Can you suggest any bodies to approach for co-funding of these trials (e.g. Private foundations, Government grants, Resource-sharing with current vector control efforts)?
11. Collaboration. List other institutions you would like to collaborate with in these studies.

[a] This Table is based on a form originally entitled *HEG-based sterile male trial: a questionnaire towards developing a proposal*, and had a layout to allow write in responses. It has been edited slightly. It was developed by the researcher with Mark Q. Benedict and Austin Burt when Target Malaria was still under the FNIH, and it refers to the homing endonuclease gene (or HEG) as an engineering mechanism used during that period of the project.

Table A2.3 Initial summary of potential partners

(used with permission of Target Malaria).

Criteria	Country A	Country B	Country C	Country D	Other
1. General regulatory context					
2. General capacity for research					
3. General ability to meet objectives of study/extend to next phase					
4. Identification of field site)s) • Mosquito population • Human population and disease incidence • Other control programmes • Logistics of working there • Other					
5. Pre-release lab studies • Facilities • Import structure • Laboratory trials					
6. Pre-release field studies • Baseline data • Ecology of population • Release methods • Other suggestions					
7. Sterile male production facility • Current capacity • Costs for expansion					
8. Field activities during and after the release period • Monitoring GMM • Monitoring wild population					
9. Capabilities • Existing staff • Contractual staff available • Social science staff • Project management					
10. Social and community engagement; communications					

11. Risk assessment requirements					
12. Project & Risk management and compliance					
13. Institutional support					
14. Co-funding (good suggestions and/or sources)					
15. Collaboration and other					
16. PI and other key staff availability					
17. Preparedness to undertake project					
18. Overall budget and timing of required funds					

Tables A2.4–A2.6 present comparisons of criteria for country, site or partner selection as discussed in Chapter 5.

Table A2.4 Scientific				
		Brown et al., 2014 - *Aedes aegypti* RILD (transgenic SIT)	Malcolm et al., 2009 - *Anopheles arabiensis* SIT	Iyaloo et al., 2014 - *Aedes albopictus* SIT
		The target species must be present at the proposed site(s).		
Entomological data	*Presence of target species (Aedes aegypti)*	Is the target species present at selected sites (proposed release and control sites)?		
		What data are available on current and historical numbers of the target species at each location (many types of data are relevant and 'ideal' information may not be available)?	**A low density of vector population amenable to inundation with released males**	**A low density vector population amenable to inundation with released males**
		How do those population sizes fluctuate through the different seasons of a year?		**Presence of a sole vector species with well characterised population dynamics**
		What is the history of the target species and how have populations changed over time (again, many types of data are relevant and 'ideal' information may not be available)?		
	Presence of other mosquito sp	Are other mosquito species present?	**Presence of one vector species**	
		Which species appear and in what estimated or relative numbers in monitoring systems to be used (from any trapping system, but particularly from ovitraps, BG-Sentinels and backpack aspirators).		
Human inhabitants		What are the approximate numbers and demographics of the human population(s) of proposed release and control sites?		
Presence of disease		Describe the nature of dengue transmission at the proposed release trial site(s), including possible transmission by species other than Ae. aegypti.	**Significant actual or potential malaria transmission**	**Significant actual or potential disease transmission**
		What is the history of dengue at the proposed locations? (Dengue incidence by year, season, location; is there laboratory confirmation of dengue fever and dengue haemorrhagic fever; age-specific incidence; circulating serotypes)		
		What is the status of chikungunya and yellow fever viruses in the proposed sites?		
		Describe the availability of facilities for monitoring dengue incidence (e.g. medical clinics, clinical research facilities) at the proposed sites, and how these are funded.		
		What are the most frequent illnesses and top medical issues for people in the target community? How often are these confused with dengue fever?		
Size(s) of proposed sites		Describe the scale of site(s) in terms of geographic area (hectares or km2). Mosquito and human populations are described in text (Entomological Data and Human inhabitants sections, respectively).		
Duration of trial		What is the capacity for commitment of the DEC partners to the duration of the trial?		
Isolation		Are the proposed sites geographically isolated by ‡ 400 meters?		
		What is the nature of the isolating terrain or other barrier(s) separating the mosquito population at the site from other known or suspected mosquito populations?	**An isolated vector population**	An isolated vector population
		If the sites have £ 400 meters isolation, what mitigations are available, e.g., barrier treatment in buffer zone?		Ecological relevance and stability [in terms of being representative of eventual field sites for vector control]
Control sites		Can a control site be identified for each potential trial site?		Presence of control sites [in terms of sites that can be monitored as a control to compare with the study sites]
		To what extent are they similar and different to the proposed release sites in aspects relevant to the trial (or to what extent are there a set of comparable sites to be used either for release or as controls)?		
Protected biotype and other significant resources		Survey and describe the protected biotypes/ecotypes and other sensitive areas that are within or close to the proposed sites.		
Other vector control activities		What vector control operations are conducted in the area?		
		Who is responsible for these activities?		
		How are these activities funded (through which agencies/bodies of government)?		
		Who are the contact people for each relevant agency?		
		What is known of their program or intentions for treating (or otherwise) the proposed trial sites? Please refer to the questions in the Regulatory section about statutory or compulsory treatment.		
Adverse natural conditions		Describe the proposed site environment in terms of risk of adverse natural conditions. As appropriate, this should include locations containing laboratory facilities, access routes etc., as well as the proposed release sites themselves.		
Adverse human activities		What is the distance to roads, railroads, airports and other possible means by which released mosquitoes can be transmitted by humans out of the trial sites?		
		Is there a real threat of civil unrest, nationally or in proposed trial area(s)?		
Next steps		If the planned trial is successful, what are the prospects for moving to a larger scale at the same or nearby site?		

Table A2.5 Regulatory Requirements					
		Brown et al., 2014 - Aedes aegypti RILD (transgenic SIT)	Lavery et al., 2008 - Ethical, social, and cultural considerations for site selection for research with genetically modified mosquitoes		Iyaloo et al., 2014 - Aedes albopictus SIT
			Regulatory considerations	**Community engagement considerations**	
Genetically engineered mosquitoes	*Legislation and permitting*	Are regulations/legislation in place governing research and other activities with recombinant DNA, etc.? - If so, what are the key relevant regulations/legislation? - Is there any risk that the research would displace individuals or communities at the preferred site(s)?	**Are there regulations governing research involving recombinant DNA, gene transfer, etc.?**	**- Is there any risk that the research would displace individuals or communities at the preferred site(s)?**	
		What is the status of the Cartagena Protocol on Biosafety (http://bch.cbd.int/protocol/) in the country and how is it being implemented? - If relevant, identify the in-country CPB contact point. - Has the country had negative experience with GMOs?	**What is the status of the law(s)?**		
		Were any relevant legislation or policies in place prior to Cartagena obligations and what is their current status?	**Is there new, original legislation governing research uses of GMOs and biosafety?**		
		Are there any specific laws/norms/guidance, etc., regarding vector control where project activities (e.g., baseline monitoring/surveying) might interact with these regulations? - Any conventional control plans (e.g., IVM, barrier treatment, risk mitigation plans) will need to take account of any such regulations.			
		Are there other known regulatory/legal issues that may affect project operations? Examples may include: - Restrictive customs regulations or delays, - Immigration (visas, work permits), - Restrictions on exporting samples (for example, biodiversity/bioprospecting law).			
		There is no widespread opposition (public or institutional) to testing genetically engineered strategies.	**Does the country have any relevant legislation/policy related to GMOs that existed before assuming its Cartagena Protocol obligations? What is the current status of these existing laws?**		
		There is a credible regulatory structure in place to sanction all of the necessary research activities, including import/export, transport and research.	**Is there a national body overseeing the development of policies based on Cartagena commitments? What is its mandate?**		
Regulatory processes		Has the country had previous experience importing GE mosquitoes for laboratory research? - If not, what about other GE insects (e.g., Drosophila for research purposes), plants or other animals? -- What are the conditions for on-going negotiations and interactions with the community?	**Has the country had previous experience importing GM mosquitoes for research purposes?**	**Are there existing data on community views regarding GMOs?**	
		What are the relevant national, state, municipal and local agencies and their specific roles? - Are there NGOs or other formal groups with experience advocating for communities?	**What are the roles of the Relevant Agencies?**		
		Is there a clear process for application and approval for the proposed research? - If so, provide an outline of the structure and process - What are the estimated time-lines for completing each of the regulatory steps? - What is the basis for this estimate? - Is there adequate infrastructure for broad public engagement?	**Is there a clear process for application and approval for the proposed research?**	**Is there adequate infrastructure for broad public engagement?**	Regulatory approval/acceptability and administrative authority
		Is a risk assessment/risk management plan required? If so, who develops it, the applicant or the authority? - Are there NGOs actively protesting GMOs and likely to respond to a GM insect trial?	**Is an independent risk assessment review required?**	**Are there NGOs actively protesting GMOs and likely to respond to a GM insect trial?**	
		What are the opportunities/mechanisms/requirements for public engagement in the regulatory process? What are the opportunities/mechanisms/requirements for public engagement in the regulatory process? - Some regulatory processes are fully confidential, some open to the public, some are a mix (for example, applications become publicly available but information identified as confidential by the applicant is redacted).			
		What are the inspection and audit regimens for compliance with granted permits? - These may be described in the legislation, but in some instances may not be known in advance of the permit being granted, for example, they may be attached as conditions of permits.			
		What are the internal approval procedures of the proposed in-country collaborating institution? - Are there precedents for prior use of these procedures? - What committees/structures are involved? - Is this a public or confidential process? - Are there interactions with governmental approval/permitting processes? With ethical, social, and cultural? - Is there sufficient capacity for regulatory compliance and reporting?			
Other regulated research		Describe the Institutional Review Boards (IRBs)/Institutional Ethics Committee (IECs) responsible for oversight of Human Subjects research at the institutions to be involved in the trials.	**Does the country have national guidelines for Research Ethics Review? Are there established Research Ethics Committees?**		
		Describe the Institutional Biosafety Committees (IBC) or equivalent review bodies responsible for oversight of research involving biohazardous agents.			
		Describe the Institutional Animal Care and Use Committee (IACUC) or equivalent institutional review bodies responsible for oversight of research involving vertebrate animals.			
		Does the country have national guidelines for research with recombinant DNA?			
		Does the in-country collaborating institution have an established research review procedure for research with recombinant DNA? - If so, what are the procedures, structures, informational requirements and projected timescale(s)?			

Table A2.6 Community Engagement (Ethical, Cultural, and Social)				
		Brown et al., 2014 - Aedes aegypti RILD (transgenic SIT)	Lavery et al., 2008 - Ethical, social, and cultural considerations for site selection for research with genetically modified mosquitoes	
			Regulatory considerations	**Community engagement considerations**
Communication	*Residents*	What are the mechanisms and conditions to facilitate interface with the trial-site residents and basis for ethical, cultural, and social (ESC) collaborations? - Describe any previous interactions of the collaborators with the community at the proposed trial site. - Is there an ongoing relationship of trust with the public health agencies and institutional scientists? - Describe proposed methods for informing and involving the community in preparation for trials. How would community opinions influence planning for the trials? - Is there any precedent or other evidence for the likely effectiveness of these methods?	**Are there mechanisms to facilitate interface with the community and basis for ESC collaborations?**	**Are there NGOs or other formal groups with experience advocating for communities?**
		How is community engagement for vector control normally conducted in the country? - What is the level of understanding by communities in the proposed trial sites regarding dengue and the role of mosquitoes in transmitting dengue? - What process is used by public health authorities for informing the community about vector control activities? Is a mechanism for community feedback in place?	**Are the preferred field site(s) sufficiently isolated? [from the perspective of defining the community]** **Is there adequate infrastructure for case studies and on-going community engagement and collaboration?**	**Is informed consent feasible with individuals in the community at the preferred site(s)?**
Communication Plan		Communications Plan will need to be put into place for both proactive and reactive communications. - Have stakeholders/influencers in the country and local area been identified? - Has a Communications Plan been developed or is one in the process of being developed? - - At early stages this may be only in draft, outline or partial form.		**Are the preferred field site(s) sufficiently isolated? [from the perspective of defining the community]**
		What is the local working language? - Do the in-country collaborators speak this language or dialect? Visiting scientists? - Is translation available as necessary?		**What is the local working language?**
Working environment	*Political environment*	What is the political system in the country/location? Relevant issues may include: - Levels of government (e.g., federal/state/municipal) - Is there conflict between levels of government likely to impose difficulties? - Is the political system relatively stable? - Are there imminent elections that may disrupt civil service (e.g., collaborators or regulators), or lead to significant shifts in policy (e.g., on GE organisms)? - If the country/site has an electoral process, when is the next election that could have a relevant impact on the proposed studies? - Who are the relevant authorities in the proposed field site? What are their mandates (may include health/ environmental authorities, general government, etc.)? - Describe the cultural leadership structure of the community (are there village chiefs, groups of elders, respected religious figures and other nongovernmental figures of respect and authority?).		**Is there an appropriate Administrative authority in the proposed field site jurisdiction?**
		Is there a political will to embrace new solutions for dengue control? - Evidence?	**Is there a political will to embrace biotechnology?**	
		What is the political/community history with introductions of GE organisms in the country? - What is the level of understanding by communities in the proposed trial-site region regarding genetic engineering? – Have there been previous interactions with non-governmental agency or advocacy group? - - Components may include an overall plan/posture, key messages, frequently asked questions (FAQ) and other question and answer documents, and include local opinion leaders and third-party spokespersons. - Are the preferred field site(s) sufficiently isolated?		**Has the country had negative experience with GMOs?**
	ESC considerations	If relevant, who has property rights at the proposed field-site location(s)? - Is there any risk that the research would displace individuals or communities at the preferred site(s)? - Is the proposed site located near to valued community resources or sites where vulnerable populations might be impacted by the trials (e.g., hospitals, recreational areas, schools)?		**Who owns the preferred field sites? Is there any risk that the research would displace individuals or communities at the preferred site(s)?**

