Modelling the Elimination of Hepatitis C Virus Infection as a Public Health Threat

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Abstract

The revolution in hepatitis C virus treatment through the development of direct-acting antivirals has generated international interest in the elimination of the disease as a public health threat. This led the World Health Organization to establish viral hepatitis elimination targets. Whether these targets can be met and how intervention programmes should be scaled up in specific settings are open questions.

This thesis details how mathematical models were developed and used to answer these questions. A model of the hepatitis C epidemic was designed and the impact of a range of intervention strategies estimated. A comprehensive package of prevention, screening and treatment interventions could avert 15 million new infections and 1.5 million premature deaths, falling narrowly short of the WHO targets. Nevertheless, achieving these gains relies on a dramatic scaling up of harm reduction interventions to people who inject drugs (to 40% coverage), continued reductions in risk of hepatitis C infection in the remaining population and implementation of screening programmes that result in 90% of hepatitis C infected people being diagnosed.

Meeting global targets will only occur if concrete strategies are implemented at the local level. We worked with policy makers in Yunnan Province, China, to devise and assess a range of screening strategies. A combined suite of interventions could reduce incidence by 49% and mortality by 56% by 2030 with treatment costs over that period of 492 million Chinese Yuan. Targeted screening that averts future infections is more cost effective than general screening; cost effectiveness hinges upon reducing DAA costs below current list prices in China. Implementing hepatitis C interventions offers a net economic benefit.

This work provides a two-sided view of tackling the public health burden of hepatitis C. Considered globally, significant steps towards elimination can be taken provided ambitious intervention targets are met. Considered locally, our analysis of the hepatitis C epidemic in Yunnan illustrates that interventions can be scaled up in a pragmatic way that offers economic benefits in addition to reducing the burden of disease ultimately borne by patients.

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Declaration

I declare that the work contained in this thesis is my own. All secondary sources have been appropriately cited. This work has benefited from the guidance and help of my exceptional supervisors which is acknowledged below.

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List of Abbreviations

AIDS Acquired immune deficiency syndrome
AIH Autoimmune hepatitis
ALF Acute liver failure
ALT Alanine aminotransferase
ANC Antenatal clinic
APRI AST to Platelet Ratio Index
ARFI Acoustic radiation force impulse
ARR Absolute risk reduction
ART Antiretroviral therapy
AST Aspartate aminotransferase

BCLC Barcelona Clinic Liver Cancer

CBA Cost-benefit analysis
CEA Cost-effectiveness analysis
CER Cost-effectiveness ratio
CET Cost-effectiveness threshold
CHE Catastrophic health expenditure
CI Confidence interval
CNY Chinese Yuan
CrI Credible interval
CT Computerised tomography

DAA Direct-acting antiviral
DALY Disability adjusted life year
DBS Dried blood spot

DILI Drug-induced liver injury
DNA Deoxyribonucleic acid

EASL European Association for the Study of the Liver
ECM Extracellular matrix
EIA Enzyme immunoassay
ELF Enhanced Liver Fibrosis
ESLD End-stage liver disease
EU European Union

FIB-4 Fibrosis-4
FSW Female sex workers

GBD Global Burden of Disease
GBP Great British Pounds
GDP Gross Domestic Product
GI Gastrointestinal

HAV Hepatitis A virus
HBsAg Hepatitis B surface antigen
HBV Hepatitis B virus
HCC Hepatocellular carcinoma
HCV Hepatitis C virus
HCVcAg Hepatitis C virus core-antigen
HDV Hepatitis D virus
HEV Hepatitis E virus
HIV Human immunodeficiency virus
HSC Hepatic stellate cell
HTA Health technology assessment

ICER Incremental cost-effectiveness ratio
IFN Interferon
IHME Institute for Health Metrics and Evaluation

IMIS	Incremental Mixture Importance Sampling
INR	International normalised ratio
IU	International units
LTFU	Lost to follow-up
MELD	Model of end-stage liver disease
METAVIR	METa-analysis of histological data in VIRal hepatitis
MRI	Magnetic resonance imaging
MSM	Men who have sex with men
NASH	Non-alcoholic steatohepatitis
NAT	Nucleic acid test
NEML	National Essential Medicines List
NGO	Non-governmental organisation
NRDL	National Reimbursement Drug List
NSP	Needle and syringe programmes
OOP	Out-of-pocket
OR	Odds ratio
OST	Opioid substitution therapy
PAF	Population attributable fraction
PCR	Polymerase chain reaction
PEG-IFN+RBV	Pegylated-interferon plus ribavirin
POC	Point-of-care
PWID	People who inject drugs
QALY	Quality adjusted life year
RBV	Ribavirin
RDT	Rapid diagnostic test
RNA	Ribonucleic acid

ROI Return on investment
ROS Reactive oxygen species
RT-PCR Reverse transcription polymerase chain reaction

SAR Special Administrative Region
SMR Standardised mortality ratio
STM State transition model
SVR Sustained virologic response

TB Tuberculosis
TE Transient elastography
TTI Transfusion transmissible infection

UI Uncertainty interval
UK United Kingdom
UNODC United Nations Office on Drugs and Crime
US United States of America
USD United States dollar

WHA World Health Assembly
WHO World Health Organization

YLDs Years lived with disability
YLLs Years of life lost

CHAPTER 1

INTRODUCTION

Chapter 1 introduces the impact of liver disease at the global scale. Viral hepatitis is highlighted as a major source of preventable cirrhosis and liver cancer deaths. The five viral hepatitis types are introduced and their contributions to global liver disease, and the ways in which they can be prevented, are summarised. Previous work modelling the impact of public health interventions on the hepatitis B epidemic, combined with advances in hepatitis C therapeutics, culminated in the establishment of World Health Organization elimination targets to tackle the burden of viral hepatitis; the high public visibility of these and the lack of previous modelling work investigating the impact of hepatitis C interventions is used to motivate the work contained in this thesis. A chapter-by-chapter overview is then given.

1.1 Motivation

Hepatitis, or inflammation of the liver, drives the development of cirrhosis which can lead to a breakdown of liver function, liver cancer and premature death [1]. The key risk factors for hepatitis are the hepatotropic viruses (hepatitis viruses A, B, C, D and E), alcohol and obesity (along with other elements of the metabolic syndrome) [2]. Complications arising from hepatitis impose an extraordinary cost on human life: in 2016, liver cancer and cirrhosis ranked sixth globally in terms of years of life lost due to premature mortality (from any cause) [3, 4]. This was an increase from being the 14th biggest cause of lost life in 1990 indicating that the proportion of global disease burden linked to hepatitis is increasing [5].

The hepatotropic viruses are responsible for the majority of global cirrhosis and liver cancer deaths (see table 1.1). This is in spite of the fact that, as communicable diseases, they are an eminently avoidable cause of liver disease [6] when compared to the other key risk factors of alcohol and obesity [7, 8]. Within the context of communicable diseases, viral hepatitis mortality is comparable to that of other major infectious disease epidemics, specifically human immunodeficiency virus

(HIV) and acquired immune deficiency syndrome (AIDS), malaria and tuberculosis (TB), see figure 1.1. Moreover, in contrast to these other epidemics, the number of deaths from viral hepatitis has been steadily rising [6].

Table 1.1 - Number of liver disease deaths by primary cause.

	Cancer (% of total)	Cirrhosis (% of total)
Hepatitis B	350,000 (42)	366,000 (29)
Hepatitis C	160,000 (19)	327,000 (26)
Alcohol	129,000 (16)	335,000 (27)
Other	191,000 (23)	230,000 (18)
Total	830,000 (100)	1,300,000 (100)

Shown are the estimates of numbers of cancer and cirrhosis deaths, and relative contributions to the total, by liver disease cause, according to the GBD study by the IHME [9].

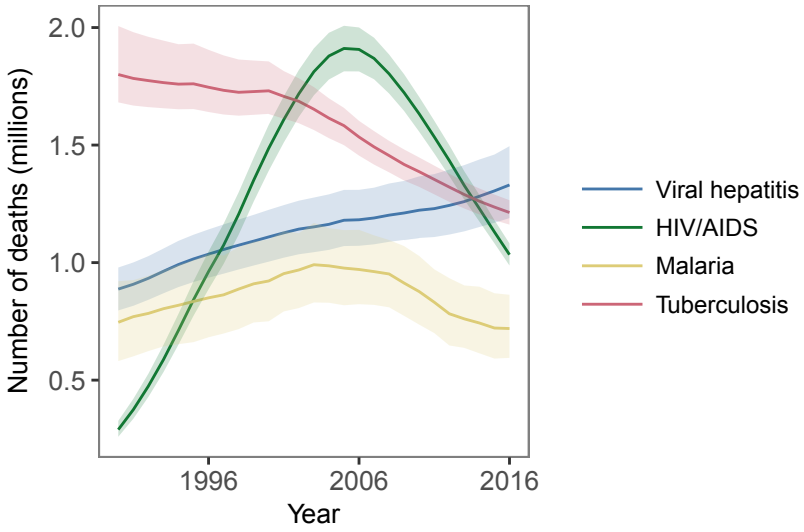


Figure 1.1 - Comparison of mortality burden attributable to viral hepatitis with other major infectious diseases. Estimates from IHME group [9].

Despite the increasing importance of viral hepatitis as a public health problem, there was no globally coordinated response until 2010. In that year a World Health Organization (WHO) commission report was released detailing the sizeable contribution of viral hepatitis to global liver disease. This report highlighted the different roles the five hepatitis viruses play (see table 1.2 for an overview), observing that a majority of cirrhosis and liver cancer deaths are a consequence of hepatitis B virus (HBV) infection, HBV with hepatitis D virus (HDV) coinfection and hepatitis C virus (HCV) infection. Hepatitis A virus (HAV) and hepatitis E virus (HEV) infections, meanwhile, were noted as driving substantial morbidity through acute but usually self-limiting disease in developing countries [10]. In addition, HAV and HEV infection contribute (along with HBV) to mortality through acute liver failure (ALF) [11].

Table 1.2 - Summary of the hepatotropic viruses.

Hepatitis type	A	B	C	D	E
Transmission	Faecal-oral	Blood & bodily fluids: sex, mother-to-child, iatrogenic	Blood: iatrogenic, injection drug use	Blood: requires HBV for expression and pathogenicity	Faecal-oral
Effect	Acute; worse in adults; self-limiting	Chronic infection, primarily in children	Chronic infection	Accelerates fibrosis in HBV	Acute; worse in adults; self-limiting
Incidence	114m	4.5m	1.75m	Unknown	20m
No chronic	N/A	257m (HBsAg)	71m (viraemic)	15m	N/A
Deaths	11k	887k	475k	Unknown	44k
Prevention & Treatment	Effective vaccine; post-exposure immunity	Antivirals suppress virus; neonate / infant vaccine	Curative direct acting antivirals	Prevention of HBV only	Experimental vaccine (licensed in China only)

Transmission, effect and prevention/treatment options information details from [1]; additional information and estimates of incidence, chronic disease burden and number of deaths from the WHO factsheets for each of the diseases [12–16]; incidence of HBV estimate from [17]. N/A = not applicable. m = million. k = 1,000.

The report culminated in a World Health Assembly (WHA) Resolution (63.18) that called for a global strategy to tackle viral hepatitis [18]. The resolution also designated 28th July as World Hepatitis Day, one of only four WHO disease-specific awareness days [19] alongside World AIDS Day (1st December), World Malaria Day (25th April) and World TB Day (24th March) [20]. This marked the establishment of viral hepatitis as a clear global health priority alongside other high-profile epidemics [21, 22]. A summary of the global viral hepatitis problem was published in 2012 [23], along with a country-by-country examination of progress made in tackling the epidemics in 2013 [24]. These reports also explored the intervention strategies that could be adopted to fight viral hepatitis (some of which are highlighted in table 1.2). The call for a global strategy was made again in a second resolution in 2014, WHA 67.6 [25].

These WHA resolutions spurred academic and political interest in taking action against viral hepatitis. The dominant contribution of HBV to liver disease worldwide, along with the existence of an effective but underutilised vaccine [26], focused initial work on investigating what the overall impact of HBV intervention strategies could be upon the epidemic at the global scale. A key modelling study made the case for increasing access to antivirals to treat infection, providing rapid birth-dose vaccination to prevent mother-to-child transmission and ensuring high coverage of infant vaccination as part of a package of interventions that could reduce incidence of chronic infection by 90%, and mortality by 65%, by the year 2030 [17]. These targets informed the WHO "Global

health sector strategy on viral hepatitis", published in 2016 followed by a "Global hepatitis report" in 2017 [27, 28]. In the language introduced by these reports, WHO targeted the "elimination of viral hepatitis as a public health threat", defined as a reduction in incidence of viral hepatitis by 90% and a reduction in mortality due to viral hepatitis by 65% [28]. Specifically, the WHO set targets of a 95% reduction in HBV incidence and an 80% reduction in HCV incidence (the mortality reduction target for both diseases is 65%) to produce the overall viral hepatitis target of 90% [27].

Such a reduction in mortality due to HCV infection would have been unthinkable prior to the development of highly effective direct-acting antivirals (DAAs) in the immediate years before the publication of the WHO strategy [29, 30]; this process of development culminated in 2015 with the approval of several different curative therapies for use in HCV-infected patients [31]. Though the previous standard of care offered the potential to cure HCV, DAAs offered vastly improved treatment success rates, better side effect profiles and shorter durations of therapy more amenable to widespread use [32–36].

By 2016 there was, therefore, a remarkable alignment of political will and pharmaceutical progress that rendered elimination of viral hepatitis (effectively HBV and HCV) as a public health threat a plausible goal. However, while rigorous modelling of HBV infection at the global scale was carried out prior to the adoption of viral hepatitis elimination targets [17], and was in fact used to inform those targets, no equivalent published work was carried out with regard to the feasibility of these elimination targets as applied to the HCV epidemic. Furthermore, while HBV modelling efforts could make use of at least one previous global model [37] of prospective intervention impact (though one that lacked a variety of desirable features [17]), no modelling of the impact of HCV interventions at the global scale had been carried out before. Prior to this project, there had not been a detailed assessment of whether WHO HCV targets could be met nor was there a suitable model available with which to attempt to answer such a question.

Within this context, the two overarching research questions posed in this thesis are as follows. Firstly, we sought to assess whether WHO elimination targets could be met and, if so, what set of intervention strategies would bring this about. To do this required filling the substantial knowledge gap represented by the lack of appropriate models with which to answer such a question, leading us to develop a first-of-its-kind global mathematical model of the HCV epidemic.

Past viral hepatitis modelling work has been effective not only as a tool for shaping or probing global policy targets, but in informing local health policy as well [38]. The second question posed in this thesis, accordingly, was what are the epidemiological and economic impacts of a range of specific HCV interventions delivered in a specific setting (Yunnan Province, China) and how do interventions compare to one another. This set of questions required adaptation of the global HCV model and the addition of economic modelling to the analysis in order to investigate the health economic impact of HCV interventions. Such analyses can provide insight into how the ambitious strategies proposed at the global level might be implemented at the local level.

The two questions therefore, complement one another: the first aims at determining the attainab-

ility of targets which have high-visibility and have driven much interest and research activity in HCV generally; the second involves describing in a level of detail not possible in a global analysis how precisely interventions might be implemented and what optimum strategies might be. Global ambitions will ultimately be met based on such local efforts and this thesis seeks to use mathematical modelling to explore the highly topical question of the impact of HCV interventions on public health at both the global and the local scales.

1.2 Overview of thesis

The following is a brief description of the chapters in the thesis. Detailed summaries are given at the start of each chapter.

Chapter 1 has given an overview of global liver disease, described the WHO targets aiming to reduce the burden of disease relating to viral hepatitis and motivated this thesis, describing its overall aims.

Chapter 2 serves as an introduction to the subjects of HCV infection, HCV epidemiology and HCV modelling. The pathogenesis of HCV is outlined followed by descriptions of the treatment cascade, modes of transmission and global epidemiology. The uses of mathematical modelling in public health are described before an overview of the HCV modelling literature is given. Mathematical modelling is shown to be a way of answering the research questions of this thesis and these research aims are restated at the end of the chapter.

Chapter 3 justifies and explains the model. Starting from the aims of the global and local modelling work summarised at the end of chapter 2, the broad approach to modelling is summarised. This is followed by the technical details of the model, including descriptions of the compartmental model structure, natural history model, transmission model and calibration. The various intervention strategies designed to investigate attainability of global elimination targets are summarised.

Chapter 4 reports our answers to the first research aim: are global elimination targets achievable? We use the model to investigate various HCV prevention and treatment strategies and report on these as part of an increasingly ambitious set of intervention packages. Our results lead to a range of policy conclusions regarding levels of scale up required to meet, or come close to meeting, elimination targets and we highlight several potential pitfalls and opportunities moving forward as individual countries start to implement comprehensive HCV elimination strategies.

Chapter 5 represents our examination of just such a local HCV strategy, specifically the prospective treatment and screening interventions under consideration in Yunnan Province, China. This chapter is our answer to the second overarching research question: what is the impact of

a range of specific HCV interventions delivered in this province? We identify several questions within this that we will seek to answer: what are the epidemiological impacts? What are the economic costs of interventions? Are interventions cost effect? Do they offer a net benefit to society as a whole? To do this, we first introduce the public health system in China, and the response in China to the HCV epidemic. After giving an overview of the health economic evaluation techniques that will be used in the subsequent analysis, we describe the methods used to answer each of the above four questions. This is followed by the results. We summarise our answers to these questions before drawing broader conclusions for the implementation of such HCV interventions in general.

Chapter 6 summarises each chapter and indicates the contributions made to policy or the literature. Limitations are discussed through the thesis where appropriate; here we highlight two sets of limitations that are of particular interest and relevance moving forward with HCV elimination programmes. A final section describes our conclusions, noting the utility of modelling at both the global and local levels before describing future work that would further add to what we have managed to achieve in this thesis.

CHAPTER 2

HEPATITIS C VIRUS INFECTION

Chapter 2 begins with a description of liver function and liver disease in general before describing the specific features of HCV infection as one of the major causes of liver disease, specifically cirrhosis and liver cancer. An overview of the biology of HCV, and an explanation of the pathophysiology of the disease, is given. This facilitates an understanding of the clinical manifestations of the disease. The HCV treatment and care cascade is introduced and key elements in reducing the burden of disease are highlighted. Modes of HCV transmission and the current and historical epidemiology of HCV infection are explained. After explaining how mathematical modelling can be used in the context of formulating public health policy, a review of the HCV modelling literature that was carried out is summarised and the key features and lessons learned from past work are used to motivate the model developed in the subsequent chapter. The aims of this thesis are then restated.

2.1 The liver

2.1.1 Overview of liver structure

The liver is the largest organ in the body and is the site of a vast array of metabolic processes [39]. Blood from the gastrointestinal (GI) tract travels to the liver via the portal vein, carrying nutrients and toxins extracted from food and drink [40]. Nutrients are processed and the blood is cleaned in the liver before it is returned to the heart via the hepatic vein [41]. The liver receives oxygenated blood directly from the heart through the hepatic artery [40]. Bile is also produced in the liver and is sent to the gall bladder via the bile ducts.

The liver is physically structured around functional units called lobules, separated by fibrous walls called septa [40]. A lobule is made up of a number of portal triads located at the periphery, each comprised of a bile duct which removes bile to the gall bladder, a branch of the portal vein which

brings blood in from the GI tract and the hepatic artery which brings in oxygenated blood. At the centre of the lobule is the central vein which drains processed blood into the hepatic vein and so on to the heart. Between the central vein and the portal triads are sinusoids along which blood travels as it is cleaned (such as by the removal of alcohol) before returning to the heart and, from there, the rest of the body, see figure 2.1.

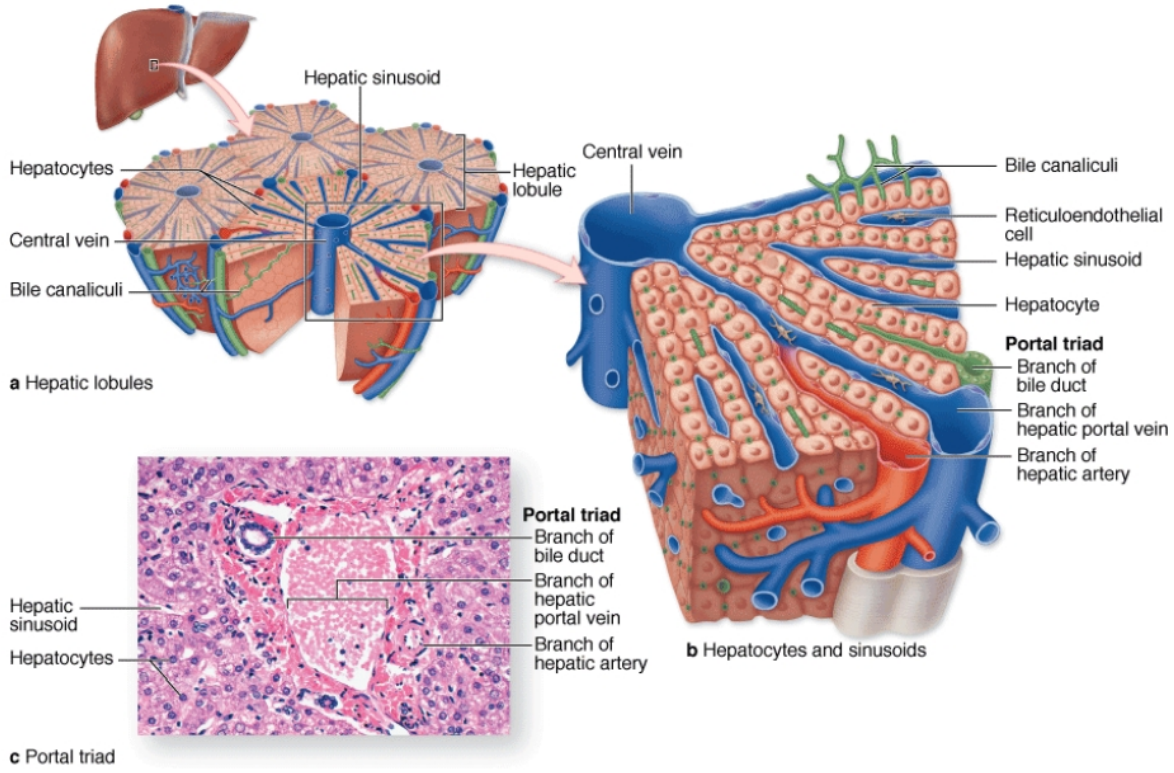


Figure 2.1 - Structure of hepatitis lobules. A shows the arrangement of adjacent lobules, centred on the central vein with peripheral portal triads, while B shows a close-up illustration of such a lobule in which the sinusoids connecting portal triads to central veins are more clear. C shows a microscopy image of a portal triad and adjacent sinusoids [42].

2.1.2 Liver disease

There are a number of agents that can damage or alter the structure of the liver and cause disease. As mentioned in the previous chapter the hepatotropic viruses, alcohol and obesity are the key causes [2]. Yet there are a multitude of other infectious agents that can promote liver injury, including non-hepatotropic viruses such as members of the herpes virus group [43], certain bacterial infections [44], while protozoal, helminthic, fungal and spirochaetal infections may also involve the liver [1]. There are also various non-communicable risk factors for liver damage in addition to obesity [45] and alcohol [46, 47], including drug toxicity [48], exposure to industrial solvents [49] or environmental toxins [50], and genetic disorders like Wilson's disease and haemochromatosis [1]. The immune system may also attack the liver itself, a condition termed autoimmune hepatitis (AIH) [1].

The nature and severity of liver disease varies considerably, as does the speed of onset. ALF is a dramatic clinical syndrome involving a rapid breakdown of liver function in an individual with no prior history of liver disease and is associated with high levels of morbidity and mortality [1]. ALF can occur as a result of drug-induced liver injury (DILI) or during the acute phase of viral hepatitis infection and is caused, primarily, by massive hepatocyte necrosis [51]; in developed countries where acute viral hepatitis is uncommon DILI will be the primary cause of ALF. While DILI is associated with a high mortality rate, resulting in death in perhaps 10% of cases due to ALF [52, 53], acute viral hepatitis is rarely so severe. In most instances, acute viral hepatitis either resolves itself (particularly in the cases of HAV and HEV infections) or otherwise progresses to chronic disease [1], particularly in the case of HBV and HCV infections but also in HEV infections of immunosuppressed individuals [54].

The course of most liver disease, by contrast, is chronic. Simple steatosis is marked by abnormal retention of lipids within hepatocytes [55] and is usually considered a benign and reversible form of liver disease [1]. Steatosis is primarily of concern when there is concomitant hepatitis, or inflammation of the liver [1, 55]. Hepatitis can arise as a consequence of accumulation of fat in the liver (non-alcoholic steatohepatitis (NASH)), alcohol (alcoholic hepatitis), iron deposition (due to haemochromatosis) or as a result of the immune response to a pathogen in the case of viral hepatitis (or otherwise in the case of AIH). Persistent inflammation leads to scarring of the liver and, ultimately, to the development of cirrhosis [56], after which breakdown of liver function may occur and there is a high risk of mortality [1]. Cirrhosis is also a key risk factor for development of hepatocellular carcinoma (HCC), the primary cancer of the liver, which is also associated with extremely poor outcomes [50]. The details of how hepatitis leads to these various outcomes varies slightly by aetiology; the details with respect to HCV specifically are given in the following section.

As was described in the previous chapter, these numerous causes of liver disease contribute to a substantial global burden of disease, both in terms of morbidity and mortality [57]. The latter is comprised principally of the burden of deaths due to cirrhosis and liver cancer (see table 1.1) [6]. In addition, acute viral hepatitis deaths (due to ALF) add an additional burden of 130,000 deaths. DILI is another major source of liver-disease related mortality but there are no global estimates for the number of deaths attributable to DILI; a very approximate value of 70,000 DILI-attributable deaths can be arrived at by multiplying the mortality rate due to DILI in the United States of America (US) by the global population in 2016 [58]. While such highly approximate estimates must be interpreted with caution [57], the major role viral hepatitis plays within the global context of liver disease is clear. In particular, HBV and HCV are the main aetiological agents driving liver-disease related mortality worldwide. As explained in chapter 1, the existence of models of the HBV epidemic to inform prospective HBV interventions, and the lack of analogous HCV models, motivated this thesis in developing such a model. A key prerequisite to developing such a model is an understanding of the biology of HCV and the pathophysiology of HCV-induced liver disease.

2.2 Hepatitis C virus infection

2.2.1 The virus

HCV is a positive-sense ribonucleic acid (RNA) virus, genus *Hepacivirus* of the family *Flaviviridae*, that was first identified in 1989 [59]. HCV virions (viral particles) travel in the blood in association with low-density lipoproteins [60] and preferentially infect the liver [61], hence the designation hepatotropic. Extra-hepatic reservoirs of the virus may also exist [62]. It is estimated that the rate of HCV virus production in infected cells is 100-fold greater than in HIV and around 10^{12} viral particles can be produced in an infected individual per day [63]; beyond this, other aspects of HCV viral load dynamics, such as the relationship between viral load and infectiousness, are poorly understood [64] particularly when compared to knowledge in the HIV field [65, 66].

HCV virions consist of RNA interacting with a shell of core (C) protein. The HCV core protein and RNA are contained within a lipid bilayer embedded in which are two envelope proteins, E1 and E2; these proteins are involved in cell entry [61]. After release of viral RNA into the host cell cytoplasm, it is translated within the host cell to produce C, E1 and E2 proteins as well as an ion channel, p7, and six non-structural (NS) proteins, NS2, NS3, NS4A, NS4B, NS5A and NS5B. These non-structural proteins are involved in all aspects of RNA replication, virion assembly and new virion cell exit as well as various aspects of host immune response evasion [67–69]. Of most interest are NS3 with its cofactor NS4A, NS5A and NS5B because these have proven to be the most druggable targets [70]: NS3-4A is a protease that breaks up the initial protein structure after translation within the host cell; NS5A plays a key role in RNA replication along with regulating replication by signalling the switch from replication to virion assembly; NS5B is an RNA dependent RNA polymerase that drives replication of viral RNA [67]. The drugs developed to inhibit the action of these proteins are described in the section on treatment below.

HCV shows high genetic variability. RNA viruses are characterised by error-prone replication, HCV has a high replication rate and the immune pressure exerted on the virus all combine to encourage numerous mutations at the nucleotide level, generating the observed genetic variability [71]. A generally accepted classification system has emerged comprising 6 genotypes (groups of viruses that have 30-50% difference in nucleotide sequence [72]) denoted 1-6, and subtypes (10-30% difference in sequences [72]) denoted using lower case letters (for the original classification see [73]; for the revised form see [74]). An extension of this system in 2014 included a seventh genotype [75] and a later discovery added an eighth genotype [76], however, these are not considered further as these genotypes are limited to an extremely small number of cases [77, 78]. In terms of viral structure, single nucleotide polymorphisms exist along the genome, even in highly conserved regions; the regions showing the greatest diversity are those coding for the envelope proteins E1 and E2 [71]. Remarkably, given the extent of genetic variation, it has not been convincingly established that pathogenicity varies between the genotypes (though genotype 3 disease progression rates might be slightly faster than other genotypes) [73, 79]. For that reason, the following section on disease progression will not delve into potential differences in disease progression by genotype

and the model developed in the following chapter will consider disease progression to be equal across genotypes. Genotype does have an important role in predicting some treatment outcomes and this will be mentioned in the relevant section.

2.2.2 Pathophysiology of disease

Damage to the liver by the virus and host responses to the virus have two key effects. Firstly, they cause Kupffer cells (a macrophage involved in the innate immune response [80]) to be activated and to release reactive oxygen species and other substances that damage surrounding liver cells [81], potentially leading to apoptosis (programmed cell death [82]) or cell necrosis. Sinusoidal endothelial cells, for example, are damaged by these [83], altering the production of vasodilators like nitric oxide and so contributing to an increased pressure in the liver sinusoids [84]. Kupffer cells also release proinflammatory cytokines and other messenger molecules [81] that, in turn, activate hepatic stellate cells (HSCs) to become activated. HSCs in turn proliferate; as HSCs can contract and relax they may act as pericytes [85], modulating sinusoidal blood flow and contributing to hypertension [86]. More significantly, activated HSCs transform into myofibroblasts [87], the cell involved in generating extracellular matrix (ECM) proteins (such as collagen), which is ordinarily produced as part of the wound-healing response [88]. ECM proteins form hard, fibrous scar tissue in the spaces between cells [89], further increasing sinusoidal intra-hepatic resistance to blood flow [84]. These various phenomena, which comprise the major elements of viral hepatitis induced liver damage at the cellular level, are illustrated in figure 2.2.

In HCV infection, fibrosis is first observed in the portal areas, causing portal areas to expand; as the disease becomes more severe, fibrotic scar tissue replaces necrotic hepatocytes and forms septa [56]. As septa grow they can bridge the gaps between adjacent portal areas (portal-portal bridging), or form bridges between portal area and the central vein of the lobule (portal-central bridging) [90]. As these bridges become more extensive, the liver becomes cirrhotic, a stage defined by "regenerative nodules" of parenchyma (functional liver tissue) surrounded and separated by "fibrotic septa" [91]. These various stages are illustrated using one of the fibrosis staging systems (see below) in figure 2.3.

Cirrhosis can be classified into two stages: a phase prior to onset of complications (described below) termed compensated cirrhosis in which the liver is still functional despite the changes in liver architecture, and a rapidly deteriorating phase termed decompensated cirrhosis after onset of complications in which the liver ceases to function [93]. The various architectural changes in the cirrhotic liver described above have the effect of increasing pressure in the portal vein (portal hypertension) due to inhibited blood flow through the liver and reducing the effectiveness of the liver in filtering toxins and performing its metabolic roles (hepatic insufficiency [94]) through the shunting of blood directly from the portal to systemic venous systems, bypassing the liver parenchyma [56]. These changes cause many complications indicative of end-stage liver disease (ESLD): portal hypertension leads to dilated blood vessels (varices), GI bleeding and accumulation of fluid in the abdomen (ascites), while hepatic insufficiency leads to yellowing of the skin due to excess

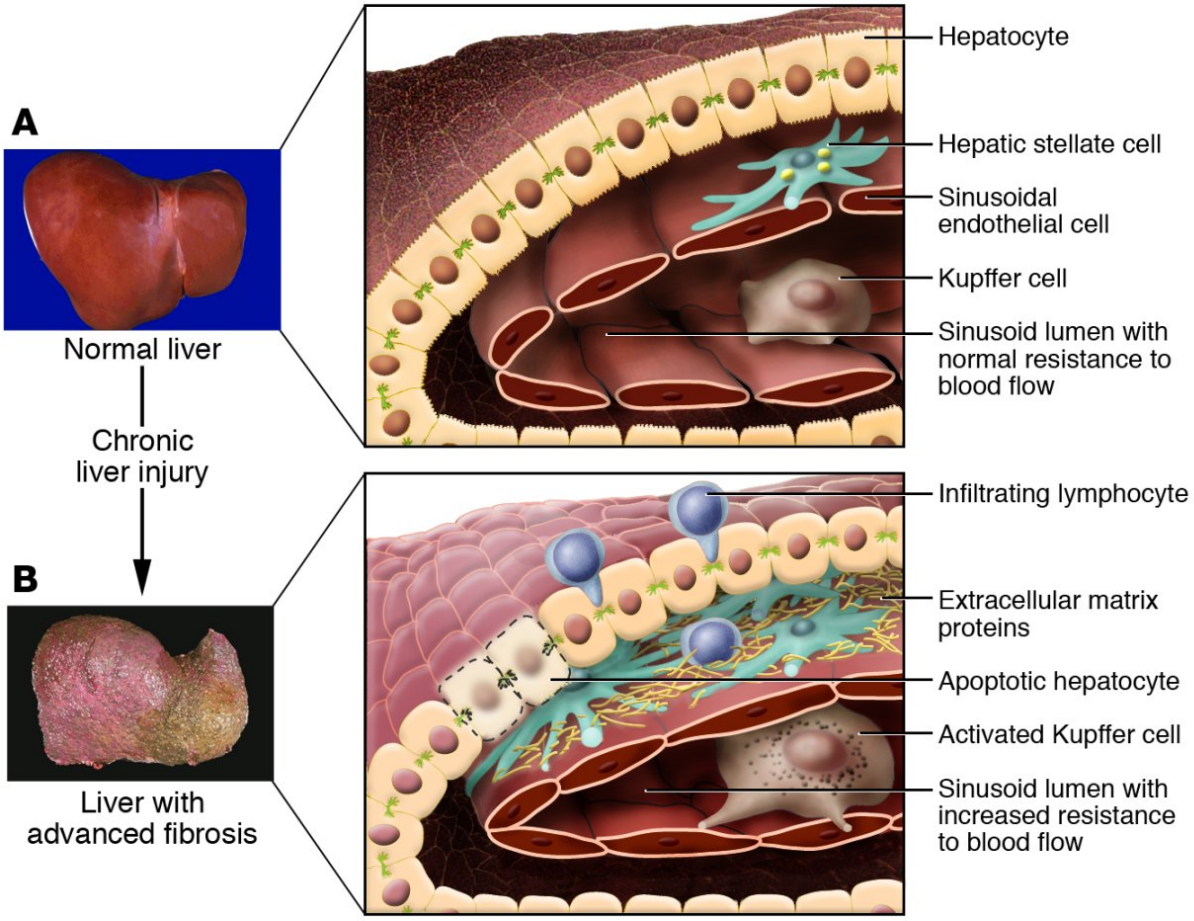


Figure 2.2 - Illustration of architectural changes undergone in the liver at the cellular level due to chronic hepatitis. (A) illustrates a normal liver, (B) shows the various changes associated with long-term liver injury, including the deposition of ECM proteins (the yellow masses around the activated HSCs), the reduced size of the sinusoid lumen impeding blood flow and the presence of hepatocytes that have undergone apoptosis. Reproduced from [89].

bilirubin (jaundice) and neurological disorders (hepatic encephalopathy) [93, 94] and a host of other complications [56].

Cirrhosis, in turn, promotes the development of cancers, particularly HCC. As mentioned above, one of the effects of HCV infection is to encourage the production of reactive oxygen species (ROS) by Kupffer cells, which can damage deoxyribonucleic acid (DNA) [95]. HCV infection is also associated with reduced antioxidant levels making the problem of increased free radical production worse [96]. Furthermore, the unusual ability of the liver to regenerate [97] and deregulated apoptosis combine to produce a high rate of hepatocyte turnover [98]. The rapid creation of new cells (so new DNA) and the presence of mutation-inducing ROS can lead to tumour development and HCC [99, 100]. In addition to the increased risk of HCC, HCV-infected patients are significantly more likely to develop B cell non-Hodgkin's lymphoma (NHL), a cancer affecting the lymphocytes [62].

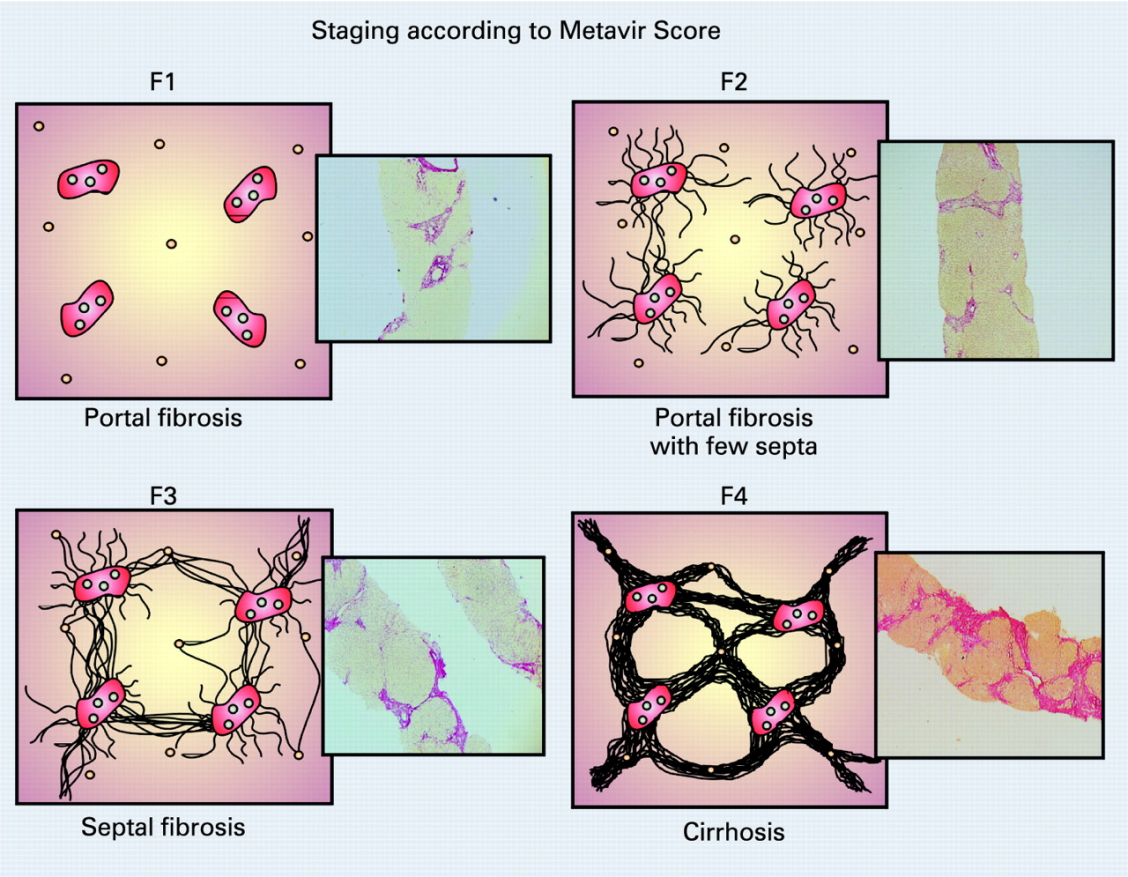


Figure 2.3 - Schematic representation of the progression of liver fibrosis with histology samples. Schematic of the development of fibrotic septa and subsequent bridging between portal tracts and central areas of liver lobules, resulting in cirrhosis. Inserts show actual examples of each of the four METAVIR (see below) fibrosis stages. Reproduced from [92].

Extrahepatic manifestations of HCV infection can occur. Principal among these is mixed cryoglobulinaemia. This condition is characterised by the production of insoluble immunoglobulins that are deposited in various tissues leading to vasculitis (blood vessel damage), glomerulonephritis (inflammation of glomeruli in the kidneys) and Sicca complex (dryness of mucous membranes) [101, 102]. Central nervous system manifestations (aside from hepatic encephalopathy discussed above) are observed with low frequency [103], with HCV potentially implicated in altering the chemistry of the blood brain barrier [104].

2.2.3 Natural history

The course[1] of hepatitis C disease is not fully understood [105]. After inoculation, an acute phase of infection leads to clinical symptoms in a minority of patients [106]. Not all patients who are successfully infected with HCV progress to the chronic stage of the disease; a recent study estimated that spontaneous clearance occurs in 25% of individuals [107]. Patients with clinical symptoms in

[1] In this section, a brief overview of the course of HCV disease is given. A detailed discussion of the parameterisation of the rates of disease progression and the onset of complications is deferred to the relevant parts of the next chapter.

the acute phase are observed to be more likely to clear the disease, perhaps due to a more vigorous immune response [106]. HCV RNA can be detected in sera one to two weeks after inoculation, and antibodies to HCV (anti-HCV) can be detected one month after that [108], though immunosuppressed individuals may not have detectable antibodies for several months [109]. In cases of spontaneous or treatment-induced (see below) clearance of the disease, HCV RNA rapidly becomes undetectable but antibodies persist [110]. It has been suggested that these antibodies confer a protective benefit, though at most this occurs in a small minority of cases [111]. Whether or not HCV infection can lead to ALF (also known as fulminant hepatitis or fulminant hepatic failure) is disputed and not considered further [112].

Acute hepatitis is deemed to have progressed to chronic disease after around six months if the virus has not been cleared [113]. Published estimates of rates of disease progression once the disease has become chronic fall into two categories: rates of progression to cirrhosis and rate of onset of complications once cirrhosis has developed. Studies often define progression to cirrhosis in terms of progression through distinct fibrosis stages. The two most common staging systems are the Ishak system [114] and the METa-analysis of histological data in VIRal hepatitis (METAVIR) system [115, 116], though other systems have been developed [90]. Both aim to provide pathologists with guidelines on how to rate the architectural disruption of the liver, which is useful both in terms of patient prognosis as well as for quantifying outcomes in clinical trials [117]. As the METAVIR system is more common in the literature describing fibrosis progression it is of greater use for modelling purposes and is the staging system adopted here[2]. The METAVIR stages can be differentiated as follows: F0, no fibrosis; F1, fibrous portal expansion; F2, few bridges or septa; F3, numerous bridges or septa; F4, (compensated) cirrhosis [90]. Illustrations of these stages are shown in figure 2.3 along with biopsy images.

Rates of progression to cirrhosis are extremely variable. As was found in a systematic review in 2001, disease progression rates vary dramatically by the study population: in liver clinic studies the proportion cirrhotic after 20 years was 22%, in post-transfusion cohorts it was 24%, in blood-donor series it was 4% and in community based cohorts 7% [119]. This reflects highly variable disease progression between individuals [120]. Due to ascertainment bias in liver clinic studies, the authors state that a community cohort approach gives the best estimates of disease progression in the average individual. Using these particular studies gives a less than 10% risk of progression to cirrhosis within 20 years for a person infected in early adulthood [119]. A more recent systematic review and meta-analysis estimated that 16% of individuals would progress to cirrhosis after 20 years [121].

As described above, once cirrhotic, there are many possible complications with associated rates of onset. From the cirrhotic state there is a 1-5% annual risk of HCC, a 3-6% risk of decompensation and a 15-20% risk of death in the first year following decompensation [105]. Risk of death after development of HCC in one paper was found to be 43% [122]. Progression rates to specific complications following decompensation have also been estimated [123]. Rates of progression to

[2]The choice is not overly restrictive since it is possible to convert between the various grading systems [118].

extrahepatic manifestations of HCV are less studied, despite a cohort study showing prevalence of at least one such manifestation in HCV patients of 38% [124]. Due to this, ignoring extrahepatic manifestations will contribute to an underestimation of hepatitis C related morbidity and mortality [125].

Hepatitis C disease, in general, is characterised by a long, asymptomatic disease period lasting decades, in which disease progression (specifically, progressive liver fibrosis) is mostly silent. This culminates in cirrhosis in a fraction of people who often present for treatment only at this late stage [105]. From here, progression may be slow or fast, with some individuals rapidly progressing to death either due to various complications after hepatic decompensation, or due to HCC; other individuals will die of unrelated causes and may never know about their infection. This natural history means that the burden of disease is often delayed decades into the future from peak incidence of infection. The presence of a large reservoir of undiagnosed individuals means preventing transmission represents a considerable public health challenge, as discussed in the following section.

2.3 The hepatitis C treatment cascade

2.3.1 Diagnosis

Diagnosis of HCV infection usually follows a two-step process: in the first step, individuals are tested serologically for antibodies to HCV followed, if positive, by a test for presence of HCV RNA [34]. The initial test for antibodies produced in response to HCV infection is an enzyme immunoassay (EIA) whereby HCV-specific antigens on an assay bind to HCV antibodies in a patient's serum sample; the presence of antibodies is determined by a characteristic absorbance signal exceeding some cut-off value [126].

The subsequent test for HCV RNA consists of a nucleic acid test (NAT) in which HCV RNA is amplified by (for example) reverse transcription polymerase chain reaction (RT-PCR), producing amplicons (the product of the amplification process) which can then be detected by a variety of techniques [127]. This produces a yes-no qualitative assessment of the presence of HCV RNA in the blood. Alternatively, it is possible to monitor the amplicons during the course of PCR to assess the amount of viral RNA present (real-time PCR) [128]. Such quantitative assessment does not necessarily have prognostic value but is useful in monitoring response to therapy [129]. Prior to the advent of pan-genotypic treatments (see below) a genotyping test would have to be carried out to inform treatment options (despite the adoption of DAAs this is still part of treatment protocols). Genotyping takes the form of either an EIA, or a PCR amplification (usually of highly-conserved regions of the genome with well-defined differences separating the genotypes [71]) followed by detection of amplicons specific to different genotypes; direct sequencing can also be carried out but this is limited to reference laboratories [127].

This 'two-step' process actually belies a series of perhaps five visits to medical practitioners (see

figure 2.4): an individual presents to a physician, is then sent to a phlebotomist for a blood draw for HCV antibody (anti-HCV) testing, returns for the anti-HCV test results, is sent again to a phlebotomist for a blood draw for HCV RNA testing and finally returns to the physician for receipt of these results [130]. This process presents multiple opportunities for patients to be lost to follow-up (LTFU). In a US study of birth-cohort screening, 73% of those with positive anti-HCV tests followed up with confirmatory HCV RNA screening [131] while among PWID in Australia only 46% had these necessary follow-up tests [132]. Another issue raised by the current process is that HCV antibodies become detectable anytime from 20-150 days after infection whereas HCV RNA can be detected 2-14 days after infection [133], with the large ranges possibly arising due to differences in the nature of exposure [134]. This means that, if tested in the early stages of infection, anti-HCV tests may be negative where HCV RNA tests would not. Similarly an anti-HCV test may be negative in immunocompromised patients such as those with HIV coinfection [34]. More importantly, a significant proportion of those who spontaneously clear HCV infection have detectable HCV antibodies decades later [135]. Due to this, HCV RNA testing is essential to the HCV diagnostic process.

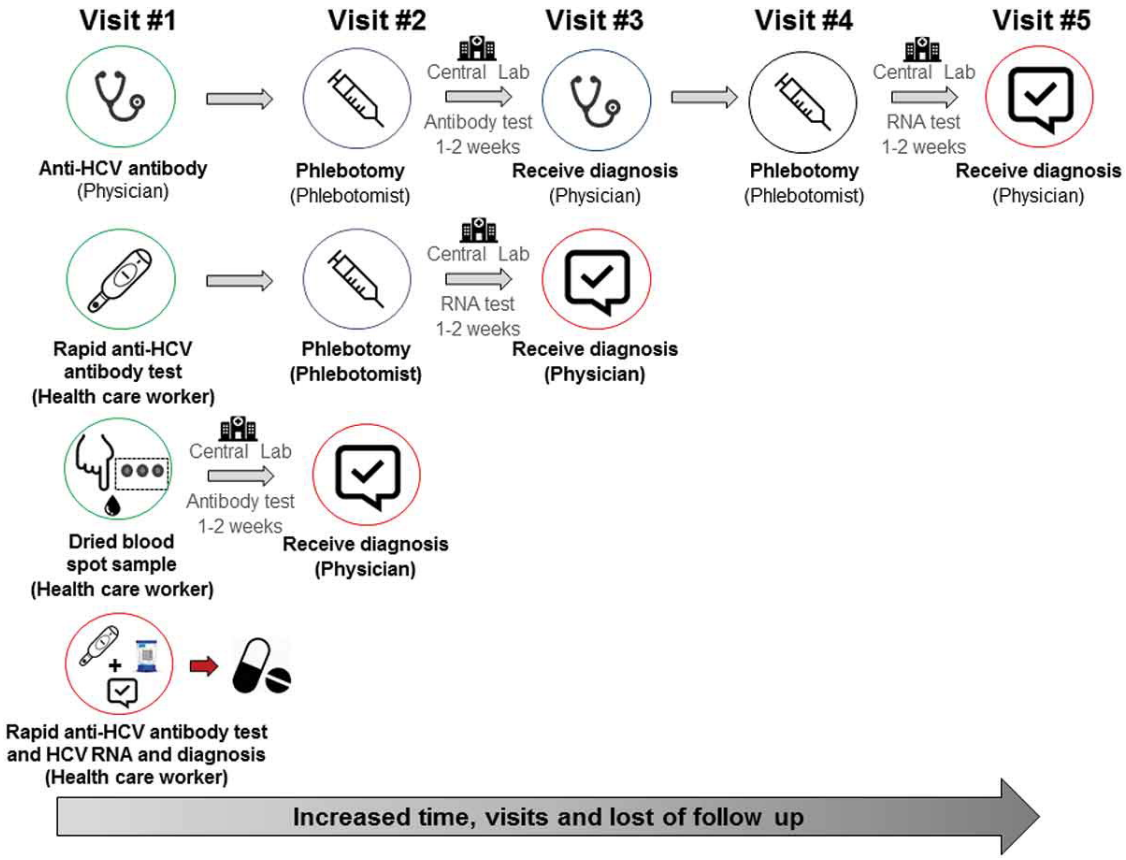


Figure 2.4 - Opportunities for being lost to follow-up in the diagnostic cascade. Illustration of diagnostic cascade (top line) and potential means of simplifying the cascade by a variety of methods described in the text. Reproduced from [130].

Elements of the above process can be combined to limit LTFU. Reactive testing using a rapid dia-

gnostic anti-HCV test (described below) can be used to combine the first three steps of the diagnostic cascade, allowing an individual to test for anti-HCV, receive the result and subsequently test for HCV-RNA in one visit (this is illustrated in the second line of figure 2.4). Nevertheless, it is worth asking why is the antibody test part of the diagnosis process at all (as indicated in every variant of the diagnostic cascade in figure 2.4)? The reasons for a complex, multi-step process that involve the anti-HCV test are partly historical: PCR tests for HCV RNA were not previously reliable and so anti-HCV serological testing was the only dependable indicator of HCV exposure [136, 137]. Nowadays with reliable NATs for detection of HCV RNA readily available, the principle reason for maintaining such a two-step process is to reduce the number of HCV RNA tests being performed. These are more expensive as they require, in particular, highly trained staff to carry out the numerous stages of the test: while an EIA can be carried out for under 10 United States dollar (USD), NAT assays may cost 30-120 USD [138]. Such tests are, therefore, to be avoided in high-income countries as a matter of efficiency and are usually prohibitively expensive in lower-income countries [138], or else the infrastructure for such tests may not exist at all.

The high likelihood of patients being LTFU, considerable expense and complex operational requirements for the current standard approach to diagnosing HCV has pushed research in a number of directions, all aiming toward a drastically simplified diagnostic cascade. One approach that has been explored is the use of dried blood spot (DBS) samples. Whereas serum and plasma samples require either refrigeration or processing within 6 hours at room temperature [139] (requiring individuals to present to clinics near such facilities [140]), DBS samples can be stored for much longer and at room temperature [141] allowing sample collection and testing to be uncoupled [142]. This has been shown to improve testing in high-risk populations [143]. One way to slim-down the cascade is to introduce point-of-care (POC) tests. Cheap POC tests are available that offer anti-HCV testing and so can expedite the route to HCV-RNA testing. Such tests are not only advantageous through offering a rapid diagnostic test (RDT) but can circumvent the need for staff skilled in venepuncture: several tests work with either finger stick blood or oral fluids [130] though the performance of the various anti-HCV POC tests available varies considerably [144, 145]. The best such option identified by a recent meta-analysis is perhaps the OraQuick RDT (OraSure technologies, Bethlehem, PA, USA) which offers results comparable to reference tests in 20 minutes and can utilise finger stick blood or oral fluids in addition to venous whole blood [145]. A trial that employed this technology significantly improved linkage to HCV care in a trial in a high-income country [146]; evidence for the impact of HCV POC testing in lower-income countries is lacking [147] but data from implementation of HIV POC testing suggest that it can increase linkage to care in resource-limited settings [148]. Simultaneously performing anti-HCV tests with other tests (such as for TB or HIV) using multiplex EIA platforms may offer a means of improving diagnosis coverage as well, by combining screening efforts across diseases and reducing the overall number of such tests required [149].

Introducing a POC anti-HCV test does not, however, mitigate the problems of patients being LTFU through the requirement for subsequent HCV RNA testing, or in lower-income settings the issue

of lack of access to such testing. Such tests would offer the possibility of one-test diagnosis, however, due to the costs of offering a POC HCV RNA test a (much cheaper) POC anti-HCV test would likely be offered first [130]; this would still offer one-visit diagnosis. While several POC HCV RNA tests are in development [150], the first to receive WHO prequalification is the HCV module to the GeneXpert device (Cepheid, Sunnyvale, CA, USA). This device performs all aspects of sample preparation, amplification and detection using RT-PCR with minimal user input [150]. Though it currently works on venous blood samples and so is not fully decentralisable [130, 151], recent work using finger-stick blood suggest that this approach to diagnosis can detect active infection and provide HCV RNA results in under an hour [152]. A considerable issue with such devices is their capital cost: the simplest GeneXpert device costs over $11,000 though the cost per test is a comparatively low $13-18 [151]. In settings with established centralised testing facilities for HCV RNA the introduction of POC testing may be more expensive [153], though a full cost-benefit analysis may demonstrate that this is acceptable in light of reduced downstream costs. In low-income settings the costs of such devices may simply be prohibitive. It should be noted that these are often multi-disease platforms that can be used for a range of disease tests [149]; accordingly, a large pre-existing install base due to HIV and TB testing expansion efforts may mitigate the problem of initial expense, requiring centres to only buy the HCV module and not the whole device [151]. Other tests are being developed, for example Genedrive (Genedrive PLC, Manchester, UK) offers a lower cost, battery operated alternative to GeneXpert though this is yet to be WHO prequalified [154].

While these technologies are being developed, a medium-term approach to increasing successful diagnosis in low-income areas may be offered by testing for hepatitis C virus core-antigen (HCVcAg). HCVcAg is released into the blood and can be detected earlier than antibodies and throughout an infection [155]. The critical point here is that as an antigen (not antibody) test, a positive HCVcAg test denotes an active infection and not evidence of past exposure. The key question is whether such tests are sensitive enough: a meta-analysis of studies suggest that core-antigen may offer a good means of testing when HCV RNA is present at concentrations of over 1,000 international units (IU)/ml [156]. This is much higher than the standard for an NAT test recommended by the European Association for the Study of the Liver (EASL) of no more than 15 IU/ml, however, a lower limit of 10,000 IU/ml would still capture 95% of viraemic infections; this suggests that this should not stand in the way of adoption where alternatives are not available [138]. This underpins WHO guidelines recommending HCVcAg testing where NAT testing is unfeasible or unavailable [147]. A caveat at present is the lack of a POC HCVcAg test, thus still requiring centralised laboratory facilities [157].

HCV diagnosis is of paramount importance as the world moves forward in implementing HCV elimination strategies. While there has been considerable focus on the incredible advances in HCV therapeutics in the last ten years that have opened up the possibility of HCV elimination (see the following section), too little attention has been paid to the fact that the majority of HCV-positive individuals do not know their status [28]. It is, therefore, pivotal that progress continues to be

made in developing cheaper, more accessible diagnostic techniques and that these allow for more rapid, if not direct, access to treatments to minimise the potential for patients to become LTFU. Funding is also required to be able to make these available in all settings [142]. As described in a 2016 WHO testing guidance document [147], in high-income countries RDTs offer the possibility of improving access and increasing the uptake of testing among high-risk groups (though trials need to demonstrate this in practice for HCV specifically [143]); in lower-income countries technologies like DBS testing can mitigate sample transport constraints, HCVcAg testing may eliminate the need for complicated NAT tests and emerging portable POC technologies could open up testing among both remote populations and at-risk groups that may not present at centralised testing facilities. Lastly, innovations to improve rates of presentation to screening will be required in addition to adoption of the above technologies. A recent contest identified means of encouraging HCV testing in a range of settings and identified numerous possible routes to improve screening, including SMS promotion of screening, social media campaigns, community empowerment and integration with existing services (PWID harm reduction clinics, HIV clinics, prenatal services); further implementation and evaluation will be required to evaluate the best means available to encourage comprehensive uptake of HCV screening to reach the WHO target of 90% diagnosed by 2030 [28, 158].

2.3.2 Staging

While diagnosis represents a key bottleneck in accessing care, subsequent steps must be carried out before treatment can begin [126]. The presence of significant coinfections must be tested for, necessitating further diagnostic tests [126]. These must be managed as appropriate and steps should be taken to manage cofactors (such as excessive alcohol use or presence of elements of the metabolic syndrome) as these may increase rates of disease progression [34, 159].

Several tests are recommended for preliminary staging of disease: international normalised ratio (INR) which measures clotting ability and so bleeding risk; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) which are elevated with hepatic inflammation; total and direct bilirubin, a compound normally removed from the blood in the liver but present at elevated levels in liver disease (a high level of which is responsible for jaundice); serum albumin levels, a protein made in the liver of which there is a derangement of levels in the blood when liver disease is present [126, 160–162].

The extent of liver fibrosis is initially assessed by using combinations of the above biomarkers to calculate indicators that have been shown to correlate with severity of fibrosis (such as AST to Platelet Ratio Index (APRI) and the Fibrosis-4 (FIB-4) index) [163]. Secondly, additional indices (such as Enhanced Liver Fibrosis (ELF) or FibroTest) can be constructed based off of additional serum biomarker tests to provide more accurate measures of fibrosis [164]. Lastly, direct measurement methods have been developed to measure liver stiffness. These are based on measuring the velocity of shear waves through liver tissue and inferring the stiffness according to Hook's law (waves will travel faster in stiffer, or more fibrotic, media) [165]. Transient elastography (TE)

was the original such method and requires a specialist (Fibroscan) device; acoustic radiation force impulse (ARFI) imaging was subsequently developed and can be integrated onto a standard ultrasound. Magnetic resonance elastography techniques have also been designed to non-invasively assess liver disease stage, which involve use of a magnetic resonance imaging (MRI) machine. These have better diagnostic accuracy, particularly for detecting earlier stages of fibrosis, but suffer from much higher costs [165].

Patients with cirrhosis must be monitored for the development of HCC [160]. Detection should be followed by computerised tomography (CT) or MRI scans; this enables cancer staging according to a variety of systems [166]. One example is the Barcelona Clinic Liver Cancer (BCLC) staging system. This stages HCC based on the tumour burden (number, size and location of tumours) and liver function according to a five-point scale (0, A, B, C, D), allowing assessment of the treatment options to be made based on stage. For example, stages BCLC 0 and BCLC A may be eligible for curative resection or ablation of tumours [167] while BCLC D may only be eligible for symptomatic treatment [166]. Staging systems for those at risk of decompensating are also employed. A common metric to calculate is the Child-Pugh score which incorporates three serological tests (serum albumin, total bilirubin and INR) and two clinical features (ascites and hepatic encephalopathy) to produce a points score converted to a class (A, B or C) with the worst survival from class C [168]. The model of end-stage liver disease (MELD) is also used, particularly in liver donor allocation [169, 170].

2.3.3 Treatment

Before discussing curative therapies for HCV, it is worth noting that liver transplantation is also a treatment option. It is indicated for those with HCV infection when liver function deteriorates beyond a specific level, usually defined by a MELD score threshold (as in decompensated cirrhosis), or in HCC patients in whom the probability of recurrence is low [171]. In both cases, pre- or post-operative treatment of HCV is required as infection of the liver graft usually occurs and outcomes for such patients (compared to non-HCV liver transplant patients) are significantly worse as a result [172]. The number of liver transplants carried out worldwide is extremely low, with estimates suggesting around 27,000 liver transplants are performed annually [173] with a quarter of these taking place in the US alone and almost none in Africa as a whole [173, 174]. The low global number compared to the overall HCV burden means that transplantation will not play a key role in disease burden reduction. It is not, therefore, considered further in this work.

A putative treatment of HCV infection was being investigated in 1986 before the virus itself had been identified (when the disease was known as non-A, non-B hepatitis) [175]. In this study, 10 patients were given recombinant interferon (IFN)-α. AST levels decreased during treatment but rebounded after treatment ceased. Despite this, larger trials were performed [176], paving the way for the establishment of IFN as the recommended treatment [177]. Regimens involved subcutaneous injections three times per week, and had extremely low success rates: the proportion achieving sustained virologic response (SVR), defined as the absence of viral RNA in sera 24

weeks[3] after discontinuing treatment [179]) was between 15-20% for 12 months of therapy [177]. The action of IFN is multifaceted: it has antiviral effects within the cell as well as promoting the adaptive and innate immune responses [180]. The low proportion achieving SVR with IFN treatment demonstrates the ease with which HCV inhibits the action of the drug. Though not well understood, possible mechanisms relate to inactivation of antiviral substances produced by the cell, for example by the HCV NS5A protein or the E2 protein, impeding the action of IFN. The second of these mechanisms has been suggested as an explanation for the lower SVR rates in genotype 1 IFN treatment compared to genotypes 2 and 3, since the genotype 1 E2 protein has a different structure [181].

Two improvements to the IFN regimen helped improve SVR rates. Firstly, ribavirin (RBV)[4] was added to the regimen in the 1990s, increasing SVR rates to around 40% [183, 184]. Though RBV has been shown to have many antiviral properties [185], it is ineffective as a therapy in its own right [186]; improvements resulting from the combination of IFN+RBV must, therefore, be a consequence of interactions between the two [180]. The second major advance in HCV treatment was the discovery that addition of a bulky polyethyleneglycol (PEG) molecule to IFN to produce (in combination with RBV) pegylated-interferon plus ribavirin (PEG-IFN+RBV) resulted in improved pharmacokinetic profiles, allowing for once weekly dosing rather than the onerous three injections per week required before [187].

This established the standard of care at the beginning of the 2000s, comprising weekly subcutaneous injections of PEG-IFN+RBV [188]. Monitoring is accomplished by measuring levels of HCV RNA in blood, with changes to duration of treatment made as appropriate. The most significant difference pertaining to the genetic diversity of HCV is that cure rates under this standard of care vary markedly by genotype [187, 189–192]. For all genotypes, PEG-IFN+RBV treatment courses are long and impose considerable burdens on patients, both due to the requirement of weekly injections and the numerous side effects [193], including general flu-like symptoms in addition to a distressing variety of neuropsychiatric symptoms, such as depression, anxiety and mood disorders [194].

Genotype 1 patients (the predominant genotype in the US) have particularly bad outcomes under PEG-IFN+RBV therapy. The plethora of adverse effects attributable to therapy encouraged the search for new therapies in the 2000s. Such searches may not have succeeded were it not for key breakthroughs in cell culture models available for the study of HCV (see [195, 196]). One of the first crucial breakthroughs in 1999 was the successful construction of a replicon system of HCV in human hepatoma cell lines (Huh-7). Replicons are RNA or DNA segments capable of autonomous replication [197]. These pushed forward the study of HCV, yet such models were

[3] 24 week SVR is only one such definition; after the advent of DAA therapies faster cure rates began to be investigated by measuring SVR rates at 12 weeks denoted SVR12 (for one example of this in use see [178]). For our purposes we simply refer to any such measure of viral clearance as SVR. Note that although reference is sometimes made to SVR rates (probably as a result of the term 'success rates') these are, in fact, proportions achieving cure and not an actual rate of achieving cure.

[4] An antiviral originally used in the treatment of respiratory syncytial virus [182].

limited [198] since they were not capable of producing infectious viruses which could be analysed to investigate how new cells came to be infected [195]. A second major breakthrough was the serendipitous discovery of an isolate from a Japanese fulminant hepatitis C patient (denoted JFH-1) that could replicate in vitro [195, 199]. Tissue transfected with this isolate produced infectious virions and allowed, for the first time, the study of the full life cycle of HCV in the laboratory. Isolates belonging to other genotypes were eventually able to be cultivated in a similar way: by adding complementary DNA (cDNA) to hepatoma cell lines, a team of researchers recently found that adding specific cDNA allowed all strains of HCV to replicate in vitro, a development that may facilitate the study of all genotypes of HCV [200]. These developments, in particular the discovery of an isolate that could replicate in vitro, revolutionised understanding of HCV and fundamentally underpinned the development of the next generation of therapeutics [201].

Armed with new cell models, researchers began to design DAA drugs that targeted HCV-specific viral proteins[5]. The advantages of such an approach would be potentially fewer adverse effects (as the drugs were more targeted) and improvements in SVR rates, with therapies possibly engineered to overcome the difficulties treating certain genotypes [204]. The first two such drugs approved were boceprevir [205] and telaprevir [206], in May, 2011 [207, 208]. Both inhibit the NS3-4A proteases which are involved in cleaving the HCV polyprotein precursor produced immediately after translation. Triple therapies with one of these two protease inhibitors in combination with PEG-IFN+RBV achieved success in large scale, early trials, with an approximate doubling of the proportion achieving SVR in genotype 1 patients [209]. The drugs were eventually discontinued, however, as they had extremely low barriers to resistance (easily achieved mutations in the HCV RNA quickly reduced the efficacy of the drugs) [210].

Continued activity has led to the development of many drugs in recent years [211], and numerous drug combinations are now approved [212, 213]. The key combinations are: sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, sofosbuvir/daclatasvir and glecaprevir/pibrentasvir (sofosbuvir/ledipasvir is currently recommended in adolescents) [36]. These treatment regimens offer 8-24 week treatment regimens that can cure the majority of patients, irrespective of genotype, HIV coinfection, disease stage or previous treatment experience [29, 33, 36, 214, 215].

As this discussion has shown, there are a great number of treatment options that open up the prospect of curing the majority of hepatitis C patients. The fight against hepatitis C has thus transformed from a question of molecular biology and drug development to a question of public health policy regarding how to ensure these transformative treatments are made available to all and what the impact of such treatments might be. A discussion of modelling efforts that have investigated this question is given below. In the following section an overview of the global epidemiology of hepatitis C disease is given. This not only feeds directly into the global modelling considerations of chapter 3, but also leads to a discussion of the various routes of transmission to which prevention

[5]Protease inhibitors had been developed before these advances (such as ciluprevir [202]) but the difficulty in designing these drugs before the advances discussed above meant they were not ultimately viable (ciluprevir, for example, was found to be cardiotoxic [203]).

efforts can be directed in tandem with increasing the testing, diagnosis and treatment of infected individuals with these new DAAs.

2.4 Epidemiology of hepatitis C

2.4.1 Modes of transmission and means of prevention

As a blood borne pathogen, any activity whereby blood or blood-derived fluid is passed between individuals is a possible HCV transmission route [216]. Any activity that prevents such transmission is referred to as prevention in this work; while disease prevention can be classified into primary ("prior to the biologic origin of the disease"), secondary ("after the disease can be recognised but before it has caused suffering and disability"), and tertiary ("practised after suffering or disability have been experienced") prevention activities [217], it seems most natural to use the term to connote only the prevention of successful transmission of HCV (while secondary prevention as defined above refers to screening and diagnosis followed by treatment and tertiary prevention refers to reactive treatment after onset of symptoms).

Healthcare transmission routes. A major source of infection is unsafe medical injections, estimated to contribute 315,000 HCV infections per year [218]. WHO defines a safe injection as one which does not harm the recipient and does not expose the provider to unnecessary risk [219]. The primary mechanisms by which injections are rendered unsafe is the reuse of needles, the reuse of syringes or the reuse of multi-dose medication vials. In developed countries these problems have been reduced through the introduction of disposal syringes/needles and single dose vials [220].

In developing countries not only are safety measures not necessarily adhered to, but the phenomenon of unnecessary injections is extremely common, making up 70-99% of injections in five countries surveyed in 2000 [220, 221][6]. These include injections of vitamins, antibiotics and analgesics like paracetamol that could be more safely (and as effectively) taken as pills. The reasons for such overuse of injections are numerous. One key factor is the perception that injections represent a significant and technologically advanced intervention; a trip to a health practitioner without an injection may be perceived as ineffective, so driving unnecessary injections even in the formal health sector [223]. In the private sector ample provision of such injections not only caters to the aforementioned demand but is seen as justifying higher prices (even when component costs do not merit it), a problem compounded by the reuse of syringes and medication vials to improve profit margins further [224]. As evidenced in developed countries, the safety of injections can be improved by adoption of disposable syringes. Auto-disable syringes that, for example, block the plunger after depression, could be introduced that physically prevents reuse [225]. Yet, without appropriate context-specific research into ways of reducing the demand for unnecessary injections, as well as adequate data collection to monitor and critique progress to reducing this demand, people will continue to be exposed avoidably to pathogens such as HCV [222]. Transmission by

[6]The use of such old estimates (from 1999) is not ideal, but is indicative of the lack of information available on this quantity, for greater discussion see the following 2013 article [222].

such means in some parts of the world may be contributing to higher HCV prevalence in regions where these routes of transmission have all but been eliminated through migration from lower to higher-income countries [226].

Blood transfusion is the second major risk factor for HCV transmission [227, 228]. Prevention of such transmission required a test to screen blood for HCV antibodies, first developed in 1990 [229–231]. Routine testing was effective in reducing incidence of HCV [232, 233] and implementation of such policies reduced risk of transmission from around 1 in 500 per unit blood transfused, to 1 in 1.6 million in the US (similar trends hold in other developed countries) [216, 234]. The outlook in developing countries is not as good: in 2007, of 141 countries surveyed by the WHO, 41 reported not screening for at least one of HIV, HBV, HCV or syphilis, resulting in 5 million new HCV infections per year [235]. The net result of these deficiencies is that in Africa the acquisition risk of HCV is 2.5 per 1,000 units of blood transfused, similar to the historical value in high-income countries [236]. This mode of transmission is, therefore, likely to remain a significant source of HCV infections in developing countries [216, 237, 238].

Other means of nosocomial (hospital-based) transmission have been documented, including improperly disinfected supplies and shared equipment during haemodialysis, cross-contamination of equipment in endoscopies and colonoscopies, inappropriate re-use of equipment such as finger stick devices, bags of saline re-used between patients and syringe misuse [239], demonstrating that ensuring blood safety alone is not sufficient for preventing HCV transmission. In developing countries such routes may contribute significantly to incidence due to lower standards of infection control [238]. Preventing transmission via these routes is increasingly being recognised as necessary to prevent HCV infection [238] in addition to efforts to reduce the number of unsafe injections and contaminated transfusions described above.

Non-healthcare transmission routes. Outside of the healthcare setting there are a range of possible indirect risk factors associated with HCV infection. These include tattooing, body piercing and beauty treatments [240–242]. The relative contributions of such minor transmission routes have rarely been investigated: one US study of blood donors suggested piercings and religious scarification were significant risk factors for HCV infection [243]. Other studies have led to opposite conclusions with a general consensus that these routes play at most a very minor role in the global epidemic [216].

Direct transmission between individuals can occur perinatally from HCV viraemic pregnant women to the child [244]. Whether transmission through sexual contact occurs is more contested [245, 246], however, a recent study demonstrated an approximately 1 in 190,000 per sex act probability of transmission between serodiscordant heterosexual couples [247]. For comparison, the lowest such estimate in a meta-analysis of HIV transmission among serodiscordant heterosexual couples is 1 in 10,000[7] [248] demonstrating the extremely low probability of heterosexual HCV

[7]This is the lower (2.5%) confidence interval for female-to-male transmission in developed countries (quoted because it is the lowest such value). Male-to-female estimates and those all estimates in developing countries are significantly higher.

transmission if it does occur at all.

Among HIV-negative men who have sex with men (MSM), it is believed that HCV prevalence is similar to the general population [238, 249]. However, among the HIV-positive MSM population, HCV incidence has been observed to be higher than in other populations in recent years [249], with severity of HIV disease positively correlated with incidence of HCV infection [250]. This suggests that this population could be a key demographic for targeted prevention interventions, particularly as the risk of reinfection after successful treatment in such a group is considerable [251].

Drug use. Sharing of needles and other drug paraphernalia among people who inject drugs (PWID) is now the principle transmission route in developed countries [216]. For example, 80% of incident HCV infections in Australia between 1990 and 2000 were estimated to be due to injection drug use [252]. In addition to dominating incidence, prevalence among PWID is extremely high: 49% of the United Kingdom (UK) PWID population, for example, was reported to be anti-HCV seropositive in 2014 [253]. HCV transmission among PWID is also an extremely important component of the epidemic in middle-income countries: a 2019 meta-analysis in China reported a prevalence of 72% among PWID [254]. The prevalence of HCV among PWID in other regions is difficult to assess, but, in Sub-Saharan Africa, it is believed that PWID do not make up a significant proportion of the number infected with HCV because overall numbers of PWID are low [255].

National estimates of high anti-HCV seroprevalence among PWID are amalgamated in a 2017 global review [256]. This demonstrates the magnitude of the HCV epidemic in this group: anti-HCV seroprevalence was over 50% (among PWID) in 53 countries out of 99 for which data were found, with over 90% prevalence reported in countries as diverse as Taiwan, Libya, Mexico and Mauritius [256]. This group must, therefore, be of key consideration in designing HCV elimination programmes and so a thorough understanding of risk factors for HCV transmission among PWID is required. As was shown previously with regards HIV infection in the PWID population, shared needles are not the only mode of transmission: HIV DNA was found in shared syringes (which can be used to mix and share out drugs, a process called 'backloading' [257]), in shared cookers (used to mix and dissolve drugs), shared cotton (used to filter particles from drugs) and in rinsing water (used to clean equipment) [258]. Such infection routes play a significant role as it is often not known that they contribute to disease transmission [259, 260].

Prevention initiatives aimed at reducing HCV transmission among PWID consist of two elements. Firstly, needle and syringe programmes (NSP) try to reduce transmission among active PWID by providing sterile needles and syringes. In addition, such schemes should provide sterile cookers and cotton as, particularly in the case of HCV transmission, transmission due to the contamination of drug-use paraphernalia may be undermining needle and syringe programmes [261]. Secondly, opioid substitution therapy (OST) services provide opioid agonists (including methadone and buprenorphine/naloxone among other therapies [262]) to reduce dependence. OST has been shown to be effective in reducing injection frequency [263] and has long been advocated

as part of a combination of measures to reduce HIV transmission [264]. The impact of these interventions on HCV transmission has been less studied, but a recent meta-analysis suggests that OST and, in particular, OST with NSP can reduce HCV transmission [265] among PWID. A variety of behavioural interventions have been investigated but the few that have been studied with regard HCV transmission have not shown any impact [266] and are only recommended as an adjunct to a comprehensive harm reduction package that incorporates NSP and OST components [267].

Unique drug taking behaviour may spread the risks of drug use from a small group to the population as a whole. For example, caffeinum natrio-benzoicum (caffeine and sodium benzoate, used in treating post-dural puncture headaches [268]) began being abused in the 1970s in parts of China. It also began being used recreationally in communal celebrations in Fuyu city, in the province of Jilin. Transmission via shared syringes used for this practice is believed to be the cause of an extraordinarily high prevalence of 43% in the city's population as a whole [269].

Summary. To summarise, in developed countries the bulk of HCV transmission is now confined within the PWID population but sporadic nosocomial outbreaks continue to occur. In developing countries there are a range of transmission routes, including sharing drug paraphernalia, transfusion, other medical procedures and unique local risk factors, the precise importance of which varies by country. If developing countries follow similar trajectories to developed countries (and the example of China strongly suggests this may be the case) then as nosocomial transmission is reduced, the number and proportional burden of disease among PWID may rise; one route by which the epidemic is maintained will be replaced by another. For this reason, better understanding of how to prevent the epidemic in PWID will be crucial for minimising the scope of the epidemic in not only developed countries but in developing countries as well.

2.4.2 Global distribution of disease

HCV infection, as a chronic and often asymptomatic disease that has multiple modes of transmission, has a complex epidemiology both within countries and globally. A 2000 study that attempted to categorise types of HCV epidemic, by drawing on national examples, described three patterns of transmission [238]. Pattern 1, examples of which include USA and Australia[8], refers to an epidemic curve with a peak in seroprevalence between 30 and 49 years (in the year 2000). Such a pattern implies minimal transmission beyond 30 years ago, suggesting the epidemic had yet to take hold; a concentrated peak of transmission among young adults at this time; and then a drop in transmission after 1990. As the authors point out, this cannot be ascribed to improvements in blood safety because sharing of drug equipment has long been the principal mode of transmission in these countries [252, 270]; the drop in prevalence at younger ages, therefore, is an unsolved problem.

Pattern 2 has low age-specific seroprevalence except in the oldest age groups, in which there is an uptick in relative seroprevalence that is sustained. This is indicative of an epidemic in which risk

[8]References follow in the text.

of infection was greatest 30-50 years ago due to risk factors not now present [271]. Examples of this pattern are Japan and Italy. Studies in these countries show geographical clustering of cases in older individuals, pointing to nosocomial transmission as the main historical route of infection [272, 273]. Increases in injection drug use in the 1990s in these countries mean that transmission is now concentrated in younger cohorts [274, 275].

Pattern 3 has rising seroprevalence by age, indicative of a continuous risk of infection over time. Egypt is the canonical example of such a trend. This is because a country-wide antischistosomal campaign contributed to an extremely high force of infection before the campaign was discontinued in the 1980s [276]; unsafe medical practices from that time, within a very high HCV prevalence population, have produced a continually high force of infection resulting in increasing seroprevalence by age.

A 2013 GBD study by Mohd Hanafiah et al. performed a review of articles containing information on hepatitis C incidence, prevalence or burden of disease; the authors fit age-dependent negative binomial regression models to produce regional age-specific HCV seroprevalence (anti-HCV) curves for the years 1990 and 2005 [277]. While current opinion is that this paper overestimated the number anti-HCV positive (see below), by reporting age-specific seroprevalence over time the work did enable an examination to be made of the development of epidemics according to the above patterns. North America was shown to adhere to a type 1 pattern, Asia Pacific to a type 2 pattern and North Africa, dominated by Egypt, demonstrated a clear type 3 epidemic [277]. It should be stressed that identifying such patterns within the context of regional seroprevalence estimates would not necessarily be expected to produce the anticipated patterns, since these schemes have been hypothesised by consideration of country-specific factors that would likely be masked by regional averaging. Nevertheless, the presence of the expected patterns in such regions as North America and North Africa suggests that the patterns described above do hold some value in understanding the broad temporal structure of different HCV epidemics.

A second recent study by Gower et al. in 2014 also attempted to estimate global HCV prevalence [278]. This study found data on viraemic prevalence for 54 countries, comprising 77% of the world's adult population, and produced global estimates by using regional averages to extrapolate to those countries with missing data. There were gaps in the data: the Caribbean represented a particular problem as no country in the region had data of sufficient quality for inclusion in their review, necessitating information sharing between regions to produce the global estimates.

These two analyses provided strikingly different values for global anti-HCV prevalence: Mohd Hanafiah et al. estimated that in 2005 there were 184 million (95% uncertainty interval (UI): 171-204 million) anti-HCV positive individuals worldwide, a prevalence of 2.8% (95% UI: 2.6-3.1%) [277]. Gower et al. estimate the number anti-HCV positive to be 115 million (range: 92-149 million), a prevalence of 1.6% (range: 1.3-2.1%) [278]. Given the increase in global population between 2005 and 2013, and since Mohd Hanafiah et al. show an increase in HCV prevalence between 1990 and 2005 (rather than a sharp decrease which could conceivably have been consist-

ent with Gower et al.), these results are evidently at odds with each other.

Gower et al. point out that the difference between the two sets of results arises principally because of differences in numbers positive in South Asia and East Asia; Mohd Hanafiah et al. estimates anti-HCV numbers over three-fold[9] higher than in the Gower et al. study. Gower et al. claim that differences in India (for South Asia) and China (for East Asia) can explain the majority of the discrepancy. In the former, overuse of estimates from the Punjab region, with a higher than average anti-HCV prevalence than the rest of India, skewed the results. In China previous work has used survey data from paid blood donors (a highly unrepresentative sample that often contains PWID and thus a higher HCV prevalence), contributing to a higher prevalence than rural surveys and voluntary blood donor surveys would suggest. By attempting to use more representative surveys, Gower et al. have found lower prevalence values in these important countries and consequently have arrived at much lower estimates of the number of people globally who are anti-HCV positive. This suggests that anti-HCV prevalence, long considered to be over 2% of the global population (as quoted in numerous high-profile reviews, for example [216, 245, 279]), is in fact a much lower 1.6%, corresponding to millions fewer infections.

A key step taken in the work by Gower et al. was to disaggregate global results from regional averages (as per Mohd Hanafiah et al.) to produce country-level results [278]. Additionally, by reviewing data on the proportion of anti-HCV infections that are viraemic (would test positive for HCV RNA) this work shifted emphasis onto active, chronic HCV infections rather than inflating the number of HCV infections by including all those who have ever been exposed. The work by Gower et al. was refined in 2017, giving a global estimate for the prevalence of viraemic, active HCV infections of 1.0% (95% UI: 0.8-1.1%) corresponding to 71 million active infections [280]. These revised results are those adopted in the most-recent WHO assessment of the hepatitis epidemic [28] and so represent the current best-estimate of the global number infected with HCV.

Since the impact of treatment has a dependence on genotype, knowledge of genotype distribution is still important to public health modelling (particularly of historical interventions). Two recent studies have estimated relative HCV prevalence by genotype [278, 281]. The reported serotype-specific prevalence values are similar. Reporting the latter, Messina et al. report 46% genotype 1, 30% genotype 3, 9% genotype 2, 8% genotype 4, 5% genotype 6 and 1% genotype 5 [281]. The distribution (by region) is shown in figure 2.5 [281]. There are key conclusions that can be drawn from both analyses: genotype 1 is the most common genotype; more individuals do not have genotype 1 than do have it; and genotype 3 is the second most common genotype. Since genotype 3 has been found to have lower treatment success rates (with current treatments) than genotype 2 [30], the full adoption of pangenotypic DAA regimens is crucial for HCV elimination in certain regions in particular as these have been disproportionately poorly served by the existing standard of care.

As discussed in the previous chapter, the burden of disease measured in terms of number of deaths

[9] This number is estimated visually from Supplementary Figure 1 in Gower et al. (2014) [278].

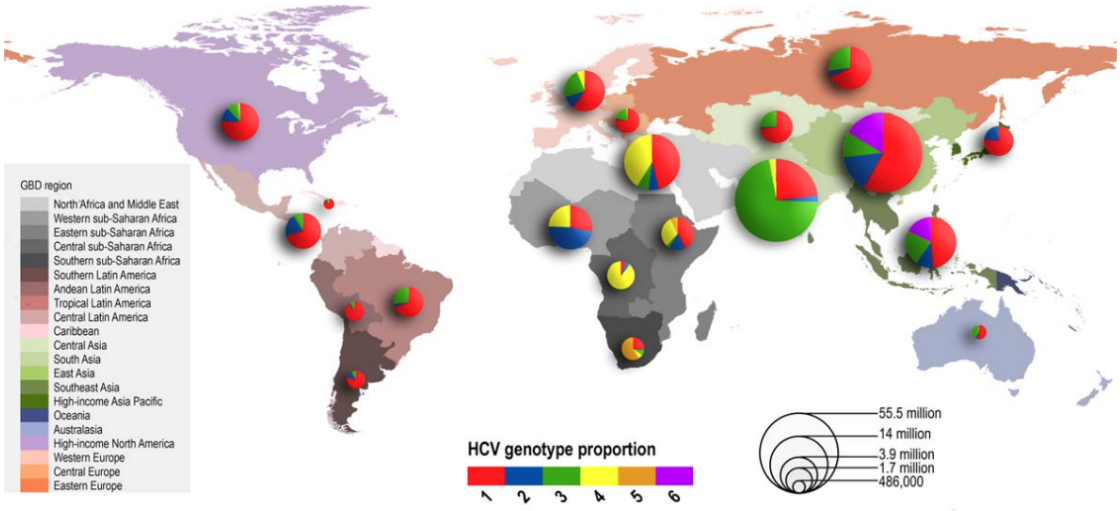


Figure 2.5 - Global HCV genotype distribution. Reproduced from [281].

has been estimated in the GBD study by IHME [6]. These estimates are calculated as follows: estimates of HAV, HBV, HCV and HEV seroprevalence are produced using the GBD disease modelling meta-regression (DisMod-MR) tool which uses available data to produce consistent mortality, incidence and prevalence estimates; this is based on non-linear mixed-effects models of the data integrated with a two state ('susceptible' and 'with-condition') systems dynamic model of the disease process (see [6] and particularly the appendix for details). These values are incorporated into the GBD covariates database which is fed into the cause of death ensemble modelling (CODEm) framework. This takes in "all-cause mortality and cause-specific mortality that are compiled from vital registration, verbal autopsy, cancer registry, and mortality surveillance sources" [6]. Using the covariates database, these values are split into different causes, producing estimates of cirrhosis, liver cancer and acute hepatitis deaths [6, 282]. These are so constructed that the overall number of deaths is fixed; specific causes of death may be squeezed such that they fit into the overall mortality envelope [3]. These age-, sex-, year- and location-specific estimates then undergo an aetiological splitting procedure using DisMod-MR: using studies on the prevalence of risk factors for cirrhosis and liver cancer, the CODEm estimates are further split into sub-causes (HBV, HCV, alcohol or other) [6].

The overall viral hepatitis deaths due to all causes of liver cancer and cirrhosis are shown in figure 1.1 in the previous chapter; figures 2.6 and 2.7 below show the distribution of disease by modality (liver cancer or cirrhosis), by sex and over time (figure 2.6), and by age in 2016 (figure 2.7). These analyses, ongoing since the initial study in 1990 [283], have provided not only age-, sex- and cause-specific mortality estimates but also indicate trends in disease over time. The ability to extract these estimates (using the online tool [4]) for any location and explore broad epidemiological trends even where other data are lacking is one of the GBD survey's key strengths [6], and the mortality estimates from IHME, along with the prevalence estimates described above, have been integrated into baseline estimates of viral hepatitis burden by WHO [28].

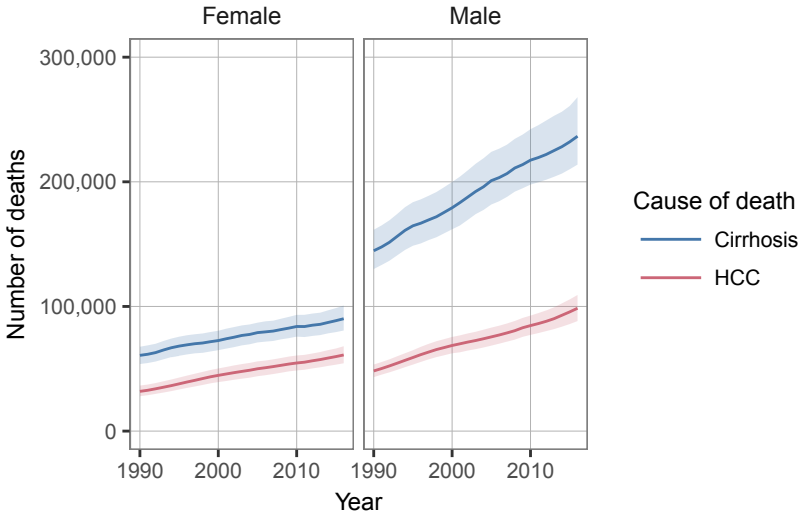


Figure 2.6 - Number of deaths by modality attributable to HCV over time. Estimates from [4].

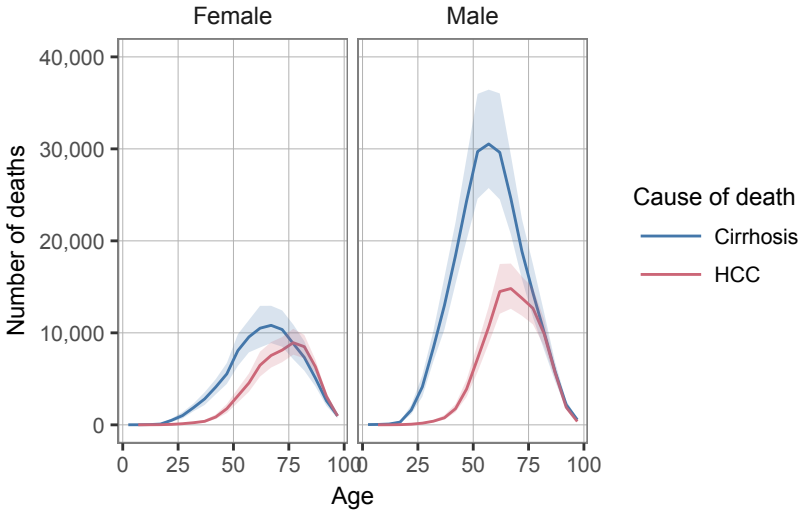


Figure 2.7 - Number of deaths by modality attributable to HCV by age in the year 2016. Estimates from [4].

Hepatitis C is a truly global epidemic, with complex regional and global epidemiology. Conservative estimates put the number of active infections at 71 million worldwide. Numbers of deaths directly attributable to the disease number in the hundreds of thousands, and reduction in quality of life due to complications of liver disease and extrahepatic manifestations can also be significant [284].

There exist numerous interventions that could prevent or cure HCV infection and reduce the this considerable burden, as described in previous sections. However, the impact of these innovations

on outcomes at the population level cannot be assessed ahead of scaling up the interventions in question. This is costly, can be practically challenging and is just one of many options available to decision makers working with limited resources and capital. One tool that has emerged to assist such decision making is the construction of mathematical models of disease and putting these to use answering a range of questions involving public health. The following section will discuss how such models have been used, illustrating their capabilities, before describing in detail the existing range of mathematical models that have been developed to investigate different features of the HCV epidemic.

2.5 Modelling the HCV epidemic

Mathematical models of disease have been a key element in formulating the public health response to disease for over a century [285]. The prototypical example is Sir Ronald Ross's work on malaria in the 1890s-1900s [286], while his work was developed into a general theory of epidemics by Kermack and McKendrick in the 1920s-1930s [287]. From these beginnings, an array of sophisticated modelling techniques has been developed to answer specific research questions related to epidemics today. A description of the myriad techniques utilised by epidemiologists would go well beyond the scope of this thesis. Rather, given how the aims of this thesis are rooted in tackling the hepatitis C epidemic, a matter of public health policy, we describe here several examples of how such models have been used to inform policy in the past. After this introduction to the policy uses of mathematical modelling, we review previous HCV modelling work focussing on those aspects of previous models that can be adopted, and those that can be improved upon, in our work. Lastly, the ways in which modelling will be used in this thesis are described, followed by a restatement of the aims of the thesis that were glossed in chapter 1.

2.5.1 Uses of modelling in public health

Mathematical modelling has played a role in public health decision making for decades. One of the first examples of this is in the work on malaria by Sir Ronald Ross (mentioned above) in 1908 [286]. In 1911 Ross wrote an attempt at general epidemic theory and identified several uses of such modelling: establishing the value of disease parameters; using the model to investigate how uncertainty in parameters might effect modelling results; and using modelling to direct "preventive measures" to be taken by the authorities [288]. Since then, though the methods have evolved, the underlying aims of such analyses are broadly the same. Here we highlight several uses of modelling, focussing in particular on their application to shaping public health policy.

As demonstrated by Ross, disease modelling can play a major role in directing prevention and control efforts [289]. His work led to the important conclusion that reducing the number of mosquitoes below a critical level could end transmission [285]. Ross even went so far as to make arguments that interventions would ultimately save money since catching malaria was preventing labourers on plantations from being able to work, foreshadowing the development of health economic ana-

lysis by decades (albeit within the context of indentured servitude) [286]. George Macdonald built on Ross' work in the 1950s and extended the recently developed concept of the reproduction number to malaria [290]. Using this, he argued that pesticides could be used not only to kill mosquitoes by annual spraying (as already happened) but also to eliminate the disease by reducing R_0 below zero; he and others also developed means of measuring transmission intensity to evaluate whether programmes targeting elimination at the time had been successful [290]. These developments, borne out of modelling malaria transmission and mosquito dynamics, directly influenced the Global Malaria Eradication Programme (GMEP), a highly ambitious public health project that ultimately foundered on lack of funding and the poor design of programmes in Sub-Saharan Africa [291, 292].

Modelling has played a major role in understanding and developing vaccination strategies. Exploring disease dynamics using mathematical models helped elucidate and develop general concepts like "herd immunity" and provided a means of quantifying the critical threshold at which this comes into effect for different diseases [289, 293]. Modelling has delivered other insights of critical importance to health officials designing vaccination campaigns. Stochastic models of measles first established estimates of the critical community size required for recurrent measles epidemics to occur [294], while later work showed that incidence would drop to very low levels directly after a mass vaccination campaign before a new period of these recurrent, albeit less frequent, epidemics emerges [295]. Modelling of rubella vaccination suggested that by increasing the average age of infection (since the risk of infection was lower), vaccination campaigns could result in more adult women being infected thereby increasing the incidence of severe complications of the disease that only affect pregnant women [296]. This modelling prediction may have led to it not coming to pass since it was instrumental in setting health policy: as articulated by WHO, rubella vaccinations should only be introduced once measles vaccination coverage (given at the same time) is high enough, and women of child-bearing age should be vaccinated before the vaccine is rolled out more broadly [289].

Mathematical modelling can be used reactively during outbreaks of different diseases. Foot-and-mouth disease was one example of such a use, with modelling analyses produced rapidly after the onset of the epidemic in the UK in 2001 [297, 298]. These made the case for culling as a means to control the epidemic, offering evidence-based analysis of the available intervention options [298]. A second wave of modelling after 2001 has led to the development of more detailed tools to try and mitigate the significant collateral damage of culling policies in the face of a new outbreak, illustrating how modelling capacity is now built as a resource to be called upon in the face of new threats [299]. More recently, models were deployed to project the possible scope of the Ebola epidemic. Nightmarish "worst-case" modelling projections involving millions of deaths focussed attention [300, 301]. Later modelling work helped monitor the disease, by offering estimates of the true number of cases and possible future impact (projected less catastrophically a shorter time into the future) [302]. Models also helped draw attention to key measures that could be monitored and improved to limit the epidemic, notably the time to hospitalisation after onset of symptoms; redu-

cing this value was shown to be correlated with reductions in the basic reproduction number in an area and led to adoption of strategies that aimed to decrease this indicator accordingly [302]. In a similar way to the foot-and-mouth epidemic, lessons continue to be learned from the modelling response to Ebola and have shaped the field in the years since. Recommendations on how to improve the response include making results available more rapidly (to bypass delays arising from publication) and creating modelling consortia (in the manner of influenza among other diseases); such ensemble modelling involves standardisation to allow cross-model comparison which would increase the confidence that can be placed in such results [303]. These developments among others illustrate how modelling is developing to meet the increasing demand for such analysis by national and international policy makers.

Estimating the number of people with disease is a key way in which mathematical modelling is put to use, with the size of the HIV epidemic in the US first inferred using simple modelling techniques [304]. Estimating the size of the HIV epidemic has evolved into a sophisticated enterprise of which modelling forms an integral part (alongside theoretical developments to improve estimating procedures and the data collection that fundamentally underpins such efforts). These modelled estimates are a critical part of the response to HIV in terms of directing resources and shaping the local and global response to the epidemic [305].

Another use case for modelling is in exploring the possible impact of new intervention approaches that have been suggested by the results of clinical trials but have yet to be implemented more broadly. One example is modelling the impact of circumcision, which had been shown to reduce transmission among men, on population level HIV incidence in both men and women [306]. This not only showed that such an intervention would modestly reduce incidence overall, but additionally the authors applied the model so developed to explore whether changes in risk behaviour (risk compensation) might outweigh the incidence-reducing benefits they had demonstrated. This type of analysis illustrates how modelling can be used to bridge the gap between trial and public health policy in an (effectively) free manner, preventing potentially perverse outcomes as well as quantifying possible population-level health benefits and providing evidence to policy makers.

Modelling may address the economic case to be made for or against introducing new (more expensive) drugs or implementing other health activities within a constrained budget. One methodology used in health economic evaluations (discussed in more detail in chapter 5) is cost-effectiveness analysis [307]. This often models the natural history of the disease among a cohort of individuals and quantifies the economic costs of different outcomes and actions (such as cost of living with disease, cost of delivering the new drug). These analyses seek to assess the trade-offs between cost and effect of new interventions (such as new drugs) and are used as a matter of course in determining purchasing decisions, in particular by national health agencies such as the National Health Service in the UK [308, 309].

Modelling can shape the global policy agenda and determine overall strategy. After it was shown that the reduction in viral load resulting from antiretroviral therapy (ART) treatment could poten-

tially reduce HIV transmission [310], modelling was used to investigate the impact of reductions in transmission on the global HIV epidemic through universal testing and treatment [311]. This galvanised interest in the potential for such highly ambitious test and treat campaigns to avert millions of infections and deaths. This work paved the way for the establishment of HIV elimination targets and modelling has, in turn, been used to test attainability of such targets and the cost of doing so globally [312], as well as to monitor country-specific progress towards the targets [313, 314]. The creation of targets with input from modelling is not unique to HIV. Modelling work informed the WHO Global Technical Strategy for malaria in 2015 by estimating what progress could be made both with current intervention strategies and with possible innovations available in the near term [315, 316]. As mentioned in the previous chapter, global HBV modelling directly fed into setting the viral hepatitis targets [17]. Modelling may also be used after targets have been established. One major analysis using an ensemble modelling approach indicated that current interventions may not result in the End TB targets being met in certain high-burden countries [317, 318]. The establishment of high-profile targets like this has become a major part of global policy across numerous infectious disease areas. Such targets focus the attention of governments and international organisations by identifying concrete targets to which countries can aspire and against which progress can be measured [319]; in terms of setting those targets, as well as in monitoring and critiquing those targets, modelling plays a significant role.

Global targets do not identify how they are to be met, however, and models often rely on specifying changes to key parameters (such as coverage of some intervention) without considering concretely how such a change may come about. This feature goes right back to the malaria models of Ross: he identified a means of tackling the malaria problem (reducing the number of mosquitoes) but lacked crucial tools with which to do it (such as pesticide sprays). Only after these were developed could Macdonald, modelling malaria at that time, plausibly countenance the eradication of malaria that Ross had simulated [290]. Even then, the Global Malaria Elimination Programme probably failed in Sub-Saharan Africa as a result of poor planning and implementation [291, 292]. Similarly, the creation of ambitious HIV targets cannot solve problems of getting ART to those who need it, the lack of data with which to monitor progress towards targets and the limited availability of appropriate diagnostics for such wide spread testing [319, 320].

This is illustrative of a whole class of practical problems in public health which can be described as the "know-do" problem or the implementation gap problem [321]: we have the tools available to tackle public health problems (the knowing) but lack the capacity to implement them (the doing). The field of research aimed at solving such problems has been called operational or implementation research by Zachariah and colleagues [322], who have defined it as the "search for knowledge on strategies $\cdots$ that can improve the results of the health programmes" [321]. They include as examples various field studies that have investigated the implementation of specific programmes and how these have led to policy changes [322]. Absent from their analysis is a description of the role mathematical modelling has played within operational research more broadly defined, in which models are built to simulate the scenario at hand and changes to parameters made to

improve efficiency and/or outcomes [323]. Yet such modelling has played a limited role in operational research within public health [324], though the capacity for such modelling to explore and suggest optimal strategies indicates a greater future role in this field is warranted [325].

This section has covered numerous examples of the public health uses to which modelling has been put as well as indicating how the field may evolve in future. In the following section, the models that have been developed and applied to questions in HCV research are described. As will be seen, the range of questions asked and the uses to which modelling has been put is relatively narrow compared to the various uses described above, with cost-effectiveness analyses dominating the literature. Nevertheless, there is much in terms of the technical aspects of the model (such as natural history model structure) that can be of use in developing new models of HCV and it is on these details that we focus in the following section.

2.5.2 Mathematical modelling of HCV

To produce an overview of the various approaches to mathematical modelling of HCV, two major systematic reviews were found that described approaches to HCV modelling within the context of cost-effectiveness analysis. Analysing the reviews (and the papers contained within them) was used as a jumping-off point for construction of the HCV natural history model in the next chapter.

These reviews were supplemented by a literature search for more general HCV models (as opposed to those whose focus was health economic analysis). This search was carried out with a view to finding analyses that investigated the epidemiological (as opposed to economic) impact of interventions and so implemented transmission models (which the models involved in cost-effectiveness analysis universally did not). Several papers were found in this search; these were variously concerned with inferring epidemic size, describing epidemiological impacts of interventions (such as prevention among PWID) and, in later analyses, monitoring progress towards WHO elimination targets (all use cases of modelling described in the previous section). The papers so found were used to inform both the natural history model as well as approaches to modelling transmission and intervention structure. The literature search was also used to ensure that the global HCV modelling work being carried out here had not been done before, thus ensuring that the work was novel.

Overview of papers from previously published reviews. The two major reviews that were found summarised features of current HCV modelling and provided lists of HCV modelling papers. Chhatwal et al. (2016) reviewed all analyses examining the cost effectiveness of introducing DAAs that were conducted after 2011[10] [326]; Townsend et al. (2011) carried out a similar analysis but with more focus on the model structures used in the analyses and the parameterisations adopted in the natural history models [327]. The former provided an up-to-date summary of current cost-effectiveness modelling while the latter provided an overview of the methodological approaches used in the field, which have not changed dramatically in the years since that study was published.

[10] (the year the US Food and Drug Administration approved the first DAAs [207, 208])

These papers were focussed on cost-effectiveness analyses and so had limitations in terms of applicability to the epidemiologically-focussed models developed in the following chapters. They were used as a starting point despite this for the following reasons: firstly, no wider reviews that focussed on epidemiological HCV modelling analyses existed; secondly, the two reviews contained transferable details on natural history modelling that would be equivalent between epidemiological and economic models; and thirdly there were more cost-effectiveness analyses available to review than epidemiological analyses. The cost-effectiveness literature, therefore, provided a wealth of usable papers with which to begin an investigation of past HCV modelling. The subsequent literature search was then used to fill in the gaps present in the cost-effectiveness literature. Economic aspects of the papers were also of value for the modelling of cost effectiveness in chapter 5 (see that chapter for details).

Chhatwal et al. found 34 papers[11] that were used as a basis for understanding current mathematical models of HCV [330–363]. All studies were set in developed countries, with only one, a study in Singapore, not in the West [343]. As the authors note, the papers found in the systematic review are extremely similar to one another. Not pointed out by the authors is the fact that several studies directly reuse the same model, applying it to different patient groups (for example treated and untreated patients [330, 334]) or applying it to different countries (Chhatwal et al. [336] and Elbasha et al. [337] use the same model applied to the US and Portugal respectively). These considerations reveal that the effective number of papers available is lower than 34 since components of the analyses are shared, and whole analyses reused, between different publications. This weakens the combined arguments of multiple publications for or against the introduction of new DAA therapies, since they are often re-statements of the same analysis, and means that a consideration of a handful of the papers will suffice to cover all those in the review.

The studies mostly adopted the same modelling structure. All but one study [355] are state transition models (STMs). STMs denote models that contain "states" (the condition that people can be in) along with "transitions" (how people move between states) and encompass a broad array of models including those with interactions and dynamic models [364]. Despite this range, all the analyses found by Chhatwal et al. were in fact non-interacting, cohort models. The similarity between models is somewhat masked by the range of language used to identify the various models in the meta-analysis, which can make effectively identical models appear different. For example, reference is made to "Individual STM" and "Cohort STM" suggesting that cohort and individual models are mutually exclusive; all the models simulated a fixed starting group and so were all cohort models regardless of whether they simulated individuals or not. Similarly, models were separately identified as "Individual STM" [352, 356], "Individual Markov" [361] and "Monte Carlo simulation" [354], possibly suggesting different modelling techniques. They are all, in fact, individual Markov models whereby individuals progress to the next health state according to a specific transition probability (whether the transition occurs depends upon a random number

[11] There were 36 papers included in the systematic review, but Tice et al. [328] was dropped as it was an unpublished report, and another paper could not be accessed [329].

hence Monte Carlo, and the transition only depends on the current state and not on an individual's history hence Markov).

The ostensible differences between the models ultimately belies the fact that all the models reviewed in Chattwal et al. are essentially the same: none considered HCV transmission and all tracked only a fixed group of people (the cohort) rather than a dynamically changing population. Such models cannot offer insight into how to model the HCV epidemic and can only be used to investigate the impact of treatment interventions. While these studies did not intend to make epidemiological projections (such as the impact of treatments on prevalence), and so such methodological choices may not represent deficiencies in the original work, failing to account for averted infections within the context of a dynamic model may have altered the estimates of cost effectiveness in the analyses. This was acknowledged by Chhatwal et al. as the primary drawback of all the studies they reviewed [326]. Averting infections adds to cost effectiveness by reducing future health costs and improving health outcomes. While this is true generally, this is particularly relevant when investigating early intervention programmes. Some studies examined the impact of beginning treatment at earlier stages of the disease (by screening before clinical manifestations): Leleu et al. [353] looked at the incremental cost-effectiveness ratio (ICER) of starting treatment at different METAVIR stages; Linas et al. [354] investigated the cost effectiveness of treating treatment-naïve patients who were non-cirrhotic as well as those who were cirrhotic. In both cases it was found that cost effectiveness was reduced with earlier treatment. The reason for this is, in part, because of discounting: treating today has an immediate (non-discounted) cost, but the quality adjusted life years (QALYs, a valuation of health from 1, perfect health, to 0, death [365]) gained may not accrue for 30 years. At a 3% annual discount rate, this reduces the impact of the QALY relative to the cost by 60%. It is unsurprising that studies would conclude that treating METAVIR stage F4 patients is preferable to treating stage F0 patients. Setting aside the debate over discounting[12] [369], dynamic modelling as described above would have, to some extent, improved the case for early intervention by acknowledging the additional gains due to infections averted.

Several other features of models were highlighted in the Chattwal et al. review. Only five studies out of 34 modelled reinfection after cure. Within the context of these cost-effectiveness analyses this is possibly justified by noting that these cohort models primarily simulated groups of individuals that resemble those in clinical trials; since these often implicitly excluded PWID (The SPRINT-1 – boceprevir – trial excluded patients with "pre-existing psychiatric condition(s)" for instance [209]) ignoring reinfection probably makes little difference to cost effectiveness as the cohort are, accordingly, assumed not to be PWID and so much less likely to be reinfected due to the absence of high-risk behaviours. Such an assumption cannot be made if considering the HCV epidemic of a country rather than a cohort. Another observation was that chronic disease is almost always simulated by way of grouping people according to their METAVIR fibrosis stage. This is due to the presence of a high-quality review of transition rates between such stages [121] and because

[12] As an example of the debate, one possible solution to the above mentioned problem is to discount future health outcomes less than costs [366, 367]. This can, however, lead to an indefinite deferral of spending, since improving future health outcomes at a given cost is progressively more cost effective [368].

clinical trials often reported SVR rates in relation to patient METAVIR stage. A last comment was that SVR rates themselves in all but one study come from trial data (or meta-analyses of trial data); the exception was a study that used US Veterans Health Administration information but only for SVR from PEG-IFN+RBV treatment, with SVR rates after DAA treatment from trial data as well [335]. As Chhatwal et al. acknowledge, there is a lack of real-world data on the impact of DAA treatments. The slow adoption of DAAs to 2018, and a general consensus that new DAAs are highly efficacious, means that studies have not materialised since this systematic review was published, forcing a continued reliance on trial data.

Townsend et al. (2011) offers a useful alternative perspective on HCV modelling through their focus on the details of the HCV natural history models used in cost-effectiveness analysis [327]. The HCV natural history model structure varies across cost-effectiveness analyses, with a handful of key choices encapsulating the differences between published models. Firstly, fibrosis progression modelling ranges in complexity from only modelling pre-cirrhotic and cirrhotic patients to simulating all five METAVIR stages, F0 to F4. This variation has mostly been eliminated in recent work [326] and studies primarily use METAVIR stages to denote disease severity for the reasons discussed above. Once cirrhotic, all models allow movement directly to HCC or else to decompensated cirrhosis. A second structural choice is whether decompensation is considered as one disease state or else is divided into specific complications (see for example [334]). This difference between models is still present in newer analyses though there does not seem to be a clear reason why the division into multiple compartments is made, given that even fewer analyses offer a means to parameterise decompensated cirrhosis complication progression rates than from the decompensated cirrhosis stage as a whole.

The choice of disease progression parameters depends upon the choices made in model structure, with either stage-specific fibrosis progression rates adopted or more general progression to cirrhosis rates used as appropriate to the model. All models implement background sex- and age-specific mortality rates which increase once cirrhosis has developed. Decompensation results in much higher rates of mortality with differential mortality according to complication in those models that explicitly simulate specific ESLD complications. Decompensated cirrhotic patients can progress to HCC in all models. Some may also implement increased year one death rates compared to subsequent years (both in decompensated cirrhosis and HCC stage individuals). Transplantation is often simulated; it is implemented in all the models in Chhatwal et al. as these were all analyses from high-income countries (even though rates of transplantation were still low). Treatment was modelled for all patients until they reached decompensated cirrhosis, at which point treatment was not offered. Various permutations of treatment duration were considered in the models along with prioritising early- or late-stage treatment. The effect of treating experienced versus naïve patients was a focus of several papers with differential rates of treatment success modelled in such analyses.

As well as summarising key model features, Townsend et al. note several limitations of these then-current models [327]. In particular, it is noted that several studies quote a single source for all of

their parameter values, a 1997 modelling study by Bennett et al. that itself assumes some key parameters (specifically progression rate to HCC and HCC mortality rate) without clear justification [370]. This illustrates two broad features of these models: reporting of parameter values is extremely poor, with primary sources often not provided. The second feature is that, as noted above, models borrow heavily from one another with the result that analyses often quote the same source, a fact that is hidden by a chain of references through secondary modelling analyses. This masks the fact that there are a small number of studies of disease progression rates and, beyond this, the available estimates have high variability. This suggests that either a clear consensus must exist when adopting a specific parameter value or else a range of parameters must be used to account for inherent uncertainty (or variability) in a particular parameter. In the studies that Townsend et al. review, parameter uncertainty is often accounted for with only one-way sensitivity analyses; in later publications, by contrast, most studies use probabilistic sensitivity analyses that incorporate simultaneous variation of all unknown parameters [326].

These two reviews of models used in cost-effectiveness analyses illustrate that there is a small set of options to be made regarding the structure of HCV natural history models. They also provide an array of parameter values to be incorporated into the model. The above discussion also reveals several issues with models that have been used to investigate HCV in the past which we will aim to improve upon (or else more clearly acknowledge and mitigate through model design than has been the case in past work). These observations are used to inform the development of the model in chapter 3 and a list of key conclusions regarding model structure is given at the end of this chapter.

Results of the literature overview. A review[13] was conducted to investigate the work that had been carried out which could provide insight for the development of a global simulation of the HCV epidemic. This was carried out with a view to finding global HCV models if they existed, or else to return studies of the impact of HCV interventions within a modelling context. These were searched for to supplement the (primarily) natural history model information garnered by the above research into past investigations of cost effectiveness. The following discussion centres on key papers found through the literature search with a view to summarising the overall trends that were identified in past modelling that either could be adopted or else adapted and improved upon.

To find relevant papers for this purpose, a literature search was carried out on PubMed [372] using the search strategy (hepatitis C AND model* AND (global OR intervention*)). This strategy was used because it returned all the expected major modelling papers in the field using a simple set of terms while returning several new documents that could be used in consideration of developing a model of HCV. The search was last updated on 23rd February 2018 and returned 616 results. As

[13]Specifically an "overview of the literature" was produced, as opposed to a systematic review according to the typology of reviews described here [371]. This entails producing a narrative description of past work without the requirement to appraise formally the quality of work or to aim at an exhaustive search strategy, since this would go well beyond the requirement here of investigating trends in past work but not to the level of producing a fully comprehensive account of previous HCV modelling.

described in footnote 13, a systematic review was not carried out in order to avoid the unnecessary complexities of (among other things) including a detailed description of exclusion criteria, but a brief discussion of how the papers were whittled down is given here for completeness.

Over half of the excluded papers fell into either the class of 'biological' papers or 'clinical' papers. 'Biological' refers to work concerning the structure of HCV, interactions in the cell, viral dynamics and so on and 'clinical' to clinical trials, case reports or investigations of some feature of the care cascade. A large number of papers were deemed irrelevant as having only a tangential link to HCV, such as studies within PWID as a whole without a particular focus on HCV. Papers that concerned purely descriptive analyses of epidemiology (such as historical trends in prevalence or distribution of genotypes) without a clear modelling component were excluded. Lastly, cost-effectiveness analyses that were found by Chhatwal et al. or Townsend et al. (or were clearly in the same vein as those articles) were not considered. This reduced the number of papers to 47. Examining these papers in detail removed a further 14 articles as they were revealed to belong in the previous categories.

The first analysis identified that went beyond the cost-effectiveness paradigm established by Bennett et al. (1997) [370] was a study of the US HCV epidemic by Salomon et al. in 2002 [373]. Like the various economic models discussed above this was built around a full natural history model; unlike those models it also simulated a full population of susceptible and infected individuals. It did not, however, dynamically model all routes of HCV infection, which would entail simulating new infections based on current prevalence [374]. Rather, it identified three sources of infection: perinatal infection (which was dynamically tied to current prevalence of infection among women) along with transfusion risk and community risk (which were not dynamically modelled). Transfusion risk was specified as an exogenous parameter that resulted in a certain number of incident infections by using data on numbers of blood units transfused and probability of infection (the latter quantity was varied between narrow limits and decreased over time as blood screening technology improved). Community infections, which include PWID transmission though no risk stratification was implemented in the model, were also modelled as exogenous parameters. Unlike transfusion infection rates, community infection rates were based on flexible parametric curves that determined incidence by age and over time. Informative prior distributions regarding the time-dependence of these curves were used to reduce the size of the parameter space and this was used to find the best fits for HCV community infection rates.

Natural history model parameters for phenomena like fibrosis progression and mortality were specified from the literature but with wide ranges. In the words of the authors: "Given the variability in findings across different natural history studies, we selected wide ranges around rates of fibrosis progression to allow the fitting procedure to identify the rates that are most consistent with observed data" [373]. These natural history model parameters, along with the shape parameters underlying the flexible incidence curves community transmission, were calibrated by fitting to data on HCV prevalence and HCC mortality. Goodness of fit was assessed by constructing binomial likelihoods for each source of data. Calibration was carried out by iteratively drawing random

samples from independent uniform distributions for the various natural history and transmission parameters and checking quality of fit, choosing the best fits for each component of the likelihood and then taking the outer product of these parameter sets to generate new parameter sets. These were simulated and the runs with the best composite likelihood score were chosen leading to a second round of this process and, ultimately, 50 parameter sets being chosen. Model fits were assessed visually and projections made based on these calibrated parameter sets.

This analysis is important as, despite not modelling interventions, it for the first time implemented a transmission model and used computationally intensive fitting techniques to allow parameter uncertainty to be propagated through to the results, rather than specifying specific values from arbitrary studies and then performing sensitivity analysis (the norm in cost-effectiveness analysis in the field). This feature is adopted by most of the following work, while future studies improve on particular aspects that were of particular importance to those studies in question.

A large class of models from 2009 were constructed to investigate the HCV epidemic within high-risk populations by the authors Vickerman, Martin and Hickman [375–386] referred to as the VMH models for ease of reference here (while it is acknowledged that many authors worked on these papers, these three authors are the only authors common to all these analyses[14]). The VMH models have explored a range of questions related to high-risk populations including the impact of HIV coinfection in PWID [385], the extent to which harm reduction alone can reduce HCV prevalence in PWID [383], the plausibility of treatment as prevention to limit the epidemic in HIV-positive MSM [378] and the cost effectiveness of screening programmes in the prison population [377].

The VMH models were the first to employ fully dynamic models in which prevalence entirely determines incidence which, in turn, determines prevalence. Initial work focussed on either treatment or prevention [380, 382–386] but in 2013 these were combined to examine the impact of combination interventions, both treatment and prevention, in PWID [381]. Focussing on this paper as it exemplifies most of the features of the VMH models as a whole, the models only simulate PWID (or the high-risk group being considered). People progress from susceptible to acute infection to chronic infection where they remain unless treated and cured. Those who fail treatment cannot be retreated. Reinfection occurs at the same rate as primary infection. Prevention is accounted for with a second layer of compartments for the group who are either on or off OST; later models added NSP (for the most recent such analysis see [375]) and the possibility to be on both. The rate at which PWID cease presenting to these services is taken to be 1/8 months (for both NST and OST with two steps required to move from OST plus NSP to no harm reduction in models that simulate both approaches to harm reduction), while the rate of entry to these services is chosen such that the particular percentage coverage level chosen in the analysis is reached.

The force of infection that relates prevalence and incidence is the ratio of infectious to total PWID

[14]Two analyses considered in this group did not feature all three authors: one by Vickerman, Platt and Hawkes in 2009 [385] and another by Vickerman, Hickman and Judd in 2007 [386], but since the VMH authors feature on all ten analyses from 2011 (and two editorials/reviews, both Martin et al. [387, 388]), the VMH designation is considered appropriate.

numbers, with reductions in transmission based on estimates of the reduction in transmission due to NSP, OST or their combined impact (particularly following this study [389]). An extra complication is added through the stratification of PWID into high- and low-risk injectors, with analyses carried out in which mixing between the two groups either does not occur at all (fully assortative mixing) or else is proportional to group size (full mixing), however, the analysis demonstrated that the overall dynamics are unaffected by such a division except in extreme limiting cases. That the high-risk group division has, under normal conditions, a minimal impact on the outcomes (such as number of treatments required to produce a set reduction in prevalence) is to be anticipated: given that prevalence data are included as part of model calibration, increasing the size of the high-risk group will simply force a decrease in the calibrated quantities determining the force of infection and negate the change in risk group size.

The VMH models demonstrated what could be achieved with dynamic compartmental models in producing simulations of high-risk group epidemics. They were, nevertheless, limited in that they still do not simulate the full natural history model. This is probably not done because, in the case of PWID, the full course of HCV infection and ESLD may be considered likely to occur after the injecting career is over (and so they have left the model), rendering a more complex model unnecessary. This feature is illustrative of the major drawback of these models. They do not simulate the full population and, correlatively, do not track PWID after their injection careers: the gains from curing individuals past their injection career in terms of reduced mortality burden is not captured in the VMH studies, which is demonstrated by the focus in these studies on reducing incidence (treatment as prevention for instance [378, 380]) and prevalence [383] but not mortality.