Table A2.7 Resources		
	Brown et al., 2014 - Aedes aegypti RILD (transgenic SIT)	Iyaloo et al., 2014 - Aedes albopictus SIT
People and institutions	What are the reasons for interest in an open-release trial?	
	There is a researcher or research team with expertise in vector biology that has local ties and is willing to be an enthusiastic collaborator.	
	What are the expectations of the collaborators?	
	Resource commitments can be met by participants and participating institutions	
	Provide the identity and nature of the proposed in-country collaborator and collaborating institution(s)? - Institution type (for example, government/university/private sector), size, identity and mission. - Previous history of international collaboration? With other project members? - Identify key individuals, for example the Principal Investigator, institute director, regulatory officer (if known) - - Provide the background and relevant experience of key personnel. - - What are their other duties, and how does this affect the time they have available for project? - As applicable, identify skill sets, gaps and training needs - Are there any known or foreseeable circumstances under which the institution or individuals might not be able to continue to collaborate for the full duration of project (e.g., short-term contracts, institution reorganizing, unstable mission/activities/funding)	
Financial/ employment	What policies govern recruitment, hiring, human resources management issues (practices and accountability) in the collaborating institution?	
	What are the relative costs of operating in the country/region? - Cost-of-living (e.g., relative to the United States or United Kingdom). - Indicate typical salaries for different grades (for example, graduate students, technicians, postdoctoral fellows, principle investigator other project personnel). - Are travel costs (flight, subsistence) and times unusually high or low?	
	Any known additional costs - Compulsory benefits, bonuses or insurance, other employment law? B Regulatory costs ('user pays') and time? - Value Added Taxes (VAT)?	
	The location does not present unacceptable risks for project staff	
Logistics	How far in distance is it from the collaborator's facility to the proposed field site(s)? - Journey time, cost, transport resources - Is there safe, reliable access to proposed facilities (e.g., laboratories, field site and travel to/between them)? (see article sections regarding adverse natural and adverse human conditions).	Practical considerations: existing infrastructure [labs, roads, etc.] Manageable size and favourable topographical surroundings
Collaborator resources	What resources does the in-country collaborator propose to provide to the project? - Of these, what will be funded by the collaborator, what from third-party sources and what will need to be provided from the project? Project contribution likely will be a mix of in cash and in kind, e.g., provision of personnel, etc. - What capacity will be made available to the project to handle regulatory issues (permitting, inspections and compliance); for example, will the collaborating institutions provide people and expertise to oversee applications through the committees? - What is the previous experience and evidence of this? - What is the capacity to manage epidemiological surveillance and treatment of dengue and dengue haemorrhagic fever?	
	What are the co-sponsorship opportunities? - Private foundations - Government grants - Resource-sharing with current vector control efforts - Who is eligible for applying and administering these opportunities?	

Mon 18/09/2017 16:59

BK

Ballen, Karen <KBallen@liebertpub.com>

RE: permission to use supplementary data table

To Quinlan, Megan M

You forwarded this message on 18/09/2017 19:34.

Dear Megan:

Copyright permission is granted for use of the requested table in your PhD thesis.

Kind regards,

Karen Ballen
Manager, Reprints, Permissions, and Open Access

From: Quinlan, Megan M [mailto:m.quinlan@imperial.ac.uk]
Sent: Saturday, September 16, 2017 12:11 PM
To: Ballen, Karen <KBallen@liebertpub.com>
Subject: permission to use supplementary data table

Hello,
I am not working out how to request through the online permission form, to use a table from the supplementary data link on your journal's article:

> **Criteria for Identifying and Evaluating Candidate Sites for Open-Field Trials of Genetically Engineered Mosquitoes**
>
> **To cite this article:**
> Brown David M., Alphey Luke S., McKemey Andrew, Beech Camilla, and James Anthony A.. Vector-Borne and Zoonotic Diseases. April 2014, 14(4): 291-299. https://doi.org/10.1089/vbz.2013.1364

I would like to duplicate (by retyping into a reordered format) their table of all criteria for sites (shown in supplementary materials, from which they prepared Box 1), in order to show a comparison to my criteria developed in the course of my PhD. It will probably be an Appendix in my thesis, to be precise.

Because it would appear in my PhD thesis, it would be available electronically in that format through Imperial College London's electronic thesis depository. I cannot estimate distribution in that sense.
Needless to say, I will fully cite the work above as the source of their own material.

Could you help me with permission on this, please?

Many thanks,

Megan Quinlan
Senior Research Fellow

Appendix 3. Posters and presentations of PhD research and findings

Calculating the costs of rearing: from laboratory to mass rearing for mosquito control. Presentation, 12th Workshop of the IOBC Global Working Group on Arthropod Mass Rearing and Quality Control (in cooperation with the International Atomic Energy Agency), Vienna, Austria, 19-22 October 2010.

Facilities readiness for containment studies of GM mosquitoes. Poster, ISBGMO13 (International Symposium on the Biosafety of Genetically Modified Organisms), Cape Town, South Africa, 9-13 November 2014

Providing a pedigree for future genetic strategy technology. Poster for Target Malaria, 3rd PAMCA (Pan-African Mosquito Control Association) Annual Conference, Lagos, Nigeria, 6-9 September 2016

Preparedness of a containment laboratory in prelude of genetic strategies studies for mosquito control in Mali. Poster for Target Malaria, MESA (Malaria Eradication Scientific Alliance) meeting, Kampala, Uganda, 19-23 February 2017

Adaptation of the invention declaration form to support commercialisation of plant biosecurity innovations. Poster for the EUCLID project, FERA (Food and Environment Research Agency), *Innovation in Plant Biosecurity 2017*, Sand Hutton, York, UK, 15-16 March 2017

Delivering change: potential release patterns and distribution systems for the release of transgenic mosquitoes in Burkina Faso. Poster, IAEA (International Atomic Energy Agency), Vienna, Austria, 22-26 May 2017

Product or service? Some distinctions arising in new product development for mosquito control. Poster, IAEA (International Atomic Energy Agency), Vienna, Austria, 22-26 May 2017

Monitoring free-flying mosquitoes for containment facility biosafety in Mali. Poster for Target Malaria, 4th PAMCA (Pan-African Mosquito Control Association) Annual Conference, Ouagadougou, Burkina Faso, 16-18 October 2017

Calculating the costs of rearing: from laboratory to mass rearing for mosquito control

Improved technology raises the prospect of control of vectors of malaria and dengue through releases of sterile male mosquitoes. Consistent with production of other insects for Sterile Insect Technique (SIT), production costs for mosquitoes will be highly affected by the possibility of genetic sexing. If genetically modified, additional costs for biosafety containment also will be incurred.

The *Model Business Plan for a Sterile Insect Production Facility* (IAEA/FAO, 2008) discusses full costing of mass rearing (Sections 6 and 7). Using historic data from fruit fly production facilities, a financial spreadsheet for costs of mass rearing was developed. The spreadsheet covers capital and operational costs, showing international averages such as for equipment. The user is allowed to fill in local costs for labour, diet, utilities, waste disposal, the interest rate for borrowed capital etc.

We adapt the financial spreadsheet to cost mosquito production, starting with laboratory figures and laying out parameters for costs of mass rearing. The resulting template will be shared globally (through the MosqGuide website, www.mosqguide.org.uk) to hold and compare data whilst researchers move from laboratory to mass rearing levels over the next few years. Further data may call for separation by species and/or genetic strategy (sterile, inheritable sterile, self sustaining but non-transmitting, etc). When field control is considered, cost trade-offs between greater numbers for release versus more accurate monitoring, will be informed by more precise costing information as captured in this template.

Rhodes, J., Quinlan, M., Knight, J. & Mumford, J. Calculating the costs of rearing: from laboratory to mass rearing for mosquito control. Presentation, 12th Workshop of the IOBC Global Working Group on Arthropod Mass Rearing and Quality Control (in cooperation with the International Atomic Energy Agency), Vienna, Austria, 19-22 October 2010.

Meeting: ISBGMO13 (International Symposium on the Biosafety of Genetically Modified Organisms), Cape Town, South Africa, 9-13 November 2014

Imperial College London

ISBGMO13
Cape Town, South Africa
9 – 13 November 2014

Facilities readiness
for containment studies of GM mosquitoes

M. Megan Quinlan[1], Mark Q. Benedict[2], Josephine Birungi[3], Mamadou Coulibaly[4], Abdoulaye Diabate[5], Luca Facchinelli[6], Jonathan Kayondo[7], Richard Mukabana[8], James Mutunga[8], Tony Nolan[1], Peter Raymond[9]

1 Imperial College London, United Kingdom. 2 Centers for Disease Control and Prevention (CDC) Foundation, Atlanta, USA. 3 International Livestock Research Institute Kenya, Nairobi (formerly with UVRI), 4 University of Sciences, Techniques and Technologies of Bamako, Bamako, Mali. 5 Institut de Recherche en Sciences de la Sante (IRSS)/Centre Muraz, Bobo Dioulasso, Burkina Faso, 6 University of Perugia, Italy 7 Uganda Virus Research Institute (UVRI), Entebbe, Uganda, 8 International Centre of Insect Physiology and Ecology (ICIPE), Mbita Point, Kenya, 9 Donald Danforth Plant Centre, St Louis, USA.

Genetic strategies for mosquito control are moving towards integration into field programmes in the Americas, Australia and Asia. Research on genetically modified mosquitoes is still new in Africa. Studies in bio containment facilities are the first step in a phased approach to evaluation of potential field interventions. Our research consortium has found that preparation for containment studies of GM mosquitoes requires a rigorous approach to facility oversight.

The consortium identified distinct themes underlying the concept of being ready to conduct GM mosquito studies: compliance, colony utility and defensible science, along with a spirit of responsible collaboration.

What comprises Facility Readiness?

Compliance	The fulfilment of all legislative and regulatory requirements and intentions for research with GMOs, or any study of novel or non-native living organisms, such as achieving the designated biocontainment level in the facility. Preparation and implementation of measures to protect workers, emergency planning, etc. as for all laboratory-based projects.
Colony utility	Relates to the quality of mosquitoes being produced so that results of studies may be compared across time (through generations and over months or years), across sites (various laboratories) and among strains or products. Identity maintenance of the mosquito strains.
Defensible science	Comprises the documentation of compliance; study designs, methods and results; and of other components of product development, in a manner which can be traced back to each event, thereby providing evidence appropriate to the interests and concerns of various stakeholders over the long term.
Other factors	Good stewardship of infrastructure, equipment and funding along with attention to building and validation of capacity. Early decisions about data analysis and ownership and publication of results support good will amongst research partners.



Although these appear to be a wide ranging and diverse set of criteria, which extend beyond facility certification requirements, we found it is the balance of these – and the authentic achievement of each – which leads to safe, reliable and collaborative research into possible future innovative interventions for malaria vector control.



The Foundation for the National Institutes of Health (FNIH) funded this work through a programme of the Bill & Melinda Gates Foundation.

PROVIDING A PEDIGREE FOR FUTURE GENETIC STRATEGY TECHNOLOGY

Quinlan MM[1], Sanou R[2], Namountougou M[2], Yagoure B[3], Sylla L[3], Balyesima V[4], Leach AW[1], Mumford JD[1]

[1]Imperial College London, United Kingdom, [2]Institut de Recherche en Sciences de la Santé (IRSS)/Centre Muraz, Burkina Faso, [3]Malaria Research and Training Center/Université des sciences, des techniques et des technologies de Bamako (MRTC-USTTB), Mali, [4]Uganda Virus Research Institute (UVRI), Uganda. Contact details of principal author: m.quinlan@imperial.ac.uk

Abstract

Aim

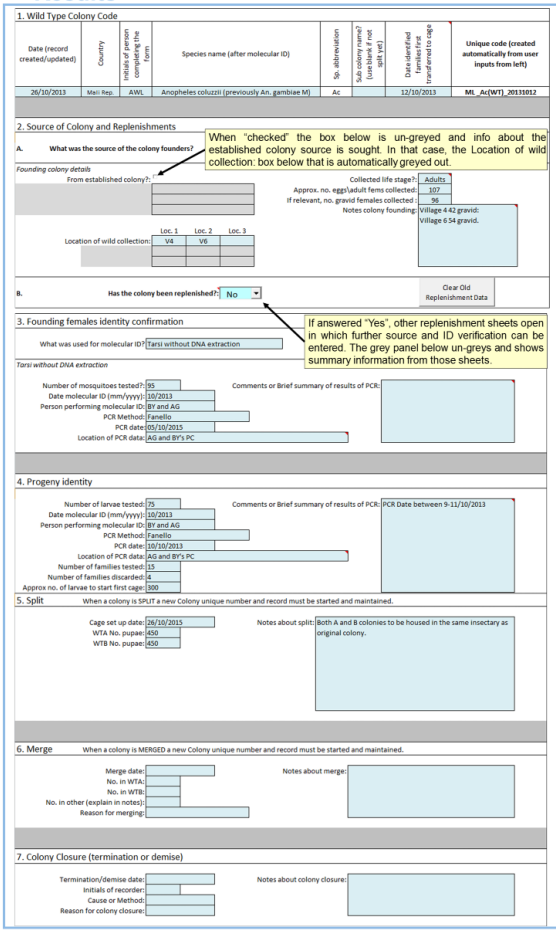
To create consistent, accessible and fit to purpose wild type colony records (WTCR) as digital records that detail the source and identity of field-caught wild type colonies of mosquitoes, which may be used as the local genetic background for genetic strategy research and eventual novel control measures. To provide an enduring and easily shared record of pedigree for mosquito colonies used in research.