Another model was developed around the same time that (coincidentally) tackled the main question not answered by the VMH models: what is the impact of interventions on HCV mortality at the national level? The model in question was first applied to estimate features of the historical US epidemic [390, 391] before being used to make projections about the impact of interventions on a range of countries in 2014 [392]. This was followed up by three more analyses for different sets of countries [393–395]. The country-level analyses have been individually spun out and examined in greater detail in a plethora of papers (examples include Belgium [396], Turkey [397]and Switzerland [398]). Lastly, in 2017 a regional analysis addressed the attainability of WHO mortality targets for Europe as a whole [226]. As the model is identical in all these papers, this last analysis is taken as the exemplar for all the others; as the work is produced by the Centre for Disease Analysis (Lafayette, Colorado, US) the model used by these papers is referred to as the CDA model.

The CDA model is described as a system dynamic model, a term used in certain fields (particularly business and management) to refer to any model based on a set of coupled, non-linear, first-order differential equations that track the values of stocks (state variables) and the flows between them [399]. The CDA model is, more specifically, a Markov STM similar in format to those discussed above. It tracks all infected people in a population with a full natural history model implemented (including METAVIR staging to indicate disease progression and the division of decompensated

cirrhosis into specific complications). The distinguishing features of the CDA model are the division of the population into narrow age categories allowing for more accurate tracking of infected people by age over the decades they may be infected (in contrast to the cruder approach taken in Salmon et al. (2002) [373]) and the simulation of an entire country's HCV-infected population.

While this approach allows the CDA analyses to project mortality burden and investigate this aspect of WHO elimination targets (specifically the target of a 65% reduction in mortality from 2015 baseline), there are several drawbacks in this body of work. Firstly, incidence is not modelled dynamically. Rather, data and estimates of prior incidence are used as guides regarding the shape of the historical HCV incidence curve and this is combined with a "back calculation" of past incidence to match the prevalence point to which the model is calibrated. This approach is problematic because it ingrains assumptions about past incidence, about which there are often strong but not necessarily evidence-based views, yet this is a critical ingredient in the CDA formula. Furthermore, the introduction of newly infected people to the model as exogenous parameters (rather than through a true dynamic modelling approach) means that, in the projections of different treatment regimens, curing individuals does not reduce the incidence of new infections. Such a model misses some of the benefits of treating people. Not only this, but the CDA model cannot be used to investigate the WHO incidence targets nor investigate the effect of disease prevention interventions of any kind.

A second limitation of the CDA methodology is that parameterisation of the model involves extensive consultations with partners in the country and reliance on expert opinion (for aspects like possible shapes of incidence curves as described above). This is a labour intensive exercise and reliant on finding in-country partners, all of which limits the potential of such a model to be extended to investigate the global HCV epidemic (to which the WHO strategy described in the previous chapter is addressed) or, indeed, to create a sustainable model for future analysis.

The CDA model has provided a complementary set of analyses to the VMH work; where VMH investigated the impact of targeted prevention interventions within high-risk groups, CDA examined the impact of treatment programmes implemented at a national level on trends in mortality. Neither model as it stands could investigate the combined WHO incidence and mortality targets.

An array of other models were found in the literature review and are worthy of note. One, a model of the non-PWID epidemic in a rural community in Egypt [400], stratified the population according to frequency of healthcare-related injections or more invasive medical procedures in a manner similar to the VMH models and is the only analysis found that has examined interventions that reduce transmission through iatrogenic transmission. The analysis is constrained by lack of data to parameterise elements of the model pertaining to these iatrogenic risk groups, however, and the analysis is a somewhat abstract study of how the basic reproduction number varies with respect to changes in certain model parameters; the relation to the community being modelled in Egypt is unclear and the model is ultimately not well designed to make concrete projections.

A later model of Egypt did make projections of the epidemic within a fully dynamic population model with risk stratification, but it only considered incidence elimination targets and relied on an opaque approach to dividing the population up into five undefined risk groups [401].

Of the remaining models found in the literature review, there were several more analyses in high-risk groups, including studies of PWID [402–404], as well as studies of the HCV epidemic in HIV-coinfected PWID [405] and HIV-coinfected MSM [406, 407]. These studies examined their respective populations in narrow subsets of the national population and were similar to studies described above. A handful of studies did look at the national picture and investigate both incidence and elimination targets. This group includes a pair of related models (in 2016 and 2017) simulating PWID and former PWID in Australia [408, 409]. The model did not included those infected with HCV in the general population, however, who make up 20% of the epidemic [410] and, by virtue of the age of this cohort, may make up a disproportionate number of HCV-related deaths in future. This model, nevertheless, represents perhaps the first nearly-national analysis of both WHO targets.

Finally, one model (published in 2018) investigated the national epidemic of Pakistan, simulated the full population stratified into risk groups, modelled incidence dynamically and examined the impact of NSP and OST provision, general population harm reduction and DAA treatment provision scale up, all within the context of the WHO targets [411]. It is the first national level model that investigates attainability of WHO targets without one or other of the major limitations discussed in reference to the models above. Nevertheless it does not provide a clear way of extending the analysis to the global scale and so cannot be readily adapted to make global epidemic projections in the manner necessary to investigate the WHO targets directly as discussed in the previous chapter.

2.5.3 Applying modelling to HCV interventions: the aims of this thesis

The previous section has described in detail the methodological approaches used by previous HCV modelling analyses showing what has and has not been achieved by these investigations. Here, in light of the general discussion about uses of mathematical modelling above, we restate the research questions posed in the previous chapter, highlighting how we intend to use mathematical modelling to answer them.

Are global elimination targets attainable? As was discussed in the previous chapter, published models informed the construction of HBV targets but no analogous one existed then (or does now in 2018) that establishes whether HCV targets can be met. A basic modelling analysis was performed internally by WHO (Timothy Hallett, Imperial College London, personal communication, 1st September 2015), but this has never been published and the methods are not public. Yet such an analysis, published transparently and in a way that can be checked and criticised, is clearly required to have confidence that the numbers are not purely arbitrary; while such targets are often aspirational and challenging, it is essential to believe that such a reduction is at least possible.

Beyond demonstrating the internal consistency of targets, a key result of such an analysis is illustrating what the key interventions are to meet elimination targets and how sensitive attaining results is to intervention success. Going all the way back to Ross in 1908, this is a typical use case for a mathematical model [286]. By developing a mechanistic model of disease transmission and progression, taking into account the lessons learned through the literature review above, we aim to not only establish the attainability of elimination targets, but to determine how they can be met, what they are sensitive to and, speaking more broadly, what the impact of achieving elimination targets might be in terms of broad measures of burden of disease such as numbers of active infections, numbers of new infections and numbers of HCV-attributable deaths. As has been stated, this requires the creation of a new model, adding in the features highlighted in the previous section. As such development of the model is given a chapter to itself (chapter 3) while the answers to the various questions stated in here are given upon application of the model in chapter 4.

What are the impacts of interventions in a specific setting? By their nature, the intervention targets established by a global analysis are non-specific: they will not indicate how they are to be brought about. To step beyond these features of the global analysis, we extended the model developed in chapter 3 to the case of a particular epidemic: that in Yunnan Province, China. China offers an ideal scenario in which to investigate HCV interventions for several reasons: it has the largest number of HCV infected people in the world and so policy decisions there have huge ramifications in terms of the number of people affected; and the government is currently engaged in reducing the prices of DAAs in order to expand access. The question of how to roll out new treatments will be critical once these become available. Working in a particular province of China allowed us to work, in microcosm, within this debate.

Our aims in this work were to explore the impact of specific interventions developed in dialogue with local stakeholders, ensuring that they are practically viable and well designed. We adapted the global model to simulate these new interventions and added economic modelling components to quantify the costs of such interventions. This work ultimately sought to answer questions of the impact, the cost effectiveness and the return on investment to society of implementing these interventions as well as comparing and contrasting the interventions developed with stakeholders. This delivers detail and resolution not possible in the global model, allowing us to answer questions pertaining both to the global and the local HCV epidemics, so tackling questions of public health on two very different scales.

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CHAPTER 3

DEVELOPING A GLOBAL MODEL OF THE HEPATITIS C EPIDEMIC

Chapter 3 begins by describing the requisite features of the model required to answer the research questions laid out at the end of the last chapter. An overview of the model so developed is then given. This is followed by a detailed description and explanation of the natural history and transmission components of the model along with justification of how these are parameterised. The way in which interventions are implemented in the model is detailed. The approach taken to calibrating the model is then summarised along with the strategy taken to investigating the sensitivity of the model to various parameters. Lastly, a list of model inputs and calibration data sources is provided followed by tables of parameter values and a list of the defining model equations.

3.1 Synopsis

3.1.1 Aims

Our research aims in this thesis are to assess whether global HCV targets can be met and what the impact a range of specific interventions in a particular setting could be. In both cases we identified that we needed a model to make the requisite projections, in the manner of similar modelling analyses described in the previous chapter.

Accordingly, we developed a deterministic mathematical model that simulates the global HCV epidemic and projects the impact of a range of interventions to explore whether or not WHO-defined elimination is possible. This model was then adapted for use in the case of Yunnan Province. The global model was built first because the intervention strategies developed in consultation with stakeholders in Yunnan would be specific and not necessarily appropriate for consideration at the global scale. As such, the model described in this chapter is the "global model" that is directly

used to answer our first research question concerning WHO HCV elimination targets. Changes to the model necessary for the Yunnan analysis and for answering our second research question are described in chapter 5.

The first consideration then, in model development, was what the requisite features of a global HCV model capable of investigating elimination targets were. While this chapter is effectively the answer to that question, we note here three crucial features that must be present in order to make progress in answering our questions. These features were identified based on the overview of the literature described in the previous chapter. In that review, it was observed that there were two classes of HCV epidemiological models. The first class was a range of models of high risk individuals which simulated prevention and treatment interventions but did not examine impacts upon mortality (rarely including detailed models of HCV natural history at all) and which did not track individuals after they left the model (after cessation of injecting for example). The second class of models took a broader national or regional perspective but only examined mortality elimination targets and did not implement dynamic models of infection preventing them being used to assess whether incidence elimination targets could be met. A final observation in the literature overview was that neither set of models could be efficiently scaled up to simulate large numbers of countries or regions. Based on these observations, our three key modelling requirements are as follows.

i. To investigate incidence targets, a dynamic model of infection must be built that simulates the whole population with susceptible and infected groups. Acknowledging the key role of high-risk groups these must be included as well so as to simulate higher rates of infection where appropriate.

ii. To investigate mortality targets, we must simulate the full natural history of HCV disease with elevated HCV-attributable mortality in the later stages of disease. The model must also be age-structured in order to model how individuals routinely take decades to die from HCV (if they experience HCV-attributable mortality at all).

iii. To investigate elimination targets at the global scale, the model must be capable of efficiently simulating all (or most) countries. To that end, the data sources required to calibrate and run the model must be available for the majority of countries. In addition, a flexible and automated fitting procedure must be used to facilitate calibrating the model to a large number of countries.

3.1.2 Summary of the model

The model constructed that meets these requirements is described in detail in the subsequent sections. Here summaries of those sections (headings given in bold) are given to provide a succinct overview of the modelling approach we took (references are given in the relevant sections).

Model structure. A mathematical model was developed to project the future course of the HCV epidemic, country by country. The model simulates the population of a country dynamically,

grouped according to infection and treatment status. HCV infection may occur (according to calibrated transmission risks) while diagnosis and treatment are simulated which can result in cure; reinfection following cure is also modelled (see figure 3.1A). Compartments are further stratified by age, sex, and risk group: PWID and non-PWID. Background age-, sex-, and time-specific mortality is simulated while PWID experience an additional mortality risk compared to other persons. Following infection with HCV, disease progression occurs according to a widely recognised natural history model (figure 3.1B). Progression occurs through the five METAVIR fibrosis stages. Increased HCV-related mortality occurs from compensated cirrhosis (F4), decompensated cirrhosis and HCC. Non-liver-related mortality is not simulated.

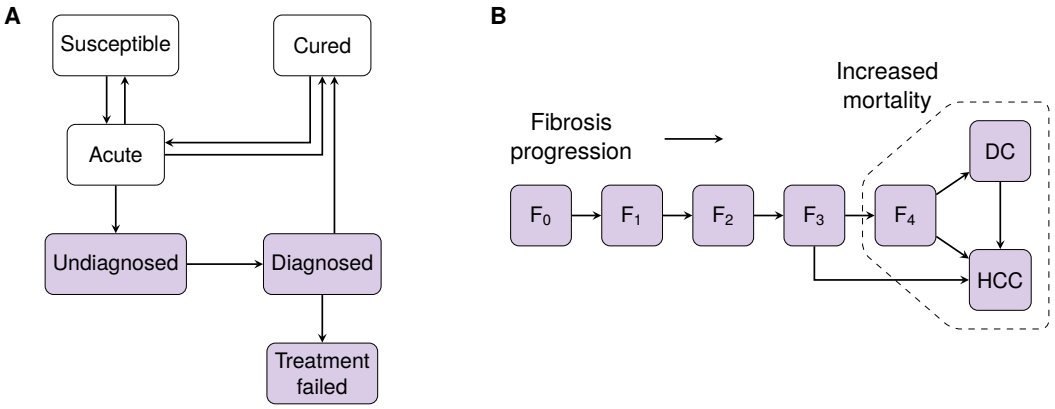


Figure 3.1 - Schematic of mathematical model. Boxes represent compartments of the model while arrows denote annual transition rates which may depend upon age, sex, risk group, or duration of infection and can vary over time. Everyone is in one compartment of the cascade of care (A). These compartments are further subdivided by age, sex, and risk group. Infection results in people entering the natural history model (B): HCV disease progresses through five METAVIR fibrosis stages. The potential impacts of age and male sex on progression and mortality rates are accounted for in calibration. Those in the cured compartment of (A) have reduced or zero disease progression rates depending on disease stage; those in the shaded purple compartments experience full natural history model disease progression.

Natural history model. The majority of natural history model parameters (rates of fibrosis progression, rates of ESLD development and increased mortality rates) are uncertain, vary by setting or potentially have dependence on key cofactors like age and sex. Possible functional dependence on cofactors is built into the model and all uncertain parameters are drawn from prior distributions informed by the literature and allowed to vary in calibration.

Transmission. Infection is specified according to HCV prevalence and a risk group-, age-, and time-dependent risk of transmission. Transmission risks are modelled as flexible splines, where the knot values are drawn from suitable prior distributions. These risks are specified separately for PWID and the remaining population. Perinatal infection can also occur. Reinfection is assumed to occur at the same rate as primary infection.

Modelling treatment and prevention. Diagnosis and treatment is simulated in the model (figure 3.1A). Treatment success depends on treatment used (PEG-IFN+RBV or DAAs). Cure leads to reduced or no disease progression depending on disease stage. Historical rates of diagnosis and

treatment are calculated such that the proportion who are diagnosed, and the proportion treated, match country estimates or WHO regional estimates where data are lacking in 2015. DAAs are implemented from 2016 in countries where their use is reported. All other countries continue to implement PEG-IFN+RBV after 2015. After 2016 (or 2015 for countries without 2016 DAA data), the future rates of both diagnosis and treatment are fixed at their 2015/2016 values (unless altered in intervention). Historical harm reduction interventions are simulated as reducing risk of infection in countries with high coverage.

Intervention strategies were constructed to assess the impact of differing levels of prevention, screening and treatment intervention scale up. A no-DAA scenario incorporating only PEG-IFN+RBV was included to analyse the scope of the epidemic if the recent adoption of DAA treatment was not maintained. The status quo scenario maintains diagnosis and treatment rates at the values reached through scale up to 2015/2016 levels and assumes no reduction in PWID or non-PWID risk. Four intervention strategies were sequentially added to the status quo starting in 2017: (I) + blood safety and infection control; (II) + PWID harm reduction; (III) + offering DAAs at diagnosis with status quo rates of diagnosis maintained (90% accept treatment); and (IV) + outreach screening[1], resulting in 90% of the HCV-infected population being diagnosed by 2030. Each intervention builds in the features of the previous strategies; intervention IV comprises all interventions and is referred to as the comprehensive intervention package.

Calibration and sensitivity analysis. We calibrated the model, in a Bayesian framework, to overall HCV prevalence, PWID HCV prevalence and HCV-attributable mortality (according to age, time and sex). 1,000 samples were drawn from the parameter posterior distributions using Incremental Mixture Importance Sampling. The parameter sets drawn from the posterior distribution were used to make forward projections of the epidemic under the above described range of intervention scenarios.

Uncertainty in natural history model and transmission parameters is accounted for in calibration by sampling from the posterior distributions. The impact of other notable model assumptions (reinfection rate, effectiveness of PWID harm reduction interventions and time to possible retreatment after reinfection) are investigated by performing one-way sensitivity analyses. Further one-way sensitivity analyses are performed on three key intervention parameters: risk reduction in the non-PWID population, coverage of PWID harm reduction services and the proportion diagnosed by 2030. Those countries that contributed most to disease burden were removed from the simulation and the model re-run to quantify the sensitivity of global results to progress made in key countries.

Model inputs. Population data used are UN population prospects estimates. Parameterising various PWID-specific quantities is achieved using several published systematic reviews. Diagnosis

[1]Intervention IV corresponds to diagnosis scale up; experience in countries like Egypt has strongly suggested that improving diagnosis coverage will require ambitious, new approaches like outreach screening [142]. The term is, accordingly, used here to emphasise that efforts required to reach 90% diagnosis coverage at the global scale will have to go beyond current measures.

and treatment cascade data are primarily obtained from published collections of values combined with WHO regional estimates to extrapolate to countries lacking such data.

Calibration data. Globally applicable datasets were chosen with respect to calibration data in order to facilitate applying the model globally: mortality estimates are from the IHME; overall and PWID-specific prevalence data are from published reviews and WHO estimates.

3.2 Model structure

3.2.1 Overview

The full compartmental model used to simulate the HCV epidemic in a given country is shown in figure 3.2 (the associated equations are given in the equations at the end of this chapter); a detailed justification of the various choices made in the structure of the natural history model is given in the following section. Parameter symbols are defined, and values given where appropriate, in the list of parameters see table 3.2.

The compartments of the model are denoted by the state variables S (susceptible to HCV infection), A (acute HCV infection), U (infected, undiagnosed), D (diagnosed, pre-treatment), T (diagnosed, on treatment), Q (diagnosed, failed treatment) and C (cured). All compartments are further subdivided according to the subscripts i (age: stratified into five-year age bands from 0 to 100 years old), j (sex: female and male) and l (risk group: general population i.e. non-PWID, PWID or former PWID). All infectious compartments (A, U, D, T, Q) are also subdivided according to the subscript g (genotype: 1-6 [281]). Superscripts denote disease stage: 0 to 4 refer to METAVIR [115] fibrosis progression stages F0 to F4, DC to decompensated cirrhosis and HCC to hepatocellular carcinoma. Compartments DC and HCC are further divided according to the subscript d (duration in stage: a binary division indicating presence of a complication for less than, or more than, one year). Subsequent references to a compartment refer to the set of compartments of a given letter (S, A, U, D, T, Q, C) with all relevant subscripts and superscripts. The term 'people' is used to indicate the average number in a particular compartment; as this is a deterministic compartmental model, individuals are not tracked.

People enter the model at birth at a rate $b(t)$. Infants join either the susceptible (S) or acutely infected (A) compartments according to the proportion perinatally infected $p^{inf.}$ (for values see table 3.2). Those susceptible can be infected according to a force of infection, $\Lambda_{il}(t)$, which depends on HCV prevalence, and a calibrated risk of transmission that varies over time (t), by age (i), and according to risk group (l), see §3.4 below. Having been infected, people either progress to undiagnosed chronic infection (U) at rate $\lambda_i^{chronic}$ or clear infection and return to the susceptible compartment according to an age-specific clearance rate λ_i^{clear}. Unless a person dies from other causes, migrates or is treated, those who develop chronic HCV infection move through the five METAVIR fibrosis stages F0 to F4 (compensated cirrhosis) and may ultimately progress to decompensated cirrhosis and/or HCC. Progression rates between compartments A and B depend (in general) on

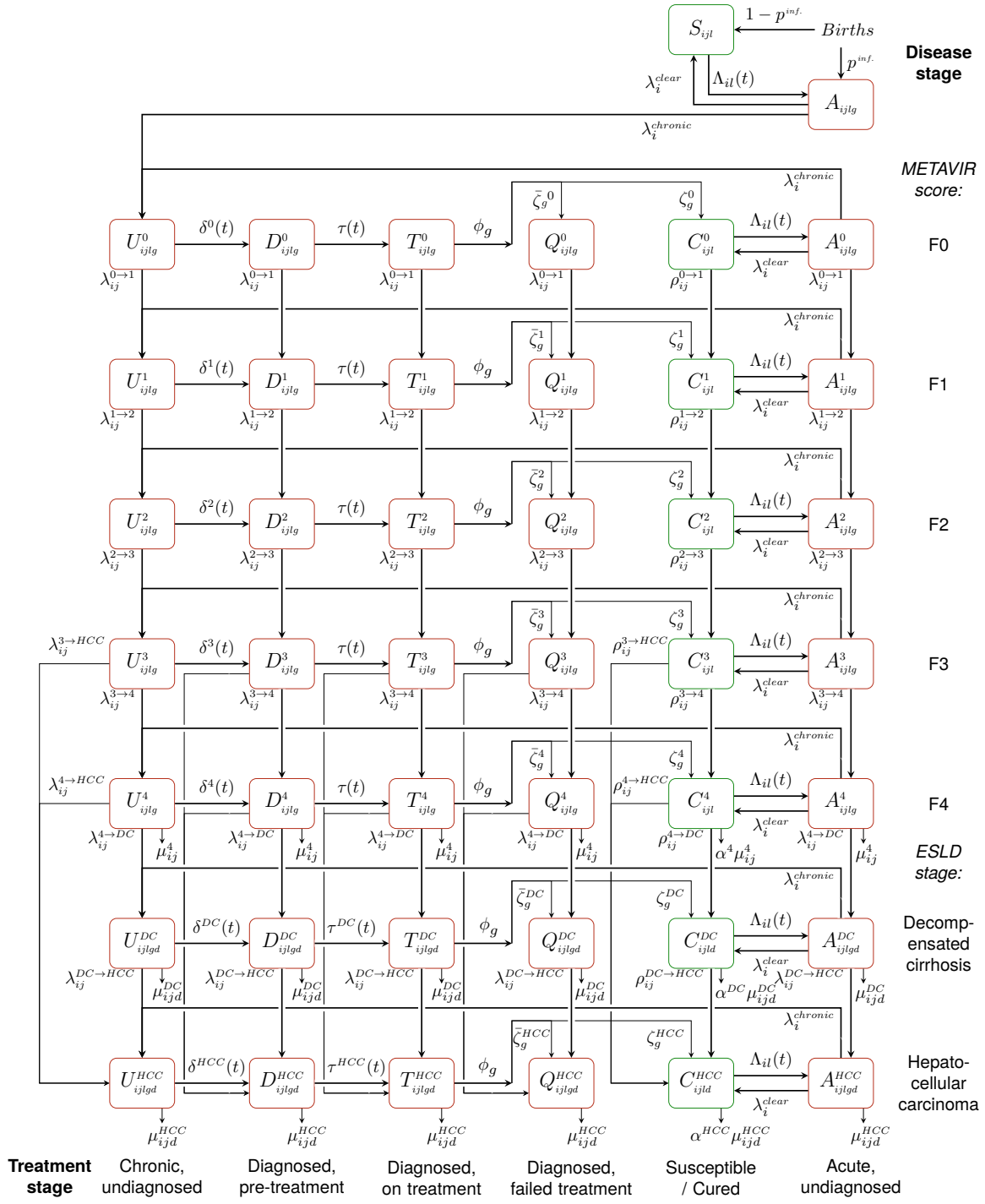


Figure 3.2 - Detailed mathematical model diagram. Full compartmental model diagram. Red boxes indicate that a compartment contributes to the force of infection; green boxes are susceptible to infection. Labels along the bottom are the cascade stages and labels along the right edge are stages in the natural history model (see figure 3.1). Functional dependence is shown where necessary. Background mortality – $\mu_{ijl}^{nat.}(t)$ – and migration – $\nu(t)$ – occur from all compartments. All symbols are defined in table 3.2 at the end of the chapter.

age and sex: $\lambda_{ij}^{A\to B}$ (see §3.3). Natural mortality $\mu_{ijl}^{nat.}(t)$ and migration $\nu(t)$ (not explicitly shown on figure 3.2) remove/add people from all compartments. Mortality depends on risk group (see below). Mortality from compensated cirrhosis (F4), decompensated cirrhosis and HCC are increased above background mortality rates by the rates μ_{ij}^{4}, μ_{ijd}^{DC} and μ_{ijd}^{HCC} respectively. Those that die from F4 or decompensated cirrhosis are recorded as dying from a cirrhosis-attributable death; those from HCC from an HCC-attributable death.

People may be diagnosed and move to compartment D. This occurs at rates of diagnosis $\delta^k(t)$ dependent on disease stage (k) that are either chosen to match the proportion of people diagnosed based on historical estimates or else are set based on the intervention being simulated (these therefore correspond to programmatic aims). The relative likelihood of seeking diagnosis increases with disease severity and is incorporated into the diagnosis rates $\delta^0(t)$ to $\delta^{HCC}(t)$, capturing the fact that individuals usually present for diagnosis after onset of symptoms. Once diagnosed, individuals may be treated with PEG-IFN+RBV or with DAAs; the rate of treatment $\tau^k(t)$ at a particular disease stage k is either determined historically or else is a programmatic aim of the particular intervention being simulated. Treatment lasts a mean duration dependent on genotype (in the PEG-IFN+RBV era) given by $1/\phi_g$. The proportion successfully treated (dependent on disease stage, k, and genotype, g: ζ_g^k) enter the cured compartment (C) and those that fail treatment ($\bar{\zeta}_g^k = 1-\zeta_g^k$) enter the failed treatment compartment (Q). Those cured progress through the disease stages at reduced rates: the rate between compartment A and compartment B is reduced to a factor $\alpha^{A\to B}$ of the original progression rate, giving a rate of disease progression $\rho_{ij}^{A\to B} = \alpha^{A\ rightarrow B}\lambda_{ij}^{A\to B}$. Mortality rates from the end stages of the disease are similarly reduced in those cured to a fraction α^4, α^{DC} and α^{HCC} of the original rates (for full details see §3.5). Once cured, people can be reinfected according to the same force of infection $\Lambda_{il}(t)$.

3.2.2 Risk groups

The risk structure of the model reflects the increased risk of infection among PWID [216, 245]. Published estimates for the proportion of the population active PWID are generally quoted relative to the size of the 15- to 64-year-old population [412]; injecting careers are considerably shorter than this, however, with survey estimates reporting injection careers ranging from 11 to 27 years in length [380]. Taking the upper end of this estimate, and acknowledging the fact that younger PWID are believed to engage in riskier behaviour [413], the model simulates increased risk of HCV infection between the ages of 15 and 40 years old.

The remaining people in the model, termed the general population (comprising never PWID and former PWID), experience a lower risk of infection. This risk of infection is calibrated to HCV prevalence estimates in the population as a whole and incorporates all non-PWID modes of HCV transmission [245].

It should be noted that HIV-positive MSM have been identified as a key HCV risk group [249, 414, 415]: HCV antibody prevalence among HIV-positive MSM (who are not injection drug users) is estimated at 6.7% [416], higher than 1.4% in the population as a whole [280]. Though sexual

transmission among monogamous, heterosexual couples is rare [246, 249], there is an increased risk of HCV infection in HIV-positive MSM [249]. On a global scale, however, the overall number of HIV-positive MSM means that this group comprises a much smaller fraction of the HCV epidemic than HCV-infected PWID. Using an estimate of the proportion of men in the US who engage in same-sex behaviour (as reported in the previous year) of 2.9% [417], multiplying by regional estimates of HIV-positive prevalence in MSM [418] and adult male population size [419] results in an estimated 7.4 million HIV-positive MSM. This, in turn, yields an estimated 495,000 HIV-HCV coinfected MSM globally [416], or 6% of the estimated global number of anti-HCV positive PWID [256]. Due to the difference in size of these risk groups globally, and the fact that overall HCV prevalence is much higher in PWID (over 50% anti-HCV positive [256]) than in HIV-positive MSM, the latter are not modelled as a separate risk group.

3.2.3 Mortality risks

We distinguish between three modes of death in the model. Two of these can be subsumed under the heading 'non-HCV mortality' which is quantified as $\mu_{ijl}^{nat.}(t) = \sigma_l \mu_{ij}^{nat.}(t)$, where σ_l is the increase in mortality attaching to PWID (when $l =$ PWID). The third source of mortality is HCV-related mortality which must be carefully defined as this has a range of possible meanings. We define all these terms now to avoid confusion regarding our use of terms.

i. **Background mortality.** That risk of death having nothing to do with HCV or being a PWID and pertaining to all persons (in a sex-, age- and time-specific manner).

   This quantity, denoted $\mu_{ij}(t)$, is derived from UN population prospects life tables; such estimates or projections (and all demographic data derived from UN sources) are available for the period 1950-2100 [419].

ii. **PWID related mortality.** The additional risk of death observed in PWID.

   PWID have a higher risk of death than the non-PWID population and this is accounted for by multiplying the background rate of mortality by a standardised mortality ratio (SMR) σ_l. To estimate this value, we examined two key sources that take a global perspective on the excess mortality risk for PWID. Firstly, a systematic review by Mathers et al. in 2013 that compiled estimates of SMRs for PWID compared to non-PWID from 67 studies and produced an overall pooled estimate of the PWID SMR [420]; secondly estimates published by the United Nations Office on Drugs and Crime (UNODC) on the global number of drug-related deaths in 2015 (derived from reports by 86 countries) [421]. SMRs were produced from these UNODC estimates by fitting an SMR in our model to account for the extra 190,900 deaths (range: 115,900 – 230,100) in PWID [421].

   Both sources have drawbacks: Mathers et al. suffer from bias since the pooled SMR relies on data from primarily high-income settings, in particular Italy, USA and UK [420]. Additionally, the SMR reported in the analysis will include HCV liver-related mortality; no disaggregation was attempted to produce an estimate of the additional mortality due to causes

other than HCV that could otherwise have been used. A previous iteration of this study (that finds almost the same pooled SMR) suggested that the majority of PWID deaths were due to overdose, while liver-related mortality (of which HCV-specific liver-related mortality is only a part) contributed around 10% (range: 4.2-15.1%) to deaths among PWID in the ten studies that reported this measure [422]. The UNODC estimates suffer from being non-systematic in the collection of results and due to countries applying different definitions of the term drug-related deaths (which may include any of: "fatal drug overdoses; deaths due to HIV acquired through injecting drug use; suicide; and unintentional deaths and trauma due to illicit drug use" [423]). This suggests that the numbers reported by UNODC probably underestimate the burden of drug related deaths. These estimates are, however, an established and endorsed source for such information and include more countries than the Mathers et al. meta-analysis.

The limitations in both sources, and the high variability of SMR values reported both between countries and between studies in the same country [420], indicates that the most appropriate approach to estimating the PWID SMR is to take a wide range of values for this quantity. To that end, the upper SMR value reported in Mathers et al. was combined with the lower value derived from UNODC to produce a PWID SMR range of 5-16.

iii. HCV mortality. The additional risk of death that is caused by infection with HCV. This is the additional risk of mortality that stems from chronic liver disease, decompensated cirrhosis and liver cancer and is simulated by increasing mortality rates in the HCC, and compensated and decompensated cirrhosis compartments.

It is acknowledged that while HCV is associated with various non-liver conditions [125, 424], the impact these conditions have on mortality is much smaller than liver-related disease arising from HCV infection: a large US study of over 9,000 people followed for an average of 14.8 years calculated mortality rate ratios between HCV-positive and HCV-negative individuals for liver-related and non-liver-related mortality [425]. This found a 26-fold increase in liver-related mortality ($p < 0.001$) among HCV-positive individuals, compared to a 1.8-fold increase in non-liver-related mortality, which was not statistically significant ($p = 0.18$). An analysis in Scotland did find a statistically significant reduction in the hazard ratio of non-liver-related mortality following HCV cure, but there was no absolute risk reduction (ARR) in non-liver-related mortality considered over a 7.5 year period (liver-related mortality, by contrast, saw a highly statistically significant ARR in the same analysis) [426]. These considerations led us only to consider an increase in liver-related mortality as an outcome of HCV infection and not to simulate an increase in other non-liver-related mortality; doing so accords with the WHO definition of mortality attributable to HCV as those deaths from "hepatocellular carcinoma (HCC), cirrhosis and chronic liver diseases" [427].

It should be stressed, however, that the narrow focus on liver-related disease ignores the considerable morbidity associated with non-liver-related conditions arising as a consequence of HCV and, by underestimating mortality as well, ultimately underestimates the potential

impact of HCV interventions [424, 428].

A potential fourth mortality risk has been suggested. It has been claimed that there may be an increase in cause-specific mortality (unrelated to HCV infection) in HCV-positive PWID above that observed in other PWID: Merrall et al. (2012) report a statistically significant hazard ratio of 0.46 for PWID without an HCV diagnosis to experience drug-related death [429]. This suggests that PWID with HCV-diagnoses have around double the drug-related mortality rate of non-HCV positive PWID. This is a sizeable increase, though less than the impact on mortality of being PWID overall as described above. Whether or not this should be modelled relies on establishing that HCV infection causes increased cause-specific mortality among PWID over and above what would be expected. Yet this causal link has not been established. HCV diagnosis is unlikely to act as an explanation for increased homicide risk for example, but, as the authors acknowledge, may simply act as a marker for other kinds of unobserved risks for drug-related causes of death. This means that HCV-diagnosis in PWID could act as "an important indicator of those needing support to mitigate a range of mortality risks" but this does not in itself mean that HCV-infection itself is responsible for these deaths. For this reason such an additional risk beyond what is already accounted for in PWID (through the inclusion of a PWID-specific SMR) and in HCV-infected people (through increased mortality in the later stages of disease) is not included in the model.

3.3 Natural history model

3.3.1 Justification of natural history model structure

HCV disease stages and transitions. The structure of the natural history model was described above (see figure 3.2). As discussed in chapter 2, there is a broad consensus regarding the natural history of HCV infection [105, 430, 431] that is reflected in the similarity of mathematical models used in cost-effectiveness analyses [326] and epidemiological analyses [373, 391]. Two notable differences were identified in that discussion that differentiated between models. Firstly, models differ in whether chronic disease is represented as one stage (chronic infection leading to cirrhosis, see for example [348]), two stages (mild and moderate chronic infection [349]) or whether progression through a full disease staging system (generally the METAVIR fibrosis staging scheme [357]) was implemented. Secondly, some models split the decompensated cirrhosis compartment into a handful of explicit decompensation events and modelled mortality differentially based on complication [392].

With regards the first choice, modelling METAVIR stages offers a more clinically grounded means of representing disease progression than wider chronic-disease categories. As METAVIR is arguably the dominant fibrosis progression scheme it seems natural to use this as means of categorising disease severity. In addition, the highest quality analysis of progression rates that has been carried out uses METAVIR stages to estimate progression rates and so adopting this scheme allows for direct application of these results [121].

The second choice concerns the structure of the decompensated cirrhosis compartment. While it is superficially more detailed to include more stages (one choice could be to include explicit compartments for ascites, hepatic encephalopathy and variceal haemorrhage, see the early CDA models discussed in the previous chapter [392]) as opposed to having just one decompensated cirrhosis compartment, this probably misrepresents the nature of disease at this stage. Patients do not progress to one stage (such as ascites) and remain there, but are highly likely to experience a second (often different) complication [432]. Models that include multiple decompensation stages do not include such transitions between complications [392]. This is problematic because an overestimate of progression rates to a complication with lower mortality rates than other complications could underestimate true disease burden. It would appear preferable, then, to employ a simpler system that aggregates complications into one compartment and estimates mortality from this compartment alone. This has the added benefit of allowing more studies to be used to parameterise this rate as there are more investigations of overall mortality after decompensation in general than from specific modes of decompensation (though such studies do exist see [433]). That this is a more appropriate means of modelling this stage of disease is suggested by the fact that the CDA group of models transitioned from using an explicit set of decompensation events in their natural history model [391, 392] to modelling only a single such compartment in their most recent work [226].

Another choice that must be made pertains to the way in which HCC is modelled. In a similar manner to modelling decompensated cirrhosis as multiple stages, HCC could be modelled according to BCLC stages (described in the previous chapter), or another liver cancer staging scheme (we comment on BCLC as this is there is a known example of this being used in an HCV model [334]). Modelling HCC in this way respects the natural history in that these stages do represent mutually independent compartments (unlike decompensated cirrhosis in which multiple complications may coexist). Yet unless interventions are simulated that explicitly differentiate between the BCLC stages there is no benefit to adding this feature. An example of a model that would benefit from this feature is one that included detailed liver cancer interventions (such as curative resection) in which it may need to be specified that only BCLC 0 and BCLC A could receive treatment. The model developed here, by contrast, does not implement such detailed liver treatments[2] and so a detailed HCC staging system is not necessary.

Models have also varied with regard to those stages from which transition to HCC can occur: most models [327] implement transition following onset of decompensated cirrhosis (as well as prior to onset of decompensated cirrhosis) whereas the CDA group of models do not. As HCC can develop during decompensated cirrhosis [432] and is a primary cause of death in cirrhotic patients [433] it would seem necessary to include this possible transition. Of course, mortality from decompensated cirrhosis could be so parameterised as to include the possibility of mortality due to HCC implicitly. However, treatment options differ based on whether HCC is present or not.

[2] As was commented with respect to liver transplantations in the previous chapter, the number and impact of such treatments worldwide is small compared to the burden of disease justifying not explicitly modelling these interventions here.

Simulating HCC implicitly within the decompensated cirrhosis category prevents this difference being accounted for and so a transition to HCC is included in our model after decompensation.

The impact of coinfection. Coinfection is another modelling aspect that must be addressed. HIV coinfection is not included in the model; while there is evidence that HIV coinfection increases fibrosis progression rates [434], it is also argued that ART mitigates this effect [434, 435]. Since the global number on ART is high in many places and increasing [436], we make the assumption that the impacts of HIV coinfection on the HCV epidemic are small and will, furthermore, decrease over the course of the model's projections. Similarly, HCV spontaneous clearance rates may be slightly lower in HIV-positive individuals (around 15% [437]) but this is only marginally different from our assumption regarding spontaneous clearance in the population as a whole and so again we assume that the effects are small [437].

Where HIV prevalence is high and ART coverage low among PWID, we will have slightly underestimated the impact of the HCV epidemic and potentially underestimated the impact of HCV interventions. This effect should be minimal: it was estimated in 2016 that the global number HIV-HCV coinfected is 2.3 million [438]. Furthermore, the number coinfected in Sub-Saharan Africa as a whole (where HIV burden is greatest) was estimated from 6 studies to be 430,000 [438] out of an estimated 10.1 million HCV monoinfected [280], while coverage of ART across Sub-Saharan Africa was 54% in 2016 [439]. The combination of a low proportion of the HCV-infected population being coinfected with HIV, even in the region most affected by HIV, along with high coverage of ART (over half of people living with HIV are receiving treatment in this region) strongly indicates that not including HIV coinfection is likely to lead to only slight underestimates of intervention impact.

Lastly, it is often noted that HBV-HCV coinfection is associated with worse outcomes than either disease alone [440, 441]. To assess the need to model HBV requires an estimate both of the impact of HBV coinfection on progression rates and of the proportion of the HCV epidemic that is HBV coinfected. With regards the latter, a common estimate is that 2-10% of anti-HCV positive patients are hepatitis B surface antigen (HBsAg) positive (used as an indicator of active HBV infection) [441–443]; a study of infection rates in PWID gives a similar coinfection rate of 9% upon very conservatively assuming that all HBsAg positive individuals are also anti-HCV positive [256]. These estimates show that it is likely only a small proportion of the overall HCV-infected population is coinfected[3]. With respect to outcomes in this group, Konstantinou and Deutsch [441] suggest a higher risk of liver disease progression in coinfected individuals than monoinfected individuals based on two studies [444, 445]. One study shows both that coinfection is associated with more severe outcomes but also suggests that "HBV superinfection in HCV chronic carriers may lead to clearance of chronic HCV infection" indicative of an interaction between the viruses [445]; the other study finds worse necrosis of the liver in coinfected individuals but not more severe fibrosis [444]. Konstantinou and Deutsch also comment on an increased risk of HCC in coinfected patients based on two studies: these meta-analyses compare cases (patients with HCC) to controls

[3]These estimates are for anti-HCV/HBsAg coinfection. Assuming 10% coinfection among anti-HCV positive individuals and given a 70% viraemic rate [278] gives a coinfection rate among HCV-RNA positive individuals of 7%.

(those without) and calculate the odds ratios (ORs) for presence of HBsAg or anti-HCV/HCV-RNA or both between the two groups [446, 447]. Both studies find higher OR with the presence of both HBsAg and anti-HCV/HCV-RNA compared to the OR for either serological marker individually. Yet these higher OR for individuals with the combination of HBV and HCV seromarkers are calculated with very few control individuals (otherwise healthy individuals who had HBV/HCV coinfection). In the study that reports a much higher OR in coinfected individuals, the number of controls is only eight, while in the study in which OR is based on 55 individuals the OR is much closer to that of monoinfected individuals. A second issue with these studies is that no adjustment appears to be made for length of infection; coinfected individuals are liable to have been infected with one or other disease longer than monoinfected individuals but duration of infection is also linked to development of HCC meaning that coinfection could be acting as a marker of disease duration (and so risk of HCC) and not be an indicator of an interaction between HBV and HCV. These remarks show that the evidence for the impact of HBV-HCV coinfection on worsening disease progression is not strong, the effect may not be as large as it is sometimes claimed to be [440] and that given the prevalence of coinfection is reasonably small the overall impact on HCV epidemiology is liable to be limited. As was argued with regard the impact of the HIV epidemic, viral hepatitis elimination efforts (whose other main target is HBV infection) should result in a reduced burden of HBV infection in the future suggesting that the impact of coinfection will diminish over the course of the model's projections. For this set of reasons HBV coinfection is not included in the model.

3.3.2 Fibrosis progression rates

The starting point for parameterising fibrosis progression rates is a meta-analysis by Thein et al. (2008) [121] that synthesised data from 111 studies (33,121 individuals) investigating HCV disease progression. This meta-analysis used the distribution of METAVIR stages, combined with known (or approximately known) durations of infection, to infer the annual transition probability between fibrosis stages using maximum likelihood methods [448]. This analysis presents results for both clinical (diagnosed in tertiary care) and non-clinical (diagnosed as part of routine screening) settings; since our model simulates the HCV epidemic across an entire country (and not just the epidemic among those presenting for care as may be relevant in certain cost-effectiveness analyses) we utilise the non-clinical results. These rates are lower than those derived from the clinical results as they are less influenced by the sample bias inherent in deriving fibrosis progression rates only from patients in need of tertiary care. Thein et al. also attempted to estimate the impact of cofactors (such as age and sex), however, we questioned their results due to the lack of strong correlation between any cofactor and fibrosis progression rates. By repeating their analysis it was shown that instead of implementing 33,121 cofactors for age, sex and so on for each patient in the meta-regression, the value of the cofactor used was an average value for each of the 111 studies included in the analysis. As such, an average of ages, durations of infections and so on were associated with one fibrosis progression value resulting in the signal for the impact of the cofactors being lost. Despite this potentially being a valuable means of parameterising the impact of sex,

age and other cofactors this aspect of the Thein et al. analysis could not, therefore, be used and the possible impact of cofactors are included in our model in a different way as part of calibration (described below).

The results taken from the meta-analysis are, accordingly, the non-clinical setting random effects model transition probabilities, quoted between fibrosis stage k and $k+1$ ($k = 0, 1, 2, 3$): $f_{l/u}^{k\to k+1}$, where l and u indicate the lower and upper 95% confidence intervals. We allow the model to explore the full range of the 95% confidence intervals in fitting by introducing a scaling factor ($\alpha^{fibr.} \in [0,1]$), varied in calibration (see §3.6.1). The fibrosis transition probability is then converted to a rate:

$$r^{k\to k+1} = -\ln\left\{1 - \left(f_l^{k\to k+1} + \alpha^{fibr.}\left(f_u^{k\to k+1} - f_l^{k\to k+1}\right)\right)\right\} \text{ year}^{-1}.$$

The scaling factor $\alpha^{fibr.}$ is introduced to acknowledge both uncertainty and the potential variability of progression rates by country. Such variation may arise as a result of, for example, higher levels of alcohol consumption or the general presence of other cofactors. In this way, a range of cofactors are implicitly built into the model. This is necessary as the quantitative impact on progression rates of many cofactors is not precisely known while data for the distribution of cofactors on the global scale are seldom available. Building the model to be flexible with regard progression rates helps mitigate this data limitation.

Two cofactors are explicitly modelled: age and sex are incorporated as part of model calibration because previous modelling studies have shown that allowing progression rates to increase with age and by male sex is necessary to account for observed trends in mortality [373, 392]; statistical analyses also indicate the significance of sex and age (specifically age at liver tissue biopsy) on progression rates [449]. Furthermore, unlike other cofactors, these could be specified for all countries based solely on demographic information and so incorporating these directly was feasible within the context of a global model.

This led to the specification of age- and sex-dependent rates of progression, denoted $\lambda_{ij}^{k\to k+1}$. To derive expressions for these, it was observed that the average age at liver tissue sample of individuals in the Thein et al. meta-analysis was 40 years old and the proportion male was close to 50% (the exact figure was 57%) [121]. Accordingly, the sex-averaged progression rate (average of rates for sex $j = f$ and m) at age 40 is set equal to the meta-analysis value:

$$\frac{1}{2}\left(\lambda_{40,f}^{k\to k+1} + \lambda_{40,m}^{k\to k+1}\right) = r^{k\to k+1}.$$

Two calibrated parameters are then introduced: one that controls the difference in progression rates between males and females and one that controls the increase of progression rates by age.

The impact of sex on fibrosis progression rates (that male progression is faster than female) is incorporated by requiring that male progression rates are up to twice as fast as female, denoted by

the relative risk $h_{sex}^{fibr.} \in [1, 2]$ [449]. The impact of age is incorporated by allowing the progression rates to vary for people between the ages of 20 and 70 years old; specifically, the 70-year-old progression rates can be equal to the 20-year-old progression rates (no difference by age), or up to ten times greater, denoted by the relative risk $h_{age}^{fibr.} \in [1, 10]$.

The fibrosis progression rates are, therefore, specified according to three calibrated quantities: the relative progression rate by age ($h_{age}^{fibr.}$), the relative rate by sex ($h_{sex}^{fibr.}$) and the speed of progression ($\alpha^{fibr.}$), in addition to the meta-analysis-derived rates of fibrosis progression ($r^{k \to k+1}$):

$$\lambda_{ij}^{k \to k+1} \propto r^{k \to k+1} \times \left\{ \begin{array}{ll} 1 & j = f \\ h_{sex}^{fibr.} & j = m \end{array} \right\} \times \left\{ \begin{array}{ll} 1 & i < 20 \\ \frac{\left(h_{age}^{fibr.} - 1\right)}{50}(i - 20) + 1 & 20 \leq i < 70 \\ h_{age}^{fibr.} & i \geq 70 \end{array} \right. ,$$

where the constant of proportionality is

$$\frac{2}{1 + h_{sex}^{fibr.}} \frac{5}{2h_{age}^{fibr.} + 3}.$$

This function is illustrated in figure 3.3.

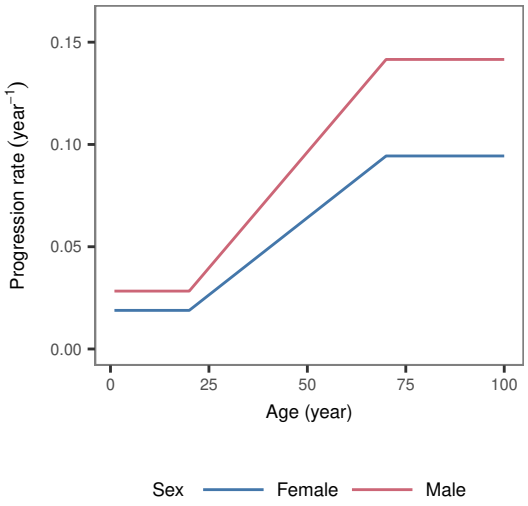


Figure 3.3 - Illustration of sex- and age-dependent fibrosis progression rates. Shown is the F1 to F2 transition rate graphed with the median value of the annual transition probability chosen (i.e. $\alpha_{age}^{fibr.} = 0.5$), a male to female relative rate of $h_{sex}^{fibr.} = 1.5$ and a 70- to 20-year-old relative probability of $h_{age}^{fibr.} = 5$.

3.3.3 End stage disease progression rates

The remaining natural history model progression rates are for the transitions to HCC ($\lambda_{ij}^{3 \to HCC}$, $\lambda_{ij}^{4 \to HCC}$, $\lambda_{ij}^{DC \to HCC}$) and the transition to decompensated cirrhosis ($\lambda_{ij}^{4 \to DC}$). Values are taken

from the literature, see table 3.2. In general, annual transition probabilities (p) are published, which are transformed to exponential rates (λ) according to $\lambda = -\ln(1-p)$.

End-stage disease progression rates are varied in calibration across a range of probabilities: where multiple sources of a parameter were available, these were used to inform the endpoints of uniform prior distributions for that parameter; where only one suitable value could be found, approximate 95% confidence intervals were constructed (assuming binomial distributions) and these were used as endpoints on the range of parameter values. The aim of this procedure was to be as conservative as possible. This was partly to reflect uncertainty even in countries where information was available regarding the relevant disease transition probabilities, but primarily this was to acknowledge lack of insight into many of these transition rates on a global scale.

The transition rate to HCC varies with age and sex [105], and there is no prior reason to assume that the other end-stage disease progression rates would not vary with these cofactors as well. Accordingly, these progression rates are varied individually by age and sex in an analogous manner to the fibrosis progression rates. The following age and sex relative risk parameters are, therefore, included in the calibration procedure (with the same ranges as their fibrosis analogues): $h_{age}^{j\to HCC}$, $h_{age}^{j\to DC}$, $h_{sex}^{j\to HCC}$, $h_{sex}^{j\to DC}$, where $j \to HCC$ indicates any transition to HCC.

Increased mortality rates due to HCV infection are specified from compensated cirrhosis F4 (μ_{ij}^{4}), decompensated cirrhosis (μ_{ijd}^{DC}) and HCC (μ_{ijd}^{HCC}). Values are taken from the literature according to duration of infection (less than, or greater than, one year), see table 3.2. Mortality rates vary by age and sex [93, 122] and this is accounted for in calibration in the same way as for other parameters, see above. This introduces the following additional parameters: $h_{age}^{cirr.\to\mu}$, $h_{sex}^{cirr.\to\mu}$, $h_{age}^{HCC\to\mu}$, $h_{sex}^{HCC\to\mu}$, where cirr. refers to both cirrhosis stages (F4 and decompensated cirrhosis).

3.4 Transmission

3.4.1 Modes of transmission

The model incorporates two forces of infection (the per-capita rate at which those in the susceptible compartment become infected [450]): the one affecting the entire population is termed the general population (or GP) force of infection and the other is the additional force of infection experienced only by PWID [258]. Transmission among HIV-positive MSM is an increasingly important transmission route in some settings [451–453], but is at present a small part of the global HCV epidemic (see Martin et al. (2015) [387] and the discussion of risk groups in §3.2.2 above for more details).

Epidemiologically the general population force of infection can be considered to comprise (primarily) transfusion transmissible infections (TTIs) with infected blood and exposure to HCV through unsafe injections [216, 245]; for a full discussion of other routes involved in HCV infection see §2.4.1 (these are not considered further as they are viewed as being of only minor importance to the global epidemic). TTIs and unsafe injections are the two routes of transmission highlighted by WHO as the most important ways in which the epidemic is maintained and a model that directly

simulated each route of infection would allow for the analysis of specific prevention interventions (such as being able to simulate specific blood safety and safe injection initiatives separately). To do this would require a strong understanding of the relative balance of the two infection routes. As discussed in chapter 2, these vary markedly from country to country with often only qualitative assessments of the primary transmission routes available. It is possible to attempt a very approximate global assessment of the proportion of HCV infections due to TTIs and unsafe injections to explore whether it is plausible to introduce two specific modes of general population transmission into the model.

Whereas global prevalence estimates directly derived from data do exist (even though these are augmented by modelling to produce estimates for a specific year [280]) no such data-driven estimates of incidence are available. Using model inferred values for incidence, WHO reports that there were 1.7 million HCV infections in 2015 [28] of which they state that 315,000 were due to unsafe injections (from this study [218]) and 390,000 infection were in PWID (based on 23% of incident infections that year being in PWID). WHO states that blood transfusions represent a small fraction of HCV infections (despite the enduring focus on this means of transmission). It is possible to estimate the number of TTIs using blood safety data: prevalence of TTI estimates are available [454] and estimates of the number of blood donations by World Bank region along with the proportion screened (see this report [455]) can be combined to produce an estimate of 90,000 HCV TTIs. Lastly, if we make some broad assumptions about perinatal infection (1% global viraemic prevalence [28], 3% transmission risk [456] and 140 million births in 2015 [419]) we arrive at an estimate of approximately 40,000 perinatal HCV infections[4].

Putting all this together accounts for 835,000 infections out of 1.7 million. In short, there is a crucial data gap with regards understanding modes of HCV transmission globally. This lack of even broad knowledge of the overall routes of infection, along with the even greater lack of country-level information on this topic, justifies not attempting to model the two specific transmission routes (TTIs and unsafe injections) while the discussion in the previous chapter concerning the lack of evidence even in the USA for the relative importance of other transmission routes explains why no attempt was made to simulate explicitly other general population routes of infection as well. Due to the uncertainty in source of infections in the general population, interventions designed to reduce infection through this means are termed blood safety and infection control initiatives. This acknowledges the key historical role played by improving, and the ongoing need to maintain, blood safety, along with subsuming a range of other potential infection routes under the broad heading "infection control" which in practice will probably refer primarily to injection safety (though encapsulates efforts to reduce infection through more unusual infection routes such as through dental procedures as well [457]).

The PWID force of infection arises through the sharing of drug paraphernalia [258] and can be

[4]Many of the infections co calculated will be cleared. However, given that the attempt here to reconcile specific modes of transmission with the overall numbers fails because there are far too few infections from such estimates, accounting for the number of viraemic infections by multiplying by a clearance rate will simply compound the problem and lead to the same conclusion.

parameterised through the wide availability of PWID HCV prevalence data (see §3.7.2). Both PWID and GP transmission routes can be considered to be driven through "engagement" with a particular activity, either injection drug use on the one hand or blood transfusion/unsafe injections/medical procedures/miscellaneous exposures on the other. The following section describes how this conceptualisation of the forces of infection is used to parameterise these quantities in the model.

3.4.2 Formulating the force of infection

Generally, the force of infection in a mass action model consists of the probability of transmission multiplied by the rate of infectious encounters [374]. In the model of HCV, susceptible individuals have a rate of engagement with a particular activity $c_{il}(t)$, assumed to vary by age i, calendar time t (see below) and risk group l. It is assumed that the rate of engagement with the activity is equal in all individuals (for a particular risk group), regardless of disease status. As such, the rate at which susceptible individuals (of age i and risk group l) are exposed to infection is equal to their engagement rate multiplied by the proportion of engagements that are with infectious individuals (the effective prevalence), denoted according to risk group as $p_l^{eff.}(t)$:

$$\text{rate of exposure}_{il} = c_{il}(t)p_l^{eff.}(t) = c_{il}(t)\frac{\sum_i c_{il}(t)I_{il}(t)}{\sum_i c_{il}(t)N_{il}(t)},$$

where $I_{il}(t)$ is the number of infectious individuals in age band i and risk group l, and $N_{il}(t)$ is the number of all individuals in age band i and risk group l (sum over all other indices and all relevant model compartments). The infectious compartments are A, U, D, T, Q. Note that those on treatment (T) are considered infectious; in the PEG-IFN+RBV era this is reasonable as treatment courses are long and failure rates high (indicating that those on treatment are unlikely to experience SVR earlier than the end of treatment [458, 459]); conversely, in the DAA era, shorter treatment durations lead to SVR in a high proportion of cases (even with adherence problems, see §3.5) indicating that those on treatment are liable not to be infectious (since cured) before the end of treatment. For simplicity and as a conservative assumption we consider all those on treatment infectious until the end of the treatment course; the impact of this assumption will be to underestimate the treatment-as-prevention benefits of therapy. However, since treatment courses are quick and the number on treatment at any one time is always low compared to other compartments of the model, this assumption will have minimal impact on the outcomes.

Denoting the probability of transmission in an engagement between susceptible and infectious individuals as $p^{transmit}$, then the force of infection can be written:

$$\Lambda_{il}(t) = p^{transmit}c_{il}(t)p_l^{eff.}(t) = p^{transmit}c_{il}(t)\frac{\sum_i c_{il}(t)I_{il}(t)}{\sum_i c_{il}(t)N_{il}(t)}.$$

The quantity $p^{transmit}c_{il}(t)$ is the transmission risk $\beta_{il}(t)$ for a particular age and risk group. Since the probability of transmission is not assumed to vary by age, we can multiply inside the sum by

the transmission probability in the numerator and denominator to rewrite the above expression as:

$$\Lambda_{il}(t) = \beta_{il}(t)\frac{\sum_i \beta_{il}(t)I_{il}(t)}{\sum_i \beta_{il}(t)N_{il}(t)}.$$

This general expression is now used in the specific cases of the general population and PWID forces of infection to derive expressions for the forces of infection that can then be calibrated in model fitting.

General population force of infection. Above it was assumed that transmission risk varied by age and over time. In the case of the general population risk this is known to be true, since age-specific prevalence varies by country, indicating different levels of exposure at different ages across time [238]. Mechanistically, the variation of risk by age may be considered a result of different engagements with healthcare (as well as other activities potentially involving exposure to blood) over the course of a lifetime; the variation over time may be a consequence of changes in infection control and blood screening measures [238]. The general population force of infection can be written as:

$$\Lambda_{i,GP}(t) = \beta_{i,GP}(t)p_{all}^{eff.}(t).$$

where $p_{all}^{eff.}(t) = \sum_i \beta_{i,GP}(t)I_i(t)/\sum_i \beta_{i,GP}(t)N_i(t)$ is the effective prevalence among all people, $I_i(t)$ is the number of all infectious people of a given age and $N_i(t)$ is the number of all people of a particular age (implicit sum over all risk groups and other indices, for all relevant compartments). The risk of transmission is decomposed into age and time dependent terms:

$$\beta_{i,GP}(t) = \gamma_i \beta_{GP}(t).$$

These quantities are fit in calibration (see §3.6.1). γ_i, the age-dependent general population risk multiplier (constant in time) is constructed as an interpolated spline with knot values at ages 33, 66 and 100 years old (ξ_{33}^{GP}, ξ_{66}^{GP}, ξ_{100}^{GP}), with uniform prior distributions specified for each of these knots.

$\beta_{GP}(t)$, the time-varying contribution to the general population risk of infection, is constructed as an interpolated spline with knots at years 1930, 1950, 1970, 1990 and 2005 (corresponding to the values: ξ_{1930}^{GP}, ξ_{1950}^{GP}, ξ_{1970}^{GP}, ξ_{1990}^{GP}, ξ_{2005}^{GP}). Before 1930, access to healthcare was limited and it is assumed that the spread of disease through medical procedures was minimal. Countries that experienced early HCV epidemics did so from the 1930s onwards [460]. The prior distribution on the 1930 knot (ξ_{1930}^{GP}) is, therefore, a sharply decreasing exponential distribution (rate $= 1.00$) implying low transmission before this time. The prior distributions on the knots for 1950, 1970 and 1990 (ξ_{1950}^{GP}, ξ_{1970}^{GP} and ξ_{1990}^{GP}) are chosen to be as uninformative as possible without permitting impossibly high rates (this was found to be an exponential prior with rate $= 0.05$). In the period before 1990, universal health care expanded but application of infection control and screening of

blood transfusions were less than adequate, hence the decision not to constrain the rate of infection in the general population over this period.

After 1990, countries began implementing blood transfusion screening. In addition, infection control continued to improve with technological and educational advances. It is a reasonable assumption, therefore, that general population risk of infection decreased after 1990. However, the roll-out of blood safety programmes and the magnitude of improvements in infection control were not uniform at the global scale. As a proxy for the improvement in iatrogenic procedure safety after 1990, the average per-capita health spending was calculated for all the countries in the model [461] and the top quartile was assumed to have significantly reduced general population incidence. This was achieved by setting the 2005 general population risk of infection proportional to the 1990 value, $\xi^{GP}_{2005} = q^{country}\xi^{GP}_{1990}$, but drawing the multiplicative factor $q^{country}$ from a high rate exponential distribution (rate $= 50$). Conversely, for countries in the bottom three quartiles, it is still assumed that some improvements have been made in terms of general population transmission, however, the prior assumption about the scale of improvement is weaker (specifically $q^{country}$ is drawn from a lower rate exponential distribution, with rate $= 5$). The general population risk of infection is held constant at this reduced rate at all later times; we do not model any further improvements in infection control in the status quo scenario [237].

PWID force of infection. The PWID force of infection is assumed to vary over time. This encapsulates the known changes of injection drug use within the injection drug use population. An individual's risk of infection is assumed to be elevated for the duration of injecting career, but not to vary with age. The PWID force of infection is, therefore, the sum of the general population risk (through engagements with healthcare and other risk factors as per the non-PWID population) and the age-constant increased risk of infection due to injection drug use:

$$\Lambda_{i,PWID}(t) = \beta_{i,GP}(t)p^{eff.}_{all}(t) + \beta_{PWID}(t)p_{PWID}(t).$$

The final term incorporates the prevalence (not effective prevalence) because of the simplifying assumption that riskiness of behaviour does not vary with age over the course of an injecting career ($c_{i,PWID}(t) \equiv c_{PWID}(t)$). The time dependent risk of transmission in PWID, $\beta_{PWID}(t)$, is composed of interpolated splines with knots at 1950 and 1980 (values ξ^{PWID}_{1950} and ξ^{PWID}_{1980}). The value of the knot at 1950 is drawn from a sharply peaked exponential prior, reflecting the lower levels of injection drug use before 1980 (exponential rate $= 1$) and the knot at 1980 is chosen to be as uninformative as possible (exponential rate $= 0.05$) to allow the model to explore higher rates of risk, reflecting increased injection drug use, following 1980 [462].

The impact of recent expansion of PWID harm reduction services is taken into account as follows. It has been suggested that NSP and OST, when implemented individually, do not significantly reduce the risk of HCV infection among PWID, but can reduce transmission by a factor of 0.75 when implemented in combination [265, 266]. Furthermore, it is recognised that "the higher infectivity of HCV compared to HIV and greater prevalence demands $\cdots$ higher coverage and greater scale-up" [463] of harm reduction interventions to reduce HCV transmission among PWID than

required to reduce HIV transmission (see also Grebely & Dore (2011) [464]). This is primarily because there is much higher prevalence of HCV than HIV in this group [256]. To capture both of these effects, we require a country not only to have implemented both OST and NSP programmes, but require NSP coverage to be high in order for there to be a harm reduction effect. High coverage of NSP is defined (following WHO targets) as distributing at least 200 syringes per PWID per year (indicator NSP.C.1c [267]). Provided this coverage of NSP is reached, coverage of effective harm reduction is then defined as the percentage of opioid-dependent PWID reached by OST programmes. This subset of PWID are, therefore, in receipt of both OST and high-coverage NSP (due to the high coverage NSP requirement) and so can be considered to experience a reduced risk of HCV transmission (which reduces the transmission risk by 75%) [266]. In 2010, only three countries (Norway, Australia and Moldova) reported high coverage of NSP services, rising to nine in 2017 [465, 466]; as global extent of high-coverage interventions is so low in 2010, we model no coverage before this year, rising to high-coverage interventions being implemented in nine countries by 2015. Details on the proportion of the PWID population opioid-dependent (and so eligible for OST) and the calculations carried out to estimate the proportion of this group receiving OST in 2015 is described in §3.7.1.

3.4.3 Reinfection

Reinfection with HCV can occur either after SVR or after spontaneous clearance of the virus. With regards the latter, evidence indicating the development of immunity following exposure and clearance is mixed with regards PWID, while in HIV-positive MSM it has been shown that clearance occurs in the same proportion of individuals for primary infection as for secondary infection [251]. Other work has shown that there are individuals who can clear the virus even upon repeated exposure, but this work indicates that those capable of clearing disease may be able to do so not as a result of post-exposure immunity but as a result of a strong cellular immune response [111]. As a result of the variable evidence regarding post-exposure immunity, the risk of secondary infection following spontaneous clearance is assumed to be equal to that of primary infection (a relative risk of one).

Work in the PEG-IFN+RBV era suggested that post-SVR reinfection occurs at an equal rate to primary infection [467, 468]. Other work in this period indicated that reinfection may be less likely to result in viraemic infection [469]. More recent articles after the development of DAAs illustrate that PWID who have been treated and relapsed to injecting behaviour are often reinfected, though in these studies comparisons with non-SVR individuals were not given preventing a formal assessment of the relative risks of reinfection versus primary infection following cure [470, 471]. Searching for information regarding potentially lower rates of reinfection among PWID (as suggested by this press release reporting on a 2017 presentation [472]) did not return robust evidence demonstrating such an effect. Reviews that have noted low reinfection rates among cured PWID also acknowledge that these studies tend to be among PWID selected as being at low risk of reinfection (in part as treatment may be withheld if an individual is an active PWID) and that

there is a lack of evidence on reinfection risk in those reporting recent injecting drug use [473].

With such a range of views regarding relative risk of reinfection, and no clear evidence one way or the other, a conservative assumption was adopted by setting reinfection risk equal to primary infection risk (a relative risk of one), an assumption followed by other modelling analyses for largely the same reasons [375, 410]. This is a conservative assumption as it serves to increase the number of infections (rendering incidence elimination more difficult to reach) than if reinfection risk were assumed lower than primary infection risk. Since this is an assumption it is varied in sensitivity analysis (described below).

3.5 Modelling treatment and prevention

3.5.1 Treatment regimens

Two treatment regimens are implemented: PEG-IFN+RBV and DAAs. Rates of SVR when treated with PEG-IFN+RBV vary by genotype: genotype 1 - 44%, genotype 2 and 3 - 73% and genotype 4 - 53% [474]. Genotypes 5 and 6 are less well studied: the SVR rate in genotype 5 is believed to be similar to genotypes 2 and 3 - 73% [192]. SVR in genotype 6 is estimated to be 75% [475]. Treatment durations are 48 weeks for genotype 1 [188], 24 weeks for genotypes 2 and 3 [188], 48 weeks for genotype 4 [476], 24 weeks for genotype 5 (based on similarity to genotypes 2 and 3 [192]) and 48 weeks for genotype 6 (as a conservative assumption [192, 476]). Note we do not simulate PEG-IFN+RBV treatment from either decompensated cirrhosis or HCC: PEG-IFN+RBV is contraindicated in patients with decompensated cirrhosis [477] and the impact of SVR on patients with HCC is contested, therefore, to be conservative, we assume no impact on survival so do not model HCC antiviral treatment (in either DAA or PEG-IFN+RBV eras) [478].

Many DAA combinations are available (see chapter 2). Instead of modelling a specific combination, we make the assumption that the best DAAs for the particular genotype, disease stage and treatment experience history are used in individual cases, leading to the best possible outcomes for the patient. Given the assumption of optimal regimens, recent work has shown equivalently high proportions achieving SVR in compensated cirrhotic and pre-cirrhotic patients, regardless of genotype, treatment experience or age [32, 33, 215, 479, 480]. Accordingly, we adopt the value 98% for the proportion achieving SVR in all patients in stages F0 to F4, regardless of genotype. In addition, studies have shown equivalent rates of SVR in active drug use patients [471, 481] and we assume that PWID receiving DAAs have the same outcomes as the general population. Lastly, we do not explicitly model HIV coinfection since coinfected patients receiving ART have equivalent SVR to mono-infected patients [214, 479, 482]; as was discussed above, assuming high (and increasing) ART coverage we are justified in not modelling differential treatment efficacy in HIV coinfected patients. DAAs can be used to treat patients in decompensated cirrhosis with 85% achieving SVR [33]. We do not model DAA treatment for patients in the HCC compartment as described above [478].

Duration of treatment is assumed to be 12 weeks up to and including compensated cirrhosis, and to be 24 weeks in decompensated cirrhosis patients [32, 33]. Treatment duration is uniform by genotype [483]. Options for even shorter durations of treatment, for example through detection of a sufficiently low viral load [34, 484], are not modelled as the requisite NATs to ensure cure would add to cost and would, moreover, not be available for a large proportion of the global HCV-infected population.

Adherence is assumed not to be a factor in determining outcomes. This is because studies have demonstrated strong adherence even among groups with multiple risk factors for non-adherence, a fact believed to derive from short treatment durations, simple all-oral regimens and mild side effects [485, 486]. Furthermore, regimens are forgiving: missing doses does not correlate with a lower chance of SVR [485]. Lastly, shorter treatment courses with more pills taken per day (two or three compared to one) have also been investigated in groups at risk of non-adherence: these regimens have high adherence and equal SVR rates to longer, 12-week courses [485]. This finding indicates that, even if adherence were a concern, measures are available to mitigate the issue, justifying not further considering adherence when assessing SVR rates and the impact of treatment overall.

Once SVR has been achieved, disease progression and mortality rates are reduced or set equal to zero. Studies have suggested fibrosis regression can take place if SVR occurs before cirrhosis, however, as a conservative measure we set disease progression rates to zero if SVR is achieved before compensated cirrhosis [487, 488] but do not model regression. If SVR is achieved in compensated cirrhosis, progression rates to decompensated cirrhosis and HCC are reduced and direct mortality from the F4 compartment is eliminated [489, 490]. Those who have achieved SVR and are in the decompensated cirrhosis compartment have no decrease in mortality but have a lower incidence of HCC [491]. Direct treatment of HCC is not possible; however, the impact of SVR on survival in HCC must be taken into account since those who have already achieved SVR can progress to HCC (though at a reduced rate). A reduced rate of mortality for those with SVR in HCC is modelled [492].

3.5.2 Historical diagnosis, treatment and prevention

The model uses estimates of the proportion of HCV-infected people diagnosed and the proportion of those diagnosed who are treated to simulate historical standards of care. 2015 values are available for select countries [392–395] and regional averages [28] used to impute the remainder; additional information on DAA use in 2016 is added into the model for select countries (see §3.7.1).

Operational definitions. The proportion diagnosed is defined by WHO as the "number of persons with chronic infection diagnosed out of the total number of persons with chronic infection" [28, 427]. This means that individuals who are cured are not included in calculations of the proportion diagnosed. When scaling up to these values the proportion diagnosed is calculated, in accordance

with the WHO operational definition, as:

$$\text{proportion diagnosed historical} = \frac{\sum(D+T+Q)}{\sum(A+U+D+T+Q)},$$

where the summations are over all indices of the given compartment. At the current modest levels of cure, this definition is stable (since the number who are cured following diagnosis is small). In interventions simulated here, particularly the outreach screening intervention (intervention IV), this definition becomes unusable because in aiming to reach a proportion diagnosed of 90%, the proportion diagnosed does not asymptote to a stable quantity; all individuals would be cured by use of the WHO definition. For this reason, an alternative definition of the proportion diagnosed is proposed and used in intervention IV to allow diagnosis scale up to be specified more meaningfully. In this definition those cured (but not reinfected) are considered as diagnosed as well, allowing targeted diagnosis proportions to be reached during diagnosis scale up (in other words diagnosing and curing people does not remove them from the calculation). In terms of the model quantities, therefore, the proportion diagnosed in intervention IV is:

$$\text{proportion diagnosed in intervention IV} = \frac{\sum(D+T+Q+C)}{\sum(A+U+D+T+Q+C)}.$$

The definition of the proportion treated is retained: "number of persons initiating treatment during a given year out of the total number diagnosed" [28, 427]. It should be noted that this definition is only implemented in the context of diagnosis scale up starting in 2017. The proportion diagnosed to 2015 utilises the WHO definition above as this is the baseline set by WHO and the point of departure for all intervention scenarios considered here. Switching the 2015 WHO definition to the intervention IV definition could be done, but given the low treatment coverage it would not significantly alter the treatment cascade to 2015 and, for consistency with WHO numbers, their definition is retained.

Historical diagnosis. Diagnosis is started in 1990, approximately the time the first HCV specific antibody assays were introduced [59, 229]. The rate of diagnosis is chosen such that the proportion diagnosed increases linearly from 0% in 1990 to the country value (or regional average value where data are lacking) in 2015. Care seeking behaviour is assumed to vary with disease stage: those with stage equal to or less than F3 have a relative rate of seeking diagnosis of 0.0025, compared to rates of 0.1 for compensated cirrhosis, and 0.4 in decompensated cirrhosis or HCC compartments. These values were found in model development to capture the trend that individuals present late for treatment, usually only after the onset of symptoms (taken here to occur from the onset of compensated cirrhosis; expert opinion); the numbers in the treatment cascade were found to be reasonably insensitive to changes in these values provided a bias towards late-stage presentation is maintained (result not shown). Unless altered in intervention, the diagnosis rate reached in 2015 is kept constant, modelling constant care seeking behaviour in the population. The bias towards end-stage diagnosis is also retained unless altered through outreach screening programmes which facilitate people entering care regardless of disease stage (this may be achieved, for example, through a birth-cohort screening campaign [493]).

Historical treatment. Historical PEG-IFN+RBV treatment is simulated as follows: after the introduction of PEG-IFN+RBV as the standard treatment for HCV infection [187, 188], the rate of treatment is chosen such that the annual proportion of those diagnosed who are treated rises linearly from 0% in the initial year of treatment, to the country (or regional) estimate of the fraction treated in 2015. The initial year of treatment is chosen, region-by-region, such that the cumulative number of treatments is approximately equal to the cumulative number of treated patients by region [28]; the minimum treatment start year is 2000 as this was the year in which PEG-IFN+RBV, the principle standard of care over the last two decades, was introduced (see chapter 2).

DAAs are implemented from 2016 in countries in which their use is reported. In these countries, the rate of treatment is calculated such that the reported number of DAA treatment courses is matched by the model [226, 494]. All other countries continue to implement PEG-IFN+RBV after 2015. This approach results in 1.76 million HCV treatment courses being delivered in 2016, of which 86% consist of DAAs [494]. The rate reached in 2015 or 2016 (depending on whether DAA information is available for a given country or not) is kept constant unless altered in intervention as described in the following section. As in the case of diagnosis, this simulates a constant treatment seeking behaviour among those diagnosed.

A list of all countries with estimates for the percentage diagnosed and treated, or the regional estimates where data are lacking, is given in appendix A, see table A.1; values for the additional DAA treatment courses given are reported in table A.2.

Retreatment. Previous models have not allowed retreatment after reinfection (following SVR) [381, 403, 408]. In the age of well-tolerated DAAs this is not considered a necessary or equitable restriction [36]. However, to prevent the possible (presumed unlikely) cycling on and off treatment (due to rapid retreatment following cure), an average delay of five years before potential retreatment was implemented in the model. As this value is arbitrary, it is varied in one-way sensitivity analyses to ensure results do not depend on it.

Historical harm reduction. Prior to 2016, blood and infection control improvements are modelled in countries with high health expenditure. Reduced transmission among opioid-dependent PWID is simulated in countries with OST plus high coverage NSP programmes, with coverage equated to OST programme coverage. See §3.4 above for details of how these are simulated and §3.7.1 below for estimates of the coverage of high-impact harm reduction interventions.

3.5.3 Intervention strategies

Four intervention strategies are simulated from 2017 above a status quo scenario (described below). We also simulated a scenario in which DAAs were not rolled out from 2016 in any countries, called the no-DAA scenario. Interventions simulated atop the status quo are cumulative: each incorporates the features of the previous interventions. If not otherwise stated, parameter values not changed in an intervention are equal to their values in the previously numbered scenario. The interventions are described here and a summary of all interventions is given in table 3.1.

No DAA scenario. DAAs are implemented in our status quo scenario but we simulated a scenario in which they are not implemented at all and all treatment courses in the past and future are PEG-IFN+RBV. This was included to investigate the benefits of DAA use even at current rates of diagnosis and treatment and provides an estimate of the future HCV epidemic were the recent rapid scale up of DAA use not to be continued.

Status quo. In the model DAAs are introduced in 2016 in those countries where use has been reported: this results in 86% of 1.76 million treatment courses in that year consisting of DAAs instead of PEG-IFN+RBV [494]. In the status quo it is assumed that all those countries in which DAAs are implemented continue to use DAAs and diagnosis and treatment rates are fixed at 2016 values. All other countries continue to use PEG-IFN+RBV at rates set to match the 2015 proportion treated as described in the previous section. Risk of transmission in the general population and PWID is kept fixed at 2015 values and no other changes are made. This scenario represents as estimate of what the HCV epidemic will look like with no changes made to improve rates of diagnosis and treatment or to reduce numbers of HCV infections.

Intervention I: + blood safety and infection control. Two of the key transmission routes in the general population are blood transfusions and infections due to lapses in infection control (such as from unsafe injections) [245]. Blood and injection safety have been targeted for elimination or reduction by WHO: by 2020 the aim is for 95% of blood donations to be screened in a quality assured manner and by 2030 for 100% of donations to be screened [28]. At the same milestones, it is intended that 50% and 90% of injections respectively are given "with safety-engineered devices in and out of health facilities" [27]; the most recent report goes further and aims for a 0% "proportion of unsafe injections" by 2030 [28]. As described in detail above, estimates of the source of infections in the general population demonstrate the considerable uncertainty regarding the precise transmission route responsible for infections in the general population [28]. Accordingly, focusing only on blood and injection safety targets alone may not eliminate HCV infection. Yet such infections have been all but eliminated in high-income countries through rigorous infection control in all settings. This indicates that overall improvements in health systems, as well as targeted interventions regarding blood and injection safety, can prevent the majority of infections resulting from medical and non-medical procedures.

These considerations make the case for simulating significant reductions in general population risk by 2030 as a plausible public health target through improvements in infection control across all settings. By contrast, the existence of HIV-positive MSM in particular as an increasingly significant at-risk group, as well as the clear challenges in eliminating medical-procedure related infection on a global scale, lead us to propose a more conservative 80% reduction in general population risk globally from 2016 values by 2020 (reached by linear scale up). As an assumption, this value is varied in our analysis (between the values of 0% and 95% reduction).

Intervention II: + PWID harm reduction. OST in combination with high coverage NSP has the most consistent evidence of reducing HCV incidence in PWID: meta-analyses suggest that such

programmes could reduce the risk of infection by 75% [266] or 71-74% (two analyses are performed that arrive at relative risks of 0.26 and 0.29 respectively based on whether adjusted or unadjusted outcomes were available) [265]. The latter study analyses data from 3,241-3,356 participants and no one study has a weight in the meta-analysis of more than 40%, suggesting that risk reductions of approximately 75% are appropriate values to incorporate when considering high quality OST plus NSP programmes.

Our intervention aims to increase all countries to high coverage NSP (defined as at least 200 syringes distributed per PWID per year) and expand OST provision to 40% of the opioid-dependent PWID population, using both of the WHO high targets for intervention coverage [267]. Countries with higher initial coverage are assumed to remain at those values (see §3.7.1). As such, 40% (or higher where appropriate) of the opioid-dependent PWID population are covered by an intervention that reduces the risk of HCV infection: $\beta_{PWID}(t)$ is reduced by 75% for 40% of the opioid-dependent PWID population. This approach to modelling risk reduction in PWID (by reducing risk of transmission according to risk reductions reported in meta-analyses) has been shown to be appropriate in other studies designed to explore the impacts of harm reduction interventions in PWID (see the discussion of the VMH models in the previous chapter, §2.5.2).

The OST coverage parameter and, therefore, the coverage of effective harm reduction, is varied in our analysis between the status quo value of less than 1% globally [466] and 95%. Following recent commentary on the challenge of reducing HCV transmission among PWID no impact of expanded NSP or OST in isolation is simulated [266, 381, 463]. There are clear limitations in extrapolating estimates of effectiveness from primarily high-income countries to the world and this is discussed in the relevant section (§4.4.4) of the following chapter; to explore the impact of potentially lower OST plus NSP effectiveness this quantity is also varied in sensitivity analysis (see §3.6.2).

Intervention III: + offer DAAs at diagnosis. In this scenario we assume that all countries introduce DAAs from 2017 so no PEG-IFN+RBV is used anywhere. Additionally, because patients engage with the healthcare system in order to be diagnosed, a logistically achievable approach to reducing the burden of HCV would be to offer DAA treatment at the time of diagnosis regardless of disease stage and without delay. In this scenario, those recently diagnosed are offered treatment and 90% accept and adhere to treatment. The rate of seeking treatment in the remainder of the population is maintained at the 2015/2016 values as described above.

Intervention IV: + outreach screening. In order to fully realise the potential of DAA therapies, diagnosis efforts must be stepped up in order to minimise the number of people unaware of their status (currently estimated at 80%). The model simulates scaling up rates of diagnosis through a countrywide programme of outreach screening such that, by 2030, 90% of the infected population is diagnosed [28]. This value is reached through linear scale up from the initial number diagnosed. As in intervention III, people are offered treatment upon diagnosis (with 90% accepting and adhering to treatment). In addition such an expansive outreach screening strategy could result in those previously diagnosed but untreated returning back into the care cascade to receive the new

DAAs. This effect is simulated as 10% per year of the previously diagnosed population returning for treatment.

A final comment pertains to the order of interventions. Interventions I and II relate to health system improvements that could occur in isolation. Indeed, it would be hoped that blood safety and infection control measures would improve by 2030 and so this is simulated first. Intervention II is more speculative but still represents a separate measure from HCV-specific interventions and so is incorporated second into the intervention package. Interventions III and IV are naturally ordered in terms of impact given that intervention IV incorporates the changes of III but goes beyond it (by scaling up diagnosis coverage to 90%). This differentiation into prevention interventions (I and II) that could take place without direct efforts to combat HCV, and treatment and screening interventions (III and IV) that are HCV-specific is arbitrary; as such, the impact of scaling up each intervention individually is explored in sensitivity analyses in order to explore the results with the impact of the other interventions removed (see §3.6.2).

Table 3.1 - Details of intervention scenarios modelled.

	Treatment	Risk of infection in non-PWID population	Risk of infection in PWID population	Treatment coverage	Diagnosis coverage
No DAA scenario	PEG-IFN+RBV	As per 2015 risk	As per 2015 risk	Treatment rate fixed at 2015/2016 value‡	Diagnosis rate fixed at 2015/2016 value‡
Status quo	DAAs from 2016	As per 2015 risk	As per 2015 risk	Treatment rate fixed at 2015/2016 value‡	Diagnosis rate fixed at 2015/2016 value‡
(I) + Blood safety &infection control	DAAs from 2016	80% reduction by 2020*	As per 2015 risk	Treatment rate fixed at 2015/2016 value‡	Diagnosis rate fixed at 2015/2016 value‡
(II) + PWID harm reduction	DAAs from 2016	80% reduction by 2020*	75% reduction at 40% coverage by 2020†	Treatment rate fixed at 2015/2016 value‡	Diagnosis rate fixed at 2015/2016 value‡
(III) + Offer DAAs at diagnosis	DAAs from 2016	80% reduction by 2020*	75% reduction at 40% coverage by 2020†	DAAs in all countries. Treatment offered within one year of diagnosis	Diagnosis rate fixed at 2015/2016 value‡

Continued on next page

Table 3.1 – *Continued from previous page*

	Treatment	Risk of infection in non-PWID population	Risk of infection in PWID population	Treatment coverage	Diagnosis coverage
(IV) + Offer DAAs at diagnosis	DAAs from 2016	80% reduction by 2020*	75% reduction at 40% coverage by 2020†	DAAs in all countries. Treatment offered within one year of diagnosis; those previously diagnosed linked back into care§	90% infected are diagnosed by 2030¶

Colours correspond to those used in the results graphs in the following chapter and are used here to indicate what is held constant from the previous intervention(s). PWID = people who inject drugs. DAAs = direct-acting antivirals. PEG-IFN+RBV = pegylated interferon + ribavirin. *General population risk reduced linearly 2017-2020. †PWID risk reduced linearly 2017-2020. Harm reduction impact based on combination OST plus NSP access as this has been shown to be effective in reducing HCV incidence [266]. 40% coverage based on WHO "high" target for OST [267]. Coverage only includes opioid-dependent PWID as suitable for OST [256]. ‡Treatment and diagnosis rates are inferred by scaling up these quantities to match the proportion treated or diagnosed where data are available [392–395] or using regional averages where data are lacking, with DAAs introduced in relevant countries in 2016 [494]; at the global scale this results in 20% diagnosed by 2015, and of those diagnosed 7% treated [28]. §Outreach diagnosis campaign facilitates return to care for those already diagnosed leading to 10% returning annually for treatment. ¶Diagnosis target reached through linear scale up to 2030.

3.6 Calibration and sensitivity analysis

3.6.1 Calibrating the model

The model is calibrated to three sets of information: HCV viraemic prevalence estimates in the overall population, data on prevalence of viraemic HCV infection in the PWID population and estimates of mortality due to HCV-attributable cirrhosis/decompensated cirrhosis (termed a cirrhosis death) or HCV-attributable HCC (an HCC death). While HCV incidence data are available in select instances, they have not been systematically combined to produce a reliable dataset that could be utilised within a global model; as such the model is not fit to incidence estimates and instead relies in calibration on the relatively stronger mortality and prevalence information available. References to prevalence in the following refer only to viraemic prevalence. The data are described in detail in Model inputs below. This section describes how the likelihood functions are constructed and how we sample from the parameter posterior distributions.

According to Bayes' theorem:

$$p(\phi\,|\mathcal{D}) = \frac{p(\phi)\mathcal{L}(\phi|\mathcal{D})}{\int p(\phi)\mathcal{L}(\phi|\mathcal{D})\mathrm{d}\phi},$$

where $p(\phi|\mathcal{D})$ is the posterior distribution of the set of parameters ϕ conditional on data $\mathcal{D}$, $p(\phi)$ is the prior distribution of the set of parameters, $\mathcal{L}(\phi|\mathcal{D})$ is the likelihood of the parameters con-

ditional upon the data, and the denominator is a normalisation constant that does not need to be explicitly evaluated [495]. The prior distributions are defined using ranges of values and distributions from the literature, see table 3.3. The likelihood function is equivalent to the probability of observing the data conditional on a particular set of model parameters, ϕ : $\mathcal{L}(\phi|\mathcal{D}) \equiv p(\mathcal{D}|\phi)$ [496]. Once evaluated, samples are drawn from the posterior distribution using Incremental Mixture Importance Sampling (IMIS) [497], described below (§3.6.1).

Calculating the likelihood. There are three contributions to the value of the likelihood: overall viraemic HCV prevalence, PWID HCV viraemic prevalence and mortality: $\mathcal{L} = \mathcal{L}^{overall\ prev.}\mathcal{L}^{PWID\ prev.}\mathcal{L}^{mortality}$. The procedure of multiplying the likelihood function together for separate sources of information is similar to that employed in the THEMBISA HIV model [498], the HIV synthesis model [499] and the Salomon et al. (2002) model of the HCV epidemic in the US (discussed in the previous chapter) in which individual log-likelihoods are calculated for HCV prevalence and HCC mortality and then summed to find the best fits [373].

The calculation of the likelihood in respect of each set of information is as follows. Overall viraemic prevalence values are 2015 country-by-country estimates, used by the WHO in formulating their global targets (see §3.7.1). The likelihood in respect of the overall viraemic prevalence is assumed to follow a beta distribution, $\mathrm{Beta}\,(\alpha, \beta)$, defined between the upper ($p_{high}^{overall}$) and lower ($p_{low}^{overall}$) uncertainty interval values (the likelihood is assumed zero outside this range). The beta distribution is chosen as a standard distribution to use on a bounded interval, while experiments in model development showed that this specification ensured the model matched WHO 2015 prevalence estimates (result not shown). The parameters are chosen to ensure the mode is located at the central estimate of prevalence $p_{central}^{overall}$, $\beta = (\alpha - 1 - p_{central}^{overall}(\alpha - 2)/p_{central}^{overall}$, and α is chosen such that 95% of the probability density function lies within 20% of the central prevalence estimate (the exact value of α varies by country). This value was chosen to produce simulated median global prevalence values that were in accord with WHO estimates (since it is WHO elimination targets that were being investigated by our model). The likelihood of a particular parameter set ϕ is calculated from the modelled prevalence, $p^{overall}(\phi)$, by computing the value of the probability density function of the above-defined beta distribution at $p^{overall}(\phi)$:

$$\mathcal{L}^{overall\ prev.} = \begin{cases} \mathrm{Beta}\left(p^{overall}(\phi); \alpha, \beta\right) & p_{low}^{overall} \leq p^{overall}(\phi) \leq p_{high}^{overall} \\ 0 & \text{otherwise} \end{cases}.$$

Where overall prevalence values are lacking, we put no requirement on this value in calibration other than requiring that the modelled prevalence is greater than the regional average; this ensures that modelled values are not lower than WHO estimates but can be higher (giving a conservative estimate rather than, potentially, an unduly optimistic view of the HCV epidemic).

The likelihood in respect of the PWID viraemic prevalence data is calculated as follows. Where data are available they comprise lower, middle and upper values. Such data are compiled from minimum and maximum prevalence values found in systematic reviews (see §3.7.2). The con-

stituent studies in the ranges of values might be conducted at different locations within a particular country, at different times or with limited subgroups within the population. To avoid applying unjustified statistical assumptions to these heterogeneous data (which nevertheless represent the best resource for modelling the global HCV epidemic in PWID), we constructed a triangular likelihood, such that simulated values must lie between the minimum and maximum values and are maximised at the central value:

$$\mathcal{L}^{PWID\ prev.} = \begin{cases} \frac{C(p^{PWID}(\phi)-p^{PWID}_{low})}{p^{PWID}_{central}-p^{PWID}_{lower}} & p^{PWID}_{low} \leq p^{PWID}(\phi) \leq p^{PWID}_{central} \\ \frac{C(p^{PWID}_{upper}-p^{PWID}(\phi))}{p^{PWID}_{upper}-p^{PWID}_{central}} & p^{PWID}_{central} \leq p^{PWID}(\phi) \leq p^{PWID}_{upper} \\ 0 & \text{otherwise} \end{cases},$$

where $C = 2/(p^{PWID}_{upper} - p^{PWID}_{low})$ is a normalisation constant and $p^{PWID}(\phi)$ is the modelled prevalence. The triangular distribution is used as it produced central estimates matching global estimates of PWID HCV prevalence in the source data. Where PWID prevalence values are lacking, no contribution to the likelihood in respect of PWID prevalence data is added.

Mortality information consists of estimates of numbers of deaths by year y, age-band a, sex j and death type t (cirrhosis or HCC), $M_{a,j,y,t}$. 95% uncertainty intervals are provided in the mortality estimates. The number of deaths is assumed to follow a log-normal distribution, with mean located at $\ln(M_{a,j,y,t})$ and variance denoted $\sigma^2_{a,j,y,t}$:

$$\text{number of deaths}_{a,j,y,t} \sim \text{Lognormal}\left(\ln(M_{a,j,y,t}), \sigma^2_{a,j,y,t}\right).$$

Log-normal distributions are a standard distribution used for modelling positive-definite quantities see [498]. The variance is chosen such that the cumulative distribution function is equal to 0.975 at the upper mortality estimate. The contribution to the likelihood in respect of a particular mortality estimate is the value of the log-normal probability distribution function at the modelled value of mortality (in the particular age-band, sex, year and death-type) for parameter set ϕ, $M_{a,j,y,t}(\phi)$:

$$\mathcal{L}^{mortality}_{a,j,y,t} = \frac{1}{M_{a,j,y,t}(\phi)} \frac{1}{\sqrt{2\pi\sigma^2_{a,j,y,t}}} \exp\left(-\frac{\left(\ln(M_{a,j,y,t}) - \ln(M_{a,j,y,t}(\phi))\right)^2}{2\sigma^2_{a,j,y,t}}\right).$$

All such points can be combined to produce the total contribution to the likelihood in respect of the mortality information:

$$\mathcal{L}^{mortality} = \prod_{a,j,y,t} \mathcal{L}^{mortality}_{a,j,y,t}.$$

The overall likelihood is then the product of the three likelihoods defined above. To reduce numerical overflow the quantity actually calculated is the log-likelihood, $l^{mortality} = \sum_{a,j,y,t} \ln \mathcal{L}^{mortality}_{a,j,y,t}$ and similarly for the other terms, giving the final expression for the log-likelihood:

$$l(\phi|\mathcal{D}) = \frac{1}{24} l^{mortality}(\phi|\mathcal{D}) + l^{PWID\ prev.}(\phi|\mathcal{D}) + l^{overall\ prev.}(\phi|\mathcal{D}),$$

where the numerical factor reduces the weight of the mortality information (for which each country has 96 values) relative to the prevalence values in order to improve the model fit (as explored when constructing the model, results not shown). A second adjustment to the likelihood is the requirement that incidence is not increasing after 2015; this criterion was implemented to prevent runaway simulations occurring whereby an acceptable calibration was achieved, but the choice of risk values was such that very soon after 2015 an epidemic explosion occurred. As found in model development, such simulations were very uncommon, contributing to raising the upper 95% credible interval but not altering the posterior median in a noticeable way compared to simulations in which incidence was not allowed to take off after 2015 (results not shown). Implementing this criterion removed this possibility ensuring all simulations represented plausible epidemics.

Sampling from the posterior distributions. The deterministic model is calibrated using IMIS, since it was designed to fit country-level HIV models and is known to be robust even in situations with multimodal posterior distributions [497]. Implementation in C++ was written for a previously published model [500] and was adapted for use here.

$N_0 = 1$ million initial samples are drawn from the prior distributions. The model is run and the likelihood calculated. The weight is calculated for all simulations (the ratio of individual likelihood to the sum of all likelihoods). The maximum weight point is chosen and a multivariate Gaussian distribution is constructed around this point from which $B = 10{,}000$ new parameter sets are sampled; the covariance of the multivariate Gaussian distribution is the weighted covariance matrix of maximum weight parameter set relative to the B nearest points (as measured according to their Mahalanobis distance [501]). The likelihood of the newly sampled points is calculated. The weights of all parameter sets previously sampled are recalculated according to the prior distribution and the sum of all previously constructed multivariate Gaussian distributions which defines a mixture sampling distribution. A new maximum weight point is chosen after carrying out this procedure, new Gaussian distributions constructed, B new parameter sets are sampled and the mixture sampling distribution updated and so on.

This process continues until a stopping criterion is reached, specifically that all points have equal importance weights. At a given iteration of the model, this is estimated by calculating the expected number of unique points that would result were resampling (from a multinomial distribution defined by all the parameter sets and their associated weights sampled so far) to take place at that point. To assess whether the stopping criterion has been reached, it is noted that, given a set of parameters labelled i with weight w_i – the probability of resampling parameter set i from a J-dimensional multinomial distribution is $1 - (1 - w_i)^J$, where J =1,000 (the number of parameter sets to be sampled from the posterior distribution). During a particular iteration of the model fit, therefore, the expected fraction of unique parameter sets sampled is calculated as $E = \sum_i (1 - (1 - w_i)^J)/J$. This quantity is compared to the case where all points have equal weight, i.e. $w_i = 1/J$, in which case it can be shown that the expected fraction of unique points is $1 - 1/e \approx 0.63$. In other words, the algorithm terminates once $E > 0.63$ and resamples (with replacement) from the multinomial distribution defined by all the parameter sets according to their

associated importance weights. Due to this self-monitoring nature, there is no stopping criterion to report, while convergence is reached by definition when calibration terminates.

3.6.2 One-way sensitivity analyses

One-way sensitivity analyses were performed on a number of parameters that were fixed in the primary analysis and are described here. These were either parameters chosen by the nature of the intervention programme (effectiveness of PWID intervention) or else parameters about which the evidence for their value was mixed or limited (relative rates of reinfection, delay in retreatment following reinfection). In the primary analysis best estimates were used for these values or where this was lacking an approach was taken with the aim of being conservative. To make it computationally feasible to perform several sensitivity analyses, these simulations were performed with a random sample of 100 posteriors (as opposed to 1,000 used in the primary analyses). Experience working with the model has shown that this has minimal impact on outcomes.

Effectiveness of PWID harm reduction interventions. Evidence for the impact of OST plus NSP (the harm reduction intervention simulated in this analysis) is of uncertain quality [265, 266]. This is reflected in the wide confidence intervals for the risk reduction of PWID on OST plus NSP programmes reported in these papers; taking the end-points of these values suggests a range of plausible effectiveness values from a minimum impact of a 20% reduction to a maximum impact of a 90% reduction (the primary analysis utilises a 75% reduction). Several analyses are repeated using these minimum and maximum effectiveness values.

Delay in retreatment after reinfection. To test sensitivity to the assumption of a five year average delay before possible retreatment (which was included in order to prevent unlikely cycling between infection and treatment in high-risk group individuals), the model was rerun with a one-year delay implemented instead. This analysis was performed with only intervention IV (the comprehensive strategy) since this involves the most treatments being delivered and so a choice regarding treatment delay would make the most difference in this setting.

Relative risk of reinfection. The impact of altering our assumptions regarding the relative risk of reinfection was investigated by running the model with relative risks of 0.2 and 0.5 (compared to a primary analysis value of 1). Additionally, a sensitivity analysis was performed in which the comprehensive intervention strategy was simulated but with varying diagnosis coverages reached in 2030. This analysis was repeated for the three values of relative risk of reinfection (0.2, 0.5 and 1).

Programme parameters. The programme parameters are those that define the extent of programme scale up in the various interventions (described in previous sections). These are varied in the comprehensive package of interventions (intervention IV) to investigate sensitivity of the results to changes in these parameters. Additional analyses looked at the impact of scaling up these programme parameters individually (all other values kept at their status quo levels) to understand the effect of prioritising different interventions.

The three programme parameters varied in these analyses are: risk reduction in the non-PWID population (range: 0-95% reduction, intervention IV value 80%); coverage of harm reduction in the PWID population (range: 0-95% reduction, intervention IV value 40%) and the proportion diagnosed by 2030 (range: base value[5]-95%, intervention IV value 90%). These sensitivity analyses estimated the proportional change in incidence rate and mortality by 2030 (to assess how close elimination targets are to being met in the various analyses) and time to elimination (if met before 2100).

Key countries. The countries that contributed most to infections and deaths averted in intervention IV were identified and the model re-run without these countries included in the intervention package (values set to status quo scenario) to quantify the sensitivity of global results to progress made in those key countries. Time to incidence and mortality elimination was calculated in these 'missing country' intervention IV simulations.

3.7 Inputs

3.7.1 Model inputs

Model inputs are taken from a variety of sources discussed below. As was emphasised in the discussion of other models in the previous chapter, the overriding factor determining the choice of sources was the requirement, as this is a global model, to find comprehensive sources that provided information (data or best estimates where necessary) for as many countries as possible. Given such sources, all countries were simulated in the same way.

Demographic inputs. UN population prospects estimates (2017 update) are used to simulate the population, country by country, from 1950-2100 [419]. The following information was used: population size in five-year age bands by sex, age-specific fertility rates in five-year age bands (between the ages of 15 and 50 years old), sex ratio at birth, migration rates and mortality rates in the ranges 0-1, 1-5, 5-10 years old and so on (calculated from life tables). Population sizes were available annually; all other values were available as five-year averages.

PWID inputs. Values of the proportion of the population PWID (denoted the proportion PWID) in the 15- to 64-year-old population were available from a recent review by Degenhardt et al. [256]. Regional averages were recalculated to be consistent with the updated population data used in the current model. It was also deemed preferable to recalculate these values (and all PWID values

[5]In status quo the proportion diagnosed by 2030 is 37%: diagnosis rates are kept fixed allowing the proportion diagnosed to vary and this is the value reached by 2030 in the simulation. Therefore, in the status quo sensitivity analysis, this is the base value when scaling up the proportion diagnosed value. When performing the sensitivity analysis with intervention IV values as described in this section as well, the base value is 42% because the implementation of prevention interventions reduces incidence and so raises the proportion diagnosed. The base value of the proportion diagnosed in the other sensitivity analyses (when GP risk reduction and PWID programme coverage) are varied also changes even when it is not part of the sensitivity analysis. This is because varying the impact of prevention interventions changes the proportion diagnosed itself. For this reason, no explicit value is given for the lower proportion diagnosed value but investigating the results show that it ranges slightly between 37-42% as described here.

described here) since a previous version of the review [502] (that had been used in the model until the newer version was published [256]) had contained significant errors that had to be corrected[6].

Countries with data comprise 81% of the global adult population. To extrapolate these country-level values to estimate the proportion PWID in the remaining countries the procedure for producing regional and global PWID proportion estimates described in Mathers et al. [412] and related papers was followed. Countries are classified by region (Eastern Europe, Western Europe, East and Southeast Asia, South Asia, Central Asia, Caribbean, Latin America, Canada and US, Pacific Island states and territories, Australia and New Zealand, Middle East and North Africa and Sub-Saharan Africa; for a list of countries by region see appendix B). Within each region an average proportion PWID is calculated, weighted by the 15- to 64-year-old adult population size. This value is then extrapolated to countries in that region without data. One exception is made for Poland. This country lacks data, but applying the proportion PWID calculated in the above way results in too many HCV-positive PWID relative to the estimates of HCV-positive individuals in the entire population. The regional average is dominated by Russia. To be able to calibrate Poland we removed Russia and recalculated the regional average to produce a revised estimate of the proportion PWID. This results in a value (0.137%) closer to countries with similar drug use profiles as noted by examining data reported by the European Monitoring Centre for Drugs and Addiction [503]. In the Pacific Islands there are no data so global averages are constructed in the same way as regional averages and these values are used for all the countries in the region. In the Caribbean, where only Puerto Rico has data, this value is combined with the global average to produce an adjusted regional estimate for the remaining countries in the region. This has the effect of increasing the percentage PWID among adults from 0.32% (the global average) to 0.43%. Estimates derived using our population data are only marginally different from the ones reported in the original paper [256] but we retain our recalculated values for consistency with our 2017 UN population figures (the original analysis used an earlier update).

The proportion of PWID who are female and the proportion of PWID who are opioid-dependent (required for modelling the impact of PWID harm reduction interventions) are reported in the same paper and we recalculated the regional and global average values according to the same procedure described above [256].

Harm reduction inputs. Countries with OST programmes and in which at least 200 needles and syringes per PWID per year were distributed are simulated as having a reduction in HCV transmission risk in opioid-dependent PWID. Larney et al. report the number of needle-syringes distributed in a given year (primarily 2014, 2015 and 2016) for 158 territories [466]. We followed their procedure in calculating estimates of numbers of needle-syringes per PWID and recalculated the regional averages to account for our use of 2017 Population Prospects population estimates (as per

[6]Specifically, some regional estimates for HCV prevalence were outside the range of values for any of the constituent countries suggesting a major mistake in calculation or presentation of the results. The 2017 update of this analysis from the same authors that was adopted after it was published contained no such mistakes but experience with the previous paper (and the desire to update for the population numbers used in this model) led to all regional and global average values being recalculated anyway [256].

all other PWID-specific inputs, see above). This provided a binary measure of whether a country had greater than, or less than, 200 needle-syringes per PWID per year by 2015 (the year in which most data are available).

To construct OST coverage, the number of OST recipients by country was found for 72 countries, as reported in Larney et al. [466]. This number includes those on OST who are both primary injection drug users and those who are not (a group which includes sniffing and smoking as primary routes of administration [503]). To derive an approximate coverage of OST requires estimating the number of opioid users in the population (of whom a subset are opioid-dependent PWID); the number on OST at a particular time can then be divided by this value to arrive at a coverage in opioid-dependent people (indicator OST.C.1c in the WHO technical guide [267]). We then assume equal coverage in opioid-dependent PWID (indicator OST.C.1d [267]).

To estimate the number of opioid users by country, data were extracted from the UNODC website on prevalence of opioid and opiate use. Opiates are drugs derived from opium while opioids comprise these as well as synthetic drugs created to emulate the properties of opiates. As such opioid use prevalence is higher than opiate use. Noting that many more countries have estimates of opiate than opioid use, we used those countries that had estimates of prevalence of both (51 countries) to calculate regional estimates of opioid to opiate use. We followed the procedure of weighting by population size as per the estimates of regional global PWID estimates in Mathers et al. and related papers used in the above calculations [256, 412, 466, 502]. This allowed the calculation of regional estimates of the ratio of opioid to opiate use in all regions (using the same regions as the aforementioned paper) except the Pacific Islands for which a global average was used. Having done this, estimates of opioid use were calculated for all countries with either estimates of opioid prevalence or values inferred using the above ratios from opiate use, resulting in opioid use prevalence in 128 countries. Regional averages were constructed from these data for opioid use prevalence and applied to countries lacking either opioid or opiate data. Lastly, the number on OST (for those countries known [466]) was divided by the estimated number of opioid users in the relevant year to calculate a coverage of OST among all opioid users.

Coverage was capped at 80%, the highest coverage achieved in Europe (see this European Monitoring Centre for Drugs and Addiction report [503]), as two countries with inferred opioid prevalence values had higher reported coverage. Lastly, we assume that the coverage among opioid-dependent PWID is equivalent to the coverage among opioid users in general as stated above. In Europe, 38% of those entering treatment inject as their primary route of administration [503], while our estimates suggest that 30% of the region's opioid-dependent people are PWID, justifying equating the coverage of OST among opioid-dependent people in general with that among opioid-dependent PWID specifically. According to this procedure, 16 countries had coverage of OST higher than 40 per 100 opioid-dependent PWID (defined as a high target coverage by WHO [267]) while globally 5% of opioid-dependent PWID received OST.

Genotype distributions. Genotype distributions were taken from Messina et al. (2015) [281].

GBD study regional averages calculated in the paper were used where data were not available for a given country. An average genotype distribution for Oceania was not calculated for lack of data; for these countries the distribution for Australasia was used.

Historical diagnosis and treatment. 67 country values for the proportion diagnosed and the proportion subsequently treated (for one of the years 2013, 2014 or 2015) were extracted from published reviews [392–395]. We updated 2013 and 2014 proportion diagnosed values to 2015 values by adding the published estimate of number diagnosed per year to the then current number diagnosed, taking into account estimates of new infections and deaths in the intervening years. We assumed that the treatment rate in 2015 was equal to the 2013 or 2014 value where necessary. In two cases (Egypt and India), significant numbers starting treatment in 2015 were reported (greater than the treatment numbers implied in our approach) [483]. We, therefore, added these treatments to the original projections of treatment numbers to estimate updated treatment rates.

To impute values for the remaining countries and territories, regional averages were used [28]. Specifically, we calculated regional estimates for the remaining countries such that the overall treatment cascade numbers in 2015 matched WHO regional estimates [28].

In countries with reported DAA use in 2016 [494], the rate of treatment in 2016 is chosen so that the number reported as starting DAA treatment in that year is matched in the model. No PEG-IFN+RBV is simulated in those countries that have transitioned to DAAs; this will underestimate treatment use in countries in which both treatments currently coexist but this effect is assumed to be small since, in those countries that have adopted DAAs already but in which PEG-IFN+RBV use continues (such as China[7]), it is expected that PEG-IFN+RBV will be rapidly phased out (particularly in light of falling prices and global advocacy pushing for increased access to these better HCV treatments [142]).

General population risk reduction. Whether or not countries experienced a reduction in general population risk was based on average healthcare spending (1995-2014) [461]. The small number of countries lacking such data were assumed not to be in the top quartile of health spending.

3.7.2 Calibration data

Mortality. Estimates of the number of deaths due to compensated/decompensated cirrhosis (defined formally as "liver cirrhosis, chronic viral hepatitis infections and hepatic decompensation events" [504]) and HCC are taken from GBD study estimates (2016 update, downloaded from [9]).

These estimates are produced by assimilating various country-level sources of information on deaths (such as death registry systems and verbal autopsy) to produce estimates of the numbers of deaths where data exist (this description follows [3, 505]). These data are adjusted to deal with

[7] This statement is based on our personal communication with Yunnan Province, China where PEG-IFN+RBV remains the only treatment available for HCV infection, while WHO reports China as having introduced DAAs (presumably only in a select number of locations) in 2016 [494].

(for example) missing cause of death information or clearly incorrect causes of death (such as back pain, referred to as a garbage code). Multiple statistical models (in particular linear mixed effects models), joined together into the Cause of Death Ensemble model (CODEm), are built up using covariates to effectively interpolate the data and produce age-, sex- and time-specific mortality estimates. This process allows extension of estimates to countries lacking data; confidence intervals associated with countries lacking data are wider than those with data, since the set of models for those countries with extensive data is not calibrated to those with minimal information on deaths. Out-of-sample predictive validation is also utilised to test accuracy of the models. A final process involves squeezing the sum of deaths produced in this way to ensure that the overall number of deaths produced by the models matches the total number of deaths (denoted the Cause of Death correction - CoDCorrect - algorithm). Estimates of mortality at the level of specific hepatotropic viruses involves estimating the proportion of deaths or infections due to each cause (HBV, HCV, alcohol and other including autoimmune) using literature searches to develop aetiological models of attributable cause [6].

As is clear from this brief summary, the IHME estimates involve significant adjustment of the raw data at every step of the process to produce estimates for all age, sex, time and location combinations; creation of HCV-specific estimates involves an extra adjustment of identifying attributable-cause that is subject to considerable uncertainty. As noted in [6], it is unclear how uncertainty in estimating HCV-attributable mortality affects the results in terms of over or underestimating numbers of deaths, precluding adjusting for possible biases. Nevertheless, these estimates are derived from a large mortality data collection exercise and the process has been refined continuously since 1990. They, therefore, represent a key source of HCV disease information particularly at the global scale, incorporating over 2,000 site years of data for both cirrhosis and HCC deaths [6]. This motivates using the IHME numbers; the limitations in the estimates led us to coarse-grain the estimates by only using values for the years 1990 to 2015 in five-year intervals[8]. In addition, estimates were binned into the age ranges 5-15, 15-50, 50-70 and over 70 years old (a standard set of age bands provided in the IHME estimates). This approach was chosen to enable the model to capture the broad trends in the numbers (both temporally and by age) but not to encourage over-fitting to what are, in most instances, modelled estimates.

Since HCV prevalence information is more limited than GBD study estimates, all countries that were simulated were required to have GBD study estimates. The value of the GBD study estimates is that they cover almost all countries and thus facilitated the development of the global model.

Prevalence. The model is fit to HCV prevalence estimates that are derived from systematic reviews. Our overarching view, backed up by a consideration of the quality and limitations of the data (described below), is, firstly, that these estimates represent sufficient quality assessments of global HCV prevalence to justify fitting our model to them; and secondly, that limitations in the data do not result in a systematic bias that could significantly alter the conclusions of our analysis.

[8] 2015 value replaced with a 2013 value for Macao Special Administrative Region (SAR) and Hong Kong SAR as these regions were not included in the 2016 GBD update so numbers from the 2013 updates were used.

Overall prevalence. HCV viraemic prevalence data for the overall population of a particular country are 2015 estimates, used by WHO in formulating their targets [28, 280].

The procedure for generating country-level estimates of anti-HCV prevalence is detailed in [280]. Briefly, a previous systematic review in 2014 brought together estimates of anti-HCV prevalence, including child-specific estimates and adult-specific estimates [278]. These were combined into regional averages (in the same way as in the Degenhardt et al. [256] analysis of HCV prevalence among PWID described below) to extrapolate to countries lacking data in order to produce global prevalence estimates. Country-level viraemic prevalence rates were derived in the same way and used to produce an estimate of the global number HCV-RNA positive. The underlying data varied. 40% of studies were within specific (but not high-risk) groups such as pregnant women, though the remainder of studies covered a broadly representative sample of the population. Of these, some only reported age-specific prevalence that had to be adjusted (sometimes without knowledge of the underlying sample's age distribution) to produce overall prevalence estimates. The last key step in the 2014 study was to assume all prevalence estimates so arrived at were constant to 2013, to produce an estimate of HCV prevalence in that year. The 2017 study extended upon this by building Markov models of HCV disease progression (a CDA model as described in the previous chapter) with which to project forward the year-specific prevalence datum to the year of analysis (2015) [280]. This 2017 study re-performed the previous systematic review, with the number of low quality studies dropping to 23%.

Our model is fit to these modelled HCV prevalence estimates. The values are derived from a range of recent individual country prevalence data (covering 86.1% of the global population) from which 2015 country-level values are extrapolated. The underlying data are in places based on age-specific samples from the population but adjustments are made to counter bias in the overall prevalence value that this may introduce. The prevalence data in some instances derive from unrepresentative groups such as pregnant woman; no correction is made to such estimates for lack of a clear approach to do so and in order to fit to the WHO baseline prevalence estimates directly [28]. Note that, where data are lacking, the only constraint on prevalence in our model is that it must be in excess of the lower bound prevalence for that country's GBD study region as estimates in [280].

PWID prevalence. HCV antibody positive prevalence data in PWID are available, see Degenhardt et al. (2017) [256]. These values are combined with the percentage HCV viraemic (the viraemic rate) to calculate a viraemic HCV prevalence. The viraemic rate is assumed equal in the population as a whole and the PWID population, and is from the 2017 global HCV prevalence study described above [280].

This analysis is a large systematic review reporting numerous data on PWID. 99 countries had at least one study reporting anti-HCV prevalence, comprising 90.2% of the global PWID population. The quality of studies varied in terms of sample methodology and coverage. 23% of studies were rated in the top (A) quality by methodology: a seroprevalence study involving more than one site and more than one sample type (out of NSP site, OST site and so on). An additional 57% of studies

were in the second tier (out of four) denoted B1: multiple sites but with only one sample type. In terms of study coverage, 36% were considered national in scope, with only 27% of studies limited to one city. As noted by the authors, the quality of studies was higher than may be expected in a marginalised group and had increased since their previous study [256]. The definition of PWID is anyone injecting in the last twelve months, though shorter time-frames are used where data are lacking. This indicates that the data reported in the study should pertain to recent injecting drug use, however, the precise definitions will vary by study and this is an unavoidable limitation of such a meta-analysis that it would be extremely challenging to correct in any systematic way.

This analysis of PWID HCV prevalence is a major, published assessment of the HCV epidemic among PWID at the global scale and, as such, is a valuable resource for calibrating the model. Specifically, our model is fit to PWID HCV prevalence in the relevant year as reported in the appendix [256]. Where data do not exist, PWID prevalence is not included in the likelihood calculation and prevalence in the PWID population is only constrained implicitly by prevalence in the population as a whole. Note that we recalculated the PWID prevalence estimates using up-to-date population estimates as described above for other PWID-specific data derived from this systematic review [256].

3.7.3 Model initialisation and technical details

The model is fit to mortality data starting in 1990. The model was run from 1890, such that a full 100-year cycle of ageing had been simulated before calibration was carried out allowing the age distribution of HCV-infected people to stabilise. The model is run with 1950's demographic information from 1890 to 1950, with a seed value of 0.1% HCV infected. The population size is rescaled in 1950 and the simulation proceeds from this date with the time-appropriate demographic parameters.

The model was coded in C++14 [506] with figures produced using ggplot2 [507] and rworldmap [508] in R version 3.4.3 [509] (additional packages [510–518]. The equations were solved using an Euler scheme, with a time-step of $\mathrm{d}t = 0.2$ years. This introduces minimal error (result not shown) as would be expected by the slow nature of both the natural history of the disease (which takes decades to manifest) and the epidemic itself (current patterns of disease burden have taken many years to develop [238]).

3.8 Tables and equations

3.8.1 Model parameters

Table 3.2 - Full list of parameters and derived quantities with values and prior distributions.