Purposes

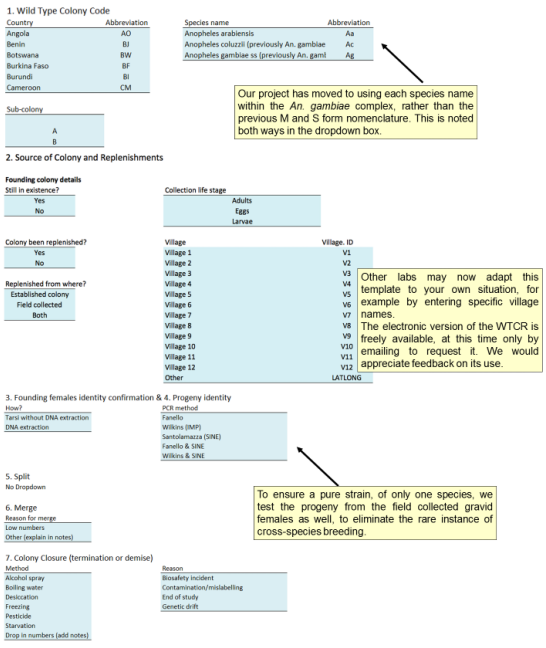
- To document the establishment of new wild type colonies, showing initial identity confirmation with clear records of methodologies.
- To document each event following establishment of a colony, including splits, merging back, replenishment and demise of each colony held in the Target Malaria insectaries. To allow project colleagues to know the status of colonies at each site, to facilitate informed decisions and analysis.
- To ensure that the study results leading to final products or technologies, and their genetic backgrounds, are fully traceable to the original wild type sources/population location and time period. To allow for consideration of the source of effects on efficacy for field use.
- To satisfy regulators that we have rigorous data frameworks to identify any genetic changes in the colony forward over time.

This template and a brief instruction manual is now available for other research groups. Requests should go to: info@targetmalaria.org

Results



Dropdown boxes for populating fields:



The WTCR was created as a simple list in a Microsoft Word™ format before we moved it to a standardised template in Excel™, which allows for dropdown menus and open/hidden cells for ease of data entry and standardised responses. The contents of a WTCR rarely need updating. (The project uses a purpose-made database for collecting information on ongoing activities, for example at the time of each cage set up or for blood feeding, or for periodic tests of insecticide resistance.)

Only mosquitoes collected in the field from native populations are referred to as wild type. Other non-transgenic lab-adapted strains may be accommodated in the WTCR by showing the source as an existing established colony, not from the field at the time the record is created.

Acknowledgments

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or visit www.targetmalaria.org

"Target Malaria is funded through a program of the Bill & Melinda Gates Foundation"

Members of the Target Malaria Consortium that contributed to this work are:

Imperial College London

TARGET MALARIA

A Vector Control Research Alliance

Meeting: MESA (Malaria Eradication Scientific Alliance) meeting, Kampala, Uganda, 19-23 February 2017

Preparedness of a containment laboratory in prelude of genetic strategies studies for mosquito control in Mali

Sylla L[1*], Benedict M[2], Diallo B[1], Hoyle S[3], Camara CO[1], Niare D[1], Camara H[1], Maiga AM[1], Yagoure B[1], Leach A[3], Facchinelli L, Clark L[3], Quinlan MM[3] and Coulibaly M[1]

[1]Malaria Research and Training Center/Université des Sciences, des Techniques et des Technologies de Bamako (MRTC-USTTB), Mali, [2]Center of Diseases Control and Prevention, US, [3]Imperial College London, UK

Abstract

Introduction:

The transgenic mosquito lab in Mali is an Arthropod Containment Laboratory Level 2 (ACL2) intended for the breeding and studies of genetically modified mosquitoes. The team working in the lab is part of Target Malaria, a not-for-profit consortium, currently active in three African countries: Burkina Faso, Mali and Uganda. The ultimate aim of the consortium is to use lab-produced genetically modified mosquitoes in an area wide release to reduce the population of targeted wild malaria-transmitting mosquitoes, and thereby reduce malaria transmission. The teams need to be well trained.

Methods:

A simulation of rearing transgenic mosquitoes in containment was carried out as part of this training with non-transgenic strains. Two strains of *An. Gambiae sl* (called color variants because of the phenotypic traits) were sent by a partner laboratory from Perugia, Italy. One of the strains has pigmentations on the back, the other does not. These traits represented the transgenic line and wild type line that will need to be backcrossed each generation for the upcoming first transgenic studies. During this exercise the team gained experience in shipping and receiving mosquito eggs, as well as, following specific containment measures and practices such as monitoring and eliminating free flier mosquitoes inside the laboratory (as a biosafety measure), following proper procedures for access to the facility and waste disposal, as well as, in carrying out a rapid termination.



Photo 1: Mosquito rearing

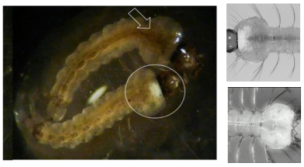


Photo 2: Strain Name: G3, MRA-112 Place of Origin: McCarthy Island, the Gambia Colonization date: 1975 Established by: Unknown Deposited by: Dr. William Collins Ref: MR4



Photo 3: Larval screening

Results

The team completed all milestones for this training over a dozen generations. An internal audit of the laboratory from the consortium partners attested to these achievements. This has led to confidence in operations within an ACL2 containment facility and in working with transgenic lines. This ensures compliance and will be complemented by regulatory reviews.

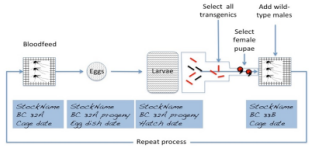


Photo 7: schema of mosquito rearing



Photo 8: Monitoring light traps for catching free flier mosquitoes

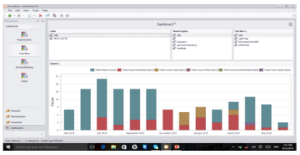


Photo 9: data management with a database designed for the project by EarthCape

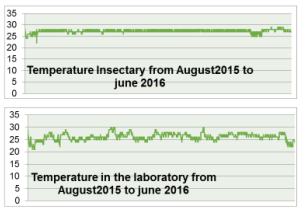


Figure 1 : temperature and relative humidity in the insectary

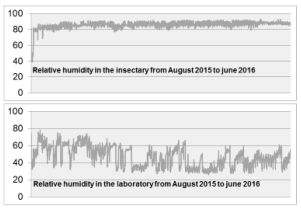


Figure 2 : relative humidity in the insectary and the lab

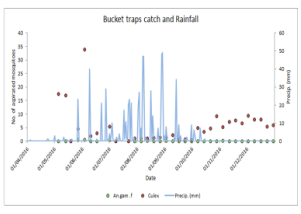


Figure 3 : Surveillance of existing mosquito populations outside the insectary using bucket traps

Acknowledgments

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"Target Malaria is funded through a programme of the Bill & Melinda Gates Foundation"

Members of the Target Malaria Consortium that contributed to this work are:

Imperial College London

CDC

TARGET MALARIA

A Vector Control Research Alliance

EUCLID
Europe China Lever for IPM Demonstration
http://www.euclidipm.org/
A Research and Innovation Action
funded by the European Commission under Horizon 2020

This project has received funding from the European Union's Horizon 2020 research and Innovation programme under grant agreement N° 633999

Adaptation of the invention declaration form to support commercialisation of plant biosecurity innovations

Megan Quinlan[1] and Léa Tourneur[2]

1 Imperial College London, Silwood Park, UK
2 INRA Transfert, Paris, France

Correspondence:
M.Quinlan@imperial.ac.uk

ABSTRACT

Standard practice across Europe in research institutes, as well as private businesses in countries such as France, is to prepare a DELCARATION OF INVENTION, or DÉCLARATION D'INVENTION form for informing management and tracking the potential for new technologies that might merit intellectual property (IP) protection. Although each organisation may have their own form, the content and purpose relates to legislation on promoting IP protection and is fairly standard in the examples we have found.

We have adapted this form for the EUCLID project, to track and consider issues for new technologies being developed through this project. For this field, advances are often built on existing practices or discoveries that may not be patentable. We aimed to tease out each aspect in order to consider the best routes to implementation and/or commercialisation in a very brief form, for use early in the technology development.

The prototype form takes into account the various types of innovations in integrated pest management and plant health today, including techniques, technologies and even behaviours or activities. These categories are based on work by Imperial College London for the same project as well as for EMPHASIS, another Horizon 2020 project.

Comments on our template are welcome, as is or uptake by other projects or research institutes. PLEASE TAKE A COPY.

INNOVATION DISCLOSURE FORM v1.0

A. Innovators' details
Terms of IP ownership by funding source or institutional policy

B. Description of innovation
Including what aspect is novel, if it relies on already protected products or is stand alone, etc.

C. Commercial considerations or pathways to uptake
A service, a product, an outcome delivered, a behaviour, etc., each have different pathways.
How could it be commercialised? How financially sustainable is IP protection?

D. Declaration— Declaration in the public domain may prevent formal IP protection

EXAMPLES FOR FORMALLY PROTECTING INTELLECTUAL PROPERTY (IP) RELEVANT TO PLANT HEALTH INNOVATIONS

Contracts:

- MTA (Material Transfer Agreement): to allow someone else to use or research the material you produce, with conditions indicated
- Confidentiality agreement: to allow discussions on confidential subjects to be shared between two parties
- Licensing contract: to allow someone else to exploit your research with some gain returning to the innovator
  - This normally presupposes the innovation is protected by some means first
  - An informal licensing might include request for registration of use, joining a users' group, or contributing to improvements
- Commercial contract or memorandum of understanding: difficult and expensive to enforce but spells out terms of agreement

Protection:

- Invention patent
- Copyright for software
  - If a tool is based on platform of existing software it is very difficult to protect IP (consider the informal license approach)
- Database: If this is the product (versus the data it holds)
  - can be protected on the structure, its architecture or composition: by copyright
  - can be protected on its functionalities: protection on the content via a patent
- Miscellaneous options: e.g. Soleau envelope: is a sealed envelope serving as proof of priority for inventions, valid in France. A Deposit on APP (Agence pour la Protection des Programmes) which is an association under the French Law of Associations (1901). APP is the European body for protecting authors' and publishers' digital works.

EXPECTED RESULTS OF HAVING A HARMONISED FORM FOR INNOVATIONS

- To support IP protection of novel plant health products, especially those arising from research outside industry
- To clarify and consider other IP protection options for services, tools and IPM packages
- To support documentation of contributions by various players, which may also apply for publications
- To better link novel approaches, systems and packages in crop protection to commercial planning tools, such as market analysis or business plans that are not always fit for purpose in this field (this objective is also being pursued through the EMPHASIS project)

Imperial College London

ID number 237

DELIVERING CHANGE: POTENTIAL RELEASE PATTERNS AND DISTRIBUTION SYSTEMS FOR THE RELEASE OF TRANSGENIC MOSQUITOES IN BURKINA FASO

F Habbel, J D Mumford, M M Quinlan, A W Leach

Centre for Environmental Policy, Imperial College London, United Kingdom
Email: fhabbel@live.com Habbel beginning May 2017 as Junior Advisor for GIZ in Lilongwe, Malawi

Introduction

Q1: How many transgenic mosquitoes should be released at a point for the release to be a 'success', how many would need to be released in all Burkina Faso?
Q2: What is the most efficient pattern of transgenic mosquito release in this area?
Q3: What are implications from centralised or decentralised distribution in this case?
Lab-reared, transgenic *Anopheles gambiae s.l.* are assumed to be released using ground transport, that these mosquitoes are highly anthropophilic and establishment in human settlements would be a priority. Assumptions are supported by literature and can be adjusted to explore other model outcomes.

Number and Pattern of Release

Two stochastic models simulate mosquito dispersal after release and test efficiency of three release patterns: discrete regular (release points at regular intervals along a road), discrete rule-based (release points by pre-set criteria), and continuous (release continuously as vehicle moves along roads). The three model patterns were run with two time periods to study dispersal: a 'One Generation Dispersal Model' (shown in this poster) and a 'Multi-Generation Dispersal Model'. Maps (Fig 1) were discretised into 900 (30x30) 1ha squares, each representing one of 21 land use types. The small scale limits complexity in the dispersal effect of location and number released. The smaller box within each map is the boundary in which mosquito releases are modelled. The function for dispersal is based on a Spatial Concept Model, developed by Leach and Mumford to explore local mosquito movement. The model has land type spatial data and values for mosquito biology, such as probability of migration distance and numbers. This model is intentionally simple and aims to give probabilistic approximations of local movement over short periods to inform release operation design. Figs 1 and 2 show maps, in which green is bushland, pink is settlement squares, blue is surface water and white is roads. Yellow shows cells where mosquitoes are released in each scenario.

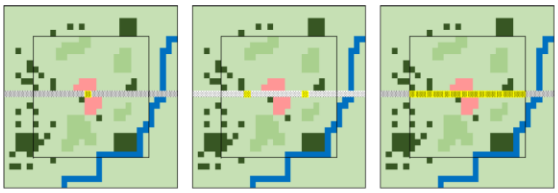


Figure 1: Release patterns: Left: discrete rule-based; Centre: discrete regular; Right: continuous.

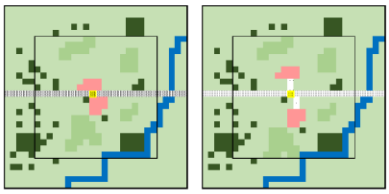


Figure 2: Settlement scenarios Left: all within 250m of road; Right: not within 250m of road.

A success was assumed if simulations showed transgenic mosquitoes establish within a settlement after one generation (Fig 3). Simulations which did not meet success are red. Fig 3a shows ratio of released mosquito occupied settlement squares to all settlement squares. Fig 3b shows efficiency, ratio of occupied settlement squares divided by total number of released mosquitoes, so the relative efficiency of each released mosquito. All release patterns work, but some patterns are more effective than others.

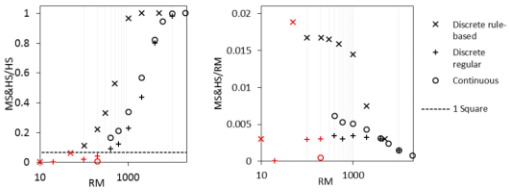


Figure 3: (a) Ratio of occupied/all settlement squares (SS). (b) Ratio of occupied SS/total released mosquitoes (RM). (MS: mosquito occupied square; HS: human settlement square; RM: Number of released mosquitoes per 2km of road).

How many mosquitoes should be released at a point for 'success' and how many for all Burkina Faso?
The 'One Generation Dispersal Model' at the scale in Fig 2 suggest a minimum of 100 mosquitoes for a discrete rule-based release pattern (1 release point), 200 per point for a discrete regular pattern (2 release points), and 20 (per 100m of road) for a continuous pattern, to reliably get establishment in a settlement near the road scenario.
For all of Burkina Faso, to establish populations in all settlements, these calculations were applied to road and settlement data from Google maps. With these assumptions, 6.1 million mosquitoes would be needed using a discrete rule-based pattern and 12.2 million for discrete regular or continuous release patterns.

What is the most efficient pattern of release?
The most efficient release pattern by mosquito numbers is a discrete rule-based pattern, with releases only near roadside settlements. A continuous pattern is more efficient than discrete regular pattern and may be the most efficient in cost because it does not involve stops or decision effort for release operators or supervisors.

Centralised or Decentralised Distribution

A 'Large Scale Distribution Model' simulates centralised and decentralised distribution systems. A distribution centre is where adult mosquitoes are reared, made ready for release, and packaged onto transport for subsequent release. The model quantifies accessible road squares around distribution centres. Inputs include maps and values for vehicle speed by road types, working hours, and maximum time mosquitoes can be chill-immobilized. The national map is set as 10,000 squares (100*100), each representing 10 km^2 (total area: 100,000 km^2). Fig 4 shows an example map based on road patterns in Burkina Faso. Road types are in shading, villages in pink, and distribution centres in yellow.

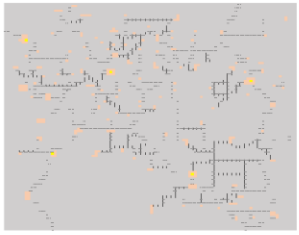


Figure 4: Map input of the 'Large Scale Distribution Model'.

A decentralised distribution system covers more road squares than a centralised system, based on road speeds (national road: 80km/h; regional road: 50km/h; departmental road: 35km/h) and the length of work day (12h). It was assumed that a truck leaves the distribution centre, follows a release route, and returns within one workday. The workday is less than the maximum time mosquitoes can survive in transport so survival does not limit the reach of distribution systems.

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PRODUCT OR SERVICE?

SOME DISTINCTIONS ARISING FROM NEW PRODUCT DEVELOPMENT IN MOSQUITO CONTROL

M. Megan Quinlan

Centre for Environmental Policy
Imperial College London

Email:
m.quinlan@imperial.ac.uk

INTRODUCTION

The push for new strategies in malaria vector control is supported by both the international position that what is presently available cannot maintain impact, and by the interest and support of private foundations. One initiative, a not for profit consortium aiming to reduce African malaria vector populations through genetic strategies, has been working through the distinctions of traditional area-wide field programmes versus development of a product that will be taken forward by others. While the IAEA/FAO Joint Division has a significant role in development of useful insect strains and methodologies, it also provides a range of services in cooperation with officially-recognised national representatives. Ultimately, however, the necessities of continual rearing and release of sterile insects has been managed more as a collaborative service, rather than provision to a specified threshold or outcome. An entity supported by project funding or shorter term resources must prepare products to stand alone more fully than might be needed in the intergovernmental treaty realm.

Area-wide control of mosquitoes – what is meant by product or service?

- **Service:** delivery of an input (e.g. given numbers field released; monitoring of populations) or an outcome (e.g. reduction in mosquito population; disease reduction), under particular terms (e.g. fitness, sterility, male/female) laid out in an agreement made in advance
- **Product:** delivery of a proven technology for use by another party (e.g. strain of mosquitoes transferred for rearing and release by a government programme), similar to off the shelf pesticides or biocontrol agents

DISTINCTIONS NOTED

Experience in one project indicates that a **product** approach requires:

1. greater documentation, validation and traceability of colony origin and confirmation of identity over time;
2. best practices for partnerships and team building across different types of laboratories and research teams (discovery, proof of principle and delivery);
3. greater harmonisation of and accessibility to data and cooperative ownership of results; and
4. deeper and ongoing engagement with a range of stakeholders who are accustomed to using products off the shelf.

In this case, area-wide vector control using a living product may be a new paradigm, beyond just 'insect as product' seen in other fields. Malaria vector control also raises the question of how much a new product must prove efficacious against disease indicators, rather than mosquito population indicators.

DISTINCTIONS EXPLAINED

1. mosquitoes as 'products' are more likely to be compared against other products, possibly registered like other products and must be consistent to a higher degree than insects released as a service;
2. an assumption may be that the well established relationships with governments, such as the collaboration by public partner researchers/implementers with IAEA/FAO Joint Division, avoids some of the cultural differences arising between new and ad hoc relationships among academic, research, field and vector control sectors;
3. the fact that any collaboration with IAEA must be through the national nuclear authority, which liaises with other public entities, may influence anticipated ownership of data;
4. traditionally the sector benefiting and involved with the area-wide control is an important partner, but other stakeholders are not as actively engaged.

Traditional area-wide control has also encountered this concept of using the 'insect as product', although in most government-led SIT programmes the sterile insects are provided as part of a service to the public or agricultural sector rather than an off the shelf product for sale.

In general, traditional SIT has been judged on efficacy demonstrated against target pest mortality rather than disease indicators.

But do you agree? What has your experience been? Is it changing?

Please leave your comments on sticky notes, next to the statements – with your name and country.

CONCLUSIONS

Emerging genetic strategies for control of mosquito vector species (including with nuclear components and without) will build on the experiences from traditional sterile insect technique. One project has been exploring the ramifications for requirements of a product development approach compared to the ongoing, long term involvement of intergovernmental bodies providing support for services.

Monitoring free-flying mosquitoes for containment facility biosafety in Mali

Sylla L[1], Quinlan M[2], Camara H[1], Camara C[1], Diallo B[1], Niare D[1], Maiga A[1], Leach A[2], Yagoure B[1], Benedict M[3], Mumford J[2], Coulibaly M[1]

[1]Malaria Research and Training Center/Université des Sciences, des Techniques et des Technologies de Bamako, Mali
[2]Imperial College London, United Kingdom ,[3]Center for Diseases Control and Prevention, Atlanta, USA

Abstract

In 2012 the arthropod containment facility at MRTC in Mali was renovated through Target Malaria, a not-for-profit research consortium, to conduct future studies involving genetically modified mosquitoes. This study shows a step taken in preparation for safe containment, before regulated contained use begins, while there are no transgenic mosquitoes in the containment facility. We present experience on achieving careful handling, verified by ongoing monitoring data within the facility. Measures to prevent unintended loss of other life stages of mosquitoes from the containment facility are also in place.

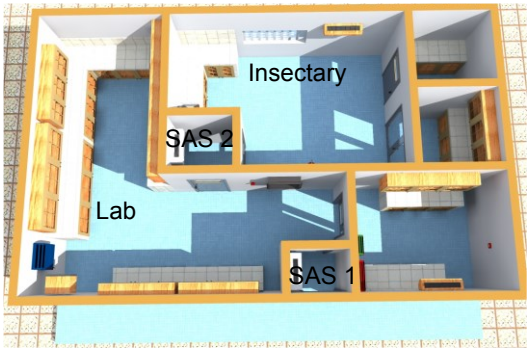
The containment facility has two sets of double doors with an interlocking system, each forming a vestibule with two doors, an interior rearing room, and a lab room between the vestibules. Fans are installed at the appropriate doors facing inwards to prevent mosquitoes from escaping the containment facility. Adult mosquitoes are handled carefully to keep them contained in mesh cages. Staff regularly watch for any free flying mosquitoes throughout the facility and kill them using electric rackets, aspirators or swatting (often making identification impossible). Four light traps also attract and kill free flying adults. Mosquitoes killed by either approach are recorded by genus and sex, where possible. Verification of procedures have taken place using colonies of unmodified mosquito strains, from November 2015 through October 2016.

During these 12 months mosquitoes were monitored inside the four rooms of the facility. Moths entering the outer vestibule from outside were also observed. As a result of this feedback, biosafety measures to prevent escape/ingress were demonstrated and reinforced. The recording, analysis and feedback on this biosafety aspect provided evidence and experience in order to reduce free flying mosquitoes even further.

Results

During the monitoring period reported, a total of 120 free flying (FF) mosquitoes were caught. Fifty-six were caught in Insectary room, and one in the vestibule connecting the Lab and Insectary (SAS 2). All but one of these were identifiable as the colony species, presumed to come from within the insectary. Three individuals of the colony species were found in the main Lab. A further 27 mosquitoes were caught in SAS 1, connecting the main Lab and an outdoor corridor, of which 23 were *Culex* and 3 *Aedes* from outside; one other mosquito caught in the outer vestibule (SAS 1) was not identifiable.

In a ten generation analysis free fliers were less than 0.02% of total adult numbers raised in the facility, and the proportion of free fliers to caged adults fell over that period of monitoring. Monitoring of this aspect of biosafety supports improvement and that more experience relates to fewer instances of adult mosquitoes outside cages.



FF captured per room

Localisation	Number and genus of FF
Insectary	55 *Anopheles* *1 Unidentifiable*
SAS 2	1 *Anopheles*
Lab	3 *Anopheles*
SAS1	23 *Culex* 3 *Aedes* 1 *Unidentifiable*
Direct search/kill (room unspecified)	33 *Anopheles*

Acknowledgments

"Target Malaria receives core funding from the Bill & Melinda Gates Foundation and from the Open Philanthropy Project Fund, an advised fund of Silicon Valley Community Foundation"

Members of the Target Malaria Consortium that contributed to this work are:

Scan me for more info!

or visit www.targetmalaria.org

Appendix 4. Featured published articles[96]

The key publications resulting from work on the PhD are listed in reverse chronological order:

*__Quinlan__, M. M., Birungi, J., Coulibaly, M. B., Diabaté, A., Facchinelli, L., Mukabana, W. R., Mutunga, J. M., Nolan, T., Raymond, P. & Traoré, S. F. (2018) Containment studies of transgenic mosquitoes in disease endemic countries: the broad concept of facilities readiness. *Vector-Borne and Zoonotic Diseases*. 18 (1), 14–20. Available from: http://online.liebertpub.com/doi/pdfplus/10.1089/vbz.2017.2189

*__Quinlan__, M. M., Mutunga, J. M., Diabaté, A., Namountouqou, M., Coulibaly, M. B., Sylla, L., Kayondo, J., Balyesima, V., Clark, L., Benedict, M. Q. & Raymond, P. (2018) Studies of transgenic mosquitoes in disease endemic countries: preparation of containment facilities. *Vector-Borne and Zoonotic Diseases*. 18 (1), 21–30. Available from: http://online.liebertpub.com/doi/pdfplus/10.1089/vbz.2017.2192

*Mumford, J. D., Leach, A. W., Benedict, M. Q., Facchinelli, L. & __Quinlan__, M. M. (2018) Maintaining quality of candidate strains of transgenic mosquitoes for studies in containment facilities in disease endemic countries. *Vector-Borne and Zoonotic Diseases*. 18 (1), 31–38. Available from: http://online.liebertpub.com/doi/pdf/10.1089/vbz.2017.2208

*Benedict, M. Q. & __Quinlan__, M. M. (2018) Genetically engineered mosquitoes for pathogen control. *Vector-Borne and Zoonotic Diseases*. 18 (1), 1. Available from: http://online.liebertpub.com/doi/pdfplus/10.1089/vbz.2018.29001.ben

*__Quinlan__, M. M., Smith, J., Layton, R., Keese, P., Agbagala, M. L. U., Palacpac, M. B. & Ball, L. (2016) Experiences in engaging the public on biotechnology advances and regulation. *Frontiers in Bioengineering and Biotechnology*. 4, 3. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4735352/pdf/fbioe-04-00003.pdf

**__Quinlan__, M. M. (2014) Assessing risk of transgenic insects. In: Benedict, M. Q. (ed.) *Transgenic Insects: Techniques and Applications*. Wallingford, CABI, pp. 283–305.

* These publications are available through Open Access.
** A copy of this publication appears in full, below. Permission to include it appears at the end of the Appendix 4.

[96] Thanks to the publishers who have allowed the inclusion of a full text copy of a publication relating to the PhD research: 'Assessing risk of transgenic insects' in *Transgenic Insects: Techniques and Applications*, edited by M. Q. Benedict (CABI, 2014).

18 Assessing Risk of Transgenic Insects

M.M. Quinlan*

Centre for Environmental Policy, Imperial College London, UK

18.1 Introduction

18.1.1 Scope of this chapter

Transgenic insects have been developed for various purposes, such as facilitating laboratory research in gene regulation. This discussion is aimed at the increasing variety of transgenic insects (e.g. see Pew Initiative on Food and Biotechnology, 2004; Beech *et al.*, 2012) developed for the purpose of control or mitigation of injurious species of insects, including agricultural pests and vectors of animal and human diseases, and some widely accepted methods to assess their risk.

In this context, transgenic insects will be discussed to some degree as outputs or 'products' of genetic modification or engineering:[1] living products which may be self-limiting or self-sustaining under natural conditions (see Mumford and Carrasco, Chapter 19, this volume). The nature of risk itself is described along with the place of risk assessment in risk analysis and policy decision-making.

The different approaches to risk of transgenic insects are considered for two conditions for use: limited by containment or confinement and open field release. These scenarios draw on experiences with similar living products, which are not transgenic. Factors that appear to be unique to transgenic insects are outlined.

Finally, the chapter touches on ideas for inclusion of social and economic issues in the assessment phase, whilst cautioning against attempting to accomplish too many objectives using one methodology.

18.1.2 Historic context for biosafety risk assessment and regulation

Risk assessment of and regulation of genetically modified organisms (GMOs) are intricately linked. Risk assessment is a valuable tool for numerous activities including planning research, project implementation, product roll-out and investment decisions, but, for this discussion, its role in regulation is of primary interest.

Although transgenic insects (*Drosophila*) were among the early model species of GMOs for research in the lab, it was some time before other insect species were transformed (Handler, 2002; Chapter 2, this volume), and the first applications for large-area commercial use of GMOs were for crop plants. This occurred at a time when the potential environmental impact of chemical pesticides was widely recognized. The public was much more informed and interested in environmental quality in general. Methods for environmental impact assessment were well developed and broadly applied. Some experts consider that this historic context led governments to apply a higher environmental standard to the assessment of genetically modified crops than had been incorporated into regulation of earlier

* Corresponding author, email: m.quinlan@imperial.ac.uk

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methods of pest control (National Research Council, 2002).