Parameter	Description	Value(s) or relation to other parameters	Justification and references
Demographic parameters			
$b(t)$	Number of births	Calculated from sex ratio, fertility rate and number of females; depends on country and time	[419]
$\mu_{ijl}^{nat.}(t)$	Background mortality rate	$\sigma_l \mu_{ij}^{nat.}(t)$	See below
σ_l	Standardised mortality ratio	l =1: 5-16	[420, 421]
		Otherwise: 1	By definition
$\mu_{ij}^{nat.}(t)$	Background mortality rate	Depends on country, age, sex and time	[419]
$\nu(t)$	Migration	Depends on country	[419]
π^{PWID}, π_{female}^{PWID}, $\pi_{opioid-dept.}^{PWID}$	Proportion PWID, proportion of PWID female and proportion of PWID opioid dependent	Depends on country	Country-specific, regional or global values used where appropriate [256]
Transmission parameters			
$p^{inf.}$	Probability of perinatal infection	0.027	[456]
$\Lambda_{il}(t)$	Force of infection; dependent on age – i - and risk group – l = GP, PWID	GP: $\beta_{i,GP}(t) p_{all}^{eff}(t)$ PWID: $\beta_{i,GP}(t) p_{all}^{eff}(t) + \beta_{PWID}(t) p_{PWID}(t)$	See below
$p_{all}^{eff}(t)$	Effective HCV prevalence; $I_i(t)$ is number infected by age, $N_i(t)$ is population size by age	$\sum_i \beta_{i,GP}(t) I_i(t) / \sum_i \beta_{i,GP}(t) N_i(t)$	[374]
$p_{PWID}(t)$	HCV prevalence among PWID	$I^{PWID}(t)/N^{PWID}(t)$	[374]
$\beta_{i,GP}(t)$	Time- and age-dependent risk of infection in general population	$\gamma_i \beta_{GP}(t)$	See below

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Table 3.2 – *Continued from previous page*

Parameter	Description	Value(s) or relation to other parameters	Justification and references
$\beta_{GP}(t)$	Time-varying contribution to general population risk of infection	Interpolated spline with risk values at years 1930, 1950, 1970, 1990 and 2005: ξ^{GP}_{1930}, ξ^{GP}_{1950}, ξ^{GP}_{1970}, ξ^{GP}_{1990}, ξ^{GP}_{2005}	See below
γ_i	Age-dependent general population risk multiplier	Interpolated spline with multiplicative values at ages 33, 66, 100 years old: ξ^{GP}_{33}, ξ^{GP}_{66}, ξ^{GP}_{100}	See below
$\beta_{PWID}(t)$	Risk of infection in PWID	Interpolated spline with risk values at years 1950, 1980: ξ^{PWID}_{1950}, ξ^{PWID}_{1980}	See below
$\xi^{l}_{i/t}$	Values of spline knots by risk group l, at time t or age i	ξ^{GP}_{1930}: exp. prior (rate = 1.00) ξ^{GP}_{1950}: exp. prior (rate = 0.05) ξ^{GP}_{1970}: exp. prior (rate = 0.05) ξ^{GP}_{1990}: exp. prior (rate = 0.05) $\xi^{GP}_{2005} = q^{country}\xi^{GP}_{1990}$ ξ^{PWID}_{1950}: exp. prior (rate = 1.00) ξ^{PWID}_{1980}: exp. prior (rate = 0.05) ξ^{GP}_{33}: 0-1 ξ^{GP}_{66}: 0-1	Pre-1930 risk of infection low so greater prior weight at lower values; risks at other times drawn from effectively uninformative prior distributions; age risks completely uninformative
$q^{country}$	Reduction in GP risk after 1990 - prior set using average healthcare spending from 1995	Spending in top quartile: $q^{country}$: exp. prior (rate=50) Otherwise $q^{country}$: exp. prior (rate=5)	Healthcare expenditure per capita from World Bank [461]; greater reduction assumed with greater expenditure
Natural history model parameters			
λ^{clear}_i	Rate of spontaneous clearance	$p^{clear} r^{clear/chronic}$	See below
$\lambda^{chronic}_i$	Rate of progression to chronic disease	$\left(1 - p^{clear}\right) r^{clear/chronic}$	See below
p^{clear}_i	Proportion clearing HCV	$i \geq$ 15 years old: 0.25 $i <$ 15 years old: 0.55	[107, 519, 520]
$r^{clear/chronic}$	Rate of moving from acute to either chronic disease or susceptible	2.18 years^{-1}	[107]

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Table 3.2 – *Continued from previous page*

Parameter	Description	Value(s) or relation to other parameters	Justification and references
$\lambda_{ij}^{0\rightarrow1}$, $\lambda_{ij}^{1\rightarrow2}$, $\lambda_{ij}^{2\rightarrow3}$, $\lambda_{ij}^{3\rightarrow4}$, $\lambda_{ij}^{3\rightarrow HCC}$, $\lambda_{ij}^{4\rightarrow HCC}$, $\lambda_{ij}^{DC\rightarrow HCC}$, $\lambda_{ij}^{4\rightarrow DC}$, μ_{ij}^{4}, μ_{ijd}^{DC}, μ_{ijd}^{HCC}	Age and sex dependent fibrosis progression rates and end stage disease progression rates	Calibrated; determined by age via h_{age}^{k}, sex via h_{sex}^{k} and annual transition probabilities $f^{k\rightarrow k+1}$ where k denotes disease stage	See below and methods for precise relationship between calibration quantities and literature-derived annual transition probabilities
$f_{l/u}^{0\rightarrow1}$	Annual transition probability	lower = 0.05, upper = 0.12	[121]
$f_{l/u}^{1\rightarrow2}$		lower = 0.05, upper = 0.07	
$f_{l/u}^{2\rightarrow3}$		lower = 0.08, upper = 0.13	
$f_{l/u}^{3\rightarrow4}$		lower = 0.05, upper = 0.13	
$\alpha^{fibr.}$	Scalar controlling rate of fibrosis progression	0-1: 0 gives lower value of all fibrosis progression probabilities in above row; 1 gives upper values	Full range of values
$f^{3\rightarrow HCC}$	Annual transition probability: F3 to HCC	0-0.02	[521]
$f^{4\rightarrow HCC}$	Annual transition probability: F4 to HCC	0.01-0.09	[122, 522]
$f^{DC\rightarrow HCC}$	Annual transition probability: DC to HCC	0.03-0.10	[432]
$f^{4\rightarrow DC}$	Annual transition probability: F4 to DC	0.02-0.06	[122]
$f^{4\rightarrow\mu}$	Annual probability of mortality from F4	0.02-0.04	[93]
$f^{DC\rightarrow\mu}$	Annual probability of mortality from DC	1st year: 0.07-0.25 Later years: 0.07-0.18	[122]
$f^{HCC\rightarrow\mu}$	Annual probability of mortality from HCC	1st year: 0.53-0.75 Later years: 0.09-0.38	[523, 524]
$h_{age}^{fibr.}$, $h_{age}^{j\rightarrow HCC}$, $h_{age}^{4\rightarrow DC}$, $h_{age}^{cirr.\rightarrow\mu}$, $h_{age}^{HCC\rightarrow\mu}$	Proportional difference 70- to 20-year-old disease progression rates	1-10	[449]

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Table 3.2 – *Continued from previous page*

Parameter	Description	Value(s) or relation to other parameters	Justification and references
$h_{sex}^{fibr.}$, $h_{sex}^{j\to HCC}$, $h_{sex}^{4\to DC}$, $h_{sex}^{cirr.\to\mu}$, $h_{sex}^{HCC\to\mu}$	Proportional difference male to female disease progression rates	1-2	[449]
Treatment, prevention and intervention parameters			
ζ_g^k (PEG-IFN + RBV)	Proportion achieving SVR by genotype g with PEG-IFN+RBV (no treatment DC or HCC)	ζ_1^k =0.44 ζ_2^k =0.73 ζ_3^k =0.73 ζ_4^k =0.53 ζ_5^k =0.73 ζ_6^k =0.75	[474] [474] [474] [474] [192, 474] [475]
ζ_g^k (DAAs)	Proportion achieving SVR by disease stage with DAAs (no treatment HCC)	F0-F4: 0.98 DC: 0.85	F0-F4 values [32] - lower confidence interval to be conservative; genotype 3 assumed equal to others. DC value [33]
$\bar{\zeta}_g^k$	Proportion not achieving SVR	$\bar{\zeta}_g^k = 1 - \zeta_g^k$	By definition.
ϕ_g (PEG-IFN + RBV)	Mean rate of treatment course by genotype g with PEG-IFN+RBV	ϕ_1 =1/48 weeks ϕ_2 =1/24 weeks ϕ_3 =1/24 weeks ϕ_4 =1/48 weeks ϕ_5 =1/24 weeks ϕ_6 =1/48 weeks	[188, 476] [188, 476] [188, 476] [188, 476] [188, 192] [188, 192]
ϕ_g (DAAs)	Mean rate of treatment course with DAAs	F0-F4: 1/12 weeks DC: 1/24 weeks	F0-F4 values [32]. DC value [33]
a_{min} (PEG-IFN + RBV)	Minimum age of treatment with PEG-IFN+RBV	15 years old	Approximate minimum age used in guidelines
a_{min} (DAAs)	Minimum age of treatment with DAAs	0 years old	Assume ongoing clinical trials will lead to all-age treatment [525]

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Table 3.2 – *Continued from previous page*

Parameter	Description	Value(s) or relation to other parameters	Justification and references
$\delta_{delay}^{PWID\ re-treat}$	Average time to possible retreatment in PWID after cure	5 years (varied in one way SA: 1-5 years)	Likelihood of multiple retreatments in PWID has not been established; we assume a 5 year average waiting time before retreatment after reinfection
$\theta_{reinf.}$	Relative risk of reinfection compared to primary infection	1 (varied in one way SA: 0.2-1)	Evidence on relative risk of reinfection mixed [467–472]; conservative value of one chosen (conservative as increases incidence so worsens outcomes)
$\rho_{ij}^{0\to1}$, $\rho_{ij}^{1\to2}$, $\rho_{ij}^{2\to3}$, $\rho_{ij}^{3\to4}$, $\rho_{ij}^{3\to HCC}$, $\rho_{ij}^{4\to HCC}$, $\rho_{ij}^{DC\to HCC}$, $\rho_{ij}^{4\to DC}$	Age and sex dependent fibrosis progression rates after achieving SVR	$\rho_{ij}^{k\to k+1} = \alpha^{k\to k+1}\lambda_{ij}^{k\to k+1}$	See below
$\alpha^{0\to1}$, $\alpha^{1\to2}$, $\alpha^{2\to3}$, $\alpha^{3\to4}$, $\alpha^{3\to HCC}$	Hazard ratio SVR vs. non-SVR: progression rates before compensated cirrhosis	0	As a conservative measure no regression is modelled [487, 488]
$\alpha^{4\to HCC}$	Hazard ratio SVR vs. non-SVR: HCC rate from F4	0.29	[489]
$\alpha^{DC\to HCC}$	Hazard ratio SVR vs. non-SVR: HCC rate from DC	0.33	[491]
$\alpha^{4\to DC}$	Hazard ratio SVR vs. non-SVR: DC rate from F4	0.26	[489]
α^{4}	Hazard ratio SVR vs. non-SVR: F4 mortality	0	[490]
α^{DC}	Hazard ratio SVR vs. non-SVR: DC mortality	1	[491]

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Table 3.2 – *Continued from previous page*

Parameter	Description	Value(s) or relation to other parameters	Justification and references
α^{HCC}	Hazard ratio SVR vs. non-SVR: HCC mortality	0.41 (only relevant if treated before onset of HCC as treatment not simulated after development of HCC since effect on mortality is minimal)	[478, 492]
$\delta^k(t)$	Diagnosis rates	No outreach screening: $\omega^k \Delta(t)$ With outreach screening: $\Delta(t)$	See below
ω^k	Relative probability of diagnosis by stage k, without outreach screening	$\omega^0 = 0.01/4$ $\omega^1 = 0.01/4$ $\omega^2 = 0.01/4$ $\omega^3 = 0.01/4$ $\omega^4 = 0.1$ $\omega^{DC} = 0.4$ $\omega^{HCC} = 0.4$	Assume majority of people come for diagnosis at the end stages of disease
$\Delta(t)$ - no outreach screening	Overall rate of diagnosis without outreach screening	Chosen such that proportion diagnosed linearly scales (from 1990) to 2015 proportion diagnosed	[28, 59, 229, 392–395]
$\Delta(t)$ - with outreach screening	Rate of diagnosis with outreach screening	Chosen such that a proportion $p_{diag.}^{max.}$ are diagnosed five years after intervention start	Programmatic aim
$p_{diag.}^{max.}$	Maximum proportion diagnosed in outreach screening strategies	Intervention IV - outreach screening: 90% Sensitivity analysis: 20-95%	Programmatic aim. Lower bound in sensitivity analysis is the approximate current global proportion diagnosed [28]
$\tau(t)$ - no outreach screening	Historical treatment rate and treatment rate in scenarios with no increase in treatment coverage	Chosen such that the annual proportion treated (of those then diagnosed) matches 2015 values or WHO regional estimates	[28, 392–395]
$\tau(t)$ - with outreach screening	Treatment rate in scenarios with outreach screening	$t <$ 2016: as defined above. $t \geq$ 2016: Chosen such that 90% of those diagnosed are treated plus 10% of those previously diagnosed but untreated	Programmatic aim
$\tau^{DC}(t)$, $\tau^{HCC}(t)$	Treatment rate in DC and HCC	DC: no treatment under PEG-IFN as contraindicated. Under DAAs, treatment rates as for $\tau(t)$, see above. HCC: impact of SVR on patients with HCC under any treatment is contested so zero treatment in this group	[477, 478]

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Table 3.2 – *Continued from previous page*

Parameter	Description	Value(s) or relation to other parameters	Justification and references
$\Omega^{intervention}_{GP\ risk\ red.}$	Reduction in GP risk in blood and infection control intervention	80%	Programmatic aim; see intervention strategies defined above for discussion
$\Omega_{PWID\ harm\ red.}$	Reduction in PWID risk in those covered by combination OST plus NSP	75%	[266]
$\kappa^{historical}_{PWID\ harm\ red.}$	Coverage of historical harm reduction interventions	Transmission risk reduced in presence of $>$ 200 needles & syringes per PWID per year plus OST; percentage coverage defined as coverage of OST provided NSP condition met	NSP values from [466]; OST coverage calculated from data in [466], [503] and [526]
$\kappa^{intervention}_{PWID\ harm\ red.}$	Coverage of NSP + OST combination in PWID harm reduction intervention	40%	WHO target, see [267]

Ranges indicate the quantity is varied in calibration or sensitivity analysis using a uniform prior distribution; single values indicated the quantity is fixed, except where an explicit prior distribution is specified. In many cases extracting values from sources required direct estimation of survival probability from Kaplan-Meier survival curves, for which WebPlotDigitizer (a graph-reading web application) was used.

Table 3.3 - List of calibrated parameters with prior distributions.

Parameter	Description	Prior distribution	Values and details
π^{PWID}	Proportion PWID	Uniform	Values drawn from country-specific low-high values or region-specific low-high values see [256]
σ_l	Standardised mortality ratio among PWID	Uniform	5-16 [420, 421]

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Table 3.3 – *Continued from previous page*

Parameter	Description	Prior distribution	Values and details
ξ_{1930}^{GP}	Values of spline knots by risk group l, at time t or age i	Exponential	Rate = 1.00
ξ_{1950}^{GP}		Exponential	Rate = 0.05
ξ_{1970}^{GP}		Exponential	Rate = 0.05
ξ_{1990}^{GP}		Exponential	Rate = 0.05
ξ_{2005}^{GP}		$q^{country}\xi_{1990}^{GP}$	NA: $q^{country}$ distribution given below
ξ_{1950}^{PWID}		Exponential	Rate = 1.00 Rate = 0.05
ξ_{1980}^{PWID}		Exponential	0-1
ξ_{33}^{GP}		Uniform	0-1
ξ_{66}^{GP}		Uniform	0-1
ξ_{100}^{GP}		Uniform	
$q^{country}$	Reduction in GP risk after 1990, by country, quantified using average country healthcare spending from 1995	Exponential	Healthcare quartile 1: rate = 50 Otherwise: rate=5
$\alpha^{fibr.}$	Scalar controlling rate of fibrosis progression	Uniform	0-1 (0 gives lower value of all fibrosis progression probabilities; 1 gives upper values [121])
$f^{3\rightarrow HCC}$	Annual transition probability: F3 to HCC	Uniform	0-0.02 [521]
$f^{4\rightarrow HCC}$	Annual transition probability: F4 to HCC	Uniform	0.01-0.09 [122, 522]
$f^{DC\rightarrow HCC}$	Annual transition probability: DC to HCC	Uniform	0.03-0.10 [432]
$f^{4\rightarrow DC}$	Annual transition probability: F4 to DC	Uniform	0.02-0.06 [122]
$f^{4\rightarrow\mu}$	Annual probability of mortality from F4	Uniform	0.02-0.04 [93]
$f^{DC\rightarrow\mu} - 1^{\text{st}}year$	Annual probability of mortality from DC	Uniform	0.07-0.25 [122]
$f^{DC\rightarrow\mu} - lateryear$		Uniform	0.07-0.18 [122]
$f^{HCC\rightarrow\mu} - 1^{\text{st}}year$	Annual probability of mortality from HCC	Uniform	0.53-0.75 [523, 524]
$f^{HCC\rightarrow\mu} - lateryear$		Uniform	0.09-0.38 [523, 524]

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Table 3.3 – *Continued from previous page*

Parameter	Description	Prior distribution	Values and details
$h_{age}^{fibr.}$, $h_{age}^{j\rightarrow HCC}$, $h_{age}^{4\rightarrow DC}$, $h_{age}^{cirr.\rightarrow\mu}$, $h_{age}^{HCC\rightarrow\mu}$	Proportional difference 70- to 20-year-old disease progression rates	Uniform	1-10 [449]
$h_{sex}^{fibr.}$, $h_{sex}^{j\rightarrow HCC}$, $h_{sex}^{4\rightarrow DC}$, $h_{sex}^{cirr.\rightarrow\mu}$, $h_{sex}^{HCC\rightarrow\mu}$	Proportional difference male to female disease progression rates	Uniform	1-2 [449]

For full details of ranges and justifications see text above.

3.8.2 Model equations

The deterministic model partial differential equations are given below. The following shorthand notations are used: i, j, l, g, d indices dropped from state vectors for ease of reading, so A stands for A_{ijlgd} and so forth; $\sum_{k'\rightarrow k}\lambda_{ij}^{k'\rightarrow k}$ implies a sum over all the disease stages k' that can move into stage k; $\sum_{k\rightarrow k''}\lambda_{ij}^{k\rightarrow k''}$ is a sum over all disease stages k'' that can be moved into from stage k (figure 3.2 shows all possible connections between the disease stages of a particular model compartment); μ_{ijd}^{k} refers to the excess mortality at disease stage k – this is zero for the majority of compartments for which there is no excess mortality due to HCV infection; the rate of change of a compartment with respect to duration, $\partial U^k/\partial d$ and so on, is zero for all disease stages except $k = \text{DC/HCC}$ since only in these stages is duration of the condition monitored; $\delta_{k,0} = 0$ for $k \neq 0$ and $\delta_{k,0} = 1$ for k =0.

$$
\begin{aligned}
\frac{\partial S}{\partial t} + \frac{\partial S}{\partial a} &= (1 - p_{inf.})\, b(t) + \sum_{g} \lambda_i^{clear} A - \left(\Lambda_{il}(t) + \mu_{ijl}^{nat.}(t) - \nu(t)\right) S \\
\frac{\partial A}{\partial t} + \frac{\partial A}{\partial a} &= p_{inf.} b(t) + \Lambda_{il}(t) S - \left(\lambda_i^{clear} + \lambda_i^{chronic} + \mu_{ijl}^{nat.}(t) - \nu(t)\right) A \\
\frac{\partial A^k}{\partial t} + \frac{\partial A^k}{\partial a} + \frac{\partial A^k}{\partial d} &= \theta_{reinf.}\Lambda_{il}(t) C^k + \sum_{k'\rightarrow k} \lambda_{ij}^{k'\rightarrow k} A^{k'} \\
&\quad - \left(\lambda_i^{clear} + \lambda_i^{chronic} + \sum_{k\rightarrow k''} \lambda_{ij}^{k\rightarrow k''} + \mu_{ijd}^{k} + \mu_{ijl}^{nat.}(t) - \nu(t)\right) A^k \\
\frac{\partial U^k}{\partial t} + \frac{\partial U^k}{\partial a} + \frac{\partial U^k}{\partial d} &= \lambda_i^{chronic}(A^k + \delta_{k,0} A) + \sum_{k'\rightarrow k} \lambda_{ij}^{k'\rightarrow k} U^{k'} \\
&\quad - \left(\delta^k(t) + \sum_{k\rightarrow k''} \lambda_{ij}^{k\rightarrow k''} + \mu_{ijd}^{k} + \mu_{ijl}^{nat.}(t) - \nu(t)\right) U^k \\
\frac{\partial D^k}{\partial t} + \frac{\partial D^k}{\partial a} + \frac{\partial D^k}{\partial d} &= \delta^k(t) U^k + \sum_{k'\rightarrow k} \lambda_{ij}^{k'\rightarrow k} D^{k'}
\end{aligned}
$$

$$- \left(\tau^k(t) + \sum_{(} k \to k^{''}) \lambda_{ij}^{k \to k^{''}} + \mu_{ijd}^k + \mu_{ijl}^{nat.}(t) - \nu(t) \right) D^k$$

$$\frac{\partial T^k}{\partial t} + \frac{\partial T^k}{\partial a} + \frac{\partial T^k}{\partial d} = \tau^k(t) D^k + \sum_{k^{'} \to k} \lambda_{ij}^{k^{'} \to k} T^{k^{'}}$$

$$- \left(\phi_g + \sum_{k \to k^{''}} \lambda_{ij}^{k \to k^{''}} + \mu_{ijd}^k + \mu_{ijl}^{nat.}(t) - \nu(t) \right) T^k$$

$$\frac{\partial Q^k}{\partial t} + \frac{\partial Q^k}{\partial a} + \frac{\partial Q^k}{\partial d} = \bar{\zeta}_g^k \phi_g T^k + \sum_{k^{'} \to k} \lambda_{ij}^{k^{'} \to k} Q^{k^{'}}$$

$$- \left(\sum_{k \to k^{''}} \lambda_{ij}^{k \to k^{''}} + \mu_{ijd}^k + \mu_{ijl}^{nat.}(t) - \nu(t) \right) Q^k$$

$$\frac{\partial C^k}{\partial t} + \frac{\partial C^k}{\partial a} + \frac{\partial C^k}{\partial d} = \zeta_g^k \phi_g T^k + \lambda_i^{clear} A^k + \sum_{k^{'} \to k} \rho_{ij}^{k^{'} \to k} C^{k^{'}}$$

$$- \left(\Lambda_{il}(t) + \sum_{k \to k^{''}} \rho_{ij}^{k \to k^{''}} + \alpha^k \mu_{ijd}^k + \mu_{ijl}^{nat.}(t) - \nu(t) \right) C^k$$

CHAPTER 4

Is Global Elimination Possible?

Chapter 4 contains the global analysis results. It starts with brief summaries of the introduction and methods detailed in full in chapters 2 and 3. Following this, calibration results are shown demonstrating model fit along with future projections in the absence of intervention scale up. The impact of all four interventions are described. The prospects for meeting elimination are investigated with respect to all four strategies. A variety of sensitivity analyses are performed to investigate the dependence of projections on key assumptions and programme parameters and these are used to obtain further insight into the model outputs. These results are then used to draw a range of conclusions regarding the policy implications of the work before comparisons to other work are made and limitations of the current analysis, and efforts to mitigate these, are delineated.

4.1 Introduction

4.1.1 Background

Globally it is estimated that 71.1 million individuals are chronically infected with HCV [28] of whom 10-20% will develop liver complications including decompensated cirrhosis and HCC [105, 121]. These complications were responsible for over 475,000 deaths in 2015 and, in contrast to the malaria, TB and HIV epidemics, the number of deaths from viral hepatitis infection has risen in recent years, a trend which is predicted to continue [6, 28]. HCV transmission is most commonly associated with blood transfusions, health-care-related injections and injection drug use [245]. TTIs and infections associated with lapses in injection safety have declined globally [24, 218], although these remain key risk factors in lower-income countries [216]. Infection associated with injection drug use is the primary transmission route in countries where other transmission routes have mostly been eliminated [216, 238]. Treatment for HCV infection used to comprise weekly subcutaneous injections of PEG-IFN+RBV [187] which had low success rates and was associated with a range of side-effects [474, 527]. A watershed moment came in 2014 with the development of

highly efficacious DAAs [29, 30]: these allow for interferon free treatment, greatly improved cure rates, better side effect profiles and shorter duration of therapy more amenable to widespread use [32, 33].

4.1.2 Motivation and aims

Advances in HCV therapeutics have led to a commitment from all 194 member states of WHO to eliminate viral hepatitis as a public health threat [27, 28]. WHO elimination targets are defined as a 65% reduction in mortality and an 80% reduction in incidence by 2030 from a 2015 baseline [27]. This is to be achieved through a combination of: preventing infection by improving blood and injection safety; extending harm reduction services aimed at reducing transmission among PWID; and expanding testing and DAA treatment for those already infected [28].

Although these targets were formulated by WHO in a consultation process [27], the feasibility of actually achieving WHO targets globally has not been demonstrated. Given the current focus on these targets it is imperative to develop a better understanding of the full effect of HCV interventions at the global scale. This work sought, therefore, to use mathematical modelling to provide the first estimates of the impact of combined prevention, diagnosis and treatment programmes on the global HCV epidemic and to determine the achievability of WHO elimination targets. This is the first overarching research aim as described in §1.1.

4.2 Methods

4.2.1 Summary of model

A deterministic mathematical model was constructed to make projections of the HCV epidemic, country by country, and to analyse the impact of a set of intervention packages at the global scale by combining individual country results. To simulate the full course of the hepatitis C epidemic in a given country, a mathematical model was constructed to incorporate: population dynamics (birth, natural death and migration); age and sex stratification; dynamic infection, by genotype, with HCV; increased risk of infection among PWID; disease progression leading to cirrhosis; increased HCV specific mortality due to complications following onset of cirrhosis; historical rates of diagnostic screening; historical rates of treatment; treatment success and treatment failure; reduced rates of disease progression and mortality following treatment success; and possible reinfection following cure.

The model is calibrated to HCV viraemic prevalence in the overall population, HCV viraemic prevalence among PWID and HCV-attributable mortality estimates. Historical and future demographic information, HCV genotype distributions, PWID data and past coverage of harm reduction and HCV interventions are used as model inputs. Uncertainty is accounted for in a statistical framework allowing disease burden projections to be made by sampling from calibrated para-

meter posterior distributions. Sensitivity analyses are carried out to assess the impact of varying programme parameters in intervention and to investigate changes in modelling assumptions.

4.2.2 Summary of interventions simulated

Four interventions are simulated along with a status quo scenario and an intervention in which no DAAs are incorporated. Each intervention builds in the features of the previous scenarios; the unique element brought in by each intervention is given in table 4.1 which gives a simplified overview of each scenario. For a full summary of the elements of each strategy see table 3.1.

Table 4.1 - Simplified overview of intervention strategies.

	Treatment	**Risk of infection in non-PWID population**	**Risk of infection in PWID population**	**Treatment coverage**	**Diagnosis coverage**
No DAA scenario	PEG-IFN+RBV	As per 2015 risk	As per 2015 risk	Treatment rate fixed at 2015/2016 value‡	Diagnosis rate fixed at 2015/2016 value
Status quo	DAAs from 2016				
(I) + Blood safety &infection control		80% reduction by 2020			
(II) + PWID harm reduction			75% reduction at 40% coverage by 2020		
(III) + Offer DAAs at diagnosis				DAAs in all countries. Treatment offered within one year of diagnosis	
(IV) + Outreach screening					90% infected are diagnosed by 2030

Colours correspond to those used in the results. Each successive intervention incorporates the elements of the previous strategy except where stated. For full details see table 3.1.

4.3 Results

The model was fit using a self-monitoring procedure (IMIS described in the previous chapter). The model was calibrated on an individual country basis to the 190 countries that could be included in the model (for countries for which there was insufficient information to calibrate within our framework see §3.7.1). Individual examples of country calibrations are given as these comprise the units of analysis that are fit directly. Global calibration results are derived from these by

summing over all country estimates. These are then compared to our estimates of the summed global mortality as well as to WHO estimates of global incidence and prevalence in 2015.

4.3.1 Calibration

Individual country calibrations. 190 countries were calibrated in the model fitting procedure. There are four levels of information available for calibration. The minimum amount of information available to calibrate a country was a set of IHME mortality estimates. This was combined with a regional lower bound estimate of prevalence (which the model was required to be above, 79.3% of global population[1]) but otherwise the overall and PWID prevalence values were unconstrained (65 countries, 7.4%). At the opposite end of the scale, the most information available was where PWID and overall prevalence values were available along with IHME mortality estimates (71 countries). The two intermediate cases were when overall prevalence values were available but without PWID prevalence estimates (28 countries, 6.8%) or the converse (PWID HCV prevalence estimates without overall, 26 countries, 6.5%). Examples of the minimum and maximum information available are given to illustrate individual country calibrations within the global model analysis and to describe those features present when fitting either to only mortality information or to full prevalence information as well. Country-level results for all countries, showing the impact of the interventions considered below, will be available online in the supplementary appendix to the published version of this work (details given in chapter 6).

The country with the largest population to which only mortality information is fit is Democratic Republic of Congo (81.3 million). The result of not specifying ranges on PWID prevalence is that the model explores all possible values for PWID prevalence, see figure 4.1. Since prevalence in PWID is known to range from very low to very high values (close to 100%) in different countries [256, 502] there is little reason to limit this quantity in any way. Mortality calibrations (figure 4.2) broadly accord with IHME estimates.

The largest country for which both prevalence estimates are available is China (1,410 million). Specifying these values not only results in a narrower range of prevalence estimates as would be expected (figure 4.3), but also a narrower range of mortality values (figure 4.4) than when such values are not included in calibration. Mortality estimates again are similar to IHME estimates but do not exactly match them (figure 4.4). This is reflective of the very different means of generating the estimates and is in keeping with our aim to follow the trends of IHME, while not attempting to match all estimates perfectly, due to the fact that these are themselves modelled values.

Global calibration results. Summing all 190 countries produces the global analysis. The model estimated 69 million (95% credible interval (CrI): 67-71 million) active viraemic infections, matching WHO numbers [28], see figure 4.5. The rise and then plateau on this graph in the number of active viraemic infections mirrors the findings of WHO historical projections of active viraemic infections, however, the findings here suggest a higher historical number of viraemic infections

[1] All statements concerning population size in the following are 2017 estimates from UN Population Prospects [419].

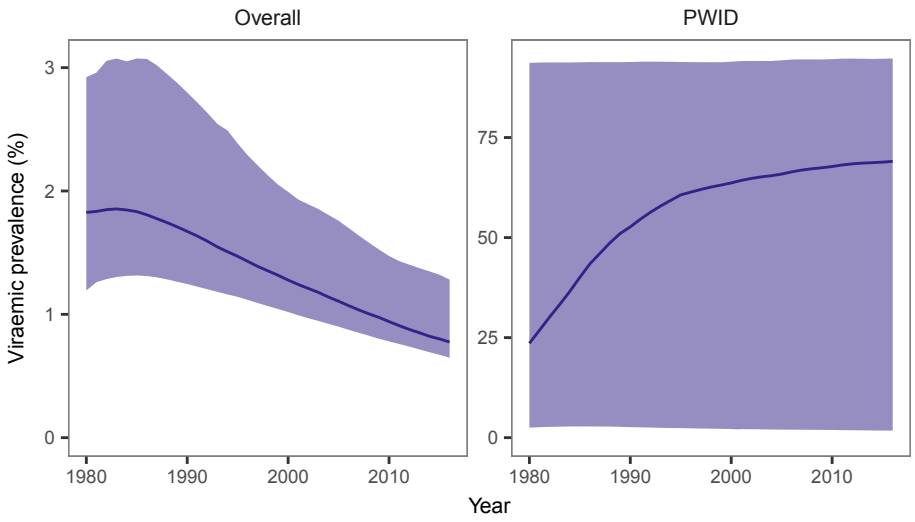


Figure 4.1 - Democratic Republic of Congo prevalence graphs. Shown are status quo historical and future prevalence curves from Democratic Republic of Congo as per the model fits. No data are shown as there were no calibration data for either overall or PWID prevalence in Democratic Republic of Congo.

[280]. This stems from the fact that the model developed here incorporates infections from before 1950 and allows the epidemic to develop prior to this time (as is known to have happened) [460]; previous historical projections used by WHO only seed the epidemic in 1950 thus producing more sharply rising epidemics prior to around 1980. Our results suggest a rising PWID epidemic to 2017, with the number of viraemic infections in active PWID making up about one tenth of the global epidemic in recent years. The overall shape of this curve (right panel, figure 4.5) is driven by the extremely high prevalence estimates observed in recent years in almost all countries in which data exist, combined with the prior assumption that the risk of transmission grows in this epidemic group from a negligible value in 1950 to a constant maximum value in 1980 during the rising years of (in particular) injecting heroin use.

The incidence rate is projected to be 277 infections per one million people (95% CrI: 262-294 per one million people) in 2015, in line with WHO estimates that year [28]. The incidence rate sharply declines in the last three decades in response to reductions in general population risk as a result of improvements in infection control and blood safety. That the epidemic is not dominated by PWID infections historically explains why reductions in general population risk could have reduced the incidence rate overall so considerably (as is shown in figure 4.6). The long plateau of infection risk following this decrease in the 1990s is indicative of the model assumption that only minor further reductions in risk occur as the epidemic progresses. The projected proportion of new infections in PWID in the model is 29% (95% CrI: 27-32%), marginally above WHO estimates in 2015 that 22% of new infections were in PWID [28].

Lastly, the model estimates that there were 512,000 deaths (95% CrI: 497,000-533,000) in 2015, in line with the summed IHME estimates for that year to which (on a country level) the model was

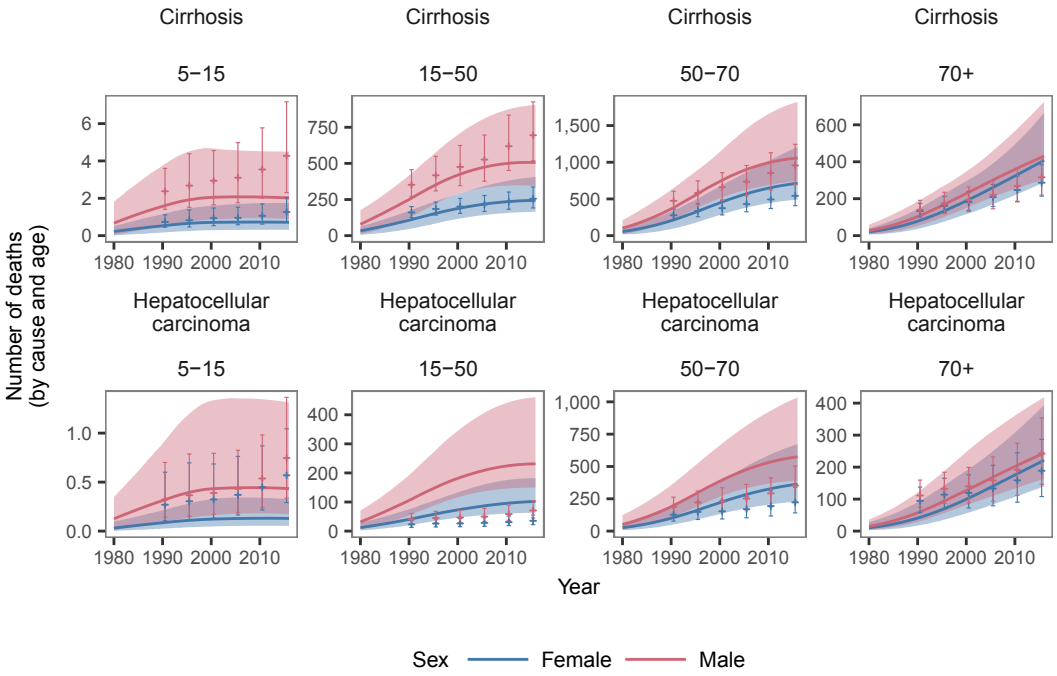


Figure 4.2 - Democratic Republic of Congo mortality calibration graphs. Shown are the mortality curves from the calibration overlaid with the individual country-level age-, sex- and type-specific (HCC or cirrhosis) mortality estimates from IHME.

fit [28]. The overall prevalence calibrations and mortality calibrations are illustrated in figure 4.7 showing good fit with WHO estimates. However, the figure suggests an underestimate of mortality in the early years of IHME estimates. It should be noted that on a country-by-country basis the relationship between mortality estimates in our model and IHME over time is much more complicated than suggested by the summed graph of mortality in figure 4.7B. In other words the model is calibrated to numerous age-, sex-, type- and country-specific points (see figures 4.2 and 4.4 above) so the lower historical number of mortality estimates on the global scale actually emerges from a complex array of effects pertaining to the age-distribution of infections over time and so on. This means that 'solving' the shortfall could not be simply done by a basic adjustment of parameters since this would alter the balance of the fits and reduce the quality of calibrations in some other way (if it could be achieved without such an outcome the calibration procedure would have already produced such a result). Moreover, a key requirement here is to be able to investigate global mortality elimination targets; these are based off of the most recent (2015) estimates of mortality. Close calibration to these values, therefore, is critical so that future model projections start from the same baseline as those used by WHO in formulating their targets. The fits in figure 4.7B fulfil this requirement.

Treatment cascade numbers are met correctly in the model: 1.7 million DAA treatments in 2016, over 5 million cumulative PEG-IFN+RBV treatments prior to this, 20% diagnosed by 2016 and

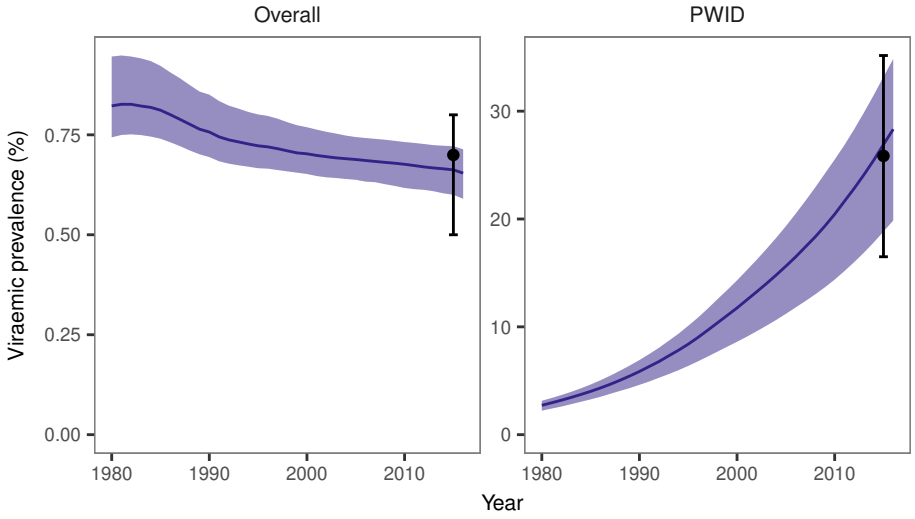


Figure 4.3 - China prevalence graphs. Shown are status quo historical and future prevalence curves from China as per the model fits. Points with error bars are the prevalence estimates to which the model was fit.

historical harm reduction coverages met (as discussed in chapter 3). Accordingly, the calibrated model produced epidemics concordant with the WHO starting point for defining elimination targets. It was deemed appropriate, therefore, to use this set of 190 calibrated countries to begin an investigation of the future course of the global HCV epidemic and of the impact of HCV interventions at the global scale.

4.3.2 Projections without intervention scale up

Figure 4.8 shows the projections of mortality, incidence and number of viraemic infections for all four interventions as well as the no intervention projections encompassing the no DAA and the status quo scenarios.

No DAA projection. Not implementing DAAs at all results in worse outcomes: even in the short term by 2030 there are 5% more infections per year than in the status quo scenario. This reflects a treatment-as-prevention effect whereby treating and curing individuals results in fewer infectious individuals which in turn results in fewer new infections. As would be expected in this scenario, not introducing the higher quality DAA treatments results in more deaths: the annual number of additional deaths is 10% higher by 2030 compared to status quo, while the cumulative number of deaths averted due to the introduction of DAAs over just the period to 2020 is 79,000 (95% CrI: 73,000-87,000). These trends are compounded in the future with rising annual mortality and incidence rates over and above what is projected in the status quo scenario.

If DAA treatment roll-out occurs heterogeneously, for example, this scenario is instructive in demonstrating how countries that are left behind could experience considerable burden of disease decades into the future. This can be illustrated by calculating the percentage increase in mortality

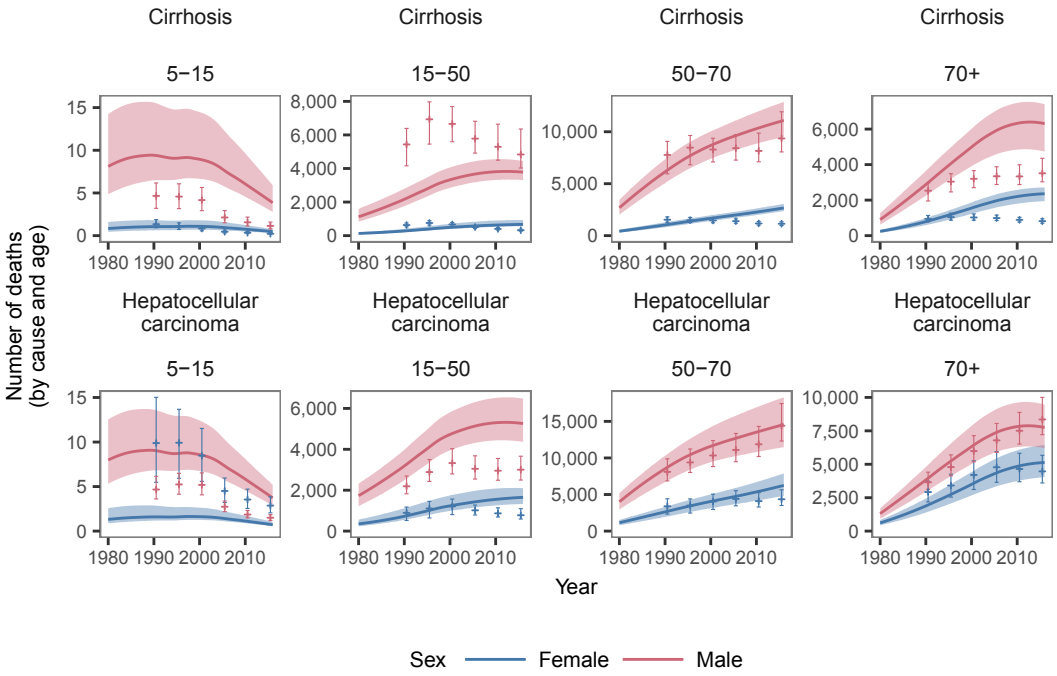


Figure 4.4 - China mortality calibration graphs. Shown are the mortality curves from the calibration overlaid with the individual country-level age-, sex- and type-specific (HCC or cirrhosis) mortality estimates from IHME.

in countries that have already implemented DAAs were they not to have done so. In Australia, for example, which had a huge roll-out of DAAs in 2016, mortality would be 476% higher by 2050 without their introduction (assuming PEG-IFN+RBV is retained as the standard HCV therapy). Even in China, which saw a modest roll-out of DAA use in 2016 relative to the size of its epidemic, there would have been 27% more deaths in 2050 compared to the status quo scenario in which the rate of DAA treatment is maintained at the 2016 value.

Status quo projection. Projecting the epidemic forward in the status quo scenario we find that the number of active infections will slowly decrease to 58 million active infections by 2050 but could rise by the end of the century. Likewise, incidence would gradually decrease to 198 infections per one million people by 2060 but may increase thereafter. Mortality from HCV decreases in the short term but can increase from that time on in line with the possible increasing numbers of active infections (figure 4.8). These results reflect our assumptions in this 'status quo' scenario that risk of infection does not decrease in any group after 2015 and that the proportion of PWID within the population will not change.

Considering the status quo just up to 2050 (before the potential worsening of the epidemic is projected to occur, see the rising numbers of deaths and active infections in figure 4.8) demonstrates the still sizeable burden of disease with no improvement in intervention coverage: there would be 9.3 million HCV-related cirrhosis deaths, 5.8 million HCC deaths attributable to HCV and 67

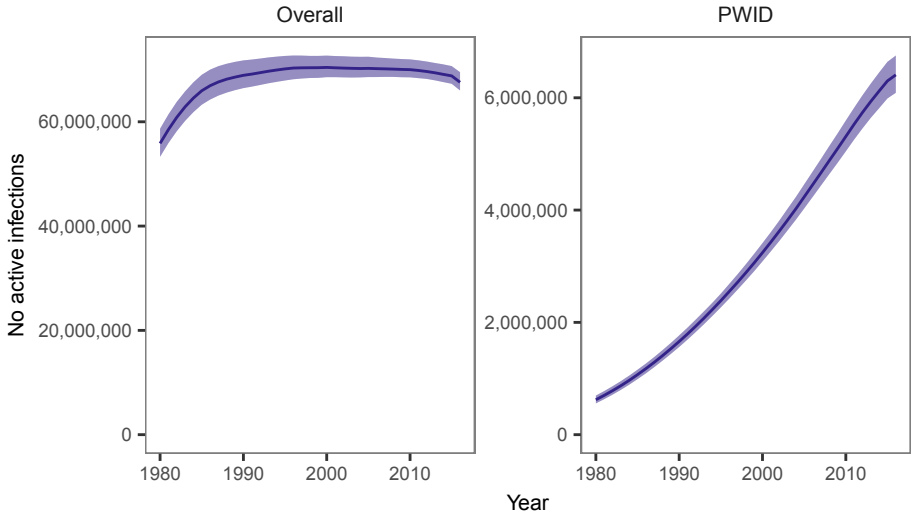


Figure 4.5 - Global historical estimates of number of active infections. Left is shown overall number of active infections and right shows only active infections among PWID.

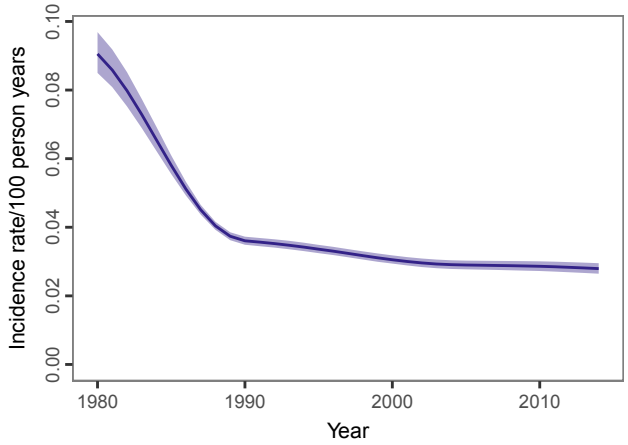


Figure 4.6 - Global historical estimates of viraemic incidence rate. Incidence rate is calculated as the number of viraemic infections divided by the size of the susceptible (never infected and cured) populations.

million new infections over this period. This burden is distributed highly unevenly: while only eight countries experience 50% of global HCV-attributable mortality to 2030, a mere four countries (China, Pakistan, India and Egypt)[2] are the site of 43% of global incident infections by the same year.

In these four countries the proportion of infections among PWID is below the global average of 29%, showing that the impact of the HCV epidemic is not concentrated in this high-risk group. In other countries, however, the epidemic is highly concentrated in PWID. Figure 4.9 shows the estimated proportion of infections to 2030 that occur among PWID as a fraction of overall HCV in-

[2]The other four are: Russia, USA, Japan and Indonesia.

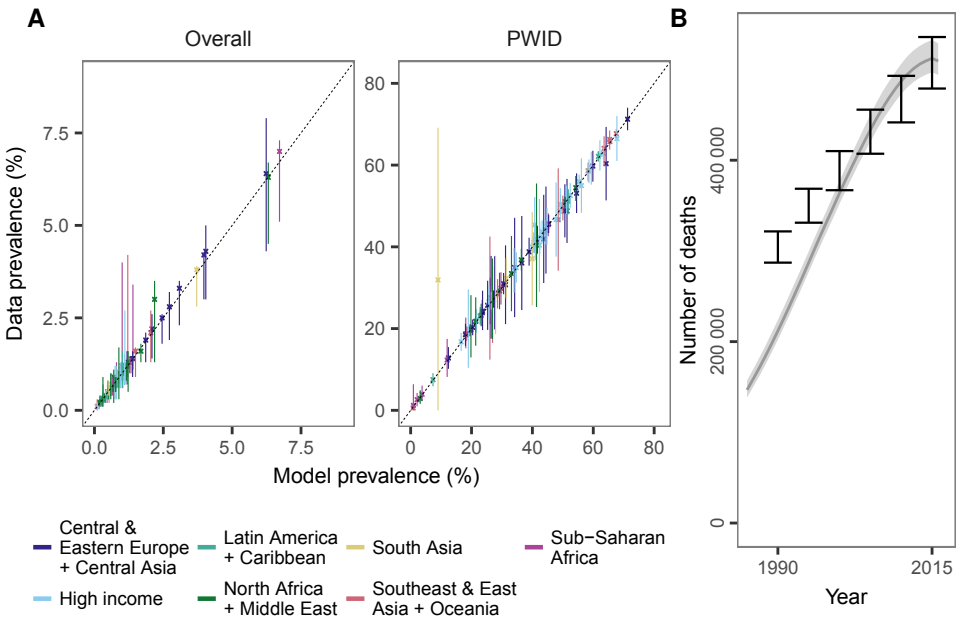


Figure 4.7 - Results of global calibration. (A) Comparison of the model's simulated prevalence of HCV with prevalence data for all 190 countries simulated [392–395], colour-coded by IHME super region (for full list of regions see appendix B). Crosses and vertical lines indicate data and associated uncertainty intervals; the horizontal location of the data value indicates the analogous modelled estimate. The diagonal (x=y) line is where the data value will lie if the data and simulated prevalence values are equal. (B) Comparison of modelled HCV mortality numbers with IHME HCV mortality estimates [6, 9]. Countries were calibrated to age- and sex-stratified mortality estimates; modelled outputs were summed into overall cirrhosis and HCC mortality numbers and compared to aggregated IHME estimates.

fections. When interpreting this graph, it should be noted that a number of the countries in certain regions countries have extremely wide confidence intervals (see, for example, countries within the Caribbean or the four Sub-Saharan African regions). This simply indicates a lack of data for the PWID epidemic; PWID can comprise a greater or lesser share of the epidemic in models generated in calibration. In such regions little can be said regarding who is most impacted by the epidemic, reflecting the overall lack of information. By contrast, several regions are marked by extremely high proportions of infections among PWID, indicative of areas in which countries have otherwise all but eliminated transmission in the non-PWID population, see in particular Western Europe, High-Income North America, Australasia and High-Income Asia Pacific. The concentration of the HCV epidemic is well known and this demonstrates starkly how, in a status quo scenario, the future epidemic (determined as it is by new infections in the coming years) will have a highly disproportionate impact upon a small group of vulnerable individuals with often unmet public health needs [528].

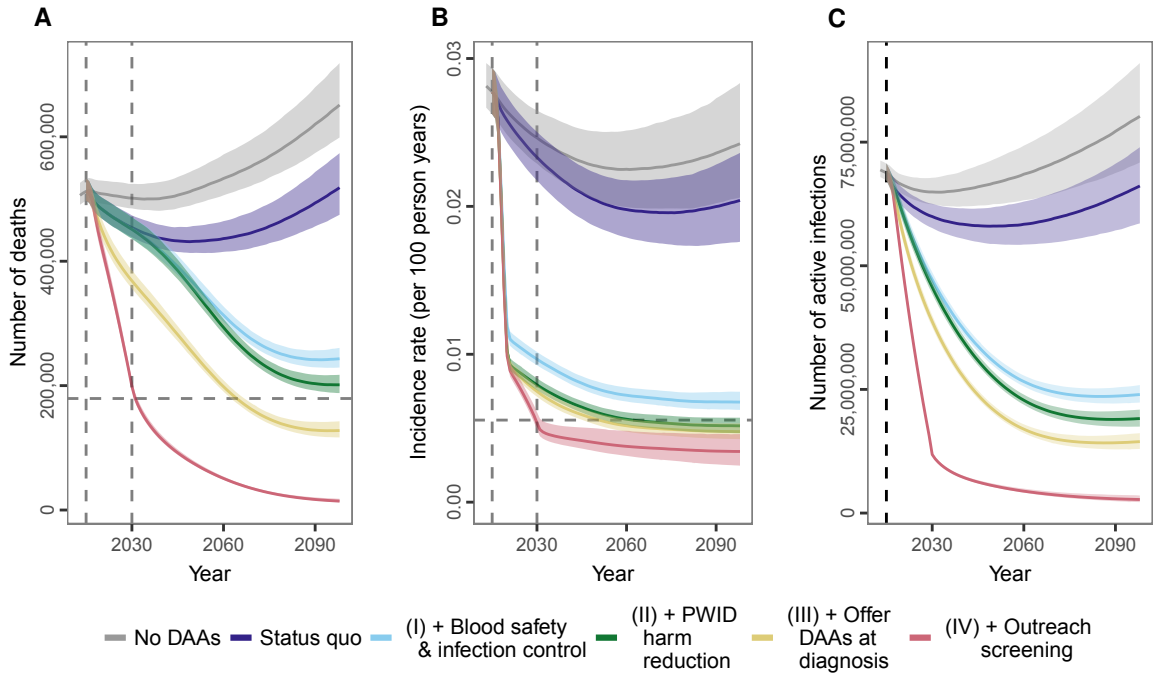


Figure 4.8 - Future projections in the intervention strategies simulated. (A) shows mortality, (B) incidence rate per 100 person years and (C) shows number of active (or viraemic) infections.

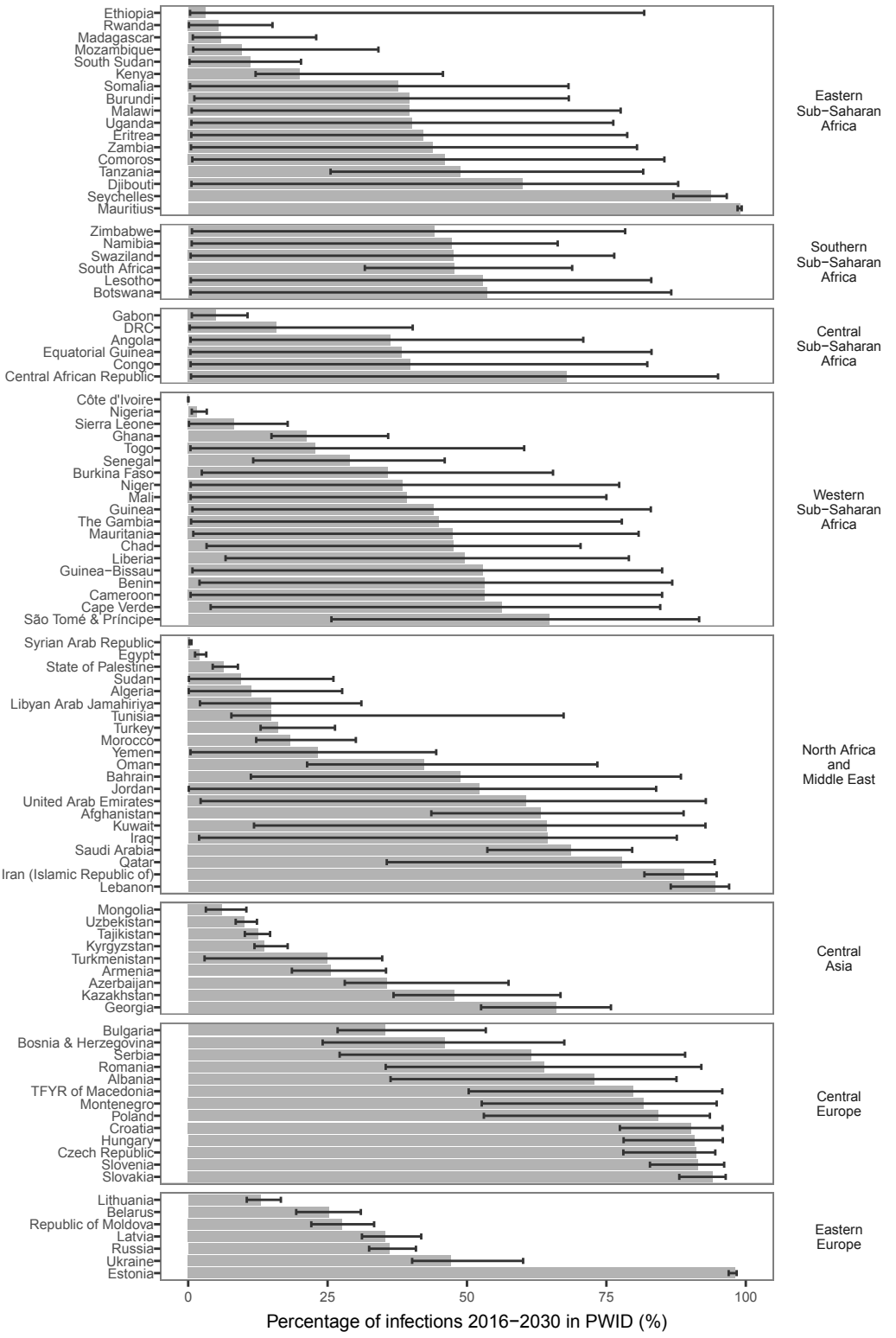


Figure 4.9 - Proportion of infections in PWID. Continued on next page.

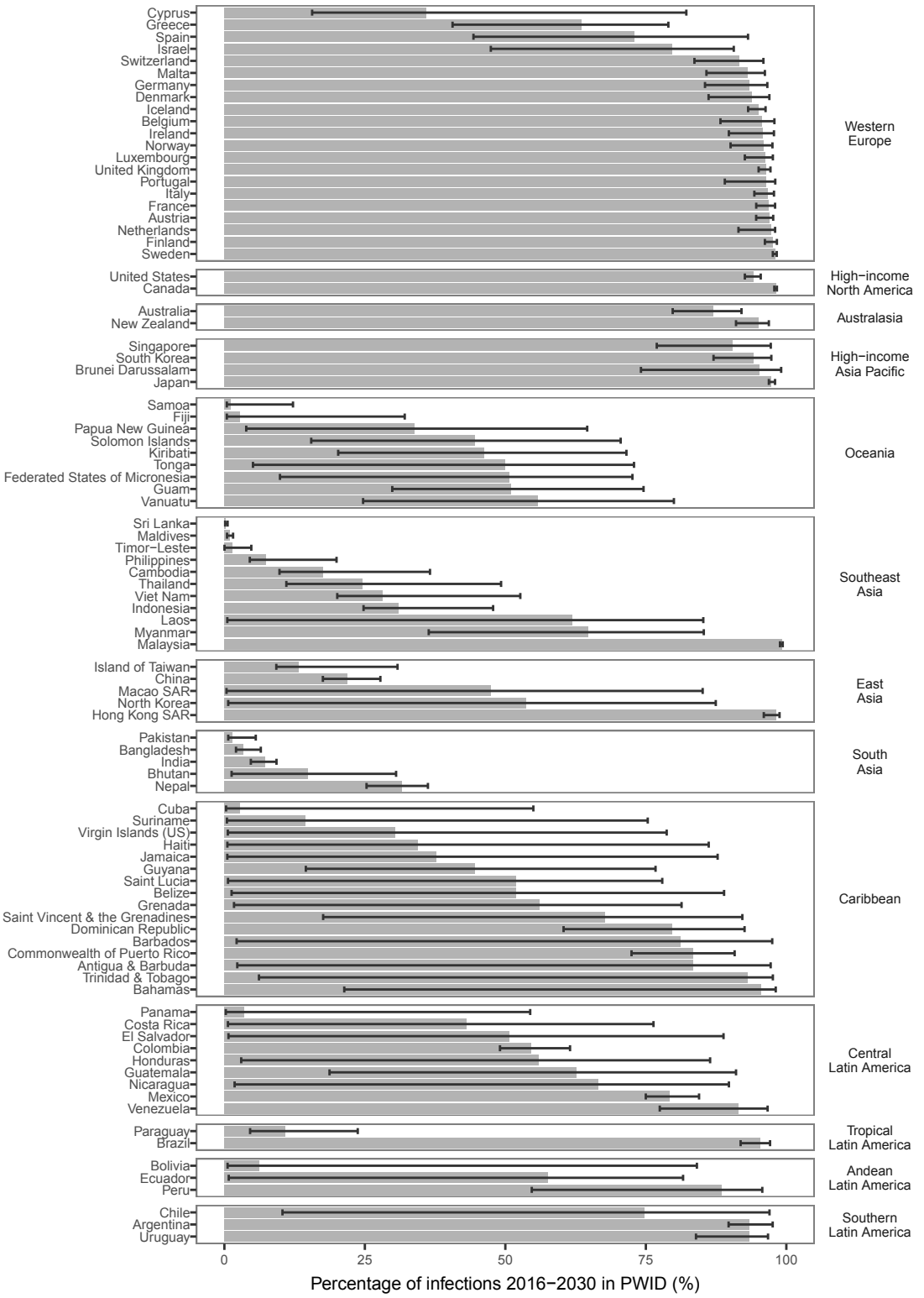


Figure 4.9 - Proportion of infections in PWID. Continued from previous page. Bars represent the median proportion of new infections in PWID (2016-2030) in the status quo, relative to the overall number of new infections. Error bars are 95% credible intervals. Country-level differences can be explained by reference to the proportion PWID and HCV prevalence values; lack of prevalence estimates in PWID produce uncertainty intervals that span a wide interval.

In short, the burden of disease measured in terms of active infections, mortality and new infections will be maintained at unacceptably high levels in the status quo scenario. The uneven distribution of burden by country and within country highlights the need not only for scale up of interventions but for implementation of a country-appropriate strategy that takes into account the specific nature of the epidemic in a given location. That the assumptions undergirding this scenario are conservative (leading to projections that get worse after 2050) should not detract from the overall message that intervention scale up is required to avert a huge number of infections and deaths in the future; if there are only modest future improvements in indicators that are held constant in this analysis (such as general population risk of infection) this would slightly ameliorate the above epidemic projections but would not bring the world close to elimination (figure 4.8). This is demonstrated in the following sections by quantifying the magnitude of intervention scale up required to make progress toward meeting global elimination targets.

4.3.3 Impact of intervention scale up

Figure 4.8 above shows estimated mortality, incidence rates and number of active infections to 2100 in the four interventions discussed here. The programmes are simulated in a stacked manner meaning each one incorporates the features of the previous. As such each intervention improves upon the previous one as can be seen in the figure. Figure 4.10 shows the annual number of DAA treatments in each scenario.

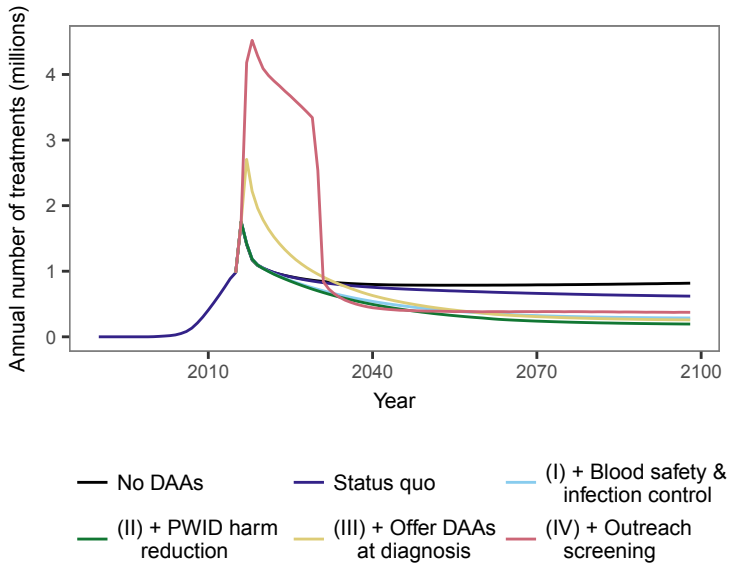


Figure 4.10 - Annual number of treatments by intervention scenario.