While the application of risk assessment is widespread, the exact approach varies. Hayes (2004) discusses the various interpretations of risk and what influences it. Glowka (2003) discusses the use of familiarity and substantial equivalence, first published by the Organisation for Economic Co-operation and Development (OECD), before the Cartagena Protocol on Biosafety to the Convention on Biological Diversity (UNEP/CBD, 2000) (or 'Cartagena Protocol', see Chapter 22, this volume) came into force. The use of substantial equivalence can give direction and increase efficiency in the burdensome process of case-by-case decision making. This approach would be subject to opposition later, causing a greater burden to the regulatory process.

The initial policy in the USA was that the *product* resulting from biotechnology, versus the method of development, was to be assessed for risk (OSTP, 1986). This policy also stated that existing laws would be sufficient to address risks from products of biotechnology. Many other national regulatory frameworks for GMOs, however, have as their basis the perception that there was something inherently dangerous about the method of achieving a novel trait, rather than by focusing on the characteristics of novel traits themselves. There was also divergence of approach regarding who has the burden of proof – and what the end-point is to be. A risk assessment cannot prove that a product is safe. The originating assumptions have a significant effect on the conclusions drawn from a risk assessment, if not also on the assessment itself.

Multilateral regimes such as those developed under the Codex Alimentarius Commission, the World Organisation for Animal Health (OIE) (both not highlighted here due to the focus on impacts to human and animal health, rather than that plus the environment; see FAO, 2011), or the International Plant Protection Convention, have achieved some harmonization due to common objectives of the various parties. These examples of multilateral guidance (see Table 18.1) discuss categories of potential hazards or harms to consider in regard to biotechnology, but do not detail the methodologies for risk assessment. Other more detailed guidance on risk assessment (not limited to biosafety) is given by most of these multilateral organizations, based on years of discussion and consultation.[2]

In contrast, there is a long-standing lack of incentive to harmonize national or regional biosafety regimes (Pollack and Shaffer, 2009). Fortunately, this has not been the case with the global research community. Researchers working with transgenic insects have been highly aware of the need to be cautious in moving out of confinement (physical, biological or environmental) to open field until broader agreement could be achieved on risk assessment, among other things. They have, to a large degree, voluntarily self-regulated through discussion, collaboration, publishing articles evoking caution and peer review. This stance is reflected in reports from the WHO Special Programme for Research and Training in Tropical Diseases (TDR) convened meetings on genetic strategies against vector mosquitoes (WHO, 1991, 2010; Takken *et al.*, 2002; Knols and Louis, 2006; Beaty *et al.*, 2009) and in various other conferences such as the Vector Biology Network (Beaty *et al.*, 2009).

An independent committee to prepare guidance was established as a result of requests at the most recent TDR convened consultation, in alliance with the Foundation for National Institutes of Health (FNIH). These guidelines will be published in 2014. The International Life Sciences Institute (ILSI) Brazil branch published a Spanish version of guidance on risk assessment of GMOs with input from authors throughout the Americas (de Andrade *et al.*, 2012). Various initiatives to address the gaps are described by Beech *et al.* (2009a, 2012).

Certainly the concurrence of the Conference on Environment and Development, or 'Earth Summit' (UNCED, 1992) and its subsequent influence on the CBD and its Cartagena Protocol on Biosafety (discussed by Pereira, Chapter 22, this volume) has had

Table 18.1. Examples of early multilateral guidance for assessing risk of Genetically Modified Organisms (not including regional initiatives).

Title and/or source of guidance	Comments
Voluntary Code of Conduct for Release into the Environment (UNIDO, 1995), prepared with United Nations Environment Programme (UNEP), the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) in consultations in 1991.	An early attempt at harmonization of biosafety guidelines. Introduced requirement to report or notify prior to field trials. It was recognized that a legally binding agreement on these issues was needed, however, and the CBD followed soon after (Zedan, 2002).
International Technical Guidelines for Safety in Biotechnology (UNEP, 1995).	Guidance developed multilaterally in anticipation of new biotech products coming into the market, when few countries had regulatory frameworks (Zedan, 2002). Proposes information requirements and points to consider in risk assessment.
Manual for Assessing Ecological and Human Health Effects of Genetically Engineered Organisms (Scientists' Working Group on Biosafety, 1998; convened by the Edmonds Institute).	More detail on hazard identification and pathways. Prepared by a group of scientists as input to the CBD for consideration when the need for a protocol on biosafety was anticipated.
OECD Working Group on the Harmonization of Regulatory Oversight in Biotechnology. General programme described in: Introduction to the Biosafety Consensus Documents of OECD's Working Group for Harmonisation in Biotechnology (OECD, 2005).	From early works (Recombinant DNA Safety Considerations (OECD, 1986), Safety Considerations for Biotechnology: Scale-up of Crop Plants (OECD, 1993), etc.) to the most recent, the OECD is a leader in guidance on risk assessment.
International Organization for Biological Control (IOBC) – Series on Environmental Risk Assessment of Genetically Modified Organisms (Romeis, 2006, 2008; Romeis *et al.*, 2006, 2008, 2011; Romeis and McLean, 2011).	Prepared by Global Working Group on Transgenic Organisms in Integrated Pest Management and Biological Control, and the Scientific and Technical Advisory Panel of the Global Environment Facility (GEF).
FAO (2004) ISPM 11. Pest Risk Analysis for Quarantine Pests including Analysis of Environmental Risks and Living Modified Organisms, developed by the International Plant Protection Convention (IPPC), Rome.	Guidance prepared through an expert working group and member country consultation process under the IPPC, in the form of International Standards for Phytosanitary Measures (ISPMs). (The IPPC operates under the FAO, thus the authorship.)
The Special Training Program in Neglected Tropical Diseases (TDR) expert consultations (see text).	These fora have provided an opportunity to agree on voluntary restrictions against moving to the field without adequate regulatory oversight.

a significant influence on the regulation of biotechnology and use of risk assessment in this realm.

Following the elaboration of the Cartagena Protocol, the majority of countries have opted for new regulation and even legislation for ensuring the safety of products of biotechnology – to the exclusion of other methods of obtaining novel traits. These legal instruments follow the guidance in the protocol, while at times requiring more, or perhaps adding greater, demands by including optional aspects as if they were obligatory (see below).

The creation of national biosafety frameworks has been a priority under international funding schemes (Johnston *et al.*, 2008; McLean *et al.*, 2012), with approximately 130 developing countries receiving support towards this aim. These frameworks arose from special funding schemes rather than from years of experience and resulting regulatory adjustment and revision. Perhaps because of this focus on

the method of development of the products, it is not unusual for biotechnology regulation to be applied in parallel to other regulatory frameworks more suited to the specific use of the organism or novel trait. There are also numerous cases in which a country has prepared a legislative and regulatory framework, yet remained hindered by 'implementation gaps' (Bulkeley *et al*., 2013) that prevented their opportunity to gain any benefits from biotechnology products (Nuffield Council on Bioethics, 2004).

Throughout the history of genetic modification of organisms, one feature universally present in biosafety guidance and frameworks is the use of risk assessment as a legitimate decision-support methodology, which also provides the opportunity for transparency in the scientific reasoning applied.

18.2 Risk Assessment

18.2.1 Understanding risk

Risk is a probabilistic concept. It is inherently predictive and is only an estimate of what is likely to occur. Risk assessment is an estimate of the probability of a hazard or harm occurring multiplied by the consequences of this event. Intrinsic to risk is uncertainty.

The evidence for what might occur can be derived from biological principles such as evolution, or historic experience based on similar situations or scenarios. Models are frequently employed to consider risk. The purpose of assessing the risk is to make informed decisions about issues such as allowing the release of a GMO, but also to formulate and implement practices which reduce the risk by either reducing the probability of the harm occurring or by reducing the consequences of the harm if it does occur. As with environmental impact assessment, the initiation of the assessment is generally because someone has seen the value in carrying out the proposed introduction or intervention. Therefore, the potential benefit is also a critical factor for decision makers.

Risk analysis has traditionally been divided into three phases: (i) identification and or classification of the hazards or harm (which is sometimes included in the assessment phase); (ii) assessment of the risk; and (iii) description of possible risk management options. Risk communication is often added as a distinct, but cross-cutting component (as illustrated in Beech and Miller, Chapter 20, this volume). Some frameworks include problem formulation as a separate phase. The Australian framework has a similar phase called 'Risk Context' in which the parameters of the assessment are set (see further discussion under section on social and political aspects; Office of the Gene Technology Regulator, OGTR, 2013).

If the risk is acceptable, compared to other existing methods for pest control for example, or if management measures can reduce the risk sufficiently, then the process continues and risk assessment informs the risk management plan, which if carried out properly reduces the risk estimate. (Another approach is that the available risk management can determine whether further risk assessment is required or the risk does not warrant concern; see Box 18.1 for an example.) Ideally, assumptions made about the risk and the management will be monitored and findings will feed back into the original assessment.

The separation of the components of risk analysis can be traced back to the principle of allowing scientific assessment of risk to take place without undue influence of political, economic, social and other factors, which are necessarily taken into account when determining policy and risk management actions.

Uncertainty may be due to natural variation, which can be estimated but not reduced, or to lack of knowledge or information, which can possibly be remedied by further research. The opportunity to clearly indicate and record where scientific evidence is conclusive and where uncertainty remains high is one reason that risk assessment and risk analysis have continued to be universally applied in governmental decision making.

Box 18.1. Risk assessment for contained or confined use of a GMO

Whereas the focus of the risk assessment for field or unconfined studies or use of transgenic insects is the safety and possible impact of the organism, the primary question for risk assessment in physical confinement is the probability and consequences of escape or accidental release from the containment facility. In fact, in many instances the risk associated with the organisms is not considered in depth, but rather the fail-safe nature of the containment is evaluated. (For exceptions requiring a comprehensive assessment, see National Institutes of Health – NIH, 2013.)

This, then, becomes an evaluation or assessment of the management measures for construction, maintenance and operation of a containment facility. Furthermore, as many countries have established regulations or guidance regarding containment facilities, the risk assessment process may be replaced largely by assurance of compliance with these existing requirements.

Containment requirements are generally presented in terms of levels assigned by a combination of criteria, such as discussed in the Arthropod Containment Guidelines developed by the American Committee of Medical Entomology (ACME, 2003). Therefore, the appropriate classification of the GMO is a key component of compliance with the risk management when in containment. An important distinction for this approach is that assignment of a particular level of containment does not necessarily equate with an equivalent probability of harm associated with the organism in question.

The classification may relate to lack of knowledge, and thus higher risk may be assumed from uncertainty, which leads researchers to take the most cautious approach readily available in order to proceed with research that will provide additional data for a more organism or product-specific assessment of risk. Containment is used for study of novel organisms to a large degree because of the uncertainty or lack of knowledge about the risk factors, rather than because of some acknowledged 'danger' from the organisms (Hilbeck and Meier, 2006).

This is a 'precautionary approach' widely used for international trade of biological control agents which were, for example, subjected to isolation for one to three generations in a quarantine facility. In this case, the requirements also allowed for detection of any contamination of the biocontrol agents with parasites or infectious agents.

Additional assessment is required if the confinement is biological (e.g. sterility, absence of mating population in the area), geographic (e.g. island, by altitude) or climatic (e.g. edge of distribution range, seasonal).

Also the evaluation of risk in regard to worker and researcher safety may require yet further assessment of the risk associated with the study organism. Indeed, as exposure increases in the laboratory setting certain risks, such as from an allergic reaction, could increase.

Additional risk management may be used when uncertainty is high, during the process of answering some of these questions. A decision-maker's response to uncertainty is at the heart of the often cited 'precautionary principle', discussed further by Pereira (Chapter 22, this volume). Various stakeholders interpret this principle in various ways, as Beech and Miller discuss (Chapter 21, this volume). Certainly there was not uniform agreement in the approach now enshrined in Annex III of the Cartagena Protocol (Kapuscinski, 2002). The risk assessment process supports making a decision, which could include additional management or precaution due to uncertainty. In general, sovereignty remains in terms of risk acceptance or aversion, although transparency and consistency are global principles.

18.3 Risk Assessment of Living Insects

Risk assessment is a widely used method for formulating and facilitating decisions regarding alternative actions for control of

insect pests (FAO, 2005, 2007; Hutchison *et al.*, 2006; EPPO, 2011). There are different attributes to risk assessment when the intervention involves intentional introduction of living organisms into the environment. In agriculture, such interventions include the introduction of biological control agents (classical and augmentative), pollinators, mycofungicides and other biopesticides. Another example is sterile insect technique, which involves the release of living insects as a means of targeting a compatible breeding population in the local environment.

Most studies and guidance on risk assessment, ecological risk assessment or environmental impact assessment of an intentional release of living insects, are referring to an open field release. In common practice, there is a phased approach to achieve reduced risk through management during the testing and development of an insect 'product', to ensure safety and efficacy prior to use in an on-going programmatic application. The typical chain of events (Fig. 18.1) is to conduct studies related to basic proof of principle and to safety in the laboratory, and then to continue to a confined release. As already mentioned, the release could be confined physically, such as in a large cage or in an insectary of lower containment level than the original testing facility. The first documented open field release of a GM insect, of GM pink bollworm, used removal of wings from adult females and pheromone traps to prevent adult dispersal (FAO/IAEA, 2006; Simmons *et al.*, 2011).

With most hazards or potential hazards, the ideal would be for none of the tested substance to remain in the environment. This equates to destruction of any plant material of a GM crop remaining in the field after the point of collection or harvest. Transgenic insects present a particular case within this category of risk assessment of introduced living organisms, especially when the GMO is self-sustaining. In the realm of public health, there are emerging programmes to introduce gut bacteria, viral or microsporidian parasites, or the target insects themselves with genetic modifications, with the aim of altering the fitness of the vector population or altering its ability to transmit the disease of concern (WHO, 2010; Brownlee, 2011). In each case, the intervention relies on the intentionally introduced organisms' survival in the environment for a specific and reliable period of time (e.g. by generations, days, months or years until the host source is exhausted), even if limited. There has been extensive debate on the precautionary approach to release of biocontrol agents, as regulatory requirements have in some cases effectively eliminated the possibility of a permit approval or of the conditions of approval being feasible.

18.4 Risk Assessment of Genetically Modified Organisms

For GMOs, risk assessment has been defined as a method to 'identify and evaluate the potential adverse effects of living modified organisms on the conservation and sustainable use of biological diversity in the likely receiving environment, taking also into account risks to human health' (Annex III, article 1, Cartagena Protocol on Biosafety).

For most public sector decision makers, despite opposition from some major trading countries and internal disagreement on some factors, the Cartagena Protocol is the primary instrument for guiding national governments in their assessment of risk from living modified organisms. The text of the protocol gives fairly general guidance based on widely accepted principles: to identify any genotypic or phenotypic

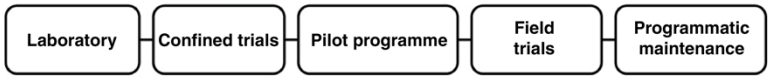


Fig 18.1. Phases in assessment of a transgenic insect.

characteristics that may negatively impact biodiversity or human health; to evaluate the likelihood of adverse events based on exposure to the modified organism and the consequences should the hazards occur; to estimate the overall risk and recommend if this is acceptable or manageable, and if so to propose management strategies; and to compensate for uncertainty by seeking additional information, adding additional management and/or by monitoring the organism once released in the environment (a paraphrase of what risk assessment entails, from Annex III, Cartagena Protocol).

The CBD and the Cartagena Protocol have afforded an important forum for on-going discussion and sharing of experiences of using risk assessment methodologies, and now through the Biosafety Clearing House as a place to find examples of risk assessments from real cases. International methods for assessing risks from alien invasive species were considered at the Subsidiary Body on Scientific, Technical and Technological Advice (Quinlan, 2001), by the Conference of Parties (COP) of the CBD. Over time, additional guidance has been provided through COP meetings for the Cartagena Protocol and by subsidiary groups. The principal contributions on risk assessment are listed in Table 18.2.

Table 18.2. Principal guidance on Risk Assessment from the Cartagena Protocol on Biosafety process.

Document	Relation to risk assessment	Other comments
Cartagena Protocol on Biosafety to the Convention on Biological Diversity (UNEP/CBD, 2000)	Annex III on Risk Assessment provides an outline of general principles, methodology and points to consider.	Entered into force 2003. As of 2013, there are 166 Parties to the Protocol.
Note by the Executive Secretary (CBD, 2005a) *Risk Assessment And Risk Management* (Articles 15 And 16)	List of resources from national, regional and multinational sources for risk assessment and management.	Supplemented (CBD, 2005b) and later additions found in subsequent reports.
Report on the Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management (AHTEG, 2005) and *Subsidiary Bodies* (Article 30) (CBD, 2006)	Provides listing of additional resources for risk assessment. Mentions IPPC guidance. Notes differences of GM animal characteristics, such as domesticated or not and how this might affect spread; example of flying versus non-flying insects. Compilation of views on need for additional guidance.	Calls for follow up on 'practical guidance on how to relate end-points of risk assessments to conservation and sustainable use of biodiversity may be appropriate.'
Part II: Specific Types of LMOs and Traits, Section C. Living Modified Mosquitoes (AHTEG, 2010) (Stand-alone annex to CBD, 2010)	Raises risk issues specific to genetic modification of mosquito species that vector disease, to complement the general 'Roadmap'.	At the first meeting of the AHTEG, the need for additional guidance specific to LM mosquitoes was agreed.
AHTEG on Risk Assessment and Risk Management Final Report (AHTEG, 2012) and *Analysis of the open-ended online expert forum on risk assessment and risk management* (CBD, 2012a)	Guidance after editing based on extensive consultation, including through regional fora.	Open-ended online expert forum provided opportunity for exchange of ideas on concepts, methods and example cases for risk assessment and management.
Training manual *'Risk Assessment of Living Modified Organisms'* (CBD, 2012b).	Linked with the Roadmap.	Developed in conjunction with educational groups participating in the AHTEG.
Guidance On Risk Assessment Of Living Modified Organisms ('Roadmap') (CBD, 2012c)	Separate document arising from Final Report, adopted at COP-MOP/6.	Undergoing testing by Parties to the protocol, governments, and relevant organizations through March 2014.

The most directly relevant guidance, the Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management report on living modified mosquitoes (AHTEG, 2010), was felt by many researchers in the field to have fallen short of the necessary guidance. The time available for preparation left inadequate distinction between assessment and management of risk (per Beech *et al*., 2012) and perhaps the expert group lacked the range of experience required. This and the other initiatives mentioned above, however, are building up resources for risk assessment of transgenic insects in complement to risk assessment of GMOs in general.

18.5 Special Aspects of Risk for Transgenic Insects

18.5.1 Phases in assessment for transgenic insects

The phased approach shown in Fig. 18.1 applies equally to development of GM insect products destined for large-scale programmatic release. Benedict *et al*. (2008) expounded on the importance of the phased approach for GM insects and suggested that a cage trial phase is imperative for GM insects containing a self-sustaining 'drive system'. However, with physical confinement provided by sterility, for example, or some fitness-reducing characteristic that results in similar mortality in the field, there is no necessity for confined trials of other types of transgenic insects to be conducted within high containment cages because confinement has already been achieved.

The advantage of larger, more natural open field studies is to more realistically determine efficacy of the intervention, which is very challenging to predict from cage studies (Robert *et al*., 2013), and to reveal ecological interactions which may not arise in the lab or cage. Benedict and Robinson (2003) proposed that sterile transgenic insects should be the first for field studies in order to gain this type of knowledge while preventing persistence in the environment.

Many countries are not yet resourced to be developing and mass-producing transgenic insects. Insects with a genetic marker, for example, could eventually be purchased through the international channels existing for sterile insect technique (described in Quinlan and Enkerlin, 2003; Enkerlin, 2007; Quinlan and Larcher-Carvalho, 2007). Current trials with GM mosquitoes have required international shipment of transgenic eggs (e.g. Government of Malaysia, 2010, 2013a, b). Therefore, an initial event to trigger assessment may be the request to import a transgenic insect (in whatever life stage) into a country. Alternatively, the transgenic living product would be created domestically, which may require a different type of permit and assessment such as certification of a containment facility. Figure 18.2 shows some of the assessment points in the phases also shown in Fig. 18.1, with the example of containment facilities as the chosen confinement step. The steps would be typical for introducing a novel product into the market or into a public programme.

There is another phase not shown in Fig. 18.2, which is scaling up of production of the transgenic insect. This requires another series of assessments: site selection for that facility/ activity, review of safe transfer from the facility to release sites, quality assurance regimes, worker safety, financial risk, etc. This is overlapping but distinct from the requirements for site selection for an outdoor cage or pilot field study, for example. Discussion of some of these issues appears in a model business plan for mass-rearing facilities, written in relation to irradiated insects (IAEA, 2008).

For each phase, a thorough analysis of results against the original assumptions in the risk assessments is required. Ideally, if similar studies are carried out over time, the data will begin to reduce uncertainty. Similarly, additional experiments may be carried out to specifically address uncertainty or concerns that arose in the hazard identification stages (e.g. although not for GM insects, see Popovici *et al*., 2010, for study responsive to expressed concerns).

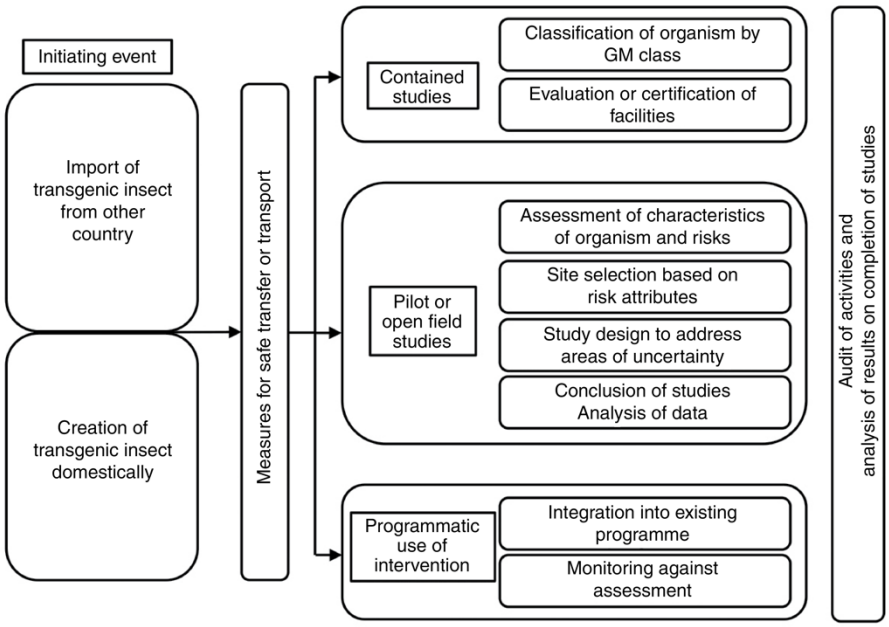


Fig 18.2. Phases in assessment, testing and approval of a transgenic insect for use in an on-going programmatic intervention for pest or vector control.

18.5.2 Characteristics of the organism

Insects can have a range of characteristics that affect control programmes and should be considered in a risk assessment for transgenic insects:

- Short generation time;
- Mobility and ability to disperse (see Box 18.2);
- Ability to diapause in unfavourable conditions and revive when conditions improve; and
- Possibility of exchanging gut symbionts, including heritably.

As with other GMOs, important factors most frequently noted for assessment of transgenic insects for field release include: the nature of the inserted gene itself (source, placement, stability, etc.) and the methodology for modification; any impact on phenotype or behaviour of the insect which is modified; and the possible effect of these changes on human health (e.g. vector competence or biting rate), the environment (e.g. non-target organisms) or on the relevant activity such as crop production or vector control (FAO/IAEA, 2006). These may be direct effects or secondary, for example through gene flow. The assessment in this step is also frequently performed as part of the application process, when seeking a permit to release (see Fig. 18.2).

18.5.3 Introduced traits

Risk also is related to the consequences or impact of a negative event. One can anticipate a higher risk from particular traits, as illustrated in Table 18.3. However, it is imperative to substantiate these assumptions with research over time, if not prior to confined release. If information

Box 18.2. Mobility of transgenic insects

The North American Plant Protection Organization regional standard (RSPM No. 27) *Guidelines for Importation and Confined Field Release of Transgenic Arthropods in NAPPO Member Countries* (NAPPO, 2007) was possibly the first official guidance specific to transgenic insects. It addresses any transgenic insect with possible impacts on plant health under consideration for import and confined field release in the three member countries (Canada, USA and Mexico). This could include biocontrol agents or other beneficial insects.

The possible mobility of insects, in contrast to GM plants, for example, poses some additional biosafety considerations. It is difficult to anticipate the impact of dispersal capacity in general regulations. NAPPO (2007) also notes the dispersal ability of a transgenic insect as a factor for consideration in risk assessment.

The regulation of (non-transgenic) butterfly releases in the USA is based on both species and origin; permits may restrict the area of release to fall within a natural barrier such as the Continental Divide (USDA-APHIS, 2012). For transgenic insects, the geographic origin of the parent organisms and in some instances the source of transgenes might be considered if reason to suspect species diversification exists.

In an unrelated regulation for setting the level of inspection of incoming agricultural trade, the European Commission has adopted a formula with mobility of the insect, at its most mobile life stage, as one parameter relating to the risk of spread from hypothetical entry of an infested product (EC, 2004); other factors relate to the amount of data available on actual interceptions. This suggests that a quantification of the mobility factor is feasible in risk assessment as well.

Lessons about the influence of humans might be learned from outbreaks of plant pests caused by amateur collectors who raise insects in unregulated conditions and, at times, release without permits.

cannot be obtained from confined release, then monitoring in an open field release may provide the necessary data. The end-points and objectives of such monitoring should be agreed in detail in advance.

Another approach is to build credible scenarios to predict possible, or even worst case, outcomes from introduced traits (Interdepartmental Liaison Group on Risk Assessment, 2013). When this is done due to insufficient data, the assumptions should be reviewed with each new piece of evidence until each scenario is better quantified in terms of probability and impact.

Mapping out the possible pathways to a negative consequence will help to clarify what might occur, what the outcomes might be and what factors will influence or prevent this. In relevant literature on risk assessment, horizontal gene transfer is almost always noted as a major risk from transgenic insects or other GMOs. Keese (2008) proposes approaches for detecting horizontal gene transfer and likely pathways, focusing on GM plants. A similar discussion focused on insects (FAO/IAEA, 2006).

It may be more appropriate to consider that genetic changes only matter if the change leads to some negative manifestation, or impact (as discussed in Keese, 2008). In this instance, gene transfer might be the pathway to an impact, but it is not necessarily a hazard. The Scientists' Working Group on Biosafety (1998), mentioned in Table 18.1, developed flow charts for decision support for a variety of possible GMOs. These flow charts are designed to ensure that all considerations have been addressed, so that conclusions to one set of assessments does not lead to a decision without review of other factors.

Genetic 'events' such as natural mutation are constantly present in the natural environment, sometimes resulting in serious consequences such as insecticide resistance. Observing genetic events in

Table 18.3. Examples of introduced traits and their anticipated relationship to risk.

Example characteristics	Expected to have increasing risk →			
Fecundity	Fully sterile	High percentage sterile	Same as target population	Greater than average reproduction rate
Mating competitiveness	Not compatible with native population	Mating compatibility less than native population	Same as target population	Preferred mate and/or able to mate with other species or molecular forms
Dispersal	Non-flying and not transported through other pathways	Disperses in immediate area (e.g. field or house)	Disperses in local area (e.g. village, river basin)	Wide ranging naturally or through other pathways
Lifespan	Lethal trait arises, larval or pupal phase	Early adult mortality	Same as target population	Extended beyond average
Genetic insertion	Demonstrated to be stable over multiple generations in laboratory conditions	Apparently stable over multiple generations in small confined space	Able to transfer to other species under forced laboratory conditions but not in studies mimicking natural conditions	Able to insert into other species in confined conditions, or after open release
Transfer mechanism	Novel genetic material not transferable	Novel genetic material may be transferred in small percentage of cases	Novel genetic material will transfer to approximately half the population through mating	Novel genetic material will transfer in greater than Mendelian percentage (gene drive)
Relation to control programme	Integrates with other control measures without changing their application and without loss of efficacy	Integrates with other control measures if they are stopped for periods of time (e.g. pesticide spraying)	Displaces some control measures but integrates with the main control measures	Displaces other control measures or reduces efficacy of integrated programme
Post-release monitoring	Trapping or detection feasible and identification routine, part of permanent monitoring programme	Trapping or detection feasible and identification routine, but relies on specific project funding	Difficult to trap but easily identified as a GMO	Difficult to trap or to identify as a GMO if caught (e.g. life form caught by trapping is not easily identifiable)
Ecosystem effects	Introduced species not closely linked with native ecosystem (e.g. anthrophilic or recently introduced)	Introduced species, which occupies niche formerly associated with a native species	Important role of predator, prey or competitor in relation to other species	Highly significant predator, prey or competitor in relation to other species of importance to ecosystems; or released species is native to area of release

transgenic insects is important, but some comparison to non-transgenic populations and understanding of the links to impacts is equally important.