Intervention I: + blood safety and infection control. Programmes aimed at curbing the spread of blood-borne infections among the non-PWID population (intervention I) can dramatically reduce incidence. Global improvements in blood safety and infection control (lowering the general population risk of HCV infection by 80%) reduce the annual number of new infections in 2030 by 58%

(95% CrI: 56-60%) compared to the status quo scenario in the same year. This reduction leads to a 21% decrease in the overall number of active infections by 2030 and a 47% decrease by 2050. Over the same time period there is a negligible reduction in the number of PWID infections (less than 1% change in either 2030 or 2050) as would be expected for a general population risk reduction intervention. Fewer new infections ultimately leads to fewer treatment courses, though the delay in treatment due to the bias towards late-stage presentation means that averted infections do not exactly equal averted treatment courses: in 2030 there is a 13% reduction in the number of treatment courses offered compared to the status quo projection while in 2050 there is a 40% reduction in treatment courses in intervention I.

Intervention II: + PWID harm reduction. In concert with these improvements in blood and infection safety, extending OST plus NSP harm reduction services to 40% of the opioid-dependent PWID population (intervention II) could reduce the number of new infections in 2030 by a further seven percentage points. The combination of general population risk reduction and PWID harm reduction interventions could avert 14.1 million cumulative infections (95% CrI: 13.0-15.2 million) by 2030 and implementing this pair of prevention interventions could avert 42.3 million infections (95% CrI: 38.2 – 46.3 million) by 2050, or 71% of the cumulative infections projected in the status quo to that year. These changes result in 17% fewer active infections in PWID by 2030 and 24% fewer by 2050.

Due to the long incubation period of HCV infection, however, such reductions in incidence will not immediately translate into reductions in mortality: by 2030 the decrease in mortality will be only marginal in either scenario (see figure 4.8A), while the combination of both interventions will only reduce mortality in 2050 by 18% (95% CrI: 17-19%), demonstrating that long term gains can accrue to these interventions in the form of deaths averted but they will not play a major role in reducing mortality burden in the 2030 elimination-target timeframe. The number of treatment courses delivered in this intervention decreases slightly (by a further nine percentage points by 2050 compared to intervention I); this intervention has less impact upon overall numbers of active interventions than general population risk reduction (since PWID comprise a minority of the epidemic) and so it would be anticipated that adding PWID harm reduction interventions would have a smaller impact on numbers in the treatment cascade than the previous intervention which affected the majority of the HCV-positive population and this effect is borne out in the results.

Intervention III: + offer DAAs at diagnosis. Expanding access to DAAs, in addition to implementing the prevention interventions of interventions I and II, is projected to cut future mortality much more substantially than those interventions alone. Replacing PEG-IFN+RBV with DAAs in every country where they have not been rolled out, and offering these at time of diagnosis to all, has a large short-term impact: there is an estimated 19% drop in annual mortality in 2030 and a 42% decrease in 2050. There is, however, only a small impact on incidence (figure 4.8B) beyond that already accounted for in intervention II, with this intervention averting only an additional 230,000 infections by 2030 (or less than 2% of the total infections averted compared to status quo in the scenario as a whole). Nevertheless, due to curing far more individuals in this intervention

there is a large reduction in the overall size of the epidemic (figure 4.8C): the number with active HCV infection is reduced to 38.7 million (95% CrI: 37.6-40.0 million) in 2030 and 20.9 million (95% CrI: 20.2-21.8 million) by 2050 (or 15% and 24% fewer active infections respectively than in the intervention II scenario).

The scenario simulated here sharply increases the number of treatment courses in the short term: in 2018, for example, the number of treatments nearly doubles to 2.2 million from 1.2 million in the status quo scenario. Yet the number of treatment courses delivered over the following decades reveals that the difference in cumulative number of DAA treatment courses between status quo and intervention III actually decreases. In 2050, at which time intervention III has reduced the size of the epidemic considerably as discussed above and averted 3.3 million HCV-related deaths (95% CrI: 3.2 – 3.5 million), only 5.0 million additional treatments have been delivered compared to status quo. By 2066 the cumulative difference in total number of treatments delivered is zero and beyond this time status quo involves delivering more DAA courses than intervention III. It should be kept in mind that these reductions in cumulative treatment numbers take place on the background of reductions in the size of the epidemic due to implementing interventions I and II. This cannot, therefore, directly be used as an argument regarding the cost-saving nature of implementing DAAs at current rates of diagnosis because large-scale improvements in blood safety and infection control along with implementation and extension of PWID harm reduction programmes are not free. Nevertheless this result indicates that there is the potential for combination interventions to not only deliver better outcomes (as would be anticipated) but also to offer compounding gains through lower numbers of treatments ultimately required. This may, in turn, improve the economic case for implementing such interventions in the first place.

Analysis of intervention III illustrates that large reductions in the burden of HCV disease can be attained by ensuring access to DAAs without otherwise changing diagnosis or treatment programmes. Such gains may, over the long run, not necessarily involve delivering huge additional numbers of treatments if combined with suitable prevention interventions, while such interventions certainly facilitate a sizeable reduction in mortality in the short-term that would not be feasible with prevention interventions alone. Such gains fall well short of WHO mortality targets, however, and the implementation of broad access to DAAs as per this intervention entails only minimal treatment-as-prevention benefits (in terms of additional infections averted through reducing the size of the infectious population).

Intervention IV: + outreach screening. Adding outreach screening in intervention IV, such that the proportion diagnosed reaches 90% by 2030, greatly reduces both mortality and incidence beyond the reductions already achieved by intervention III. This scenario incorporates all prevention, screening and treatment elements of the previous strategies. With this comprehensive package of interventions there would be a 61% reduction in mortality by 2030 compared to the baseline 2015 value, corresponding to 1.5 million deaths (95% CrI: 1.4 – 1.6 million) prevented. The decrease in mortality from baseline is 85% in 2050, a dramatic increase from the 42% reduction achieved in intervention III.

There is a more marked treatment-as-prevention benefit compared to intervention III (see figure 4.8B): while that intervention reduced the incidence rate in 2030 by 73% (95% CrI: 71-74%), intervention IV leads to an 81% (95% CrI: 78-82%) reduction in incidence rate compared to the baseline 2015 value (this corresponds to a 28% reduction in absolute incidence rate between interventions III and IV, far greater than the 5.6% decrease in incidence rate observed between interventions II and III). This additional incidence reduction stems from the greater treatment-as-prevention benefit arising from massively increasing the coverage of diagnosis and treatment by 2030: fewer infectious individuals leads to fewer new infections. Compared to prevention interventions alone (intervention II), the extra treatment courses delivered in intervention IV (the comprehensive package of interventions) averts 950,000 additional infections by 2030 meaning that, in total, there are 15.1 million new infections (95% CrI: 13.8 – 16.1 million) averted in the comprehensive intervention package. Treatment interventions can be seen to play a small but not insignificant role in reducing the burden of disease due to new infections.

Averting infections and, primarily, curing individuals results in a sharp decline in the number of active infections by the year 2030. Whereas with no intervention in the status quo there were a projected 60.0 million active infections (95% CrI: 57.6 – 62.5 million), while after implementation of both general population and PWID prevention interventions in intervention II there were 45.7 million (95% CrI: 44.3-47.2 million), upon implementation of the comprehensive package of interventions (intervention IV) there are only 11.8 million (95% CrI: 11.5-12.2 million) active infections (an 80% reduction from status quo). Considered in terms of prevalence of viraemic infection, the comprehensive package of interventions entails a reduction from 0.70% in 2030 in the status quo scenario, to 0.53% due to implementation of prevention elements of the strategy (as per intervention II), to 0.14% with all elements of the strategy (intervention IV). As commented on above, implementation of intervention IV would mean fewer future infections and a large reduction in mortality. Though the model did not explicitly quantify this, such a reduction in the number of active infections would also lead to an improvement in quality of life for millions, not only through averting debilitating ESLD symptoms but also through reducing the number who have a reduced quality of life at earlier stages of the disease either as a result of additional symptoms [529] or even solely as a result of knowing their HCV status [530].

Achieving such an impact requires a massive outreach screening program and demands a rapid increase in new treatment courses in the short term (see figure 4.10): 51.8 million courses of DAA treatment (95% CrI: 50.5-53.3 million) by 2030. The specification of the model produces a very sharp increase in number of treatments as can be seen on figure 4.10 that should be explained. Considering first intervention III, all those being diagnosed are offered treatment in addition to those who would otherwise have been treated (at the past rate of treatment which is assumed to depend on treatment seeking behaviour). The additional number of treatments offered in this scenario rapidly depletes the pool of already diagnosed individuals and, accordingly, the annual number of treatments eventually reaches a new, lower equilibrium than in status quo, corresponding to approximately the number newly diagnosed per year (less those who do not accept treatment

and plus those who present for treatment in the latter stages of disease). In intervention IV the surge in numbers treated is partly a result of this effect (as intervention IV builds in the features of intervention III) but also is due to the feature that the outreach screening campaign facilitates 10% of those who have been diagnosed in the past to return to care and receive treatment. As the pool of diagnosed and untreated individuals is greatest in 2017 (when the interventions begin) this corresponds to a significant 'warehousing' effect whereby there is a large pool of individuals immediately available to be treated. The plausibility of this feature of the model is discussed in more detail in the discussion.

In contrast to the large outlay of treatments to 2030, the number of treatments required in the subsequent 20 years is a much more modest 12.0 million courses. Comparing this to status quo shows that while by 2030 there are an extra 37.0 million DAA treatment courses delivered cumulatively, by 2060 this number drops below 30 million and continues to decline suggesting compounding benefits whereby treatment courses are averted in the future. Unlike in the case of intervention III, however, there is never a point at which the cumulative number of treatments in the comprehensive package of interventions 'breaks even' with the number in status quo. This is simply because the magnitude of the undiagnosed epidemic is such that the required treatments to tackle it outweigh gains potentially seen over the following 75 years when considered purely in terms of numbers of treatments. Nevertheless, the huge impact on mortality and incidence, as well as the modest treatment requirements reached in the long run (after 2030), indicates that rapid testing and treatment scale up is a means to controlling the epidemic rather than merely dealing with its consequences. This is clear from the way in which only this intervention package brings WHO-defined elimination within reach as will be discussed below.

Variation in impact between countries. Before discussing global elimination, the impact of interventions at the country level are examined. The different strategies simulated do not have a uniform impact across the globe. Figures 4.11 and 4.12 show the country-by-country reductions in incidence and mortality in 2030 for the four interventions as compared to a counterfactual of the status quo scenario in the same year[3].

The impact of prevention interventions on incidence is dependent on local epidemiology. Upon reduction of general population risk such that risk of HCV transmission is reduced by 80% (intervention I) incidence is greatly reduced in countries in which this mode of transmission dominates (figure 4.11). For example, in 2030 Mongolia, Egypt and Pakistan all experience at least 80% reductions in incidence rates as compared to the counterfactual status quo scenario in that year (comparing to 2015 baseline values shows that these countries all reach WHO incidence elimination targets upon implementation of this intervention alone as well[3]). Other countries with a large

[3]While WHO targets are framed in terms of the 2015 baseline mortality and incidence rate, it is helpful here to compare the interventions to status quo counterfactuals in the same year (2030). This highlights the impact of each intervention compared to a 'do nothing' scenario. If baseline comparisons are used, then doing nothing would still have an effect since the epidemic evolves from 2015 to 2030 leading to changes in incidence and mortality. Our discussion here, therefore, focuses on the impact attributable to the interventions and not to the changing nature of the epidemic. All discussion of elimination targets, however, specifically use the 2015 values as the comparator value as this is how WHO targets are specified.

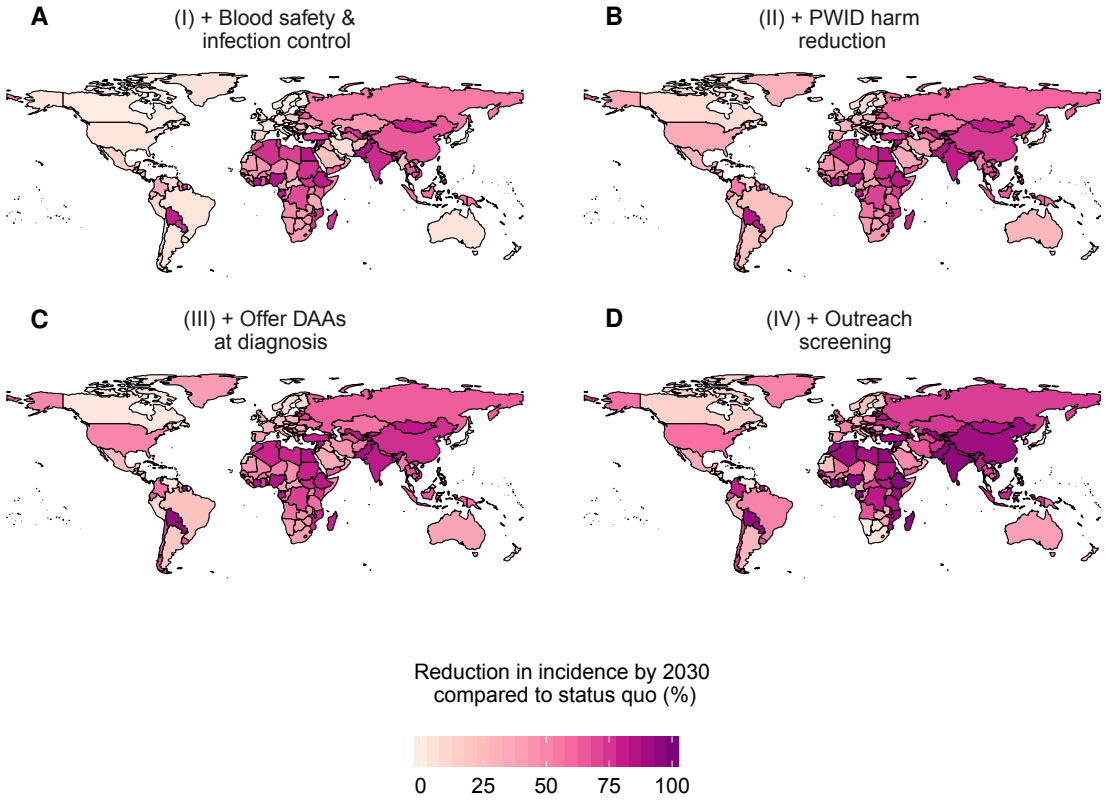


Figure 4.11 - Incidence reductions by country and intervention in 2030. Reduction in annual incidence, calculated for 190 countries by intervention, as compared to the status quo in the same year. Each graph shows the incidence reduction comparing the status quo to: (A) intervention I – status quo + blood safety and infection control, (B) intervention II – status quo + blood safety and infection control + PWID harm reduction, (C) intervention III – status quo + blood safety and infection control + PWID harm reduction + DAAs in all countries and offer DAAs at diagnosis, (D) intervention IV – status quo + blood safety and infection control + PWID harm reduction + DAAs in all countries and offer DAAs at diagnosis + outreach screening.

proportion of the HCV epidemic concentrated in PWID (such as Australia, USA and Spain) show notable improvement upon expansion of PWID harm reduction services; they experience at least 28% reductions in incidence compared to counterfactual in 2030 (compared to minimal changes upon implementation of intervention I). The overall impact is, however, lower than that due to implementing general population risk-reduction measures since the model simulates extension of harm reduction to only 40% of opioid-dependent PWID (already an extremely ambitious target, see the discussion below). The impact upon mortality from these prevention interventions at the country level by 2030 is negligible as would be expected for reasons discussed above with regards the global epidemic.

Upon all countries rolling out DAAs and offering these at time of diagnosis (intervention III), the majority of countries in Africa, along with South, East and Southeast Asia experience smaller reductions in mortality than countries in other regions. This reflects the lower current diagnosis

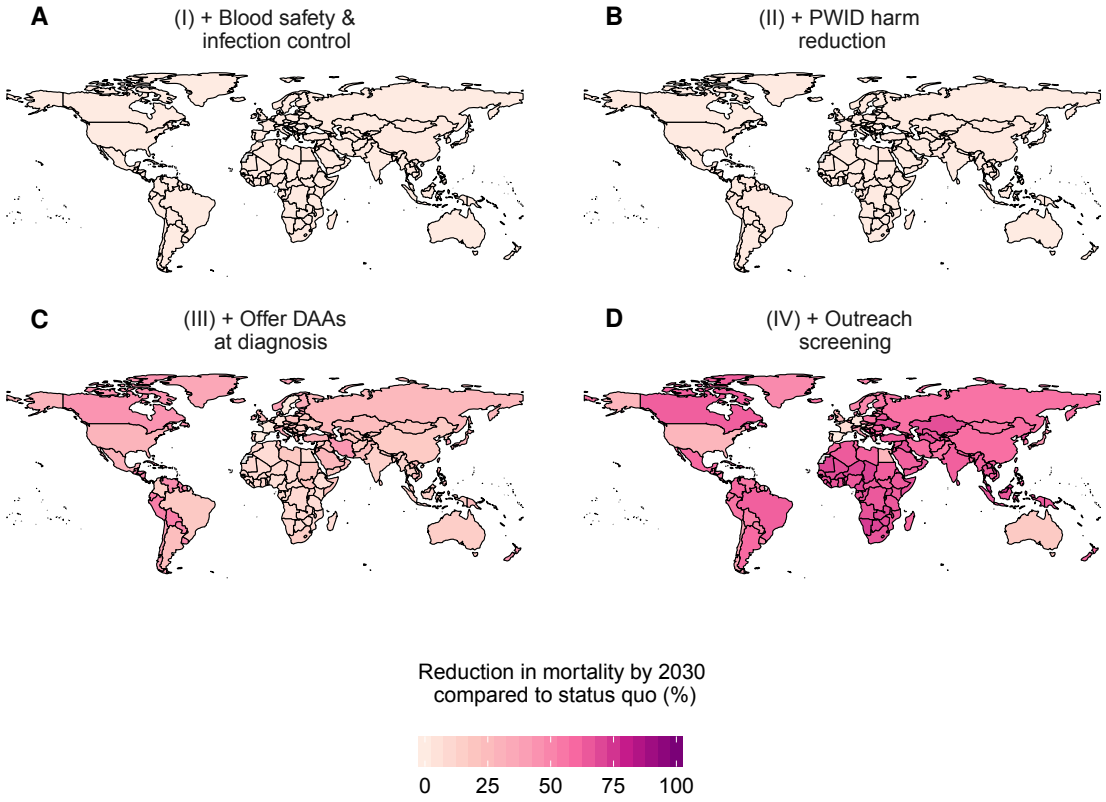


Figure 4.12 - Mortality reductions by country and intervention in 2030. Reduction in annual mortality, calculated for 190 countries by intervention, as compared to the status quo in the same year. Each graph shows the mortality reduction comparing the status quo to (A) intervention I – status quo + blood safety and infection control, (B) intervention II – status quo + blood safety and infection control + PWID harm reduction, (C) intervention III – status quo + blood safety and infection control + PWID harm reduction + DAAs in all countries and offer DAAs at diagnosis, (D) intervention IV – status quo + blood safety and infection control + PWID harm reduction + DAAs in all countries and offer DAAs at diagnosis + outreach screening.

coverage in those regions. More specifically, countries with high diagnosis rates and relatively low treatment rates (such as South Korea) or even countries with high treatment rates but that have not yet implemented DAAs (such as Qatar) experience large reductions in mortality (of over 30%) simply upon expanding access to DAAs to all those being diagnosed. The impact upon incidence in intervention III is highly varied. Countries with high risks of infection (particularly among PWID) can experience increases in incidence rates as a result of curing individuals who are then at risk of subsequent infection (such as Venezuela). Other countries, in which infection risk is lower, experience a reduction in incidence in intervention III. One example is the United Kingdom, in which incidence rates drop an additional 23 percentage points by 2030 compared to intervention II. This is a result of curing PWID, reducing prevalence and thereby reducing incidence.

The majority of countries experience big reductions in both mortality and incidence upon implementation of the comprehensive package of interventions, reflecting the high impact a multifaceted

approach to tackling the epidemic can have. There is still a heterogeneity of responses between countries. Those that had high diagnosis and treatment rates in status quo have small improvements in mortality rates in intervention IV as would be expected (examples include Austria and France).

The impact upon incidence is even more varied, with a handful of countries actually experiencing increases in incidence rates when comparing the 2030 status quo counterfactual with intervention IV (Venezuela is an example of such a country as per intervention III). In this scenario the overall incidence rate rises as a result of a large number of PWID being cured and a proportion of them subsequently being reinfected, raising the number of infections in intervention IV over that of the status quo. It should be noted that incidence rates within the PWID group itself fall in intervention IV, reflecting the lower prevalence and lower risk of being infected that results from the intervention; it is the growth in the susceptible group that leads to an increase in the number of infections overall[4]. Notably, the countries that experience an increase in incidence rates in intervention IV are those for which data are generally lacking. In calibration, these countries have explored a wide range of epidemics including epidemics characterised by very high prevalence among PWID. Additional testing revealed that, if the lower credible value (2.5% estimate) of number of infections were used to calculate the proportional reduction in incidence rate (rather than the median value), then implementation of intervention IV does reduce incidence rate overall as would be expected.

This demonstrates that the point estimates reported on figure 4.11 that show a negative outcome upon implementation of intervention IV mask a wide range of possible outcomes including possible reductions in incidence rates. This feature ultimately reflects the lack of knowledge regarding prevalence in a small number of countries, since the vast majority of countries do not experience increases in incidence upon implementation of intervention IV. In fact, the total number of infections to 2030 in those countries that experience increases in incidence in intervention IV comprise only 2.6% of the global value. It is concluded from this that the uncertainty in these countries (and the simulated worsening of the epidemic that can happen) will not affect conclusions at the global scale. This discussion also emphasises that the PWID epidemic plays a key role in determining incidence reductions moving forward (this will be explored more thoroughly below).

To summarise, there is a heterogeneity of responses to the individual components of all four interventions considered in this analysis. Local epidemiology will, accordingly, be critical to understand and take into account when designing appropriate national HCV elimination programmes. Where data are lacking the requirements for HCV elimination programmes will, accordingly, be less clear and in scenarios with potentially very high incidence rates among PWID the possible impact of reinfection in driving up the absolute number of new infections should be taken into account and mitigated by appropriate measures (such as by ensuring treatment is only offered within the framework of a comprehensive set of prevention intervention services [531]).

[4]Mathematically, while the number of infections rises, the number susceptible rises even more as a result of curing PWID. This leads to the counterintuitive result that incidence rates in PWID decrease in intervention IV but overall population incidence rates (and indeed number of infections) increases.

4.3.4 Prospects for meeting elimination targets

Figure 4.13 shows the year in which elimination targets are met, by region, for all the intervention and no-intervention scenarios considered. Considering the global results (figure 4.13) it can be seen that only interventions III and IV make reaching the mortality target possible before 2100. This would be expected since, in the short run, the prevention interventions (interventions I and II) would not be anticipated to reduce mortality due to the slow, progressive nature of the disease. Incidence elimination, meanwhile, is brought in from 2100 to 2063 only upon expansion of both general population and PWID harm reduction interventions (intervention II), is brought marginally closer (2051) upon introduction of DAAs at diagnosis rates (intervention III).

Only upon implementing the comprehensive package of interventions (intervention IV) are elimination targets even close to being met in 2030: while the incidence elimination target is met in 2030 itself, the WHO-defined mortality elimination target is narrowly missed (it is reached in 2032). As discussed above, the comprehensive package of interventions does lead to a large 61% reduction in mortality in 2030 compared to the 2015 baseline value; moreover, not only is elimination reached in 2032 but the reductions in mortality simulated in intervention IV soon go well beyond the WHO target (figure 4.8A). At the global scale, the key conclusion of this analysis is that all components of the interventions simulated (prevention, treatment and outreach screening) are required to come close to meeting elimination targets.

As would be expected given the discussion above regarding the impact of interventions at the country level, the prospects for meeting elimination targets vary widely by region; the particular nature of the HCV epidemics by country lead to large variations in the importance of the different intervention components. Those regions with (on balance) high rates of access to DAAs already (particularly Western Europe) can reach mortality elimination soon in just the status quo scenario. Other areas with large, concentrated epidemics in PWID can reduce mortality in the future through expansion of PWID harm reduction interventions though, as discussed above, mortality elimination due to prevention interventions tends to happen much later than through scale up of treatment and diagnosis interventions (see Australasia and High-Income North America). Epidemics with much smaller PWID components (North Africa & Middle-East) can reach mortality elimination targets before 2100 with general population risk reduction measures (intervention I) only. A number of regions do not reach mortality elimination except after implementation of the comprehensive package of interventions (see all Sub-Saharan African regions for example). These regions are characterised by very low diagnosis and treatment rates preventing intervention III in particular leading to mortality elimination, while even with prevention interventions implemented there is not enough diagnosis and treatment to bring mortality under the 65% mortality reduction target. All regions reach the mortality elimination target at similar times after implementing the comprehensive package of interventions (figure 4.13A). This indicates that, regardless of the underlying nature of the epidemic, if diagnosis rates are increased, such that 90% of HCV-positive people are diagnosed, huge reductions in mortality are possible.

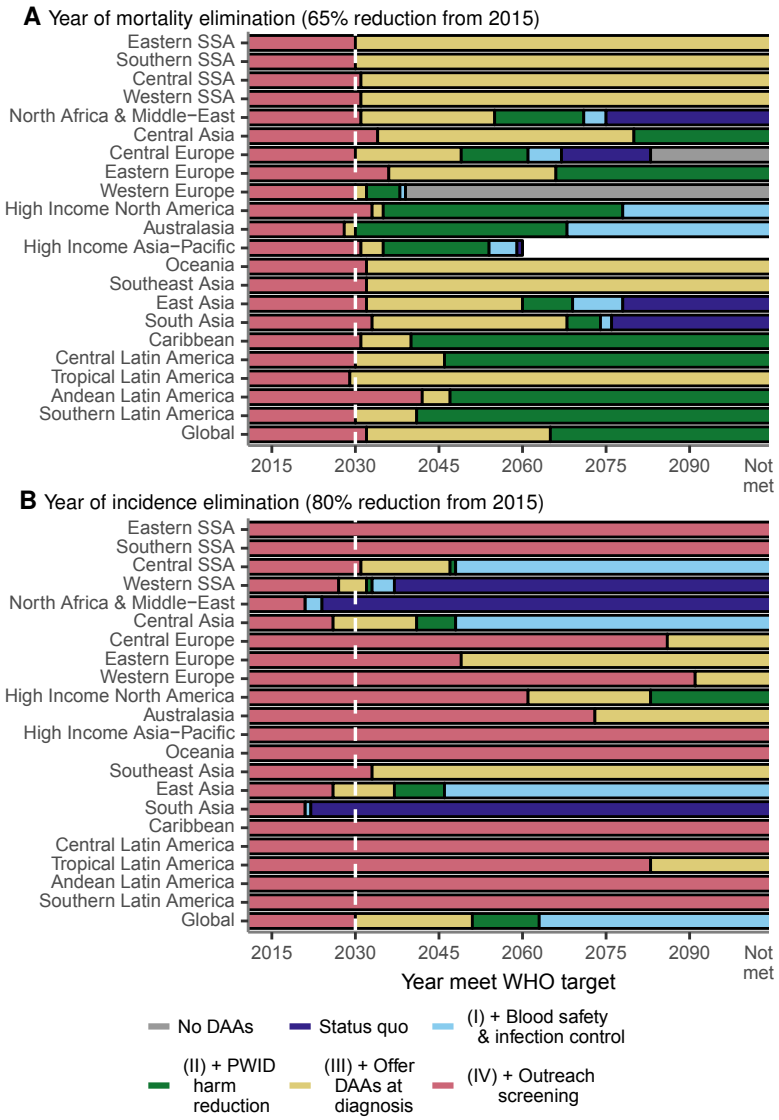


Figure 4.13 - Time to elimination globally and by region in all interventions. (A and B) End of each bar represents the median year in which A mortality and B incidence elimination occurs. All interventions are shown: where a colour extends to the end of the graph it means that that intervention does not lead to elimination and, by extension, none of the previous interventions do (at the regional level there is no case where a higher numbered intervention pushes back elimination year). Where a red bar (intervention IV) extends to the edge of the graph, elimination was not achieved in any scenario before 2100. Elimination is defined as a 65% reduction of mortality and 80% reduction in incidence by 2030 (marked by the dashed white vertical line).

The year in which incidence elimination targets are met largely follow what would be expected from the discussions above regarding the impact of interventions in individual countries. Regions whose countries are characterised by large general population risk of infection (North Africa & Middle-East and South Asia) experience large reductions in incidence upon implementation of further general population risk reduction measures. PWID harm reduction interventions alone only bring the year of incidence elimination closer in Central Asia. It is surprising that such measures

do not potentially make elimination possible in what are thought of as the regions with primarily PWID epidemics, such as Australasia or Eastern Europe. The reason these interventions do not lead to elimination in those regions is that their epidemics are dominated by PWID transmission and PWID harm reductions are not extensive enough to reduce incidence by 80%. Countries in Central Asia, by contrast, have both high prevalence in the general population and in their large PWID populations. General population risk reduction will tackle the high burden in the population as a whole but the PWID epidemic prevents incidence targets being met; PWID harm reduction interventions then push incidence rates below the elimination threshold because the HCV epidemic among PWID also represents a significant component of the overall epidemic. This region, therefore, is somewhat unique in maintaining large epidemics in both the general population and PWID and so benefits greatly from the combination of interventions present in intervention II (leading to incidence elimination in 2048).

Considering the comprehensive package of interventions, while global incidence targets are met, eight regions still do not reach the incidence elimination target before 2100, even with this extensive scale up of all intervention components (figure 4.13B). The key determinant of whether incidence elimination is achieved is the proportion of infections by risk group; the regions that reach incidence elimination before 2030 are characterised by low numbers of infections in PWID relative to the rest of the population (see figure 4.9). This is the case because efforts to reduce incidence in PWID are assumed to reach only 40% of the eligible PWID population and so are inherently limited in the impact they can have. Another key aspect is uncertainty, with those areas lacking prevalence data (such as Caribbean and Oceania) exploring a wide range of possible epidemics including those dominated by PWID transmission. This results in incidence elimination targets being potentially very difficult to meet. However, following the discussion of Venezuela above, many epidemics in these simulations do not offer such a pessimistic outlook. In short, while the overall size of the regions dominated by uncertainty means they will not have a large impact on the overall results, greater knowledge of these epidemics is essential to formulate intervention strategies and to understand the prospects for elimination in these regions and their constitutive countries.

4.3.5 Sensitivity analyses

Impact of intervention coverage. The sensitivity of incidence and mortality reductions to changes in intervention impact were investigated by varying one of general population risk reduction, PWID harm reduction programme coverage and the proportion diagnosed by 2030 while leaving the other two parameters at their original intervention IV values, see figure 4.14. From figure 4.14A and 4.14B it is clear that reductions in risk in both the general population and PWID are critical for reaching incidence elimination targets, with the 80% reduction target met almost exactly at the intervention IV values of general population risk reduction and PWID harm reduction coverage. Slight reductions in the impact or coverage of either of these components limits the possibility of reaching elimination. Figure 4.15A and 4.15B illustrate how the year in which incidence elimination is met is pushed back to beyond 2040 without substantial reduction in general population risk,

while not expanding PWID harm reduction coverage to close to 40% pushes the year of elimination even further back. Notably, the uncertainty in the latter projection is particularly great, reflecting the greater variability of simulated PWID epidemics where data are lacking (less constrained as they are by mortality or overall prevalence estimates). Yet at the 40% coverage considered in the primary analysis, uncertainty is reduced leaving conclusions drawn about the impact of intervention IV at the global scale robust.

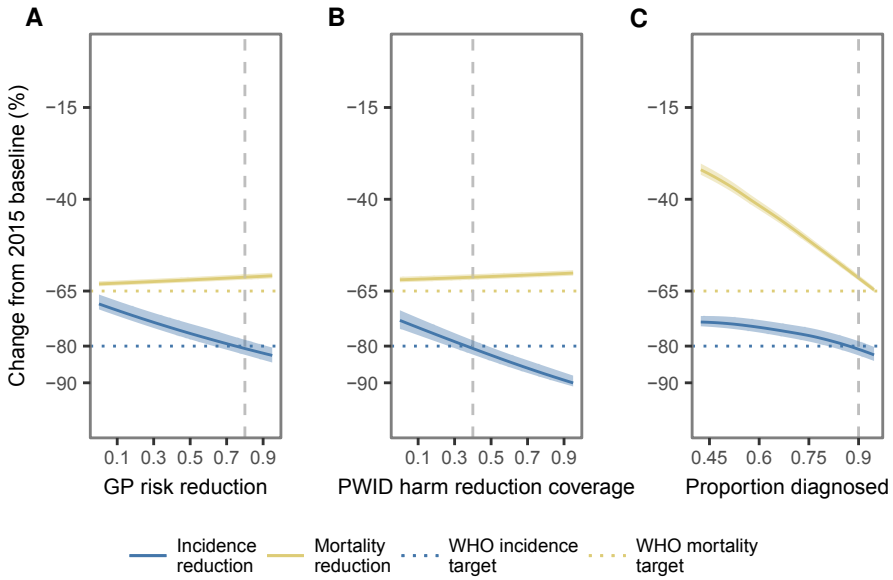


Figure 4.14 - Sensitivity of reaching WHO elimination targets to changes in programme parameters with the comprehensive package of interventions. Sensitivity of reaching elimination targets in 2030 in the comprehensive package of interventions (intervention IV), expressed as change in 2030 value from 2015 baseline, by (A) reduction in general population risk, (B) coverage of PWID harm reduction intervention and (C) proportion diagnosed. The values of all variables aside from those varied in sensitivity are equal to their original intervention IV values and are indicated by the vertical dashed lines on each plot. The slight decrease in mortality reduction with rising prevention intervention coverage may be due to more treatment slots being used on those who are sicker (as there are fewer early-stage infections) in high compared to low coverage prevention interventions. This, in turn, could lead to deaths being deferred rather than fully averted since those in the later stages of disease can still die of HCV infection following cure. If these deaths were then to occur in 2030 (as opposed to earlier), this could explain the marginally higher mortality as prevention coverage increases. As the effect is small, it was not explored in further detail; additional modelling could have been performed to understand this more fully had time permitted.

Running simulations with greater general population risk reduction (to 95% reduction) is seen to have only a marginal increase in terms of further reducing incidence or moving the incidence elimination year closer. By contrast, considerable further incidence reduction is possible by increasing PWID harm reduction coverage: if coverage is increased above 80% for example, incidence rates can be reduced by nearly 90% compared to 2015 baseline values (figure 4.14B), with elimination year brought as close as 2023 (at 95% coverage, figure 4.15B). We do not adopt such a high value in our analysis because we simulate combined OST plus NSP, the method of harm reduction with the strongest evidence of reducing HCV transmission among PWID [265, 266]. A suitable coverage for this intervention is the WHO "high" target for OST of 40% [267] which is, nevertheless, far

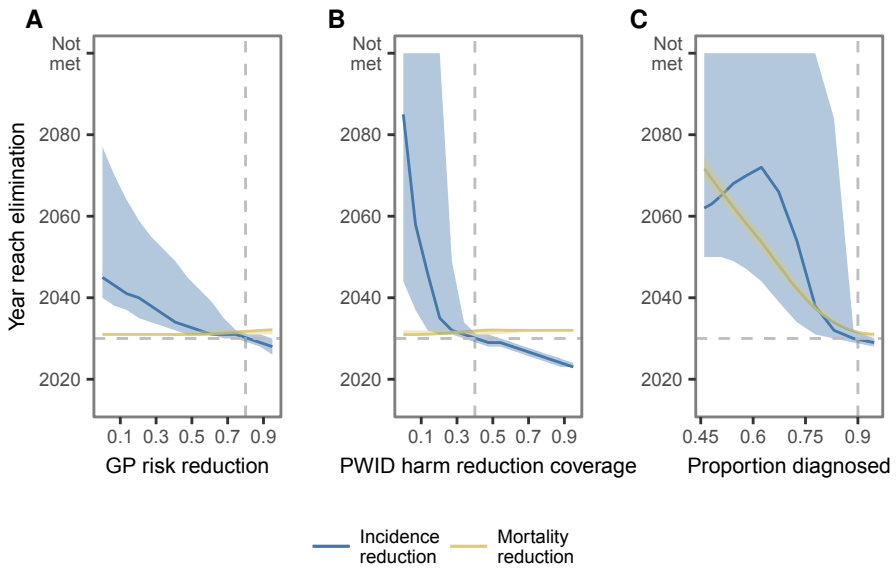


Figure 4.15 - Sensitivity of reaching WHO elimination targets to changes in programme parameters with the comprehensive package of interventions, as a function of year of elimination. Sensitivity of reaching elimination targets before 2100 by (A) reduction in general population risk, (B) coverage of PWID harm reduction intervention and (C) proportion diagnosed expressed in terms of year of elimination. The values of all variables aside from those varied in sensitivity are equal to their original intervention IV values and are indicated by the vertical dashed lines on each plot (see table 3.1). Horizontal dashed line shows 2030 (the year in which elimination is targeted).

beyond that reached in most countries to date [466].

Mortality elimination targets are only made possible by expanding access to treatment and increasing the proportion diagnosed, as has been shown above. Figure 4.14C illustrates how the mortality reduction by 2030 is a linear function of the proportion diagnosed. Mortality elimination could be reached by 2030 if the coverage of diagnosis were increased to 95%, rather than the 90% assumed above (figure 4.14C). Mortality reductions are considerably reduced with lower diagnosis coverages: At 42.3%, the value of diagnosis coverage reached when only status quo diagnosis rates are maintained from 2017 onwards (in the comprehensive package of interventions), the mortality reduction in 2030 is only 27% and mortality elimination is not met until 2077 (95% CrI: 2074-2082).

Increasing the proportion diagnosed also plays a key role in reducing the incidence rate in 2030, though the effect is sub-linear indicating an indirect role for this variable in driving incidence reductions: the gains from increasing diagnosis rates are only felt above a certain threshold at which point the increase in the number being cured does indeed drive a treatment-as-prevention effect. Below this threshold point, a more complex effect is manifested: the relationship between the level of diagnosis and year of achieving the elimination target is found to be parabolic (figure 4.15C). That is, intermediate levels of diagnosis lead to lesser future reductions in incidence after 2030 (leading to later elimination) than either no increase or enormous increases in diagnosis rates. This is because we have assumed that cured persons are at risk of reinfection and at lower levels

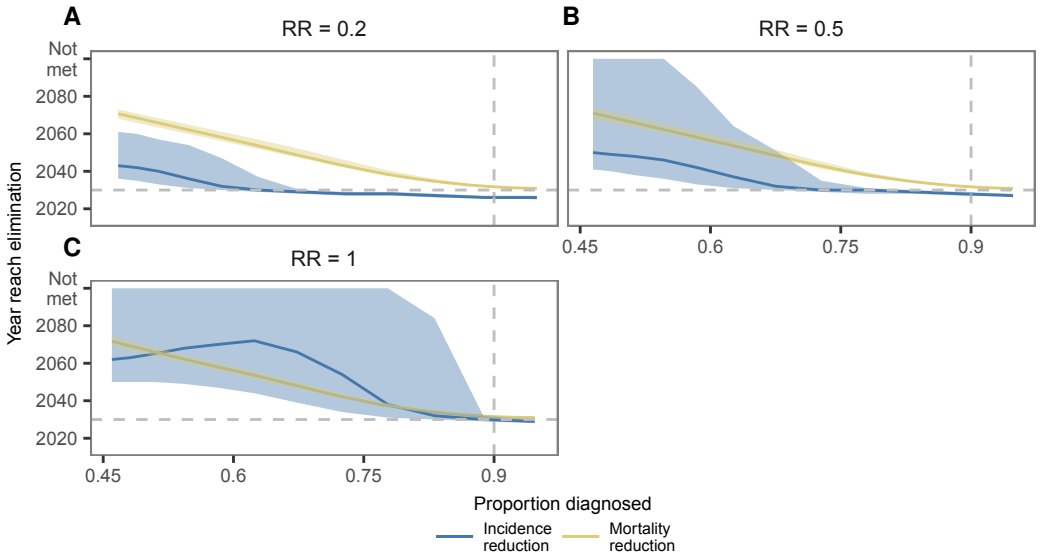


Figure 4.16 - Impact on elimination year (in comprehensive package of interventions) upon varying the relative risk of reinfection and the proportion diagnosed. Shown are the times to elimination in the comprehensive package of interventions at varying diagnosis coverages (reached by 2030) with a reinfection relative risk (RR) of (A) 0.2, (B) 0.5 and (C) 1 which is the value used in the primary analysis (see panel C in figure 4.15).

of diagnosis coverage, infection risk for PWID remains high and so there can be more infections than with no intervention. At high levels of diagnosis, this effect is overwhelmed by the reduction in infection risk that is brought about by the reduction in the numbers of infectious persons. That this effect is related to reinfection was demonstrated by running additional analyses in which reinfection risk was reduced leading to the parabolic profile disappearing, see figure 4.16A and 4.16B (4.16C shows the original curve with reinfection risk equal to primary infection risk). This is important because if reinfection risk were lower than the risk of initial infection then the year of elimination could be reached much sooner than we have estimated above (figure 4.16). Such values were not chosen as there is no clear evidence for a reduced risk of reinfection in those who have achieved SVR (for a full discussion see chapter 3).

It should be made clear how figure 4.14C and figure 4.15C are consistent. By 2030 any increase in diagnosis proportion leads to a decrease in incidence (figure 4.14C) whereas at intermediate levels of diagnosis the year in which elimination occurs can be pushed back compared to the year of elimination with lower levels of diagnosis (figure 4.15C). At intermediate levels of diagnosis, the prevention interventions have driven the reductions observed in incidence and changes in the proportion diagnosed by 2030 have had little impact. This is shown by the minimal changes in incidence by 2030 upon changing the proportion diagnosed up to a threshold value of around 60-65%, as described above (figure 4.14C). Epidemiologically, this stems from the fact that the given proportion diagnosed is only reached in 2030 itself, giving little time for reinfection to play a role. This means reinfection cannot create a parabolic profile in the incidence reduction curve in 2030

(figure 4.14C). However, the higher diagnosis and cure rates at these intermediate levels of diagnosis do generate the possibility of reinfections in the future (after 2030) thus preventing further reductions in incidence that would otherwise facilitate incidence elimination targets being met in the years soon after 2030. In this way the intermediate diagnosis levels can seemingly have no adverse effects by 2030 but push back elimination year in the years following. It should be noted that, while incidence elimination varies considerably, the mortality elimination year is always brought closer upon expansion of diagnosis coverage (figure 4.15C); treating and curing always reduces mortality but can have complex impacts upon incidence where risks of infection are either known to be, or are potentially, high.

Impact of implementing single interventions only. Analyses were carried out in which each of the three programme indicators (general population risk reduction, PWID harm reduction coverage and the proportion diagnosed by 2030) were scaled up from status quo values to their intervention IV values, but with the other two kept at their status quo values. This was to investigate the role played by each intervention component in the absence of any other improvements.

This analysis demonstrated that all three categories of intervention highlighted by WHO [28] play a key role in reducing disease burden, see figure 4.17. Firstly, improving blood safety and infection control, such that the risk of infection in the general population decreases by 95%, can reduce incidence in 2030 by 72% (95% CrI: 70-73%; figure 4.17A). Secondly, although HCV-positive PWID comprise only a minority of global HCV-positive individuals (and of new infections), programmes that can reduce PWID transmission would have a global impact upon incidence: expanding PWID harm reduction coverage to 95% could reduce global incidence by 33% in 2030 (95% CrI: 31-36%; figure 4.17B). Lastly, screening and treatment interventions carry a double benefit (figure 4.17C): increasing the proportion diagnosed and treated reduces both mortality and incidence (through a treatment-as-prevention effect). Despite this, treatment alone has less impact than when combined with prevention interventions: the comprehensive package of interventions reduces incidence in 2030 by 81% compared to only 65% when prevention interventions are not implemented.

Sensitivity to outcomes in key countries. To assess the impact on elimination prospects of the key countries driving global burden of disease, the numbers of infections averted and deaths averted in intervention IV between 2017 and 2030 were calculated as a proportion of the global total (see figure 4.18). The top ten such countries are shown in figure 4.19. The primary contributors to future disease burden measured in terms of new infections are China, Pakistan and India. The impact upon removing these countries from the comprehensive package of interventions (and setting them to status quo only) was investigated.

Figure 4.20 illustrates the changes in future mortality and incidence upon removal of each of these systemically important countries from the comprehensive package of interventions. The year in which the mortality elimination target is reached is pushed back to as much as 2036 (upon removal of China from the intervention package), though the impact of removing the other countries is only minimal. This suggests that mortality burden is spread out, with progress in many countries key

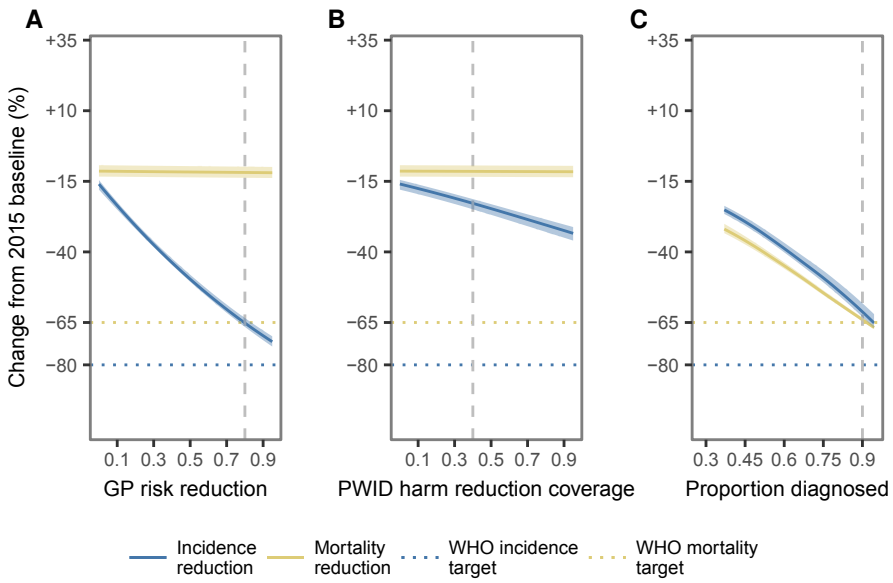


Figure 4.17 - Reduction in mortality and incidence in the status quo scenario upon improving prevention or screening intervention coverage. Changes in mortality and incidence by 2030 upon increasing (A) the reduction in general population (GP, i.e. non-PWID) risk, (B) the coverage of PWID harm reduction interventions and (C) the proportion diagnosed by 2030, from status quo values. The vertical dashed lines show the values targeted in the relevant intervention scenarios.

to meeting mortality elimination targets. Conversely, removing China, India or Pakistan from the intervention package pushes back the attainment of incidence elimination targets to at least 2047 in the case of India, and well beyond that in the case of China or Pakistan. Even in 2030, not implementing the comprehensive package of interventions in these countries would result in global incidence reductions of only 69% as opposed to an 81% reduction when all countries implement the interventions. This suggests that a handful of high incidence countries will play a major role in potentially maintaining the epidemic in the future and in determining whether targets are met or not.

Sensitivity to other model assumptions. As discussed above, the year in which incidence elimination is reached is very sensitive to assumptions made about the risk of reinfection (see figure 4.16). Yet the lack of evidence conclusively suggesting a lower reinfection risk compared to primary infection risk means it would be unjustifiably optimistic to use a lower reinfection risk value and propose that incidence elimination targets could be met much sooner than in the primary analysis presented above. Accordingly, the choice to assume equal reinfection to primary risk is the appropriate one taken. In addition, there is little uncertainty regarding year of elimination or incidence reduction by 2030 in the comprehensive package of interventions anyway, suggesting the projections of impact in this scenario are robust to assumptions regarding relative reinfection risk (see figure 4.16). This is because the extent of intervention scale up in this scenario is such as to overcome variations in outcomes due to possible changes in relative risk of reinfection.

A related quantity is the delay in retreatment after reinfection. The choice of a five year average

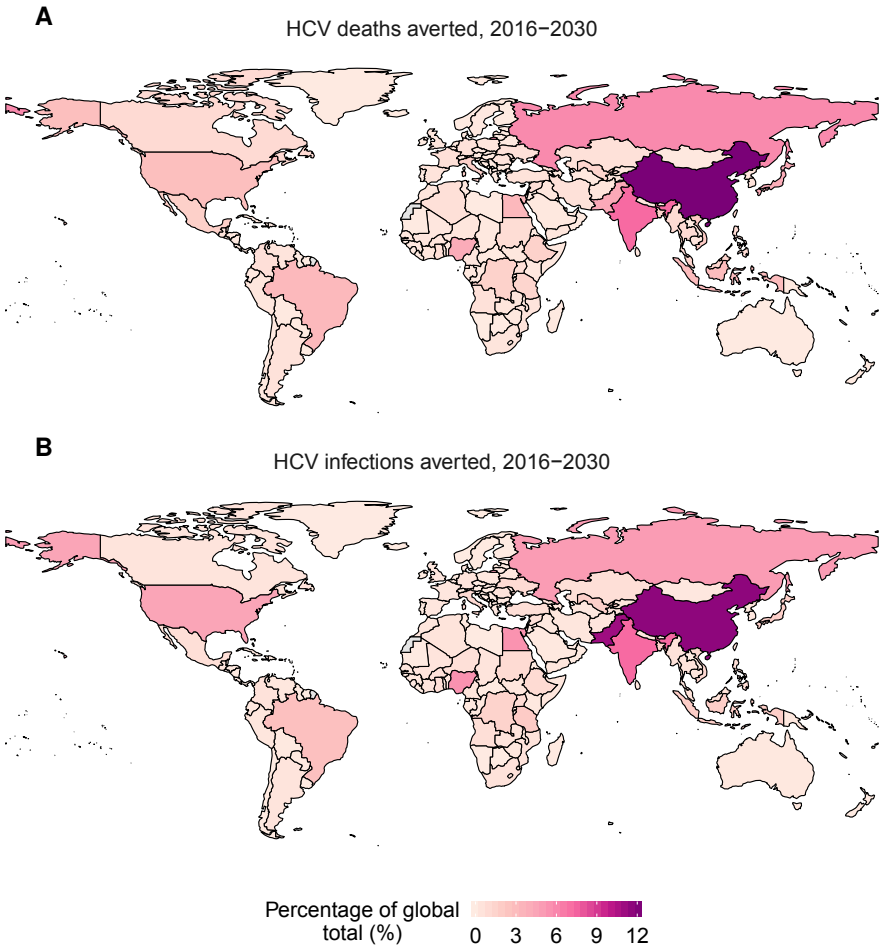


Figure 4.18 - Distribution of global deaths averted and infections averted when implementing the comprehensive package of interventions compared to status quo. Graph (A) shows the cumulative deaths averted and (B) the cumulative infections averted 2017-2030, by country, as percentages of the global total number averted, when comparing the comprehensive package of interventions (intervention IV) to status quo.

waiting time before retreatment was arbitrary but was so chosen in order to prevent a (presumed unlikely) cycling between cured and infected via successful treatment. To test this assumption, the model was re-run with a one-year delay instead. In the context of intervention IV, reducing the delay to one year did not alter the global incidence or mortality elimination years (still 2030 and 2032 respectively), while by 2050 the difference in incidence rate between the five year delay and one year delay simulations is only 3.5%, implying that there is a very small increase in incidence with the smaller treatment delay time. This is due to the greater rate at which people are offered retreatment and so subsequently able to be reinfected. This effect marginally increases the number of treatments in intervention IV: by 2050 there are an additional 200,000 treatments delivered on a total number of 64 million DAA treatment courses. In other words, a possible cycling effect does not manifest noticeably in the results and the choice of delay time has a negligible impact on outcomes.

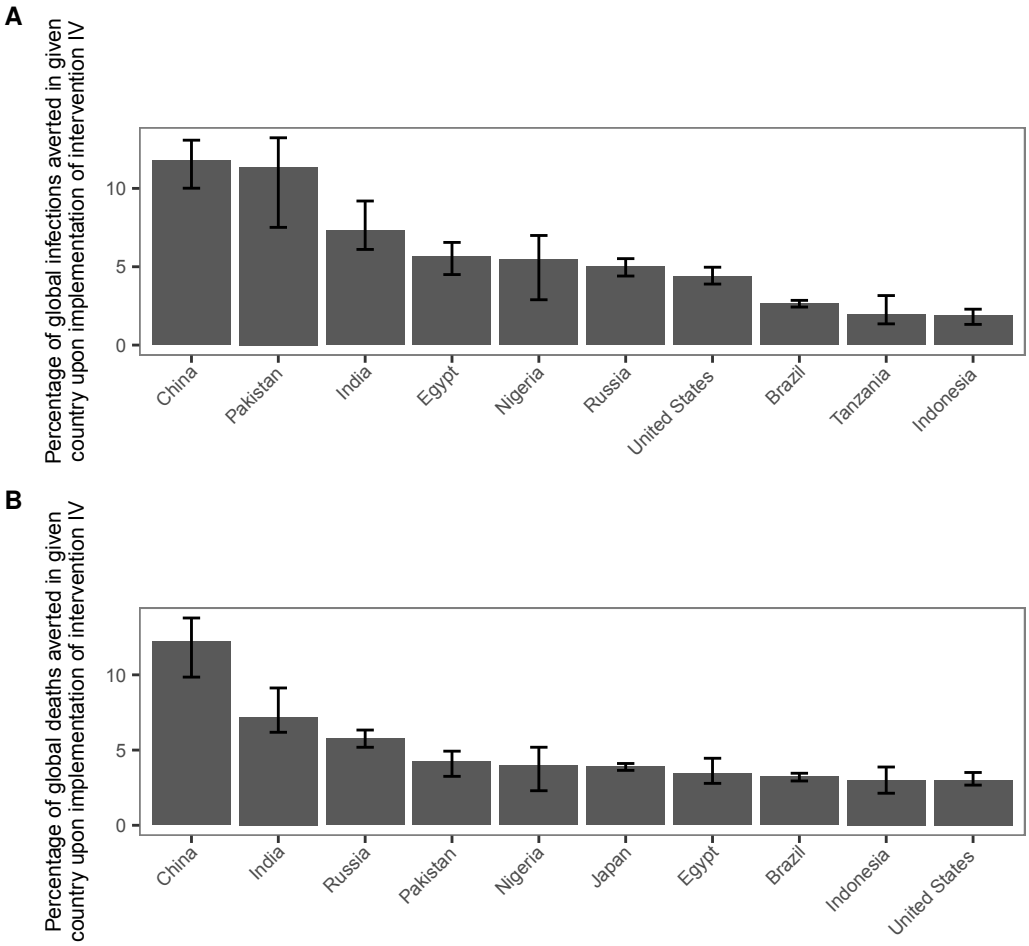


Figure 4.19 - Ranking of countries in terms of contribution to global HCV burden reduction. Shown are the top ten countries in terms of contribution to global reduction in (A) numbers of infections and (B) numbers of deaths upon implementation of the comprehensive package of interventions as compared to a status quo scenario.

The degree of effectiveness of PWID harm reduction programmes is more uncertain than, for example, the effectiveness of DAA treatment, while the effectiveness of such programmes probably varies substantially between settings. Due to these various uncertainties, sensitivity analyses were performed to investigate the dependence of the results on this parameter of the model, see table 4.2 which summarises the results of this analysis. Reducing the effectiveness of OST plus NSP interventions to 20% (from 75% in the primary analysis) pushed back the year of incidence elimination to 2052 (table 4.2D). As shown by the breakdown by region this is driven by delays in elimination in regions in which HCV-positive PWID comprise a large proportion of the HCV epidemic (such as Western Europe, High-Income North America and Australasia).

The impact of varying PWID harm reduction programme effectiveness on various outcomes was calculated for both the 20% effectiveness scenario and a putative 90% effectiveness scenario, see table 4.2. Varying effectiveness from the lower to upper values results in 1.5 million more infections

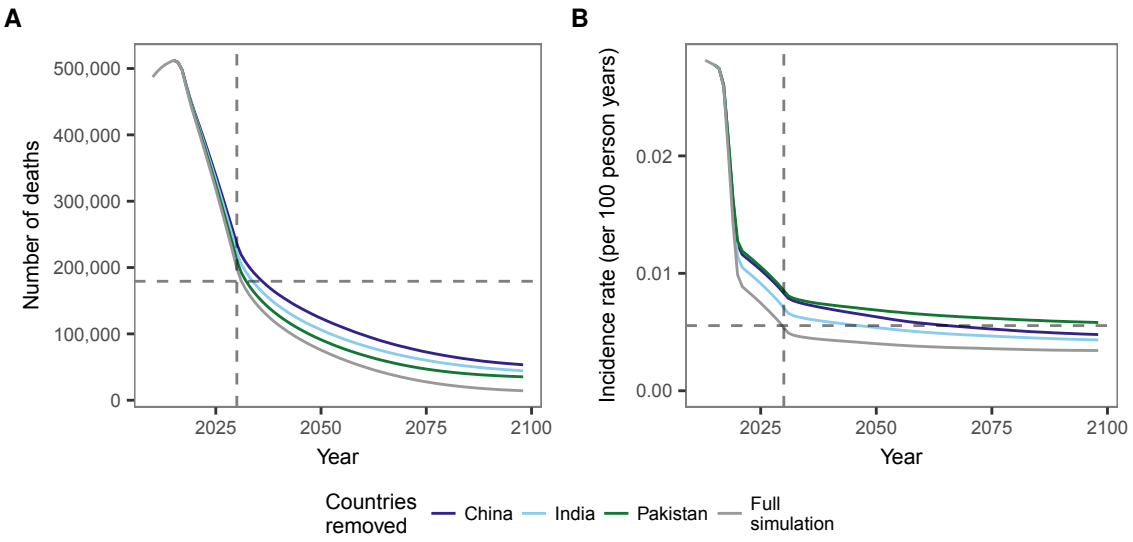


Figure 4.20 - Sensitivity of reaching WHO elimination targets upon removal of systemically important countries. Number of deaths (A) and incidence (B) for the comprehensive package of interventions and for the comprehensive package of interventions upon removal of the three countries that are projected to contribute most to number of infections averted in intervention IV (2017-2030). Credible intervals not shown for ease of interpretation.

being averted upon implementation of intervention II. 180,000 additional infections are averted in intervention IV (between the lower and upper effectiveness values); those being cured in intervention IV are less likely to be subsequently reinfected (due to higher harm reduction programme effectiveness) resulting in more infections averted relative to the status quo scenario. Compared to the primary analysis, simulations in which PWID harm reduction effectiveness is improved (to 90%) could result in 470,000[5] fewer courses of treatment being delivered in intervention IV by 2030. This highlights the cost savings that PWID prevention efforts may entail, even in the short term, through reducing the number of treatment courses delivered. This effect is even more pronounced by 2050 (table 4.2).

4.4 Discussion

4.4.1 Summary

The revolution in HCV treatment through the development of DAAs has generated international interest in the global elimination of the disease as a public health threat leading, in 2017, the WHO to establish elimination targets for 2030. By developing a dynamic transmission model of the global HCV epidemic, the worldwide impact of scaling up interventions that reduce risk of transmission, improve access to treatment and increase diagnosis rates for HCV were estimated.

By 2030 interventions that reduce the risk of transmission in the non-PWID population by 80% and

[5]The values in table 4.2 are rounded hence why values quoted in the text may not exactly equal values calculated from table 4.2 directly.

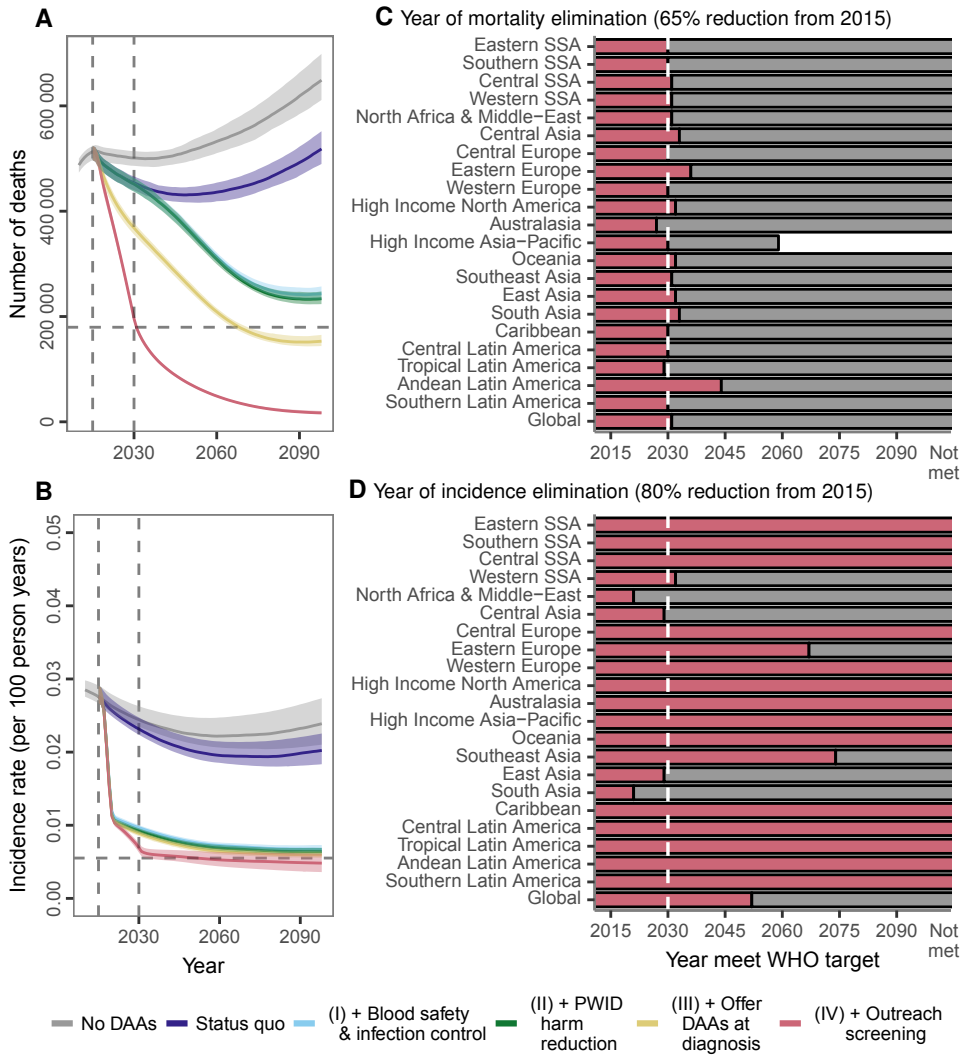


Figure 4.21 - Impact of all interventions on global HCV epidemic with assumption of lower PWID programme harm reduction effectiveness. Impact of interventions when assuming that PWID harm reduction programmes reduce risk by only 20%. Note that the green and blue curves in figures (A) and (B) are mostly coincident reflecting the fact that the impact of adding PWID harm reduction is much lower as would be expected. (A) Number of deaths due to HCV by scenario. (B) Incidence of viraemic HCV infection (number of chronic infections divided by number susceptible) by scenario. Note that the incidence curves for interventions II and III are almost coincident. Vertical dashed lines indicate baseline (2015) and the year for targeted elimination (2030). Horizontal dashed line indicates elimination targets: 65% reduction of mortality and 80% reduction in incidence. (C and D) End of each bar represents the median year of (C) mortality and (D) incidence elimination. Grey bars show no DAA scenario; red bars show the comprehensive package of interventions (intervention IV). Where a red bar extends to the edge of the graph, elimination was not achieved in any scenario before 2100. The dashed white vertical line indicates the WHO elimination year target (2030).

increase coverage of harm reduction services to 40% of PWID (intervention II) could avert 14.1 million new infections. In addition, offering DAAs at time of diagnosis in all countries (intervention III) could prevent 640,000 cirrhosis and liver cancer deaths, equivalent to almost two years' worth of HCV-attributable deaths today. Combining these strategies with a paradigmatic increase in the

Table 4.2 - One-way sensitivity analysis upon varying PWID harm reduction programme effectiveness.

Outcome	Lower (20%)	Primary (75%)	Upper (90%)
Infections averted by 2030 in intervention II	12.8 million	14.1 million	14.3 million
Additional infections averted by 2030 in intervention IV	780,000	950,000	960,000
Deaths averted by 2050 in intervention II	510,000	570,000	590,000
Treatment courses required by 2030 in intervention IV	52.9 million	51.8 million	51.4 million
Additional treatment courses required by 2050 in intervention IV	14.6 million	12.0 million	11.3 million

Median values shown. Intervention II refers to the general population risk reduction plus PWID harm reduction intervention; intervention IV is the comprehensive strategy involving these elements as well as DAA treatment introduction worldwide and screening scale up such that 90% are diagnosed by 2030. Values averted are as compared to values in the status quo scenarios (with the values of PWID harm reduction effectiveness as listed in the column heading).

proportion diagnosed and subsequently treated (intervention IV) results in WHO targets being only narrowly missed: such an intervention reaches the WHO incidence reduction target of 80% but is just short of the mortality reduction target of 65% (it could be reached in 2032). Despite the fact that even with this stark improvement in prevention and treatment indicators WHO elimination targets are missed, such a programme would be a tremendous stride forward, averting 15.1 million new infections and 1.5 million HCV-related deaths by 2030.

Reducing global burden depends upon success of prevention interventions, implementing outreach screening and the progress made in key high-burden countries, in particular China, India and Pakistan. Results in intervention IV, the comprehensive package of interventions, are sensitive to changes in the effectiveness of PWID harm reduction programmes. Analysis of the impact of reinfection risk reveal that reinfection plays a key role at lower intervention coverages in pushing back the year in which incidence elimination is reached, though this is within the context of considerable uncertainty. At the intervention coverages simulated in intervention IV results are robust to changes in various model parameters and assumptions. Investigating the impact of scaling up interventions in isolation or in concert demonstrates that further improvements in blood and injection safety, expansion or creation of PWID harm reduction services and extensive screening for HCV with concomitant treatment are all jointly necessary to reduce the burden of HCV and bring elimination within reach.

4.4.2 Policy implications

There are many important challenges that must be met in attempting to roll out the various elements of intervention IV, though, and the analysis presented above raises several points of direct relevance to policy and programme development. Firstly, the benefits of DAAs will only be fully reaped with an exceptional increase in diagnosis coverage to 90% by 2030; the treatment of only those already in care will not translate into significant reductions in HCV deaths or incidence (as was demonstrated with the analysis of intervention III). However, in only one country (Malta) is the estimated proportion of persons living with HCV who have been diagnosed at such a high level [226]. Progress could be made by a variety of methods in the coming years: innovative means of increasing awareness and encouraging HCV testing in a range of settings are being explored [158] and new technologies, such as POC viral load finger-stick tests [130], should soon be available as was discussed in chapter 2 [130]. It is conceivable that awareness raising initiatives and simpler diagnostics could facilitate an increase in HCV-status knowledge similar to that achieved in the HIV-arena.

Secondly, the HCV epidemic among PWID plays a deciding role in determining whether incidence elimination targets are met. The modelled strategy that resulted in incidence elimination being achieved in 2032 relied upon coverage of OST plus NSP increasing to 40%: however, only 1% of PWID live in countries with such high coverage of these harm reduction services [466]. If the effectiveness of those programmes is lower than has been estimated in some settings [265, 266] then elimination becomes a much more remote prospect, with elimination not being reached until after 2050 even with high coverage of other interventions. Reinfection was shown in our analysis to play a key role in delaying the year of incidence elimination in intervention IV, particularly where the proportion diagnosed does not meet the highly ambitious intervention IV diagnosis-coverage goals. Greater knowledge of the state of the HCV epidemic among PWID would help reduce the uncertainty in elimination year projections, though if target coverages can be reached the impact of intervention IV on incidence is likely to be considerable regardless of this uncertainty.

These results highlight the fact that efforts to tackle the epidemic among PWID must be central to HCV policy. One approach that could be implemented more extensively is treatment as prevention. The model results presented here illustrate the potential for treatment interventions to reduce incidence even in regions in which the epidemic is concentrated among PWID (this has been shown in other models as well [387]). Such approaches are potentially contentious (as they were when first considered in the early days of universal ART interventions to tackle the HIV epidemic [532]), particularly among vulnerable groups. Such an approach must be done in a manner respectful of the needs of PWID, in the context of enhanced harm reduction interventions and with community involvement [531]. Other means exist for improving outcomes that go beyond the HCV-specific measures considered in this analysis including eliminating structural barriers (criminalisation of PWID) or systemic barriers (treatment restrictions on active drug users) which can improve access to health services [528, 533]. A concrete example of an HCV PWID intervention is given by the Hepatitis C Action Plan programme in Scotland. This has shown that national reductions in in-

cidence are possible through an integrated approach involving scaling up of OST plus NSP along with increasing awareness and provision of HCV testing for PWID (including ever-PWID) [534]. Such progress relies on political will and reliable sources of funding which, in low- and middle-income countries in particular, are often lacking. This lack of funding and political will represents a serious challenge for implementing effective HCV programmes in many settings and is one of the key policy issues that must be addressed [535].

Thirdly, continued improvements in blood and injection safety remain key components of the global elimination intervention package as they drive a large reduction in new infections. While proven blood and injection safety measures exist and have played a major role in reducing infections in many settings [455, 536], only 39% of countries worldwide operate haemovigilance systems [455] and, as was described in detail in chapter 2, unsafe (often unnecessary) injections continue to be a major source of HCV infection [218, 537]. The reasons for the persistence of unsafe injections as a transmission route are complex [223] (see chapter 2) and context-specific management methods are necessary if there are to be continued reductions in the risk of HCV transmission via these routes [222]. More data concerning the source of infections are also required to direct efforts at those transmission routes most responsible for HCV infections. This is particularly pressing given uncertainty in the acquisition route of a sizeable fraction of HCV infections at the global scale (see §3.4.1).

Lastly, the global HCV epidemic is concentrated in a set of countries that may face myriad challenges in implementing the PWID harm reduction, blood and infection safety, and outreach screening initiatives simulated in our analysis. This may make talk of elimination seem more tenuous but this feature of the results is important as it can focus attention by illustrating that major progress can be made with policy changes in just a few places. In terms of global HCV epidemiology, and given the stated aims of the WHO and the UN Sustainable Development Goals to "combat hepatitis" [538], progress made in these settings should be of primary concern to bring about global reductions in HCV disease burden.

4.4.3 Comparison to other work

These policy points reinforce and augment the conclusions drawn by other studies. Several modelling analyses (in particular the VMH family of models described in chapter 2) have highlighted the challenge of reducing transmission among PWID and have advocated simultaneously scaling up prevention and treatment interventions to reduce prevalence, a key policy prescription in the current work [375, 403]. Moreover, our work extends this to demonstrate that, even on the global scale where incidence is dominated by non-PWID transmission, reducing incidence among PWID plays a key role in determining whether elimination targets are met. A recent study has incorporated dynamic modelling of PWID into a full population model of the HCV epidemic in Pakistan [411]. The authors find that only with extremely high coverage of interventions can elimination targets be met. This agrees with what we have shown on a global scale that even with exceptionally high intervention coverage, elimination targets are difficult to meet.

A European Union (EU) modelling study has suggested that mortality elimination targets can be met in this region (for a list of countries in this region see appendix B) [226]. Similarly, we find that, provided there are ambitious increases in screening and treatment, mortality elimination targets are met in most regions by around 2030. The EU study did not, however, model incidence dynamically and could not draw conclusions regarding incidence targets. Our analysis has shown that even with extensive scale up of prevention interventions the majority of regions do not meet incidence elimination targets before 2100, due in large part to ongoing PWID transmission. Even after implementation of the comprehensive package of interventions, numerous regions struggle to meet incidence elimination targets. This demonstrates why a focus on meeting mortality elimination targets (particular in a region like the EU where a majority of transmission is due to injection drug use) creates a very distorted view of the plausibility of meeting elimination targets as a whole (i.e. considered as the composite of incidence and mortality targets). Conversely, failing to incorporate transmission in analyses such as those by the CDA group prevents an acknowledgement of the treatment-as-prevention impact of curing HCV-infected individuals that our analysis has taken into account which will understate the benefits of treatment itself.

Methodologically our analysis brings together many features of various other analyses to produce an integrated model to assess the dynamics of transmission and prevention simultaneously, thus going beyond previous work and offering a first example of a global HCV-epidemic model that can be used to investigate the impact of HCV-intervention strategies. One area in which our model appears superficially more simple is in the specification of the PWID harm reduction intervention. Numerous modelling papers [375, 376, 381, 383] have modelled OST and NSP as separate programmes which have associated rates of initiation, rates of cessation and have differing effectiveness in reducing HCV transmission risk. There is also a 'coverage' parameter defined as the proportion of the PWID population that is 'in' harm reduction programmes at any particular time. This 'coverage' is taken as the lever which policy makers adjust and the initiation rate is varied in the model in such a manner that the desired coverage level is reached.

We eschewed such an approach, despite the frequency with which it has been applied in the literature (see all the VMH family of models, discussed in chapter 2), for a number of reasons. Firstly, the cessation rate is not really known; several analyses base it on an indication of times on treatment in the UK [539] but the range of values reported was very wide. This rate will also vary from place to place. Secondly, evidence for the effectiveness of OST, NSP or OST plus NSP is of low quality and modelling several different harm reduction programmes simply compounds this problem: whereas in our model we have just one effectiveness parameter, splitting out the components of harm reduction interventions introduces three that are then combined in a complex manner to produce the results. Such complexity renders it harder to explore the impacts of overall effectiveness on outcomes than the approach taken here and reduces the transparency of the approach. Lastly and most importantly, when the initiation rate is adjusted to match a particular coverage value, as is done in the aforementioned papers, the cessation rate has minimal effect. This is because a higher cessation rate induces a higher initiation rate to produce the desired coverage value, lead-

ing to more 'cycling' on and off of these programs. Therefore, the introduction of such complexity is ultimately negated by the calibration of the model to produce a given coverage. In short, the simple model of reducing risk of transmission for a proportion of the PWID population that has been implemented here was utilised to avoid introducing extraneous parameters and allows the discussion to focus on the two key variables: coverage of PWID and the effectiveness of the harm reduction programme. This framing is entirely in keeping with WHO indicators that focus on how many PWID are currently accessing services and on the quality of services themselves [267].

4.4.4 Limitations

To produce a global analysis, we have managed a variety of data and modelling limitations. We have used modelled estimates of mortality from the GBD study from the IHME [6, 9]; these have been produced for the majority of countries and are instrumental in allowing basic epidemic trends to be inferred even where other data are lacking. To manage the uncertainty this introduces, we built the model to be flexible when calibrating to these inputs since they are estimates rather than data. A related limitation is the lack of prevalence data for many countries globally making calibrations rely on mortality estimates alone. This was deemed acceptable because overall prevalence estimates and PWID prevalence estimates cover 86% and 90% of the global and PWID populations respectively. While this means that we can have confidence that global results are not driven unduly by the wide variety of epidemics explored in the remaining countries, it does lead to considerable uncertainty in particularly data-sparse regions such as the Caribbean, Oceania or Sub-Saharan Africa that could only by improved upon with further data collection.

A potential modelling limitation is in the specification of the transmission model. It is possible that choices in the structure of the risks, or in the overall timeframe chosen for the analysis, influence the results of the model. This, in turn, may explain deviations from IHME estimates of mortality as discussed above. The question of deviating from IHME estimates is discussed in the previous paragraph. With regards the potential for the model structure to unduly influence outcomes, it was observed in model development that the key outcomes of the model (reduction in mortality and incidence by 2030; progress to elimination) are relatively insensitive to changes in the precise nature of the risk model used (observed by changing the years or the prior distributions of the risk spline knots). Further testing could have been carried out to fully establish this result had time permitted.

To simulate the treatment cascade we used regional estimates to extrapolate to countries without data. This process necessarily smooths out country-level differences in diagnosis and treatment coverage, introducing error in some individual country projections. This is particularly problematic where WHO regions mix disparate countries, for example the Caribbean countries share information with USA and Canada, resulting in the assumption that they have extremely high values of 45% diagnosed and 14% treated (this is deemed implausible because the majority of Caribbean countries are upper-middle-income while these treatment cascade values are the highest of all the regional values). Country-level cascade information is, however, available for countries that ac-

count for about 60% of the global viraemic population, giving good resolution on the treatment cascade for a majority of the globally infected population. This should prevent such regional data pooling altering the overall results (though it will reduce the applicability of regional results that pivot on treatment cascade estimates, in particular the results of intervention III). More importantly, low overall treatment numbers compared to the size of the epidemic mean that the error introduced through extrapolating to the remaining 40% of the HCV-infected population will have a small impact on those intervention projections that rely on cascade numbers (primarily intervention III).

There is considerable uncertainty about the source of infections among the general population which makes it impossible to be sure about the extent to which this route of transmission is being, and can be, reduced (this was described in detail in chapter 3). While WHO calls for 0% unsafe injections and 100% of blood donations screened with quality assurance [28], both the difficulty in reaching these targets and the many ways of being infected with HCV beyond these two routes (see chapter 2) led us to specify only an 80% risk reduction among the general population (in intervention I and above) in order to be conservative regarding what is a necessarily vague intervention strategy. We varied this in sensitivity analysis to explore the impact this programme parameter had on outcomes to acknowledge this uncertainty.

Similarly the impact of PWID harm reduction interventions is uncertain outside of the primarily North American and European settings in which OST plus NSP initiatives have been studied [265, 266]. We vary this quantity in sensitivity analysis to account for this, but in implementing PWID harm reduction globally we are making the strong assumption that such programmes can have equal success in all regions. This is deemed acceptable since there does not appear to be any other approach justifiable in simulating harm reduction interventions in countries that have not been explicitly studied other than from published formal evidence syntheses of OST plus NSP programmes. It might be claimed that harm reduction interventions cannot be effective in all settings and so the model is overly optimistic in implementing a high-impact harm reduction intervention in all settings. In response to this potential limitation, we believe that it is not a priori certain that high quality programmes cannot be delivered in diverse settings. Rather, the key issue on the global scale appears to be a lack of (or instability of) funding and the failure of political leadership to set up and maintain such programmes in the first place [540]. Additionally, if past experience in certain countries has not always been encouraging regarding the possible benefits of harm reduction (due to sudden removal of funding for example) [533, 540], the conclusions drawn here highlighting the importance of PWID prevention for global HCV elimination reinforces the need for focussing attention on improving effectiveness in all settings.

Lastly, we do not model changes in the proportion of the population who are PWID. There is growing concern about potential increases in the number of PWID in the USA for example [541], yet the relationship between non-medical use of prescription opioids and initiation of injection drug use is not well understood [542]. Conversely, in other regions like Europe the proportion of the population who are PWID may have decreased [543], such as in Scotland which has reported a decline

in injecting drug use over the last decade [544]. With such uncertainty regarding the direction of possible changes in the proportion of the population who are PWID we kept this quantity fixed and did not simulate possible increases or decreases in the future. Future structural interventions (or simple changes in behaviour) that could reduce the number of PWID [545] would have a substantial impact on the HCV epidemic. The possible impact of such changes can only be built into the model once such trends have been established which is why future changes in the proportion PWID were not simulated in the model.

4.4.5 Conclusion

To conclude, reaching WHO elimination targets is an extremely challenging aim that requires a multifaceted approach combining screening, prevention and treatment with a focus on those countries in which burden is greatest. Such efforts will entail considerable practical challenges and have large cost implications (running into the tens of billions of US dollars by 2030 for a complete viral hepatitis strategy [27]). Yet many countries have made substantial progress despite this: Egypt empowered local facilities, created numerous opportunities for HCV screening and treated 700,000 HCV-infected individuals with DAAs in 2016 [142, 494]; Australia negotiated a volume-based pricing model for DAAs which encourages, rather than rations, the prescription of expensive DAA treatment courses [546]; and Scotland has successfully coordinated national expansion of harm reduction services with HCV testing and treatment provision resulting in a sharp increase in people achieving SVR [547]. By using new tools and the examples of relevant countries like these to devise ambitious integrated interventions, this modelling work has shown that substantial progress towards global elimination can be made while greatly reducing the burden of new infections and premature death worldwide.

CHAPTER 5

Modelling the Epidemiological and Economic Impacts of Hepatitis C Interventions in Yunnan Province, China

Chapter 5 specialises the global model to the specific case of the HCV epidemic of Yunnan Province, China. The chapter begins with an overview of the public health system in China followed by an examination of the response to HCV in the country. Several economic analysis tools are introduced for use in evaluating a set of intervention strategies suggested by partners in the province. The nature of these interventions, along with details on how the global model was adapted, is described. The epidemiological and economic impacts of the interventions are presented and cost-effectiveness ratios and returns on investment are calculated. Sensitivity analyses on a range of economic modelling parameters are carried out. These results are used to make conclusions regarding the set of interventions available in Yunnan from a health economic standpoint, as well as to make comments about the challenges facing countries in scaling up HCV intervention programmes in general.

5.1 Introduction

5.1.1 Overview

China is widely considered to have the largest number of HCV infections in the world, with the most recent WHO estimates suggesting 10 million viraemic infections in 2015 [28, 280]. The modelling of the previous chapter has demonstrated that if China fails to make progress in implementing an array of interventions to tackle the hepatitis C epidemic then global elimination will not be met until decades after the 2030 targets. China's importance in the global drive towards HCV burden reduction and elimination is, therefore, not in doubt.

Beyond the sheer size of its epidemic, China has rolled out major HIV treatment and prevention initiatives in the past [548]; a consultation between the Chinese government and WHO on a national viral hepatitis programme was carried out in 2014 which demonstrates an interest in improving access to treatment for people with HBV or HCV [549]. These developments indicate that there exists political will and capacity to take significant steps in reducing the burden of major diseases in the country. Very recent developments (described below), furthermore, indicate that the national government in Beijing is currently moving towards the creation of an HCV strategy; other developments indicate this might be supported by a large reduction in the cost of DAAs in the country. All of which illustrate that China has the need and the willingness to introduce precisely the sort of ambitious scale up of interventions required to tackle the HCV epidemic in the manner described as necessary in the previous chapter.

Yunnan Province, in south-west China, is a region of 47 million people. The province is poor: it is second to last in a 2017 ranking of China's provinces by Gross Domestic Product (GDP) per capita [550]. The region shares a 2,500 mile border with Myanmar, Vietnam and Laos (primarily the first two). Yunnan's proximity to Southeast Asia explains why three of the four counties in China with the highest malaria incidence are in the province [551]; the province also has a high TB burden, possibly due to the high proportion who live in rural areas (over 70%) and poor economic status compared to China as a whole [552]. Parts of Yunnan lie within the region known as the "golden triangle" [553], a term for the area centred on the intersection of Myanmar, Laos and Thailand which was the world's largest producer of opium for most the second half of the twentieth century (it is now the second largest after Afghanistan) [553]. As a result of this, the majority of heroin trafficked into China arrives via Yunnan [554], and the province has the epidemiological distinction of being the first region of China to report HIV among indigenous people (as opposed to cases in tourists), specifically among non-Han PWID [555, 556]. Yunnan remains one of the provinces hardest hit by the HIV epidemic and ethnic minorities are still disproportionately affected, with PWID the main high-risk group [557]. HCV has been primarily studied among PWID in the province, with comparable anti-HCV prevalence to the rest of the country [557].

Yunnan has been a leader within China in terms of steps taken to combat and prevent disease. The first NSP was implemented in Yunnan in 1999 [556], one of the first OST clinics was established in 2004 and the first mobile clinic was introduced shortly afterwards (followed by roll out of the scheme to nine other provinces) [558], while an OST training centre was established in the capital Kunming in 2005 [559]. The province has led in promoting safe sex among commercial sex workers [556]. Non-governmental organisations (NGOs) also play a role; a recent call for new means of increasing screening and treatment of viral hepatitis received only one entry from China, specifically from an HIV NGO in Yunnan carrying out operational research into HBV screening for pregnant women and their partners in maternal and child health clinics (alongside HIV screening) [158].

It is within this context of multiple competing disease priorities, a significant PWID population and a proven track record of scaling up public health programmes that the Yunnan CDC invited

us to work with them in analysing the impact of prospective HCV interventions. This afforded us an opportunity to study HCV interventions on a local scale, giving greater resolution on the specifics of interventions and allowing more insight into the details of HCV interventions than is possible in a global analysis. In addition, past experience modelling HBV in the country has demonstrated how local disease control initiatives can ultimately influence national policy, suggesting that working with a specific province of China may allow us to inform the policy debate at the level of the country itself [560]. In short, Yunnan itself offers an ideal backdrop to explore and implement novel interventions to tackle the burden of HCV given its history of implementing such schemes, while such a China-based analysis has the potential to drive policy in the most significant HCV epidemic in the world.

This introduction will provide a description of HCV in China before detailing the current state of the response to the epidemic. An overview of the health system in China, past and present, is given within this discussion to help frame the public health response to HCV. Since various health economic evaluation methods will be applied in this chapter, a brief introduction to these techniques is given, followed by a description of the aims of this work.



Figure 5.1 - Provincial map of mainland China. Map made in R using the procedure and shapefile described in this reference [561].

5.1.2 Hepatitis C in China

Debates are ongoing and unresolved about the best estimate of anti-HCV prevalence[1] for China as a whole [563, 564]. The first documented instance of HCV (known then as non-A, non-B hepatitis because HCV was not identified until 1989) was a 1985 outbreak in blood plasma donors [565]. Voluntary, non-remunerated blood donation is the gold standard for blood collection because it encourages donation from the lowest risk individuals [235, 566]; not only did China not move to a voluntary scheme until 1998 (when commercial collection was made illegal [567]) but a practice existed in the country whereby frequent blood plasma donors were reinfused with red blood cells to avoid anaemia and enable more frequent donation [556, 568]. Though illegal, it was reported in 2005 that such practices may endure and could still be contributing to infection in rural China (though this is conjectural) [568].

In addition to blood donors, several risk groups with associated transmission routes have been identified in China: a 2002 study described higher than average anti-HCV prevalence in several groups including haemodialysis patients, female sex workers, transfusion patients and PWID [569]. Other studies have identified invasive procedures such as endoscopy as risk factors for HCV [570]. In addition, drug use practices other than opioid injecting drug use have been linked to HCV (as mentioned in chapter 2) [269, 571]. Lastly, an excess of potentially unsafe healthcare-related injections pose an ongoing risk for the transmission of blood-borne infections [572, 573] and have been linked to HCV outbreaks specifically [574], though the precise contribution that unsafe injections make to the HCV epidemic is unclear [219]. Of these higher risk groups, recent estimates based on case reporting have shown that the highest anti-HCV seroprevalence is among PWID [571].

This discussion suggests a dominant role for HCV transmission among PWID in terms of maintaining the current epidemic, while past infections were probably a result of unsafe blood products, a route that has been mostly eliminated through screening of blood products since 1993 [575]. Haemodialysis patients, MSM and persons undergoing invasive medical procedures are all groups at higher risk of HCV infection compared to the general population [571].

While these various transmission routes have contributed to China being host to probably the largest HCV epidemic in the world, the HBV epidemic in China has arguably garnered more national and international attention. This may simply be as a result of the existence of an effective vaccine with which to tackle the HBV epidemic. Whatever the cause, concern over HBV led to the first national survey of hepatotropic virus seroprevalence in 1992 [575]: this produced an estimate of 3.2% anti-HCV seroprevalence [576]. A follow-up survey in 2006 found a massive reduction to 0.43% seroprevalence (95% confidence interval (CI): 0.33% - 0.53%) [577]. Such a sharp decline,

[1] For the rest of this section anti-HCV prevalence is adopted as the measure of the HCV epidemic size since all but the most recent estimates utilise this measure and it simplifies discussion. WHO estimates themselves started with such results and ultimately converted to HCV RNA positive prevalence values according to a viraemic rate from Chinese data of 60% [562].

if not due to sampling error[2], is epidemiologically implausible due to ongoing HCV transmission [568], the lack of treatment availability over most of this period and the long-term, chronic nature of HCV disease. Explanations have, therefore, been sought for the discrepancy. Two recent proposals have been made [563, 575]. One argues that the original survey relied on early anti-HCV tests that are known to have low specificity (so delivered many false-positive results) and thus overstated the extent of the epidemic in 1992 [575]. The other explanation counters that the later study itself was flawed: the 2006 survey originally investigated only HBV infection and the blood samples were then frozen. Anti-HCV tests were not performed until 2011 resulting, it is argued, in an underestimate of the true positive rate (presumably as a result of sample degradation) [563].

The controversy and ongoing debate illustrates that utilising estimates at the smallest possible scale offers the best route to calibrating and using an HCV model in China: there are better estimates available and greater resolution regarding the possible public health response [579]. In the following section a summary of the health system in China is given before describing the specifics of the response to the HCV epidemic. These discussions demonstrate the types of interventions that could plausibly be rolled out in China given the context of its health system and the existing state of the response to HCV.

5.1.3 Chinese public health policy

In the 1950s the Communist Party of China eliminated private provision of medical services and introduced a centrally funded system of healthcare that made access to basic services virtually universal [580, 581]. This system oversaw huge improvements in public health indicators, albeit from the extremely low base set during the 'Great Leap Forward' of 1958-1962 (during which time tens of millions of Chinese people died as a result of famine): between 1962 and 1982 infant mortality decreased three-fold while life expectancy rose from 45 to 68 years [419]. These improvements took place on the backdrop of Mao's cultural revolution (1966-1976) that saw doctors forcibly relocated to collective farms and medical schools closed (standard five-year medical degrees were not reinstated until 1977) [580]. Part of the reason for improvements in coverage was Mao's focus on the peasantry; he launched an initiative in 1968 whereby individuals without prior medical training were given 3-6 months training and then sent out into the countryside to improve access to services [582]. These so-called barefoot doctors helped improve coverage of immunisations and safe delivery of children along with bringing about improvements in sanitation [582].

Despite the gains achieved during those decades, market-oriented reforms introduced by Deng in the 1980s led to the rapid dismantlement of this successful health system [581]. Policy and funding were decentralised to the provinces resulting in the proportion of healthcare spending met by central government being halved [581]. This had the effect of reducing the risk-pooling and redistributive benefits of centralised funding and control. Furthermore, health coverage, particularly in rural areas (with smaller tax takes), declined: the number of rural health workers (primarily

[2]This is deemed unlikely due to the number tested and broad geographical coverage through over 100 disease surveillance sites [576, 578].

barefoot doctors) fell from 3.5 million in 1970 to around 60,000 in 1986 [582]. A secondary problem was the implementation of regulation that created price ceilings to ensure access to basic health services did not become prohibitively expensive in the newly-created private markets. To counteract these restrictions, newer drugs and services could be offered with 15% mark-ups while at the same time doctor salary structures were modified to an activity-based model (based on fees-for-service payments) resulting in three quarters of doctors' income coming from such payments [583]. Both of these changes led to higher cost services being pushed on patients and, ultimately, to rapid increases in health spending [581]. Another feature of the health system that drove up costs (and continues to do so) is that general practitioners often work in hospitals and seldom act as gatekeepers meaning patients can refer themselves to expensive outpatient specialists [583].

As a result of these changes, in addition to the concentration of hospitals in urban areas and the difficulty in encouraging doctors to work in rural areas [583, 584], the period of privatisation in the 1990s was marked by a widening gap between rural and urban areas: the uninsured population grew from 29% in 1981 to 79% in 1993, primarily as a result of increases in the rural uninsured; the gap in health outcomes between people in rural and urban areas grew (such as in the ratio of rural/urban mortality rates); and a large disparity emerged between the proportion of rural patients who could not follow medical advice as a result of inability to pay [585]. Health system indicators reached a nadir in 2000, with out-of-pocket (OOP) expenditure reaching 59% as a proportion of total health expenditure [586].

The Chinese government responded to this array of problems in the health sector by successively introducing three social health insurance schemes. The first scheme in 1998 targeted only the urban employed. A subsequent scheme launched in 2003 provided insurance to rural households but with low financial commitments from the government and extremely high deductibles for inpatient expenses. The third scheme instigated in 2007 was aimed at urban residents not included in the employment-linked insurance scheme [581, 586]. Evidence suggested that shortcomings in public health provision in rural areas were impeding poverty reduction efforts, which galvanised political will and led to further investment in health insurance schemes [581]. While coverage did drastically increase, by 2006 growth in OOP and overall expenditure still outpaced government spending on healthcare [587].

A 2009 initiative aimed to change this and set targets for universal health insurance coverage [588]. This set of reforms led to a doubling of central government healthcare spending [586], reduced OOP payments to less than 30% in 2016 [589] and by 2011 close to universal insurance coverage had been reached [590]. Yet catastrophic health expenditure (CHE) remains a key problem particularly in rural areas [591]: universal insurance coverage does not necessarily mean universal access to affordable services. The most recent set of reforms, accordingly, aim to improve affordability of healthcare: the "Healthy China" plan was introduced in the 12th five-year plan and reaffirmed in the 13th five-year plan (covering 2016-2020). Though light on specifics, one concrete commitment is to expand the severe illness coverage, which greatly increases the reimbursements available to those experiencing severe illness (such as liver cancer), with the aim of reducing CHE [592]. Such

efforts suggest an awareness at the highest levels of government regarding the aspects of the health system that are not working and a willingness to attempt to deal with growing Chinese dissatisfaction with their health system [583].

In addition to this complex web of schemes, specific disease intervention programmes have been implemented. Of particular importance is the response to HIV in China as it was the first programme to offer free treatment. Attention was focussed on HIV in China when then-premier Wen Jiabao visited HIV patients on world AIDS day in 2003 [593]. At this time free HIV treatment programmes were being trialled in a handful of counties [594] and these were then rapidly expanded nationwide, with 97% of eligible patients receiving free ART by 2008 [548]. China has followed the evolution of WHO ART treatment guidelines (that specified treatment only for those at specific stages of disease) leading, in 2016, to free treatment for all people living with HIV regardless of disease stage [595, 596].

It remains the case, however, that the majority of disease is dealt with in a health system that is fragmented and inefficient, a consequence in part of the existence of three independent insurance schemes that are decentralised to the provincial or even county levels. Various trials of integration, both vertical (from provincial to national level) and horizontal (between adjacent insurance schemes), have been carried out and it seems likely that consolidation of these schemes will be necessary to reduce further the healthcare equity problems that persist in China [586, 597]. In addition, alterations to the fee-for-service model of payments could better align incentives between patients and doctors and reduce the inducement of demand that drives up costs for the system as a whole [588, 598]. Lastly, the response to HIV has shown what can be achieved when political will is focussed on a particular disease. It is within this complex and changing framework for healthcare provision that the response to viral hepatitis as a whole has been developed and it is to this that we now turn.

5.1.4 The response to hepatitis in China

The HBV epidemic has met with a large public health response in China: infant vaccination was recommended in 1992, provided at a small cost from 2002 and made free of charge and mandatory for all infants from 2005 [599]. These measures among others resulted in HBsAg seroprevalence decreasing by 90% in children under 5 years old between 1992 and 2006 [599]. Public health policy regarding HBV has since evolved from being a matter of prevention to a matter of treating the millions of people in China chronically infected with HBV. To that end, in 2016 the government negotiated lower prices of the drug tenofovir which suppresses the HBV virus (no cure exists) [600]. The following year the drug was included on the National Reimbursement Drug List (NRDL) which, though not making the drug free as was the case with HIV (see above), still renders it much more affordable (providing 80% reimbursements to those eligible through certain insurance schemes) [601]. The government has not rested on this progress: HBV is the first of only six diseases mentioned explicitly in the most recent five-year plan and the only hepatotropic virus included [592][3].

[3]The other five (in order) are HIV/AIDS, tuberculosis, schistosomiasis, malaria and leprosy.

This focus on HBV extends down to the provincial level: in Yunnan Province, for example, integrating HBV screening into a provincial HIV/AIDS programme was trialled as a means to increase diagnosis rates for the disease [158].

HCV, by contrast, has been a focus of attention only comparatively recently (probably due to the lack of effective treatments) [549]. There are low levels of HCV serostatus awareness in the country [602] along with low knowledge of HCV itself: only 25% of newly diagnosed individuals report knowing about the disease at all prior to testing [603]. A particularly concerning issue in China, revealed by a 2014 survey carried out by the World Hepatitis Alliance, is the reported stigma associated with the disease [603]. This is illustrated by the fact that only 11% of HCV-positive respondents had told their close family about their diagnosis (compared to 75% in Malaysia and 99% in Japan) [603]. These features of the epidemic point to the challenges that will be faced in the following years when scaling up HCV intervention programmes in China. Yet the success of HBV interventions (which attracts similar levels of reported stigma as HCV [18]) indicate that these issues are not necessarily an impediment to programme success.

In addition to low status awareness, access to treatment has historically been low, with the aforementioned national survey suggesting that very negative perceptions regarding PEG-IFN+RBV treatment (on the part of patients) may have reduced uptake of treatment in the past [603]. A large number of patients have had to meet outpatient PEG-IFN+RBV costs entirely OOP and even those covered by one of the three insurance programmes described in the previous section will likely have had to pay for a significant fraction of their HCV care costs [602, 604]. In addition, as has happened elsewhere, patients are delaying treatment in light of the (presumed) imminent availability of DAAs [603, 605].

Considering the new treatments, China may have treated around 200,000 people with DAAs[4], but as of February 2018 DAAs were not reported as being included in national insurance schemes [606]. In September 2018, a sofosbuvir-based HCV drug was listed on the National Essential Medicines List (NEML) [607]. This may pave the way for expanded access; inclusion in the NEML is supposed to lead to reduced copayments and the elimination of drug mark-ups [608, 609]. This is, however, not always the case [610] and corruption may be undermining the aims of the NEML [611], while it is not yet known whether, and to what extent, the drug will be reimbursable by health insurance agencies (Chan Polin, WHO Western Pacific Regional Office, personal communication, 7th September 2018). Ultimately, there will not be wide-scale access to DAAs until they are included in these schemes and OOP payments are minimal. Such access is required to achieve significant burden reduction: nearly 7 million treatment courses were delivered by 2030 in China in the comprehensive package of interventions described in the previous chapter (and this is within the context of extensive reductions in transmission as a result of implementing prevention inter-

[4]It was reported in a WHO access to treatment report in 2016 that (as of September that year) 200,000 DAA treatment courses had been delivered in China [483], however, a 2018 update stated the same number of treatment courses had been delivered by the middle of 2017 [494]. This suggests at best stop-start progress in rolling out these effective new therapies or else a lack of concrete knowledge concerning the scale of implementation.

ventions as well); this will not be achieved without integration of DAAs into national healthcare provision.

A key impediment to wide-scale roll out of DAAs in China, as in other upper-middle-income countries, is cost. These countries are excluded from voluntary licensing agreements that would allow them to either make or otherwise purchase generic DAAs such as sofosbuvir or daclatasvir [483, 494]. This leaves China in the position of having to pay a reported 8,900 USD for a 12-week regimen of Sovaldi (the tradename of Sofosbuvir from originator company Gilead) [612], which must then be combined with (for example) daclatasvir which costs 3,900 USD for an equal-length supply [494]. Such costs are prohibitive for universal coverage given the scale of China's epidemic and go a long way to explaining why, despite inclusion in the NEML, HCV drugs have not yet been made widely available within reimbursable schemes as was the case for HBV.

Encouragingly, substantive progress has recently been made with regards to reducing the costs of DAAs in China. In August 2018 Gilead withdrew its patent application for Sofosbuvir in China which had been mired in court proceedings [612, 613]. The US-based advocacy group I-MAK (Initiative for Medicines, Access & Knowledge) argued successfully that the company's patent application was so broad as to impede any competition via development of similar drugs; pharmaceutical companies (including Bristol-Myers Squibb who make daclatasvir) often register multiple patents for related compounds (prodrugs) to prevent development by competitors, a procedure known as 'evergreening' [614]. That the patent was withdrawn suggests that the prospects for Gilead of successfully defending the original patent in court were poor, paving the way for legal production of generic versions of DAAs as early as 2019 [613]. Similar developments have enabled DAAs in Egypt and India to be produced and purchased at radically reduced prices [142, 612, 613]. The withdrawal of a key DAA patent comes in the wake of reports that China is increasing pace of development of new DAAs as well, which would avoid patent issues altogether [606].

These changes, in combination with recent developments such as the inclusion of HCV drugs on the NEML, suggest that a paradigm shift in HCV treatment access could well be in progress [606]. Past changes in policy, such as the move to cheaper HBV drugs, have been motivated not only by medical need and epidemiological impact but also by economic arguments such as the potential for cost savings [615]; such economic assessments have continued to be used to argue for various policy changes (such as those concerning HIV programmes) in the country [616–618]. Making the case for interventions in this way not only relies on producing estimates of public health impact (often by mathematical models) but also on constructing economic metrics to evaluate the programme under consideration. To that end, the following section introduces several economic evaluation techniques for use later in this chapter.

5.1.5 Methods for health economic evaluation

To evaluate HCV public health interventions in Yunnan Province will involve adapting the existing epidemiological model and producing relevant economic analyses to evaluate the programmes under consideration. Here the basics of economic evaluation techniques are described; the precise

methods and means of using them that are adopted in the work on Yunnan will be summarised below in the methods. Following Drummond et al. (2015) [307], approaches to economic evaluation of health care programmes, sometimes called health technology assessments (HTAs), can be divided into several sets of techniques including cost-effectiveness analyses (CEA) and cost-benefit analyses (CBA). The costs included in these analyses vary with the 'perspective' taken.

Perspective. All economic analyses of health interventions involve an assessment of relevant costs. What constitutes a "relevant" cost varies with the perspective taken. A patient perspective could be taken which includes only those costs accruing to the patient. These costs may include what are sometimes termed direct medical costs (such as costs of treatment met OOP) and direct non-medical costs such as transport to medical facilities. Beyond these, a patient will experience a loss of net income associated with time off from work due to illness and this may or may not be included in economic analyses from the patient's perspective [619]. A healthcare provider perspective, by contrast, would examine costs accruing only to a particular payer within the health system itself, for example, by specifying a National Health Service (NHS) perspective in the UK [620].

Analyses from such 'one-sided' perspectives can lead to undesirable outcomes such as cost-shifting, whereby an intervention is deemed beneficial but in reality shifts the burden from one sector to another [621]. To avoid this, another approach is to take a societal perspective in which all costs and effects that are impacted by an intervention are included [622]. Precisely what is included in such a societal perspective is not well defined and analyses often report inconsistently on their perspective [622]. Following Neumann (2009), a broad definition of societal perspective is any analysis that includes in its costing both direct medical expenses and at least direct non-medical expenses (travel costs or OOP expenses) or productivity losses through lost labour (due to morbidity in terms of sick days or mortality) [622]. This latter quantity can be assigned a cost through the human capital approach (described below).

Cost-effectiveness analysis. CEA assesses the cost difference associated with implementing a particular intervention compared to a base case comparator scenario (such as the status quo). This cost difference, Δcost, is then combined with a measure of health outcome changes given the implementation of the intervention, Δhealth outcome. Two common measures for quantifying the change in health outcomes are the quality adjusted life year (QALY) and the disability adjusted life year (DALY). QALYs measure utility on a scale of one (perfect health) to zero (death). Similarly, DALYs measure disease from zero disease (a DALY of zero) to death (a DALY of one). Both quantities are estimated in different ways but a detailed discussion of the differences between DALYs and QALYs is beyond the scope of this thesis. The key point is that these generic measures combine information about quality of life with quantity of life and allow for comparisons to be made regarding different health interventions [307][5].

[5]It should be noted that, while Drummond et al. (2015) draw a sharp distinction between cost-utility analysis (CUA) [307], which is what has just been described, and CEA, the terms are used interchangeably [623] and the terminology of CEA is far more common in health economic evaluation, hence we adopt the term CEA rather than the arguably more accurate CUA.

Given an estimate of the changes in costs and health outcomes, the quantity most often calculated by CEA is the incremental cost-effectiveness ratio (ICER):

$$\text{ICER} = \frac{\Delta\text{cost}}{\Delta\text{health outcome}},$$

A positive ICER, accordingly, can either indicate a more costly but beneficial programme or a cheaper but less beneficial outcome. A negative ICER indicates either a less effective and more costly intervention (which would never be chosen) or a cheaper, more effective intervention (which is always chosen).

ICERs are calculated where a range of interventions are being considered and an order is established by identifying the most cost-effective intervention (lowest ICER), and then identifying the most cost effective given that the first intervention is already implemented: each intervention is, therefore, considered incremental to the last. Where the comparator in the CEA is just the status quo, and calculations are not performed incrementally between interventions considered, the quantity calculated is the cost-effectiveness ratio (CER).

Cost-effectiveness thresholds and ICERs. Given a positive ICER, a decision must be made as to whether to implement an intervention or not, commonly by comparison of the ICER to a set value termed the cost-effectiveness threshold (CET). When investments are made in a particular public health activity, those resources are not then available for use in other parts of the healthcare system. The health benefits foregone due to the commitment of resources to particular interventions define the opportunity costs of the intervention [624]. The opportunity cost is, therefore, the ratio of the cost reduction resulting from displacing other interventions in the healthcare system to the health benefits lost as a result [624].

The CET should equal these opportunity costs; it can then be used to determine whether or not an intervention offers greater, or lesser, health benefits than those lost by the redirection of resources. The word 'should' is used because a variety of rules of thumb have been used to set the CET (such as in lower- and middle-income countries that the CET is $1-3$ times a country's GDP) [625], which are often more aspirational than reflective of the true opportunity costs. Such notions are problematic because if they are followed in systems where the actual opportunity costs of spending are lower than the CET value used, interventions will be adopted with net benefits lower than the interventions they displace, harming overall public health [624–626].

For this reason empirical methods for estimating the CET (considered as the foregone benefit of displaced spending) have been developed. These attempt to calculate the opportunity costs (and so an appropriate CET) by investigating how changes in health spending affect health outcomes. The method was first applied to the UK and gave a result of approximately 50% of GDP in that year, less than previous estimates [627]. Such estimates have since been made for a number of other countries [624, 626]. Though such methods have been developed, it ultimately falls upon national agencies to determine how to utilise estimates of ICERs, and guidance relating to CETs is usually framed in such a way as to allow considerable leeway in decision making [627].

Cost-benefit analysis. Where CEA facilitated the comparison of interventions across different disease areas through the specification of a general measure of quality of life, CBA facilitates cross-sectoral comparisons (within and without the health setting) by assigning a money value to health outcomes themselves [307]. This enables construction of benefits in time-period t as $b(t)$ in the same units as costs $c(t)$. The conversion of health benefits to money values is a topic fraught with controversy. One approach to evaluating health benefits is to adopt the human capital approach whereby the value of additional life is quantified according to the additional contribution to the labour market using the average wage. The above net benefit corresponds, then, to assessing a health "investment" in terms of the pay-back on this investment via an individual's "increased production in the market place" [307]. The human capital approach was disputed by welfare economists (who are concerned with individual preferences) because it does not ultimately reflect what an individual is willing to sacrifice in order to gain from the proposed health programme [628, 629]. Various methods have since been adopted to try and estimate the value of goods an individual would actually forgo in order to gain an additional year of life, sometimes termed the value of statistical life (VSL) [630, 631]. These studies have led to concepts such as "full-income" whereby national income is part of the calculation of the VSL (as in the human capital approach) but with a multiplicative factor included (estimated at 2.3 times the per-person income in low- and middle-income countries). This is designed to "[go] beyond national income accounting to also assess the direct welfare gains of improved life expectancy" [632].

By adopting such methods in CBA, health intervention programmes can be assessed in a way that is comparable to other interventions (such as investments in environmental interventions). Probably due to difficulties in interpretation and the challenges of valuing human health directly in money terms, CEA is a more commonly utilised tool for HTAs than CBA [307].

Return on investment. Within the context of CBA, the benefit-cost (B/C) ratio may be calculated. If the (discounted) sum of benefits is denoted B and of costs C then the B/C ratio is defined as:

$$\text{Benefit cost ratio} = \frac{B}{C}.$$

From this can be defined the return on investment (ROI):

$$\text{ROI} = \frac{B}{C} - 1 = \frac{B - C}{C}.$$

This is the net benefit divided by the costs. What constitutes the 'cost' is to some extent arbitrary (since in CBA everything is cast into money terms) [629], however, a natural 'cost' to consider is the cost of the intervention components specifically, termed the investment costs, while the benefits constitute the sum of all other cost changes and benefits that result from this investment. Investment costs, so considered, may refer to the costs of expanding harm reduction interventions for PWID, for example, or changing treatment drugs to DAAs. Benefits refer both to the evaluation of health benefits as described above with regards CBS, as well as any other cost changes, for example those related to disease care. This distinction is intended to highlight those components of costs that are directly under control by, for example, a government agency or entity responsible for the

intervention and who may bear the investment costs. These can then be considered a public health "investment" while the overall balance of costs (Δcosts) viewed from society as a whole constitute the net returns on that investment.

Summary. A range of methods are available that link the economic with the epidemiological and clinical benefits of health intervention programmes and attempt to ascertain whether they should be adopted or not. CEA is the most common method, which delivers an assessment of the cost changes due to a programme relative to the health benefits it offers. Such an assessment (the ICER) must be incorporated into a decision process that determines whether or not, given a particular value for the ICER, an intervention should be implemented. One way is to assess the ICER against an empirical estimate of the opportunity costs. CBA offers a more integrated way of assessing health interventions by eliminating the calculation of health measures (like QALYs or DALYs) by using the value of a statistical life to quantify all benefits in monetary terms: this analysis may be expressed in terms of the ROI which can be used to investigate the economic return on health investments. The assessment of costs in all methods depend on whether a societal or more narrow healthcare provider perspective is used.

Application to HCV interventions in China. A small number of health economic evaluations investigating HCV interventions in China have been carried out [633–635]. Like those described in chapter 2, these publications are all cohort models that investigate the cost effectiveness of providing DAAs in place of PEG-IFN+RBV to a cohort of diagnosed individuals. Chen et al. (2016) investigated the cost effectiveness of providing DAAs to genotype 1b patients in China from a health sector perspective [633]. The high costs of DAAs (96,000 USD in that study) prevented the intervention being cost effective and only an 81% reduction in price led to the intervention being cost effective at a threshold of 1 times China's per-capita GDP. Chen and Chen (2017) and Lu et al. (2018) both performed similar analyses, though the progressively lower DAA prices (12,000 USD and 4,400 USD respectively) led to the conclusion in both papers that providing DAAs in place of PEG-IFN+RBV is highly likely to be cost effective [634, 635]. In the latter paper the cost had dropped sufficiently far that DAAs were cheaper than PEG-IFN+RBV leading to a cost-saving conclusion [635]. Implementing DAAs in this situation should happen automatically; the only reason for not doing so is lack of access to drugs at these low prices, a problem that will potentially be circumvented by the recent developments described above.

5.1.6 Aims

Chinese government interest in DAA production and the putative development of an HCV strategy (as indicated by the inclusion of an HCV drug in the NEML), combined with continuing efforts to improve overall healthcare provision, indicate that national scale up of HCV treatment programmes is both feasible and even likely in the near term.

The global model has demonstrated the importance of increasing the rate of diagnosis and subsequent treatment; practical national and sub-national strategies are now required to determine how to screen, diagnose and ultimately treat more HCV-infected individuals. We worked with

Yunnan CDC to explore alternative screening and testing strategies that could be used to improve access to DAAs.

Given this suite of intervention options, we aimed to answer the following questions: what are the epidemiological impacts of implementing these interventions in Yunnan Province? What are the economics costs? Are these interventions cost effective from a health care sector perspective and how do they compare to each other? Lastly, what are the possible societal returns on investment delivered by these interventions?

5.2 Methods

The key changes to the global model that allow us to answer these questions are described in this section. In short, these include epidemiological model extensions, such as incorporation of local data and the addition of new risk categories that were required to model the interventions unique to our work in Yunnan; alterations to the calibration procedure; and the development of an economic modelling component to allow health economic evaluations to be carried out.

5.2.1 Modelling the epidemiological impacts of HCV interventions in Yunnan

This section describes how the epidemiological components of the global model were adapted to simulate the HCV epidemic in Yunnan and how interventions were modelled. First we describe the interventions themselves. These were developed in collaboration with Yunnan CDC during a week of meetings in the provincial capital Kunming; we developed the following set of intervention strategies in an iterative process. This involved understanding the available capacity for HCV interventions, suggesting means of improving screening or treatment, receiving feedback from staff in the CDC and then honing the strategies until they were agreed upon.

Intervention scenarios. Following this process, three 'levels' of scenario (scenario sets) were considered. Scenario set 1 considers the impact of introducing DAAs and then improving uptake among those recently diagnosed. Scenario set 2 simulates additional screening in a range of groups who are termed "within the system", meaning they have regular contact with health professionals, either public or through NGOs and are available to be tested for HCV. Scenario set 3 introduces further screening and diagnosis measures that go beyond the high-risk groups considered in scenario set 2 but were deemed practical within the consultation process.

In estimating the epidemiological impact of interventions, we added intervention elements successively in simulation, following the order in which Yunnan CDC deemed interventions were liable to be rolled out (scenario set 1 is most likely and scenario set 3 is the most ambitious). This allowed the full impact of all interventions to be investigated, which is a probable outcome once HCV programmes begin to be scaled up in China as a whole. All interventions begin in 2017. It is assumed that intervention strategies will be maintained and are projected to 2100 (to allow lifetime benefits to be calculated in the health economic analyses, see below). The three sets of scenarios are summarised in table 5.1 and described here.

Status quo. Estimates of the number of HCV diagnoses in 2015 and 2016 were available (10,000 diagnosed HCV-RNA positive); values before 2015 were assumed zero as they are believed to be small compared to recent years. The rate of diagnosis in 2015 or 2016 was chosen to match the given numbers. This rate was then left fixed in the following years modelling a constant rate of care-seeking behaviour (the number diagnosed thus depends on the number infected).

Treatment in status quo is specified according to a fixed proportion of those who have just been diagnosed progressing to treatment. The proportion of those who are diagnosed being treated is based on local data that 30% were treated with PEG-IFN+RBV in 2015 and 2016 of whom 50% dropped out of treatment; we assumed that all those who drop out of treatment are not cured and remain within the diagnosed and untreated compartment (compartment D according to the state variables defined in chapter 3). The remainder progress to diagnosed, failed (compartment Q) or cured (compartment C) according to genotype-dependent SVR rates (see chapter 3). This proportion completing treatment (15%) is kept constant from 2015 onwards in status quo.

Scenario set 1. In scenario set 1 DAAs are introduced.

Scenario 1a: Switch to DAAs. Switch PEG-IFN+RBV to DAAs in status quo.

Scenario 1b: DAAs to newly diagnosed. Increase the proportion of newly diagnosed persons accepting and completing treatment from 15% to 90% in line with local targets for successful completion. This is plausible based on evidence that patients in China (as elsewhere) avoid treatment with PEG-IFN+RBV due to the difficulty of completing the regimen; in a DAA regime they are more likely to accept DAA treatment [603]. Furthermore, as discussed in chapter 2, treatment regimens involving DAAs are much shorter and easier to tolerate leading to an increase in the proportion completing treatment.

Scenario 1c: DAAs to previously diagnosed. 25% of the those diagnosed in past years are successfully found and offered treatment. This represents a warehousing effect, whereby those who have not started treatment when they were first diagnosed are able to return to care and seek treatment once DAAs become available. Indeed in surveys in China this has explicitly been cited as a reason to avoid treatment now since DAAs are not yet widely available but may be soon [603].

Scenario set 2. This set of scenarios introduce a screening component within a range of groups who are at higher risk of transmission of HCV. Individuals are available to be tested through being "in contact with an existing programme" as a result of interactions with NGOs or public health services that work with MSM, PWID, FSW or people who are HIV-positive. Using data on the size of these groups a set of scenarios were simulated in which screening was rolled out, successively, to each group.

The simulation of the four scenario set 2 interventions is broadly similar; to illustrate how these scenarios are simulated we take the example of the MSM screening strategy. The details apply to the other three scenarios which are described briefly below. A "reachable" group

size was specified by the Yunnan CDC and this number of people are screened for HCV in the model. For example, the number of MSM reachable through such groups is estimated to be 7,000; this is translated into a proportion of MSM screened for HCV in 2017 in the model. In subsequent years, it is not deemed practical to keep screening such a large initial fraction of MSM. Rather, it is assumed that each year there are new entrants to the programme and that the same proportion of these will be screened as were screened in the first year. To estimate the rate of new entrants to the NGO programme, we approximate it as equal to the rate of leaving the MSM category as a whole (as a result of premature death, migration or cessation of sexual activity). This rate is calculated dynamically in the model; these values were observed in model development to be reasonably constant and so approximate averages were estimated and used as model inputs so that the exact number being screened could be specified explicitly; the Yunnan CDC have agreed with the suggested number of annual screens indicating that the screening numbers produced by the model are plausible.

Scenario 2a: Screen MSM. It is estimated that 7,000 MSM could be reached via NGOs in year one. In subsequent years 375 MSM are screened.

Scenario 2b: Screen in HIV care. It is estimated that 100,000 people are HIV-positive in Yunnan of whom 70% are in treatment (or accessible to healthcare professionals through routine testing) yielding 70,000 HCV screenings in 2017 [636]. To estimate the rate of entry to this group (in order to estimate the possible annual number of people newly presenting in HIV care), it is noted that the number of new infections in 2016 was approximately 12,000 [637] (similar to the 10,500 in 2012 suggesting the value is reasonably stable [636]). Multiplying by the proportion in treatment provides an approximate number newly available for HCV testing of 8,750, which is adopted as the annual screening rate from 2018 onwards.

Scenario 2c: Screen PWID. 38,000 PWID are available to be screened in 2017 (resulting from accessing various support or treatment services). The annual number screened (from 2018) is set at 2,500 based on the rate at which PWID leave this group (as calculated by the model, see discussion above).

Scenario 2d: Screen FSW. 20,000 FSW are available to be screened through contact with NGOs in 2017, dropping to an annual number screened for HCV of 4,500 based on the leaving rate from this group estimated by the model.

Scenario set 3. This scenario simulates increasing screening beyond high-risk or vulnerable groups to the general population.

Scenario 3a: Screen pregnant women. Following the procedure for calculating HCV prevalence in pregnant women (detailed below), the estimated number of women presenting to antenatal clinics (ANCs) each year is estimated from 2017 onwards and it is assumed that 90% of them accept HCV tests. 90% of those accepting tests will then go on to

complete HCV treatment. For reference, the number of women available to be tested in 2015 (the number of births that year) was approximately 600,000 [419].

Scenario 3b: Screen male partners of pregnant women. This scenario modelled reaching 90% of the male partners of those women who accepted HCV testing, and of whom 90% accept treatment. The male partners were assumed to have the same age distribution as their partners (from which the HCV prevalence of men screened was derived).

Table 5.1 - Yunnan intervention scenario details.