18.5.4 Receiving environment

Some of the characteristics to consider when choosing a site for confined release are outlined in the NAPPO (2007) guidance, including:

- Proximity to populations of the same species as the transgenic arthropod and closely related species;
- Proximity to sensitive or protected ecological areas;
- Presence of susceptible hosts;
- Presence of non-target organisms, beneficial arthropods, and endangered or threatened species in the confined field release site. This should take into account the seasonal presence of these organisms, particularly at times of migration and mating; and
- Presence of aboriginal populations of the arthropod or closely related species that may be centres of genetic diversity.

Similar considerations should be made for pilot field releases. However, for programmatic use additional considerations may be required (see section 18.5.5 regarding intended use).

For transgenic insects/transgenes designed to persist and/or spread genetic material, another consideration will be the similarity of the gene insertion site to other non-target insects; the stability of the insertion and the possible consequences if transfer does occur. In these scenarios, even without scientific evidence of any probability, there may be reason first to perform well-controlled, multi-generation laboratory experiments to eliminate the possibility of creation or transfer of insecticide resistance, acquired ability to vector additional diseases etc., due to the extreme consequences that could occur. The phased studies, explained above, and use of any methods for mitigating or stopping spread of a gene-drive GMO should be used in case of unanticipated outcomes in the field.

Such studies and contingency planning is best done with peer review by a group of experts representing all relevant scientific subjects, but who also are cognizant of the limitations of budgets, detection levels and other feasibility factors so that the desire to address concerns does not prevent progress for an intervention that has a high probability of societal benefit.

18.5.5 Intended use or application of the GMOs

Because the purpose of most research on pest species ultimately will be to improve control efforts in an on-going programmatic intervention, the effect of the transgenic traits on integration into such an operational control programme, as well as worker safety issues during research and for the production facility that will be needed, are additional points of consideration in any assessment (Hoy, 2000; James, 2005).

Hoy (2000) concludes from her own experience that the efforts for introducing a transgenic insect into a pest control programme can be divided into three similarly demanding phases: (i) the planning and technological development of the product; (ii) field testing; and (iii) the integration of the product into a pest management programme. This last phase includes public education, cost-effective mass rearing, and additional research on possible hazards when conducting large-scale releases over longer time periods.

An adequate assessment must also recognize any limitations inherent to the monitoring and regulatory system available at the site. A review of the international code for release of biological control agents showed that few countries were conducting the post-release monitoring as prescribed (Kairo *et al*., 2003), this lack of oversight itself forms an additional risk factor. (The review also revealed the value of clear guidance on the roles of each party and the need for a highly engaged leadership to

ensure it is taken into account.) It has been long-recognized that proposing management measures that are not feasible in the local context invalidates the plan (World Bank, 1999).

18.5.6 Interactions and cumulative risk

As already suggested, it is very difficult to predict all interactions that may affect risk after field release. Furthermore, the same receiving environment may undergo changes from the time of the original evaluation and risk assessment. It is not realistic to require the original developer, research team or project which introduces the product for public sector uptake be responsible for monitoring and observing all of these future interactions in order to revise the original assessments. Even a commercial entity with long-term presence in the market does not control and may be unaware of the multiple changes to the receiving environment which could alter the behaviour or performance of the living product.

Therefore, the national or local government will be required to consider these issues when approving a release. One way to facilitate efficient review of decisions is to prepare a table of possible trigger events or conditions for changes in the risk. This could be related to climate (e.g. drought, floods, increasing average temperatures), species complex (e.g. introduction of another species, loss of species diversity, shift in keystone species), demography (e.g. increase in density of human population, change in movement of people), pest control practices (e.g. over use of a particular insecticide, substitution of pesticides with biocontrol agents) and so forth. By identifying possible triggers, with credible mechanisms for affecting the transgenic insect, the burden on the public sector to review their decisions is alleviated.

The key elements of an Integrated Confinement System have been identified (National Research Council, 2004) as:

- Commitment by top management;
- Establishment of written plans to be implemented, including those for documentation, monitoring, and remediation;
- Training of employees;
- Dedication of permanent staff to maintain continuity;
- Use of standard operating procedures and good management practices;
- Periodic audits by an independent entity;
- Periodic internal review and adaptive management; and
- Reporting to an appropriate regulatory body.

It would seem that, in addition to environmental factors, these elements are key throughout pilot and open field releases and even after the transgenic insect has become part of an on-going programmatic intervention. People will always be one of the most important factors in all work with transgenics – both as sources of risk and as resources for the prediction and management of risk.

18.6 Documentation of Risk Assessment

Documentation of assumptions, uncertainty, end-points and data or data sources is critical to get the most from a risk assessment. Adequate documentation extends the value of the assessment from decision support at one point in time, to a range of purposes over time: a record which can be taken up by others to confirm or adjust risk assumptions as new information is obtained; a communication tool to, for example, inform the public how their concerns were taken into account or to interact with regulators and politicians on cross border issues; as a transparent record of the process to provide legitimacy of permit decisions if questioned over time; and to support development of risk management and standard operating procedures.

Final conclusive reports are important, but risk assessment may be carried out at

several steps in the development of a product, as shown in Fig. 18.3. A risk assessment may be required as a part of each of the documents noted: an import permit application, a field release permit application, an ethics review, an environmental impact assessment, an impact evaluation and a monitoring plan. Similarly, these studies may contribute sections to a comprehensive risk assessment. The exact nature of documentation will be set by the national or, at times, local regulatory requirements.

18.7 Social and Political Aspects of Risk

Article 26 of the Cartagena Protocol states that Parties '*may* take into account … socio-economic considerations' and in Article 23, 'that they *shall* promote and facilitate public … participation … [and] consult the public' [emphasis added]. De Andrade *et al*. (2012) warn that the former may cause conflicts with rights and responsibilities for other international agreements. This level of public participation is often new for regulators. Mumford and Carrasco (Chapter 19, this volume) discuss precedent and ways to consider economic factors in a large transgenic insect release programme.

Macer (2003) identified key social and ethical issues in regard to release of GM mosquitoes. Researchers themselves have recognized the need for broader agreement on social, ethical and legal aspects of moving from laboratory to field applications of transgenic insects (WHO, 2010). Some advances along this line have been made in confined and pilot research and release site selection and community engagement (Lavery *et al*., 2008, 2010). An important question is how much of this process should be taking part in the risk assessment phase, versus through other mechanisms.

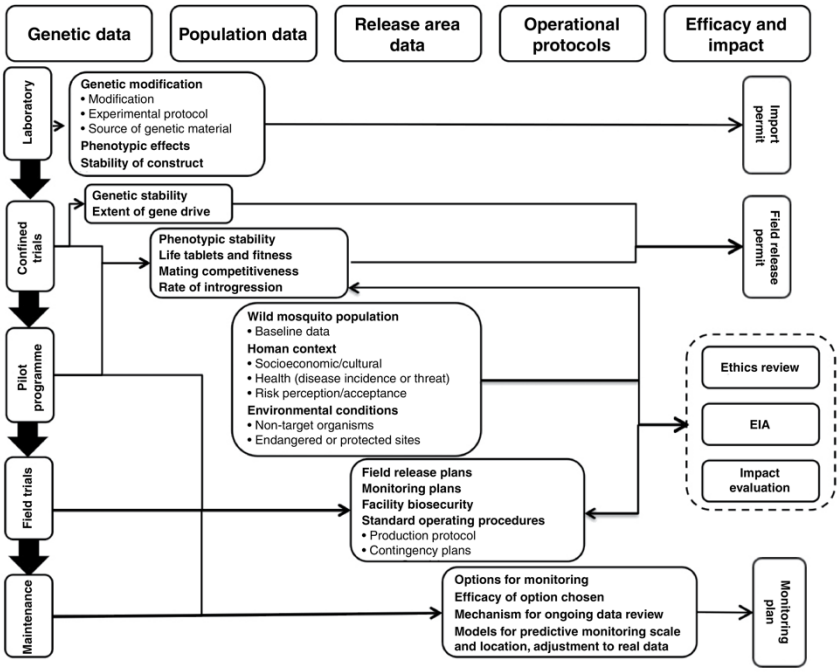


Fig. 18.3. Phases of technology development, data types and requirements and resulting documentation for deployment of a GM mosquito (Knight *et al*., 2010).

The hazard identification step (which can be separated from the assessment phase) is an important point at which to obtain broader input, so that valid concerns will not be left out of the analysis process. The Environmental Security and Governance Research Group at Imperial College London has developed a series of opinion elicitation and graphic representational tools for policy formulation based on risk analysis with high uncertainty or lack of data (e.g. Leach and Mumford, 2008; Mumford *et al*., 2010). Presenting opinion as a distribution and eliciting certainty about opinion as an additional dimension (e.g. Holt *et al*., 2012, 2014; Rindorf *et al*., 2012) has allowed for the identification of clusters and trends in concerns, which may inform hazard identification. (Concerns which have no scientific evidence may be included in this type of exercise, but these are then identified as hazards in terms of the possible impact from people believing in the concern rather than as a scientifically supported hazard in and of itself.) This method seems to work best with expert groups who are at least somewhat familiar with the topic and able to express opinions in quantitative scales and evaluate their own certainty. The research group is working on more community-oriented tools of a similar nature.

The Grand Challenges in Global Health-supported project for release of *Wolbachia*-infected mosquitoes has used a hierarchical mathematical modelling system, which can express relationships of cause and effect, structuring this as a Bayesian network, in order to capture public input in the same risk assessment-style study as the biological, epidemiological and programmatic concerns identified through focus groups and surveys (Murphy *et al*., 2010). This method of representing hazards or concerns and their probability (initially as predicted by the stakeholder raising the concern) has been taken up by Vietnamese project implementers in a 3-month process of elicitation from expert groups, workshop and final analysis (Truong *et al*., 2011).

Risk assessment case studies were developed for transgenic tephritid fruit flies, pink bollworm and *Aedes aegypti* mosquito at a UNDP-sponsored workshop in Malaysia on Risk Assessment of Transgenic Insects (Beech *et al*., 2009b). Hazards were identified with a time frame, mechanisms or pathways to the hazard, and estimate of the likelihood. It was found that most experts outside the field of risk do not readily distinguish between hazard, consequence, risk and uncertainty. This study concludes that a risk assessment is not generally familiar to even technical audiences and that it may not be the appropriate tool for capturing ethical, social and cultural concerns.

For frameworks that distinguish a separate, initial phase of problem formulation, this is another opportunity to incorporate public opinion, social and cultural issues and political priorities. Some hazards, such as pathogens, are already classified through international systems which are employed by most governments. Risk acceptability for transgenic insects is not so clearly described or known. The Australian Office of the Gene Technology Regulator begins their decision process with definition of the risk context (OGTR, 2013). This includes the development of a consequence assessment criteria matrix, which uses descriptors that could be tested against public acceptance of risk and concerns.

An illustrative consequence matrix for a serious agricultural pest is shown as Table 18.4. This would allow stakeholders to express their concerns and acceptance or aversion to risk in terms of the context of the problem or challenge. This type of matrix may be developed in advance of a risk assessment, so as to provide input on risk acceptance and community views.

Recent analysis of the application of the Cartagena Protocol (McLean *et al*., 2012) suggests that the precautionary principle has been used to restrict decisions to environmental criteria rather than all of the criteria, or even the top priority criteria, at hand. The balance of benefit and risk allows for scientific, social and economic development rather than single sector authority over national decisions (Nuffield Council on Bioethics, 2004).

Much remains to be developed in terms of inclusion of social and political factors in

Table 18.4. Illustrative Consequence Assessment Criteria Matrix for use in determining community acceptance of a novel plant protection intervention (such as a GM crop).

Level of harm	Challenge	Impact
Marginal	New plant pest or disease incursion, being addressed with existing control measures.	Minimal impact on market prices, consumer availability or quality of food items.
Minor	New plant pest or disease established and affecting entire production sector for a preferred food item.	Some food items not available or too high cost, but can be substituted with others.
Intermediate	New pest or disease established, not responding to available measures, and affecting entire production sector for a core food item.	Core food items only available at significantly higher prices.
Major	Serious pest or disease established and spreading through the region. Control measures not effective or causing other damage and/or are not feasible for significant portions of the population.	Country-wide impact on availability of core food items, significant increase in prices.

a decision regarding use of transgenic insects. Certainly, the degree to which public good needs to be demonstrated or agreed and the concept of community consent require further study. Although hazards and concerns may be identified by the public, it would seem that the step of estimating risk should be handled by risk assessors rather than requiring such estimates from the general public.

18.8 Conclusions

Assessing risk of transgenic insects can be informed by long-established practices in risk assessment as applied in other fields, particularly for release of living organisms such as biocontrol agents or to some extent for GM microorganisms that are self-sustaining. (For laboratory research and contained studies, existing guidance already encompasses most risks associated with transgenic insects.)

The same concepts – including use of risk assessment – are the bases for all of biosafety resource documents, e.g. from OECD, IOBC and the three intergovernmental treaties referenced in the WTO SPS Agreement. To date, however, guidance was focused on general principles and GM plants and seed. Guidance relating to GM animals gave little detail regarding any unique aspect of risk assessment. The first official guidance on GM insects has been published in the past 2 years by the Cartagena Protocol, reporting on issues in Risk Assessment of Living Modified Mosquitoes (AHTEG, 2012) and is still somewhat imprecise in concepts. The European guidelines (EFSA, 2013) do not have regulatory status, but were developed with the characteristics of GM insects in mind.

A number of contributions from academic, research, business and development sectors propose greater detail on risk features of transgenic insects and useful methods for quantification of risk. Additional guidance is anticipated from TDR in conjunction with FNIH. Voluntary 'precaution' has been a hallmark of the research community since the first studies with GM insects.

Some factors are more specific to assessing risks of transgenic insects. In these cases, national biosafety regulations may require adjustment to be fit for purpose. Harmonization of data requirements would benefit commercial and public research. In addition to biological risks, it is important to consider the role and impact of novel technologies on the current insect control programmes in agriculture or public health. Vector control poses additional concerns in relation to disease dynamics.

Multilateral guidance documents provide a window into shared ideas and values, whilst some national or regional regulatory regimes retain variations on concepts so

that harmonization is unlikely. The vast majority of developing countries are Parties to the Cartagena Protocol and have established biosafety frameworks under the auspices of the CBD and the Global Environmental Facility, and are relying on the Cartagena Protocol for capacity and guidance. Thus environmental criteria may continue to dominate what should be a cross-sectorial decision. Capacity in risk assessment will likely develop more quickly if linked with actual uses of biotechnology for commercial or public good.

Most would agree that the 'regulatory polarization', attributed by Bernauer (2003) and others to differences in public opinion and risk acceptance, has caused barriers to beneficial use of biotechnology and wasted valuable resources for governments already challenged with food security and public health challenges. Yet a fresh look at how to incorporate some of these factors comprising risk acceptance could possibly advance the discussion on harmonization of methodology. A positive result of the higher standards imposed on biotechnology at the beginning of harmonized regulation is that assessment of novel organisms can provide a catalyst for thought on issues previously not addressed for other agriculture or health interventions (Macer, 2003).

Societies should guard against requiring too much of risk assessment, however. Political pressures on an essentially technical and scientific exercise will weaken the decision process. Legitimate issues related to social, political, environmental and other priorities can be taken into account during selection of the risk management options and policy formulation. If risk assessment is required to support decision-making, provide a mechanism for public engagement and legitimize the overall regulatory process (National Research Council, 2002), the methodology will surely fall short of expectations.

Notes

[1] The terms transgenic organism, genetically engineered organism, genetically modified organism, product of biotechnology (biotech) and living modified organism, while not precisely equivalent, are used interchangeably in this text. For a discussion of distinctions made between terms by some others, see FAO (2011, 2012), ICPM (2001), Article 3 of the Cartagena Protocol and Royal Commission on Genetic Modification (2001).

Similarly, the term biosafety is employed despite its controversies and confusion. For comments on the term 'biosafety', its relationship to 'biosecurity' and lack of harmonization of the term's use, see Quinlan *et al.* (in press).

[2] It is erroneous, therefore, to consider that the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) of the World Trade Organization (WTO, 1995) is inferior to the Cartagena Protocol in providing detailed guidance, because the SPS simply referenced existing intergovernmental treaties which had already elaborated more detailed guidance on risk assessment and management methods, terminology, roles of Parties and dispute settlement.

Similarly, organizations such as the OECD have a history of developing consensus documents, following an agreed and documented procedure.

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All statements and certainly any errors are the sole responsibility of the author.

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Susan Philcox
Rights Coordinator
CABI Head Office
Nosworthy Way
Wallingford
Oxfordshire
OX10 8DE
United Kingdom

Telephone: +44 (0)1491 829394
Fax: +44 (0)1491 833508
Email: s.philcox@cabi.org
Visit us at: www.cabi.org

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Appendix 5. A roadmap for potential users of this research

Orientation to this study for various decision perspectives in the delivery of a novel intervention for vector control

Discoverers or Novel Researchers external to DEC[97]

Decisions about the timing of seeking a partner

- Consider the lead time and possible capacity development needs (Table 5.1)
- Consider criteria described throughout Chapter 5 for finding a suitable partner. If there an option of data transferability from early studies on efficacy and safety?
- Technology Readiness Levels are presented in Figure 5.7 in terms of entry point for a partnership; a conscious decision about timing should be made.

Choice of IP protection

- Results of the EMPHASIS and EUCLID projects inform this choice when considering a biologically based product (Chapters 3 and 5)

Consideration of shared liability and benefit

- For questions of liability, see suggested topics for a Legal Review (Table 6.2)
- For shared benefit consider suggested approach to the Nagoya Protocol (Box 3.3) and negotiate in advance with national regulators
- Shared benefit also requires negotiation on data ownership and similar roles, responsibilities and researcher relationships (Chapters 5, 10)

Style of partnership and degree of transfer of ownership

- Chapter 5 addresses a number of considerations in regard to finding a partner (e.g. Tables 5.3 and 5.5)
- Cultural differences in style should be considered (Box 5.2) along with the objectives of both parties
- Chapter 10 addresses some ways that partners can take on more ownership
- Criteria for the different meso and micro level decisions appears as Table 5.6
- Judge investments against the basis for defensible science, and the premise that people form the foundation of good research (Figure 7.4)

DEC laboratory researchers (containment studies)

Decisions about participating in novel research that may require additional resources

- What are the options for funding proposals and formation of partnerships? Is there an institutional mechanism for supporting researchers during this phase?
- Aim for advance agreements on data ownership, publishing and similar issues (Chapter 5)
- Follow a systematic review to consider what is needed for product level stewardship (such as the components in Figure 10.1)
- Consideration of the benefit of high visibility publications (Figure 5.9) in terms of reputation of the research institute

[97] Categories of decision makers and the list of their key decisions comes from Table 2.1. The bullet lists of possible frameworks comes from throughout the study.

- The outcome of a Legal Review (Table 6.2) should inform the local partner as much as an external one, in terms of potential vulnerabilities related to conducting the research

Decisions about commitment of staff and facilities for dedicated use

- Consider the challenges of Table 5.1 and if these can be overcome to the benefit of the research team or institution
- Position achievements against indicators under control of the DEC researchers, as well as project outcomes that may be beyond their control (Asking this question within the proposed criteria of Table 5.6)
- Prepare statements of mission, vision and values (such as Table 4.2) against which new proposals can be evaluated
- Review and follow steps for preparation of facilities (Figures 7.2, 7.3) to ensure appropriateness of the investment
- Ensure all components of guidance are met (Figure 7.5)

Balancing institutional or national priorities or research needs

- Explore mechanisms for supporting ongoing needs such as the cost of preparing bids for new funding, the gaps between funding, institutional oversight for estates and equipment, more stratetegic training provision
- Document decisions affecting learning systems and tools (e.g. Table 9.2) in order to easily replicate these or adapt to new projects or funding, with different objectives

Choice of approaches to ethics or research review system

- Consider the challenges of Table 5.1 and seek support in addressing these early on
- Facilities review could follow Table 7.1, but with a clear choice of approach and parameters for success and using best practice (Table 8.3) for internal reviews

<u>DEC decision makers –Regulators and others</u>

Appropriateness of technology in the national context

- Ask whether guidance is in place for engagement with the public and other organisations or there are mechanisms for debate outside of case level regulation (Figure 6.1)
- Follow best practices when creating such guidance or system (Table 6.1)
- Create a system for monitoring any disruption to facilities readiness, in the style of a learning system (Table 10.1)
- Create a national level Theory of Change designed to reach the key national priorities, and review how each new technology or innovation fits within this planning structure

Risk and benefit issues in context of existing interventions

- Pre define the range of risks and what response might be required (e.g. Table 10.2)
- Choose the level of identity maintenance and other record keeping required early on in research timeframes (Table 9.1)

Evaluations related to permitting, facility certification and a system to move from contained studies to field studies and use

- Ensure all international obligations of the country are met
- Consider gaps or weakneses of the national system, in the context of international discussions and debates (Box 6.1)
- Decide in relation to Figure 7.1 at what point and with what method to review and certify a research facility and what specific areas will be covered by regulation or

inspection (e.g. from Table 8.2) rather than left as individual lab management decisions

DEC decision makers for uptake – not addressed in depth in this study

Priorities for health spending
- Keep track of developments for evaluating early stage interventions (Box 3.2) and those using novel approaches

Compatibility with other technologies in ongoing vector control
- Criteria for appropriate field sites might influence technology choices (Figure 5.8)

Confirmation of safety and efficacy
- Decide on the best approach to provide direction and monitor compliance (in the style of Table 8.1)

Feasibility of costs and delivery

Appropriate existing policy and regulatory framework for evaluation of the novel research

Funders – not addressed in depth in this study

Compatibility of proposed intervention with Funder priorities and policies

Potential value, benefit and imact of the technology

Timeframe for support

Likelihood of success
- Consider if there is a champion that will progress the intervention (Box 3.1)
- Plan for resources required to build the capacity and have collaborative and multidisciplinary planning for vector control research

International or regional policy makers and sources of guidance – not addressed in depth in this study

Decision to recommend novel technologies

Choice of best practices or standards (e.g. for laboratory, biosafety, operations) – differences amongst locations and types of technologies
- Consider building on existing guidance (e.g. Table 7.2 on revisions to the Arthropod Containment Guidelines) in the development of future guidance or sectoral standards, e.g. for accreditation of insectaries
- Support technical experts, including DEC based teams, to identify appropriate indicators for research and translation success, and to participate in developing and using appropriate management tools such as a Theory of Change (see Chapter 4)
- Indicators and thresholds may vary according to the national context (Box 6.2) and cannot simply be copied from international agendas

All decision makers should allocate or secure resources for extensive literature review (consider Table 4.1); participation in relevant conferences and workshops; learning from others through study tours, visits, exchanges; and invited mentoring. This will inform the development of frameworks, templates, tools and other methods for organising information and data. More importantly, frameworks should be designed to answer questions.

The nature of learning systems (Section 4.6) can be risk based, based on mathematical or relational models, or simply descriptive for routine and intentional updating, consideration and reflection on lessons learned.

Stakeholder engagement should be planned and funded beyond the public consultation context considered under the scope of this study. Truly multidisciplinary teams may require more funding and time, but can better represent various perspectives in the delivery of a novel intervention for vector control, in particular. Further research on social factors such as the basis of trust, appropriate metrics for considering trust and confidence (Box 4.1), socio economic factors of importance to the society; and ways to support transfer of ownership of the research problem may be justified.

Key messages by chapter

Chapter 1
Novel interventions in vector control are needed to sustain the progress against malaria. The scenario of having an innovation discovered or developed externally to the disease endemic countries (DEC) where it will be used appears to be a common one, and is the paradigm studied by the researcher without endorsing the approach.

Chapter 2
Decision making in the context of novel interventions for vector control is more complex than in similar or component fields, particularly when the intervention is based on a mosquito strain itself, or other living organisms, and when transgenic mosquitoes are employed. The complex decisions faced are further hindered by challenges in the overall research context in many resource restricted countries.

Chapter 3
Other sectors can offer useful insights into these challenges and suggest good approaches to decision making for innovation in vector control.

Chapter 4
Research on the introduction of novel vector control requires a multi disciplinary approach; such pragmatic and operational research in particular requires a combination of methods. The research was based on outcomes from an action research process that took place over several years, complemented by literature review, interviews and an online survey. Study questions included micro level (e.g. containment lab), meso level (regional or national) and macro level (international influencers) and were framed as explorations into current practice and possible enablers and barriers. Using a Theory of Change to map the overall direction of activities and outputs, or other project management tools may support ongoing monitoring and reaching the outcomes desired in this complex topic.

Chapter 5
Progressing novel interventions in mosquito vector control requires partnership with research teams in disease endemic countries. National (meso) level criteria and biological criteria are key to identifying field sites, but a number of other factors arise for early phase delivery (import and containment studies). The researcher found that personal characteristics were often cited as much as national level criteria when considering good parterships from the perspective of an external researcher wanting to introduce a discovery. The technology readiness level at the time of introduction to a DEC context has a significant impact on the nature of the partnership. Styles of partnership along a continuum of early involvement and responsibility of a DEC research partner are described from the perspective of two European country examples of originators of innovation. Although there is no single best approach to partnerships among researchers, there are some recommended principles and practices.

Chapter 6
Regulators are restricted to their mandate, and cannot fulfil roles outside of that. Public input to decisions on novel interventions is more valuable when guided by a pre determined scope, focusing on what is within the mandate of the relevant decision makers. Other forms of stakeholder engagement are critical, but possibly beyond the mandate of a regulator.

Chapter 7
For the first stage studies taking place in containment facilities, the decision to import (when interventions are originating outside the disease endemic country doing the research) should be based on a combination of factors. Facilities readiness includes research team capacity as well as compliance with regulations, norms and the terms and conditions of any permit. The colonies of mosquitoes need to be maintained in a way that supports the usefulness of study

results. New calls for authentication of research organisms applied to this sector. Due to the nature of the research as product development, additional documentation may be required.

Chapter 8
An internal audit of these factors for facilities readiness is a useful method for supporting the decision to proceed with containment studies in a DEC setting. It can also support compliance over time.

Chapter 9
For novel interventions using the mosquitoes themselves as products, identity maintenance is particularly important and exceeds the level of record keeping generally applied. A good practice may include establishing a new field caught colony, so as to know the actual source and identity of the lab mosquitoes representing the target mosquito population.

Chapter 10
Attention and resources should be dedicated to developing all of these practices by a research team in DEC, to ensure biosafety and delivery of useful study results. One avenue for embedding practices is to develop a process of incident reporting and analysis as a means to inform risk management. This is only effective among teams with a culture where learning for improvement is valued above blaming. If the culture is in line with this, specific types of documents and guidelines are recommended to support the learning.

Chapter 11
The researcher offers a suite of new and adapted frameworks to support current decision making and provide the results of this learning for the next decision makers. The opposing views on use of any genetic modification will not be resolved with these. For those considering areawide control with modified mosquitoes, however, the frameworks will add transparency and possibly confidence in the reasoning behind decisions. While largely an exploratory study, the research has identified some key challenges, opportunities and those decision makers within a public health and research system. Her record of one example consortium working towards a novel intervention using transgenic mosquitoes can inform others starting on this path of delivery from an external discovery lab to meaningful involvement of a DEC based research team.