Scenario	Name	Details
SQ	Status quo	PEG-IFN+RBV only. 10,000 diagnosed 2015 & 2016; constant rate of diagnosis thereafter. 15% complete treatment 2015 onwards.
1a	Switch to DAAs	All those receiving PEG-IFN+RBV treatment in status quo receive DAAs.
1b	DAAs for newly diagnosed	90% of those newly diagnosed complete treatment.
1c	DAAs to previously diagnosed	25% of those diagnosed in previous years return for treatment.
2a	Screen MSM	7,000 MSM screened in 2017; 375 screened each year thereafter.
2b	Screen in HIV care	70,000 HIV+ people screened in 2017; 8,750 screened each year thereafter.
2c	Screen PWID	38,000 PWID screened in 2017; 2,500 screened each year thereafter.
2d	Screen FSW	20,000 FSW screened in 2017; 4,500 screened each year thereafter.
3a	Screen pregnant women	90% of pregnant women accept HCV test and 90% of those positive complete treatment.
3b	Screen male partners of pregnant women	3a + 90% of the male partners of those women who are tested in 3a accept an HCV test and 90% of those positive complete treatment.

Listed are those elements that change intervention scenario to intervention scenario. Colours are those used on the graphs in the following. In the primary analysis, each scenario incorporates all elements of the previous scenarios. Where interventions are considered independently they do not, except in the case of scenario 3b which always incorporates scenario 3a.

Changes to the global epidemiological model. Demographic data were available for Yunnan

Province specifically [638]. The majority of necessary demographic parameters were available (population size by sex and year, number of deaths by year and the sex ratio), however, these were not available with the age-stratification used in the model. Furthermore, projections (for future demographic parameters) were not available. To solve this, age-distributions and percentage annual changes past 2016 from the overall China data used in the global model were combined with the Yunnan-specific data to produce comprehensive demographic estimates for use in the model. Where data were lacking entirely, China national estimates were used. Table 5.2 shows the new parameters in the Yunnan model and describes changes to existing parameters. Parameters not in table 5.2 retain their original formulations or values, see table 3.2 in chapter 3.

Given our aim to model more risk categories in order to simulate the interventions developed with the Yunnan CDC, two new risk groups were added to the model: MSM, and female sex workers (FSW). The MSM group contains the higher risk (for HCV infection) HIV-positive MSM group in which prevalence would be expected to be higher; heterosexual transmission is not modelled (see chapter 2 for discussion of transmission routes) [639], however, FSW may well have higher HCV prevalence as a result of other risk behaviours such as non-injection drug use [640]. The proportions in the risk groups were available from sentinel surveillance surveys carried out in the province (table 5.2); the assumption is made that the groups are mutually exclusive based on discussions regarding the data with the Yunnan CDC. These two groups are included in the model, in addition to PWID (as in the global model); the general population is redefined to comprise the population excepting PWID, FSW and MSM. These are incorporated into the model defined in chapter 3 by extending the index l (risk group) to encompass these new risk groups (changing the number of compartments accordingly): $l \in$ general population, PWID, MSM or FSW.

The risk of infection in the new risk groups (such as FSW) was modelled in the same way as PWID, namely by specifying an increased risk of infection additional to that experienced in the population as a whole:

$$\Lambda_{i,FSW}(t) = \beta_{i,GP}(t) p_{all}^{eff.}(t) + \beta_{FSW}(t) p_{FSW}(t),$$

and similarly for MSM. Terms in this equation are as defined in chapter 2 or table 5.2 below. $\beta_{FSW}(t)$ is the additional risk of infection accruing to FSW. This is modelled as a flexible two-level spline in the same way as PWID, with a constant value in the past (before 1950) changing to a new constant value in 1980. The assumption is that risks of infection in the risk groups are low in the past (achieved by drawing values from high-rate exponential prior distributions) and can be any value now (achieved by drawing values for the risk spline from uninformative low-rate exponential prior distributions). The same approach is used to simulate increased risk in MSM. An increase in risk in FSW and MSM begins at age 15 and finishes at age 65, following HIV models in modelling various high-risk behaviours between these ages [641, 642].

Additional outputs calculated. With the additional risk group structure, we included in this analysis a means of investigating the relative importance of different risk groups to the epidemic. In addition to reporting the proportion of active infections in each risk group, we estimated the population attributable fraction (PAF) of incident HCV infections in the different risk groups. PAFs

were calculated by turning off additional infection risk in each group individually and comparing incidence rates with that of the original analysis (following the procedure described here [643]) between the years 1990-2017. We also report on the number of infections in 2018 from each risk group.

Changes to the calibration procedure. Estimates of anti-HCV prevalence among pregnant women, PWID, FSW and MSM were available over 2-year intervals between 2010 and 2016 (Yunnan CDC sentinel surveillance surveys 2010-2016); point estimates were converted to viraemic prevalence values according to a viraemic rate of 60% (as used in the global model) [562]. The prevalence in a particular high-risk group is calculated as the ratio of positive to total number in the respective group. To calculate prevalence among pregnant women, the number of women in each age group was multiplied by annual age-specific fertility rates and multiplied by the average length of a pregnancy to estimate the number of current women pregnant. Taking the ratio of those HCV-positive to the total number provides an estimate of HCV-positive pregnant women.

The calibration approach described in chapter 3 involves calculating the likelihood of a particular set of parameters conditional on a particular datum. The likelihood is equivalent to the probability distribution of this datum conditional on a particular set of model parameters. The prevalence data were all assumed to be beta distributed (as was the case for the overall population prevalence in the global model). To produce a beta distribution appropriate for each prevalence datum, 95% confidence intervals were constructed around the prevalence point estimates and then a beta distribution was fit to the point estimates (using the central prevalence estimate as the mode and requiring that 95% of the distribution falls between the upper and lower confidence values). 95% confidence intervals were not available from the original data and so these were imputed from Chinese data: PWID confidence intervals were used to impute the percentage width of the high risk group values (PWID, FSW and MSM) while the overall population width was used to impute the pregnant women prevalence confidence intervals.

Additionally, numbers of cirrhosis and HCC deaths were available in the same age intervals (5-15, 15-50, 50-70 and 70+ years old) as in the global model, for all the years between 2014-2016 (cirrhosis) and 2008-2016 (HCC) inclusive from the Yunnan death registration system. From these values, estimates were made of the proportion of such deaths attributable to HCV. 5-25% of cirrhosis deaths (with a central value of 15%) were estimated as due to HCV following literature searches in Chinese databases[6] along with English-language sources; 10-30% of HCC deaths were estimated as attributable to HCV with a central value of 20% [644, 645]. These ranges were deliberately chosen to be wide reflecting the broad variations in estimates of these quantities and the lack of Yunnan-specific data. A crude measure of the applicability of these measures is to compare the total HCV-attributable cirrhosis or liver cancer deaths in Yunnan to GBD estimates of China as a whole (by multiplying by a factor of 30, the relative size of Yunnan compared to China): doing this shows that the central values are approximately in line with GBD estimates (compared in 2016)

[6]Citations are in Chinese and are not shown.

[9] showing that the central estimates and the overall mortality numbers for Yunnan are consistent with estimates derived for China as a whole.

Calibration to mortality values followed the same approach as in the global model. This is because, while in the global model the calibration is to IHME estimates and here calibration is more directly to data (which could suggest the use of a different approach in calibration), the Yunnan data have to be adjusted to produce HCV-attributable estimates of cirrhosis and HCV mortality. As a result, there is considerable uncertainty in the mortality estimates despite deriving more directly from data than the IHME estimates used in the global model. Therefore, the same calibration approach is adopted in the Yunnan model: the numbers of deaths were assumed to follow log-normal distributions and the likelihood of a particular set of parameters is calculated relative to the known number of deaths given this assumption (see chapter 3 for details). The standard deviation of the distribution was calculated in the same way as in the global model using the ranges of values and central values described above.

Table 5.2 - List of additional or altered epidemiological parameters in Yunnan model.

Parameter	Description	Value(s) or relation to other parameters	Justification and references
Demographic parameters			
$b(t)$	Number of births	Calculated from sex ratio, fertility rate and number of females; sex ratio and number female available at Yunnan level, fertility rate used values for China as a whole. Future values assumed to follow the same period-to-period percentage changes as China values as a whole	Yunnan-specific values [638]; values for China as a whole [419]
$\mu_{ij}^{nat.}(t)$	Background mortality rate	Number of deaths overall for Yunnan available from 1950. Adapted UN mortality rates for China to match these overall numbers. Future values assumed to follow the same period-to-period percentage changes as China values as a whole	[638]; values for China as a whole [419]
π^{MSM}	Proportion of males MSM	0.005	Survey results of community resident's household in Yunnan by Yunnan CDC (2015)
π^{FSW}	Proportion FSW	0.0011	Yunnan CDC (2016)

Continued on next page

Table 5.2 – *Continued from previous page*

Parameter	Description	Value(s) or relation to other parameters	Justification and references
π^{PWID}	Proportion PWID	0.0029	Data from the dynamic control and supervision system of the department of public security
π^{PWID}_{female}	Proportion PWID women	0.08	Sentinel surveillance conducted by Yunnan CDC (2015)
Transmission parameters			
$\Lambda_{il}(t)$	Force of infection; dependent on age – i - and risk group – l	FSW: $\beta_{i,GP}(t)p^{eff.}_{all}(t) + \beta_{FSW}(t)p_{FSW}(t)$ MSM: $\beta_{i,GP}(t)p^{eff.}_{all}(t) + \beta_{MSM}(t)p_{MSM}(t)$	See below
$p_{FSW}(t)$	HCV prevalence among FSW	$\frac{I^{FSW}(t)}{N^{FSW}(t)}$	[374]
$p_{MSM}(t)$	HCV prevalence among MSM	$\frac{I^{MSM}(t)}{N^{MSM}(t)}$	[374]
$\beta_{FSW}(t)$	Risk of infection in FSW	Interpolated spline with risk values at years 1950, 1980: ξ^{FSW}_{1950}, ξ^{FSW}_{1980}	See below
$\beta_{MSM}(t)$	Risk of infection in MSM	Interpolated spline with risk values at years 1950, 1980: ξ^{MSM}_{1950}, ξ^{MSM}_{1980}	See below
$\xi^{l}_{i/t}$	Values of spline knots for FSW and MSM by risk group l, at time t or age i	ξ^{FSW}_{1950}, ξ^{MSM}_{1950}: exp. prior (rate $=$ 1.00) ξ^{FSW}_{1980}, ξ^{MSM}_{1980}: exp. prior (rate $=$ 0.05)	Pre-1950 risk of infection low so greater prior weight at lower values; risks at other times drawn from effectively uninformative prior distributions

Ranges indicate the quantity is varied in calibration.

5.2.2 Estimating the economic costs of interventions

This section describes the methodology that allows us to investigate the cost of implementing the above-described interventions in Yunnan. We identified several cost components of relevance to HCV interventions (which apply to all the scenarios). We used these first to analyse how different cost components change between interventions. How these costs are used within the context of the health economic evaluations is discussed in the following two sections. The cost components

can be split into four categories:

i. **Treatment costs.** Cost of drugs plus cost of treatment monitoring.

ii. **Screening and diagnosis costs.** Unit test costs and staff costs.

iii. **Care costs.** These comprise:
   a. **Direct medical costs.** Inpatient and outpatient costs.
   b. **Direct non-medical costs.** Transportation to health care facilities.
   c. **Indirect medical costs.** Costs due to time off work.

iv. **Productivity losses.** Cost to the economy associated with premature death leading to lost labour productivity.

Costs and perspective. To carry out health economic evaluations we must identify to what perspective (societal or health care sector) each cost category belongs. All costs are part of the societal perspective. We identify the following as the health-care sector perspective: treatment costs (item i in the list above), screening and diagnosis costs (item ii), and direct medical costs (item iiia). It should be noted that while "who pays" for health care sector costs is a complex question to answer in the case of China (as was illustrated in the introduction) the Gates Reference Case recommends including OOP payments for health services/interventions within the health care sector analysis where these would otherwise fall on the health system [646]. To that end, we assume that all medical costs can be considered as part of the health care system, even though some may accrue to the patient and some to government insurance agencies. Lastly, we identified treatment and monitoring costs and screening and diagnosis costs as "investment" costs for use in the ROI analysis described below.

The relationship between the cost components, the perspective and the identification of investment costs is shown in figure 5.2.

Costings. The values assigned to each cost category are figure 5.2 is detailed here; all values (or ranges) are given in table 5.3 below.

i. **Treatment costs.** Treatment consists of the drug cost (DAA or PEG-IFN+RBV where appropriate) and a weekly cost of monitoring:

$$c_{treat,DAAs} = c_{DAA\ course} + w_{DAAs} c_{treat\ monitoring},$$

where w_j is the length of treatment courses, set equal to 48 weeks for all PEG-IFN+RBV courses and 12 weeks for all DAA treatment courses. The cost of a course of DAA treatment was estimated by the Yunnan CDC at 13,000 to 20,000 Chinese Yuan (CNY) per course (or 1,930 to 2,960 USD using the 2017 average exchange rate of 1 USD to 6.75 RMB [647]). PEG-IFN+RBV costs were estimated at 5,000 USD (or 33,750 CNY). Weekly monitoring costs were

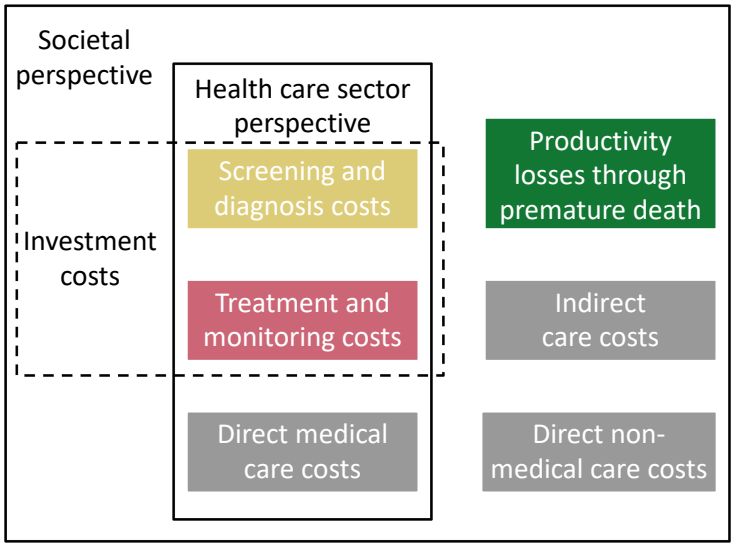


Figure 5.2 - Costing inventory. Shown are the six cost categories considered in the economic analysis of HCV interventions in Yunnan. Colours refer to the colours shown used to denote the four groups of costs used on results graphs. The grey set of boxes are referred to as the "care costs" in later figures.

estimated in a 2017 paper at 25 USD (converted at the above exchange rate to 170 CNY). Overall treatment costs in a particular scenario (year y) are then expressed as:

$$c^{sc.}_{treatment}(y) = N^{sc.}_{treat,DAAs}(y)c_{treat,DAAs} + N^{sc.}_{treat,PEG-IFN+RBV}(y)c_{treat,PEG-IFN+RBV}.$$

ii. **Screening and diagnosis costs.** The model distinguishes two types of diagnosis: diagnosis through routine testing (as occurs in the status quo and scenario set 1 interventions) and diagnosis as a result of screening programmes (scenario sets 2 and 3). Diagnosis through routine testing occurs at a rate set in the status quo scenario (which persists in all intervention scenarios simulated). To assign a cost, we sum the cost of anti-HCV test, HCV RNA test, HCV genotype test and a cost of diagnostic work up (for a discussion of the full details of these tests see chapter 2). The three constituent test costs were 20 CNY, 150 CNY and 135 CNY respectively (Xiu Jiezhang, Yunnan CDC, personal communication, 25th April 2018). Diagnostic work up costs were based on HBV modelling work [648] and adjusted (so as to remove HBV-specific tests), giving a value of 375 CNY (Shevanthi Nayagam, Imperial College London, personal communication, 10th September 2018).

We neglect routine anti-HCV and/or HCV-RNA tests for those testing negative as a result of background screening. Accordingly, background HCV-RNA positive diagnoses have an associated cost of:

$$c_{HCV-RNA+,background} = c_{anti-HCV\ test} + c_{HCV-RNA\ test} + c_{diagnostic\ work\ up}.$$

Diagnosis associated with screening programmes (scenario sets 2 and 3) includes additional anti-HCV tests associated with those testing anti-HCV negative in the screening programme:

$$c_{HCV-RNA-,screening} = c_{anti-HCV\ test}.$$

We incorporate additional HCV RNA tests employed on those anti-HCV positive but HCV RNA negative (according to the viraemic rate):

$$c_{HCV-RNA+,screening} = c_{anti-HCV\ test} + \frac{c_{HCV-RNA\ test}}{v} + c_{diagnostic\ work\ up}.$$

The overall cost of screening in a given year y in scenario $sc.$ is then the sum over all these constituent costs (as appropriate in the given scenario):

$$\begin{aligned} c^{sc.}_{screening\ \&\ diagnosis}(y) = & N^{sc.}_{HCV-RNA+,background}(y) c_{HCV-RNA+,background} \\ & + N^{sc.}_{HCV-RNA-,screening}(y) c_{HCV-RNA-,screening} \\ & + N^{sc.}_{HCV-RNA+,screening}(y) c_{HCV-RNA+,screening}. \end{aligned}$$

iii. Care costs.

a. Direct medical costs. These are incurred as a result of inpatient care (to manage the symptoms of cirrhosis for example) or outpatient care required as a result of illness (such as the prescription of medications to treat HCC). Cost estimates were available for the annual medical costs that arise as a result of being in particular disease stages F0-F3, F4, decompensated cirrhosis and HCC (see table 5.3) (Xiu Jiezhang, Yunnan CDC, personal communication, 25th April 2018). The HCC quantity was estimated per hospitalisation, and this was converted into an annual cost by using a value of 1.6 hospitalisations per year as reported in Beijing in a 2009 study of HBV patients [649]. These costs were applied to all those diagnosed with HCV. The direct medical costs in year y are denoted:

$$c_{direct\ medical}(y).$$

The set of medical costs made available by the Yunnan CDC are within the range of values reported in a study of HCV direct medical costs that utilised data from eight hospitals in four regions of China [633]. As reported by the authors, prices are set by provincial-level Bureau of Commodity Prices and so are fairly homogeneous by province (justifying utilising single results across Yunnan). Additionally, this result suggests that central providers of care in China are likely to have a good understanding of direct medical costs, indicating that such data provided by the Yunnan CDC should be accurate. We also vary these costs in the analysis (along with all care costs) between 0.5× and 2× the central value to acknowledge the potential for limitations in the Yunnan CDC cost data.

b. Direct non-medical costs. Hu et al. (2009) estimates the direct non-medical costs by liver-disease state for people with HBV; we make the assumption that these costs are the same for HCV (more recent analyses specific to HCV interventions exist but these are carried out from the "payer" perspective and do not include estimates of non-medical or indirect costs [633, 635]). Included in our analysis is the cost of additional health

products purchased by the patient and the costs of transport to and from medical facilities (which can be substantial to centralised tertiary care centres) in the stages F0-F3, F4, decompensated cirrhosis and HCC (these estimates incorporate frequency of hospitalisation) [649]. These are denoted:

$$c_{direct\ non\text{-}medical}(y).$$

c. Indirect medical costs. Hu et al. (2009) also estimated the economic burden arising as a result of patient or family time off work in the aforementioned stages [649]. This constitutes the indirect economic burden. These 2009 values were converted to CNY according to that year's USD exchange rate (1 USD = 6.83 CNY [647]) and then converted to 2017 values according to the consumer price index (corresponds to multiplying the 2009 CNY value by 1.22) [650]. These values are presented in table 5.3. Such costs are denoted:

$$c_{indirect\ medical}(y).$$

Change in care costs post SVR. After cure, care costs are reduced. For those in stages F0 to F3 disease severity is assumed low enough to incur zero disease costs (based on medical opinion). Disease states F4, decompensated cirrhosis and HCC have costs multiplied by a factor $\alpha_{cost,SVR}$ =0.709 [651].

The overall cost of care is:

$$c_{cost\ of\ care}(y) = c_{direct\ medical}(y) + c_{direct\ non\text{-}medical}(y) + c_{indirect\ medical}(y).$$

iv. Productivity losses. This is quantified according to the human capital approach using the average income in Yunnan Province of 18,000 CNY (Xiu Jiezhang, Yunnan CDC, personal communication, 25th April 2018). Unemployment in China has persisted at 4% [652] and so any year of life lost between the working age years (assumed to be 18-65) is associated with a cost ($c_{year\ of\ lost\ working\ life}$) of 17,280 CNY. By assuming the burden of HCV is equally spread, we assume that a year of life lost due to premature HCV-attributable mortality (of someone of working age) would have contributed this amount to the overall economy. As such, the cost of productivity losses in a particular year y is given by the number who would have been alive in a given year were it not for premature deaths due to HCV. This is denoted $N_{premature\ HCV\ death}(y)$:

$$c^{sc.}_{productivity}(y) = N^{sc.}_{premature\ HCV\ death}(y) c_{year\ of\ lost\ working\ life}.$$

The quantity $N^{sc.}_{premature\ HCV\ death}(y)$ is tracked in the model by moving those who die prematurely from HCV into an additional compartment from which natural mortality is simulated. The annual average occupancy of this compartment, therefore, corresponds to the number who would have been alive were it not for HCV, taking into account that they may have died already due to natural mortality.

Table 5.3 - Costing and methodological values.

Parameter	Description	Value/range (distribution)	Justification and references
Cost values			
$c_{anti\text{-}HCV\ test}$	Cost of anti-HCV test (unit cost)	20 CNY (Uniform: $\pm$20%)	Local stakeholders
$c_{HCV\text{-}RNA\ test}$	Cost of HCV-RNA test (unit cost)	285 CNY (Uniform: $\pm$20%)	Local stakeholders; sum HCV-RNA (150 CNY) and genotype test (135 CNY)
$c_{diagnostic\ work\ up}$	Cost of diagnostic work up	350 CNY (Uniform: $\pm$20%)	Cost of diagnostic work up for HBV less HBV-specific tests (Shevanthi Nayagam, Imperial College London, personal communication, 10th September 2018)
$c_{DAA\ course}$	Cost of course of DAA treatment	13,000 - 20,000 CNY (Uniform)	Local stakeholders
$c_{PEG\text{-}IFN+RBV\ course}$	Cost of course of PEG-IFN+RBV treatment	33,750 (Uniform: $\pm$20%)	Local stakeholders; approximate value of course 5,000 USD converted to CNY at 2017 average exchange rate of 1 USD = 6.75 CNY
$c_{treat\ monitoring}$	Cost of treatment monitoring per week	170 (Uniform: $\pm$20%)	[634]
$c_{F0\text{-}F3}$	Cost of care for patients in care stages F0-F3	2,800 CNY (Lognormal: 95% CI 0.5-2$\times$)	Direct medical: 800 CNY (local stakeholders) Direct non-medical: 1,200 CNY [649] Indirect: 800 CNY [649]
c_{F4}	Cost of care for patients in care stages F4	8,000 CNY (Lognormal: 95% CI 0.5-2$\times$)	Direct medical: 5,000 CNY (local stakeholders) Direct non-medical: 1,400 CNY [649] Indirect: 1,600 CNY [649]
c_{DC}	Cost of care for patients in care stages DC	18,300 CNY (Lognormal: 95% CI 0.5-2$\times$)	Direct medical: 9,000 CNY (midpoint of data from local stakeholders) Direct non-medical: 5,400 CNY [649] Indirect: 3,900 CNY [649]

Continued on next page

Table 5.3 – *Continued from previous page*

Parameter	Description	Value/range (distribution)	Justification and references
c_{HCC}	Cost of care for patients in care stages HCC	38,800 CNY (Lognormal: 95% CI 0.5-2×)	Direct medical: 24,000 CNY (midpoint of data from local stakeholders) Direct non-medical: 10,000 CNY [649] Indirect: 4,800 CNY [649]
$\alpha_{cost,SVR}$	Multiplicative change in care costs following SVR	0.709 (Lognormal: 95% CI 0.592–0.855)	[633, 651]
$c_{year\ of\ lost\ working\ life}$	Average cost of year of working life lost	17,280 (Uniform: ±20%))	Local stakeholders; original value adjusted for assumption of 4% unemployment [652]
Methodological parameters			
r	Discount rate	3%	Standard value, see [653]
$t_{horizon}$	Horizon length: the time over which costs and health outcomes are evaluated when calculating ROI and CER (see the text)	2100	Maximum length in model; chosen as facsimile for lifetime horizon

Ranges shown indicate the range of values explored in the primary analyses. Where only direct medical costs are used (in CEA) the appropriate sub-costs of the care costs are used.

Incorporating uncertainty. Uncertainty in epidemiological parameters was incorporated inherently as a result of the calibration procedure: 1,000 epidemiological parameter sets were sampled from the posterior distribution. To incorporate economic uncertainty, these parameter sets were sampled with replacement and combined with 1,000 economic parameter sets, resulting in 1 million parameter sets per intervention scenario considered. Economic parameter values are drawn from the prior distributions defined in table 5.3. Prior distributions are informed either by the literature or else a plus/minus 20% uniform distribution is constructed around the given value to incorporate uncertainty in parameter values. Care costs are varied in unison according to a single care cost multiplier. All values described are sampled when the model is run and combined to produce the quantities detailed above.

5.2.3 Calculating and comparing the cost effectiveness of interventions

Approach to calculating and comparing the cost effectiveness of interventions. To assess the cost effectiveness of the differing interventions, we calculate the changes in costs and health outcomes between each intervention scenario and a comparator scenario and calculate CERs defined below; this is done in two different ways. Firstly, we estimate CERs of the cumulative (or 'stacked') set of interventions relative to status quo. This allows us to determine how cost effective it is to introduce anything from just DAAs (scenario 1a) to the full suite of interventions (scenario 3b). This provides Yunnan with a set of numbers that indicate how implementing an increasingly comprehensive intervention strategy compares to the current health opportunity costs of spending in the healthcare system (estimated using CET values for China as a whole).

Secondly, to disentangle the effects of each intervention (considered collectively in the stacked analysis), we simulate each intervention element independently and calculate a new set of CERs. A nuance here must be dealt with: when calculating CERs for the 'stacked' interventions, because we introduce DAAs in scenario 1a, all subsequent interventions include DAAs. Since we would not implement increased treatment or screening interventions (all of scenarios 1b-3b) in the absence of DAAs, it does not make sense to consider (for example) implementing scenario 2a (screen MSM) within the context of the status quo scenario (in which PEG-IFN+RBV is the default treatment). For that reason, when modelling interventions independently, the correct comparator scenario from is scenario 1a, that is, the status quo but with DAAs introduced. Simulating scenario 2a independently then means screening MSM in the context of having already introduced DAAs.

CERs are reported for both the cumulative (stacked) and independent CEA analyses. The independent CERs are given in one table only; all other results are those for the stacked interventions whose comparator scenario is the status quo (as described above). The focus is kept on the stacked interventions relative to status quo because this represents the actual cost effectiveness based on the current situation in Yunnan Province. The CERs derived for each scenario independently relative to scenario 1a are used to compare strategies; they do not represent the cost effectiveness of implementing the given strategy because, by construction, they neglect the cost savings inherent in implementing DAAs as in scenario 1a. Nevertheless, the analysis of interventions considered independent from one another will provide necessary insight into the relative differences driving the changes in CERs observed when carrying out the stacked analyses.

Perspective and costs included. The change in health outcomes is specified using DALYs (described below). The Gates Reference Case recommends performing analyses with direct health costs [646]; following this guidance, this analysis calculates CERs from a health care sector perspective. This means that values of CERs can be compared to CETs that equal the opportunity costs of spending in the health care system as was noted above. The costs included are treatment costs, screening and diagnosis costs, and direct medical care costs (see figure 5.2 above).

Calculating the DALYs. DALYs were estimated by summing the years of life lost (YLLs) and the years lived with disability (YLDs) according to the current approach of not adjusting these values

by age [654]. Though DALYs are usually presenting without discounting, it is inappropriate to estimate costs with discounting (as is standard) but not DALYs [646] and so these are discounted at the same rate as costs (see below). The key quantities to evaluate the DALYs are, therefore, the disability weights used to assess YLDs which are denoted δ_k for different disease states k (described below). These weights are combined with the average annual number with each sequela $N_k(y)$ to produce an overall number of YLDs in that year. This follows the prevalence approach rather than the incidence approach (adopted in the past) which is now the standard [654]. YLLs are calculated using the value of $N^{sc.}_{premature\ HCV\ death}$, described above, which tracks the average number of people who would be alive were it not for premature HCV death; this is thus also a prevalence measure of YLLs [655].

Disability weight values are from the most recent GBD update and presented in table 5.4 [4]. In this update, weights have been estimated for chronic hepatitis C (δ_{F0-F3} =0), compensated cirrhosis (δ_{F4} =0), and decompensated cirrhosis attributable to hepatitis C (δ_{DC} =0.178) and liver cancer due to hepatitis C (which we take to indicate HCC, δ_{HCC} =0.451) [4, 656]. On the assumption of minimal access to advanced HCC treatments or curative therapies, we assigned the metastatic disability weight for HCC attributable to HCV (0.451) as opposed to the "controlled phase" (0.049) or the "diagnosis and primary therapy phase" (0.288) which are lower, or the "terminal phase" (0.54). Upon cure, HCC disability weights are assumed equal since HCV cure is not assumed to alter mortality risk in this compartment (see chapter 3). Disability weight in the decompensated cirrhosis compartment is assumed reduced to the compensated cirrhosis value (δ^{SVR}_{DC} =0). The values are fixed at their central estimates for all primary analyses in which they are used (the calculations of the CERs). In sensitivity analyses they are varied between the limits estimated in the 2016 GBD update. For those states with zero weight we varied from this value to an upper bound of 0.051, corresponding to the generic moderate infectious disease disability weight [657]. The overall number of DALYs can be decomposed into the YLLs and YLDs and evaluated (in a particular scenario $sc.$) as:

$$d^{sc.}(y) = \text{YLLs}\,(y) + \text{YLDs}\,(y) = N^{sc.}_{premature\ HCV\ death}(y) + \sum_k \delta_k N_k(y).$$

Calculating the CERs. The CER is calculated from the health care sector perspective by only using the costs of treatment, and diagnosis and screening. The cost difference is evaluated between the comparator scenario (status quo when calculating the CERs for the full stacked set of interventions, or scenario 1a when simulating interventions independently) and the particular intervention scenario ($sc.$) considered. The quantity we are calculating is a CER (not ICER) because we use the same comparator in all ratios. Denoting the health care sector costs in a particular scenario as:

$$c^{sc.}_{health\ care\ sector} = c^{sc.}_{treatment} + c^{sc.}_{screening\ \&diagnosis} + c^{sc.}_{direct\ medical},$$

where $c^{sc.}_{treatment}$ is the net present value (the discounted sum) of the future treatment costs to the

Table 5.4 - Disability weights.

Parameter	Description	Value/range (distribution)	Justification and references
Heath utility values			
δ_{F0-F3}	Disability weight F0-F3	0	[4, 656]
δ_{F4}	Disability weight F0-F3	0	[4, 656]
δ_{DC}	Disability weight F0-F3	0.178	[4, 656]
δ_{HCC}	Disability weight F0-F3	0.452	[4, 656]

Disability weights are varied in one-way sensitivity analyses, see table 5.5

horizon time (set to 2100)[7], according to a discount rate $r = 3\%$:

$$c^{sc.}_{treatment} = \sum_{y=2017}^{y_{horizon}} \frac{c^{sc.}_{treatment}(y)}{(1+r)^{y-2017}},$$

and similarly for the other costs c and DALYs d. DALY and cost discount rates are set equal [368]. The CER is, therefore, given by:

$$\text{CER}^{sc.} = \frac{c^{sc.}_{health\ care\ sector} - c^{comparator}_{health\ care\ sector}}{d^{comparator} - d^{sc.}}.$$

Sensitivity analyses. Uncertainty in epidemiological and economic parameters is incorporated into the main analyses reported here as described in the previous section. In separate analyses, we test the variation in the stacked CERs when varying the analysis time horizon (the horizon over which costs and DALYs are evaluated and summed), the discount rate and the disability weights (which are fixed in the main analysis). This follows standard recommendations on health economic evaluations [646, 658]. Disability weights are varied between minimum and maximum values in two groups: the fibrosis stages F0-F4 are varied simultaneously, and the ESLD stages (decompensated cirrhosis and HCC) are varied simultaneously. The ranges explored in these sensitivity analyses are given in table 5.5.

5.2.4 Evaluating return on investment and net benefit to society

The final aim in this analysis was to estimate the net benefit to society of these interventions by calculating the ROI. Benefits from interventions accrue beyond the health care sector. It is appropriate, therefore, to incorporate these additional economic benefits by performing an analysis from the societal perspective. This is done in the framework of CBA by constructing an ROI for each intervention. The investment costs are equated to the additional spending on treatment, diagnosis

[7] 2100 is a time suitably far in the future over which to integrate such that future benefits accrued after this time are sufficiently small (given discounting) that they can reasonably be neglected.

Table 5.5 - Ranges of values explored in methodological sensitivity analyses.

Parameter	Description	Range of values	Justification and references
Methodological parameter ranges			
r	Discount rate	0-12%	Wide range chosen; includes no discounting approach (nominal values)
$y_{horizon}$	Horizon length	2030-2100	Time of WHO elimination targets chosen as shortest length over which to evaluate outcomes; maximum is time horizon used in model
Heath utility value ranges			
δ_{F0-F3}	Disability weight F0-F3	0-0.051	[4, 656]
δ_{F4}	Disability weight F0-F3	0-0.051	[4, 656]
δ_{DC}	Disability weight F0-F3	0.123-0.25	[4, 656]
δ_{HCC}	Disability weight F0-F3	0.307-0.600	[4, 656]

These ranges are only explored in secondary analyses; reporting of all values in the text except where stated use the fixed values for these quantities, see tables 5.3 and 5.4

and screening (items i and ii above). The benefits are the sum of: the changes in direct medical care costs (item iiia) and the changes in patient spending and indirect costs (items iiib and iiic respectively) both of which are anticipated to decrease; and the health benefits of the intervention quantified according to the human capital approach (one year of lost working life is equated to one year of lost income), referred to as the productivity losses (item iv above). The identification of the investment costs and the societal perspective are illustrated in figure 5.2.

Calculating the ROI. The overall investment costs can be expressed in the particular scenario under consideration as the difference in treatment, and screening and diagnosis costs between the scenario and the status quo (note that the sum of these two cost components is sometimes referred to as the intervention costs to distinguish it from costs less directly related to the intervention scenario being considered):

$$c^{sc.}_{investment} = c^{sc.}_{treatment} + c^{sc.}_{screening\ \&\ diagnosis} - (c^{status\ quo}_{treatment} + c^{status\ quo}_{screening\ \&\ diagnosis}).$$

The return on investment is assessed by calculating the overall benefit $b^{sc.}$ relative to the investment, which consists of the changes in care costs and health benefits (evaluated according to overall productivity gains):

$$b^{sc.} = c^{status\ quo}_{cost\ of\ care} + c^{status\ quo}_{productivity} - (c^{sc.}_{cost\ of\ care} + c^{sc.}_{productivity}).$$

The ROI is, therefore:

$$\text{ROI} = \frac{b^{sc.} - c^{sc.}_{investment}}{c^{sc.}_{investment}}.$$

Understanding the drivers of ROI. To understand what cost components influence ROI, we calculated the partial correlation coefficients (using the ppcor package in R [659]). By identifying that the two main drivers were DAA cost and care costs, we recalculated ROIs with DAA costs and the care cost multipliers extended beyond the values used in the main analysis: DAA costs are explored up to the reported value of DAA costs in China noted in the introduction (approximately 80,000 CNY) and the care cost multiplier range is expanded to vary the costs of care simultaneously from 20% to 500% of the central value (see table 5.3 for the central values).

Sensitivity analyses. We recalculate the ROIs upon varying the time horizon and discount rate used in the analysis. The ranges explored in these sensitivity analyses are given in table 5.5.

5.3 Results

5.3.1 Epidemiological impact of HCV interventions in Yunnan

The model fit to HCV data in Yunnan is shown in figures 5.3 to 5.5. Figure 5.3 demonstrates that prevalence values are matched closely through time. The exception is one MSM prevalence point to which the model does not fit as it is located well outside the envelope of the other MSM prevalence points. The consistency of three out of four data points suggests that the close model fit to only these points is appropriate. Figure 5.4 shows calibration to mortality; the broad patterns of age-, sex- and type-specific estimates are mostly reproduced by the model. Figure 5.5 similarly demonstrates fit to overall HCV-attributable mortality numbers.

By 2016 (the year before interventions start) the overall number of viraemic HCV infections is 190,000 (95% CrI: 169,000-223,000), of whom 18% are PWID, 0.3% are MSM and 0.1% are FSW. Given the group size estimates of MSM and FSW, the absolute number of HCV-positive MSM and FSW is extremely small and projected to decline in line with trends in general population risk. In the same year there are an estimated 1,770 (95% CrI: 1,460-2,290) HCV-attributable deaths, of which 62% are cirrhosis deaths and 38% HCC deaths, while there are 3,700 (95% CrI: 2,700-4,578) incident viraemic infections. The population attributable fractions between 1990 and 2017 are 89% (95% CrI: 80-94%) in PWID, 0.5% (95% CrI: 0.2-0.8%) in MSM and 0.5% (95% CrI: 0.3-3.6%) in FSW. In 2018, of the next 1,000 infections, 930 (95% CrI: 880-950) are in PWID, 2 (95% CrI: 1-3) in MSM and 1 (95% CrI: 1-2) in FSW. While the epidemic has been driven historically by infection without the PWID group, shown by the relative low fraction of current active infections among PWID, the future course of the epidemic will be determined by response to the epidemic in that group.

The impact of interventions implemented from 2017 onwards are shown in figures 5.6 to 5.8.

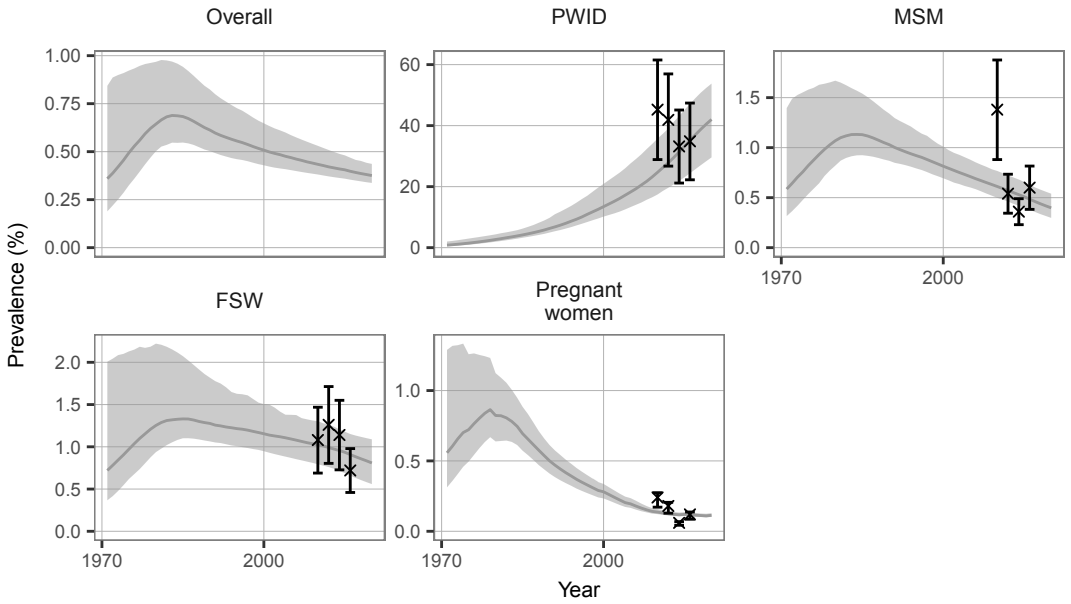


Figure 5.3 - Calibrated viraemic prevalence by risk group in Yunnan Province. Solid line shows median and ribbons show 95% credible intervals of 1,000 parameter sets sampled from the posterior distributions. Crosses indicate data; error bars are estimated confidence intervals based on Chinese data.

By 2030 in status quo incidence rates have risen slightly, mortality has declined by 6% while the number of active infections has dropped 13%, suggesting that declines in prevalence are driven by deaths of those infected rather than reductions in incidence. By 2050, incidence has moderately declined though only to 3,100 (95% CrI: 2,800-3,400) infections in that year, a decrease of 16%. Prevalence and mortality continue to decline, by 22% and 26% respectively, with 149,000 (95% CrI: 133,000 – 164,000) active infections that year and 1,300 (95% CrI: 1,100-1,600) deaths that year. There is, overall, a high cumulative burden of HCV on Yunnan in status quo: by 2030 there are 24,600 HCV-attributable deaths and by 2050 there are 54,000 such deaths along with 129,000 new infections cumulatively by that year.

Switching DAAs for PEG-IFN+RBV and ensuring that 90% of new diagnoses receive them (scenario 1b) drives down prevalence by curing more individuals than in status quo (scenario 1a is similar but the effects are much more muted as fewer people are treated): in 2017 alone 6.0 times more treatment courses are delivered (which are the much more effective DAAs rather than PEG-IFN+RBV). Despite this reduction in prevalence, there is a minimal impact upon incidence by 2030, though the long-term trend in overall incidence (as opposed to risk-group specific incidence) is counterintuitive: while scenario 1a reduces incidence rates across all risk groups, the overall incidence rate rises relative to status quo after 2037. This is a manifestation of an effect observed in the previous chapter (with regard PWID) whereby, within a high risk group, curing individuals results in a large number of susceptible individuals available for reinfection relative to the overall size of the group. In the group itself the rate of new infections relative to the susceptible popu-

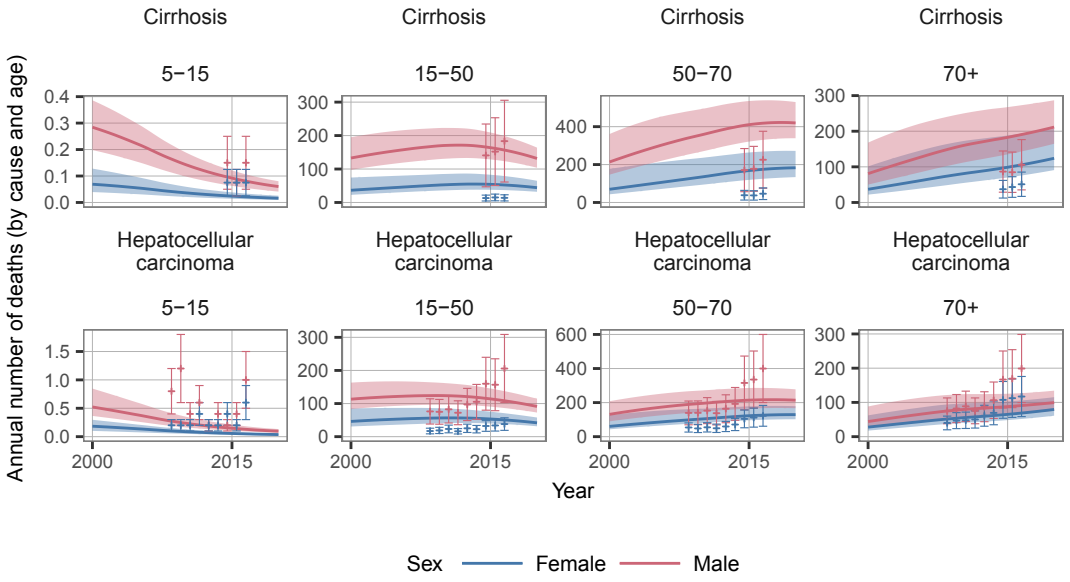


Figure 5.4 - Calibrated mortality by age, sex and mortality type in Yunnan Province. Solid line shows median and ribbons show 95% credible intervals of 1,000 parameter sets sampled from the posterior distributions. Crosses indicate data; error bars are calculated based on variation in proportion of deaths attributable to HCV.

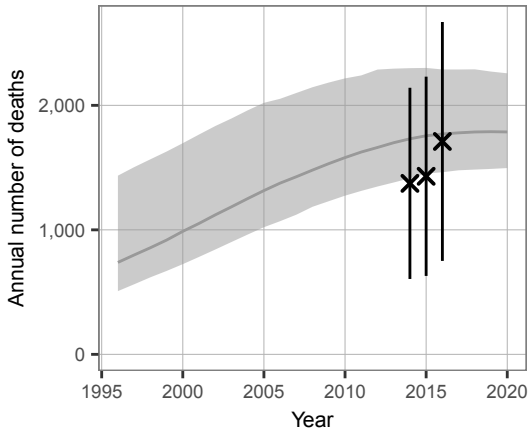


Figure 5.5 - Calibrated summed mortality graphs. Total mortality (only shown are the three points for which both cirrhosis and HCC data were available).

lation declines but, considered from the view of the whole population (in which the susceptible population size is effectively constant) incidence rates rise in line with the additional reinfections. As is visible on figure 5.7 the effect is extremely modest even by 2050, with scenario 1a experiencing only a modest increase in overall incidence rates of 6.0%. Lastly, scenario 1a reduces mortality burden considerably, reducing HCV-attributable mortality by 45% (95% CrI: 39% - 51%) by 2030, a reduction of 5,500 (95% CrI: 5,000-6,200) deaths cumulatively. Improving access to DAAs by such

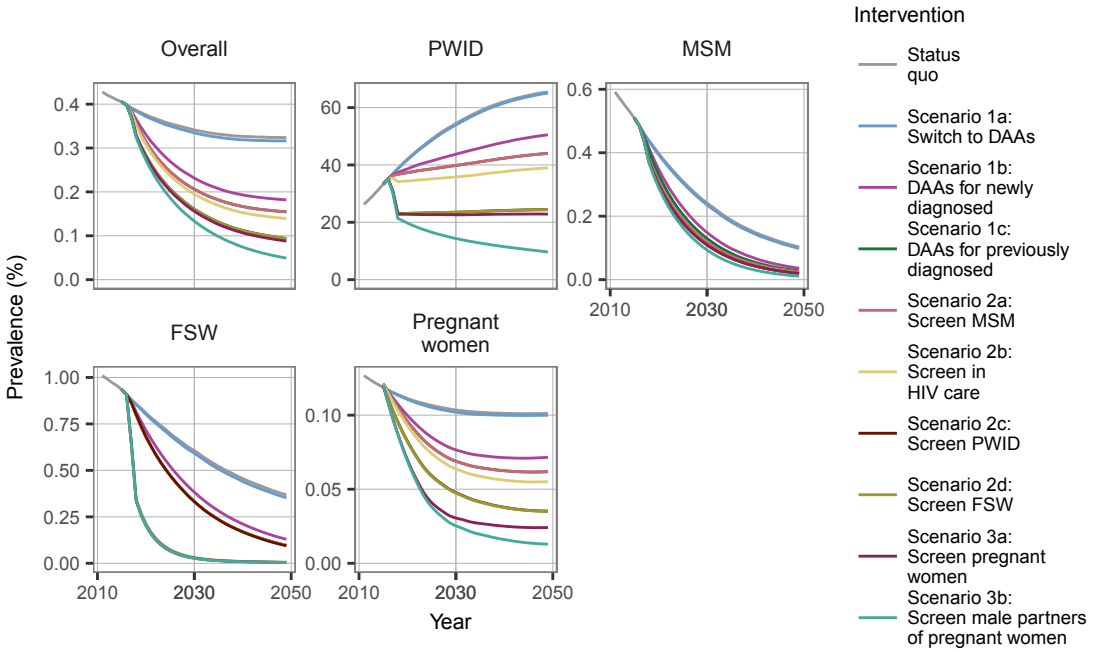


Figure 5.6 - Prevalence projections by risk group in Yunnan Province for each intervention scenario. Credible intervals are not shown for ease of interpretation; their comparative size is similar to that seen on figure 5.3 (result not shown).

that an annual 25% of those previously diagnosed are offered treatment (scenario 1b) further reduces mortality by an additional 8.2 percentage points (corresponding to 1,500 additional deaths averted).

Scenarios 2 interventions, by contrast, only marginally reduce mortality due to the fact that these are screening intervention that will pick up early infections that would not have led to premature death by 2030. Scenario set 2 interventions have a much greater impact upon risk-group specific incidence than scenario set 1 interventions (see figure 5.7), though the same counterintuitive result of rising overall incidence is observed in scenarios 2a and 2b (see above for an explanation). Scenarios 2c and beyond reduce both risk-group specific incidence and overall incidence alike. This is primarily because scenario 2c introduces PWID screening, among whom HCV prevalence is much higher; this leads to much higher treatment rates (there are 10,300 more treatment courses delivered in scenario 2c than 2b by 2020 alone). These additional treatments within the highest risk group stabilises PWID incidence (figure 5.7) and prevents reinfection causing an overall rise in incidence rates as in the previously considered scenarios.

Scenario set 3 interventions (which involve screening either pregnant women alone – 3a – or pregnant women and their male partners – 3b) lead to further reductions in incidence and prevalence. Most notably, scenario 3b, which incorporates all intervention components, reduces incidence by 49% (95% CrI: 41-56%) by 2030 compared to status quo. In this scenario the number of active infections is driven down to 65,000 (95% CrI: 55,000-81,000) in 2030, a 61% reduction compared to status quo. The significant marginal benefit of this intervention compared to scenario 3a (for example,

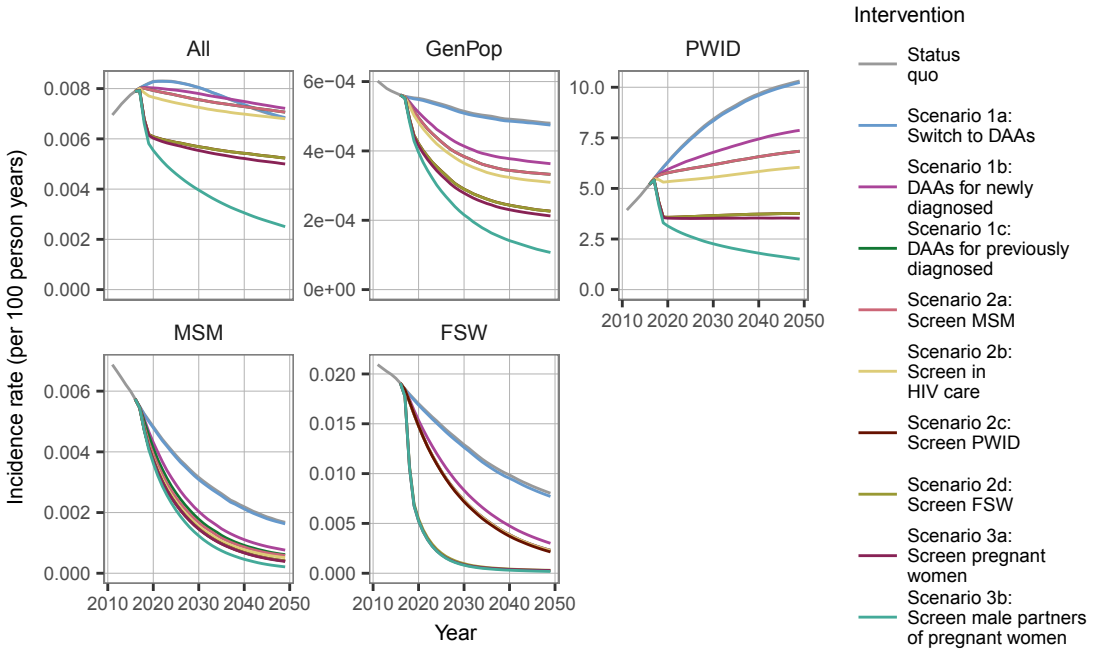


Figure 5.7 - Incidence projections by risk group in Yunnan Province for each intervention scenario.

scenario 3b reduces the incidence rate by 28% relative to scenario 3a) is because the majority of new infections are in PWID (as shown above). Yet only 8% of PWID are women; screening a large number of men annually (the annual number of births in 2015 is approximately 600,000) leads to a larger number of PWID being screened than when only pregnant women are being screened (scenario 3a). This explains the larger decrease in PWID prevalence (figure 5.6) and PWID incidence (figure 5.7) upon implementation of scenario 3b (which incorporates all intervention elements including screening male partners) compared to scenario 3a (which includes all elements except male partner screening). Whether PWID would present to ANC in this manner for screening in equal proportion to other men is an open question and we have not made any assumptions regarding this. Prevalence and active infections continue to decline after 2030 in this scenario relative to status quo, see figure 5.6, illustrating how a comprehensive set of interventions can drive down the burden of disease well into the future.

Figure 5.9 demonstrates the impact on disease burden of the nine interventions compared to status quo quantified according to the YLDs and YLLs averted in each intervention along with the overall annual DALYs averted. YLDs plateau because curing those in ESLD (the only contributor to YLDs) reduces YLDs for them for only a few years before they otherwise would have died, at which point they contribute to YLLs. Correspondingly, YLLs rise over time as each death averted continues to contribute to YLLs, potentially for decades depending on the age of the person treated in intervention. Figure 5.10 shows the total infections, deaths and DALYs averted by intervention compared to status quo to the year 2030. As has been noted above, deaths averted are driven almost entirely by scenario set 1 intervention components; infections averted are dominated by the contribution made

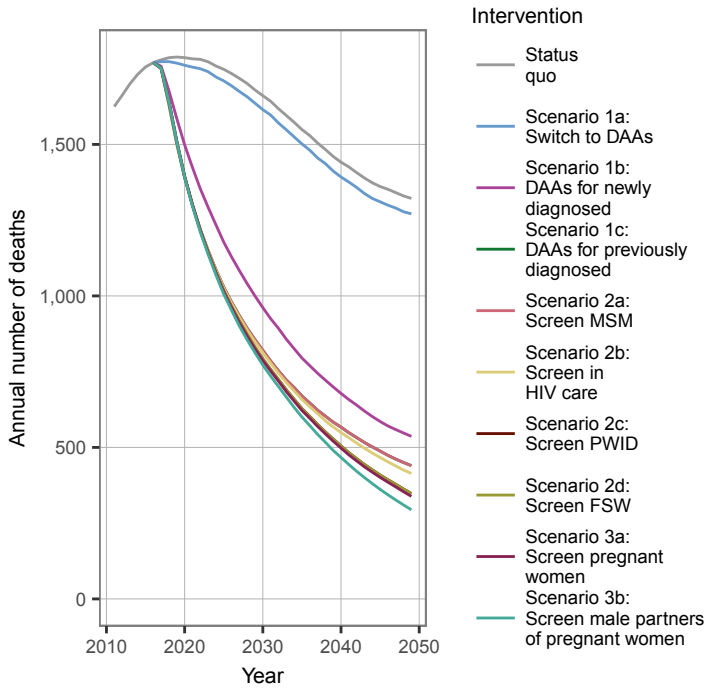


Figure 5.8 - Mortality projections in Yunnan Province for each intervention scenario.

to reducing PWID incidence either directly (scenario 2b) or indirectly by screening men (scenario 3b). DALYs averted are determined primarily by the trend in deaths averted, which contribute to YLLs, the primary contributor to DALYs (see figure 5.9).

5.3.2 Economic costs of interventions

The costs by component in each of the nine interventions are shown in figure 5.11. In status quo, care costs comprise the largest fraction of overall costs related to HCV, reaching over 300 million CNY by 2035 (or approximately 30 million Great British Pounds (GBP)). Spending on treatment is 60 million CNY in 2017 and declines from that point as the pool of those diagnosed and available to be treated decreases. In scenario 1a, there is no increase in treatment rates but DAAs are implemented, producing a significant drop in treatment costs in 2017 to 26 million CNY. In scenario 1b, despite the adoption of the cheaper DAAs, the large increase in number being treated drives up costs to 158 million CNY; treatment costs in this scenario persist above the status quo as a result of the greater access offered to treatment. Despite this, the offset in other costs, notably in care costs but also productivity losses associated with premature death, lead in scenario 1b to reduced overall spending of 501 million CNY by 2021 compared to 503 million CNY in status quo, see figure 5.12; by 2050, total spending is 48% lower in intervention 1b compared to status quo.

This general pattern is mirrored in the other interventions, but the initial spike in treatment costs is greater as a result of adopting new methods of reaching patients driving increased treatment volume; in scenario 3b (which incorporates all screening strategies considered) treatment spend-

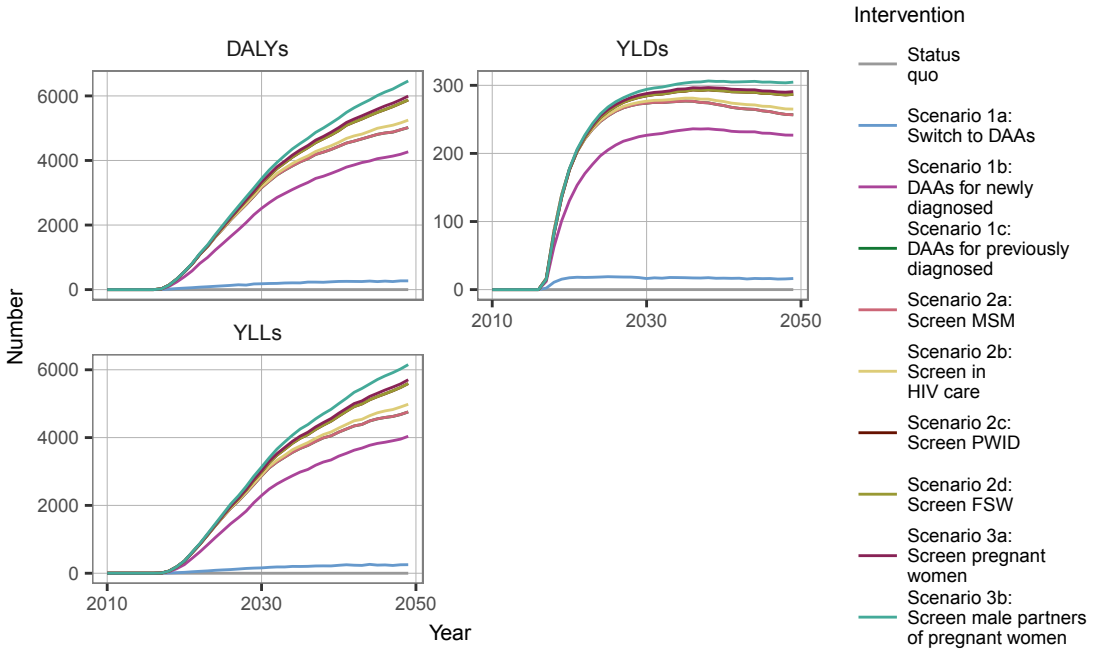


Figure 5.9 - Annual DALYs averted in Yunnan in each intervention by year. Shown are the annual DALYs averted and its components: years lived with disability (YLDs) averted and years of life lost (YLLs) averted. Note that YLLs are modelled as a prevalence measure: in every year in which one person would be alive were the intervention adopted compared to the status quo, 1 YLL is added to this value. This contrasts with the approach sometimes taken in which all the 'saved' life years are added as an incidence measure at time of premature death. For this reason the YLL measure here grows slowly as the benefits of averting premature mortality accrue over the prolonged lifespan of that person. The values shown here are not discounted; all calculations involving these quantities are discounted at the standard rate of 3% per year.

ing peaks at 492 million CNY. As in scenario 1b, the treatment costs persist above status quo to 2050, a result of the increase in treatment volume despite lower DAA costs. In all scenarios, total costs (including all elements i to iv) drop below status quo by 2023 at the latest. In scenario 3b by 2050, costs are 68% lower. These cost decreases are driven by two factors: reductions in overall care costs and reductions in productivity losses. In scenario 3b, for example, reductions in care costs comprise the majority of the reductions in overall costs (177 million CNY lower in 2030 compared to status quo), while reductions in productivity losses due to premature death contribute 53 million CNY of cost savings in scenario 3b compared to status quo in 2030. The contribution of productivity losses progressively rises as YLLs accrue; whereas in 2030 changes in total cost as a result of productivity losses are 30% of the savings in care costs, this has risen to 44% by 2050. These offsetting costs not only outweigh treatment costs but also additional costs of screening and diagnosis which, as can be seen from figure 5.11, are small. That these costs are small is driven by the design of the individual elements of the intervention scenarios; they integrate within other programmes keeping screening costs to a minimum, even in scenarios 3a and 3b in which substantial increases in testing occurs.

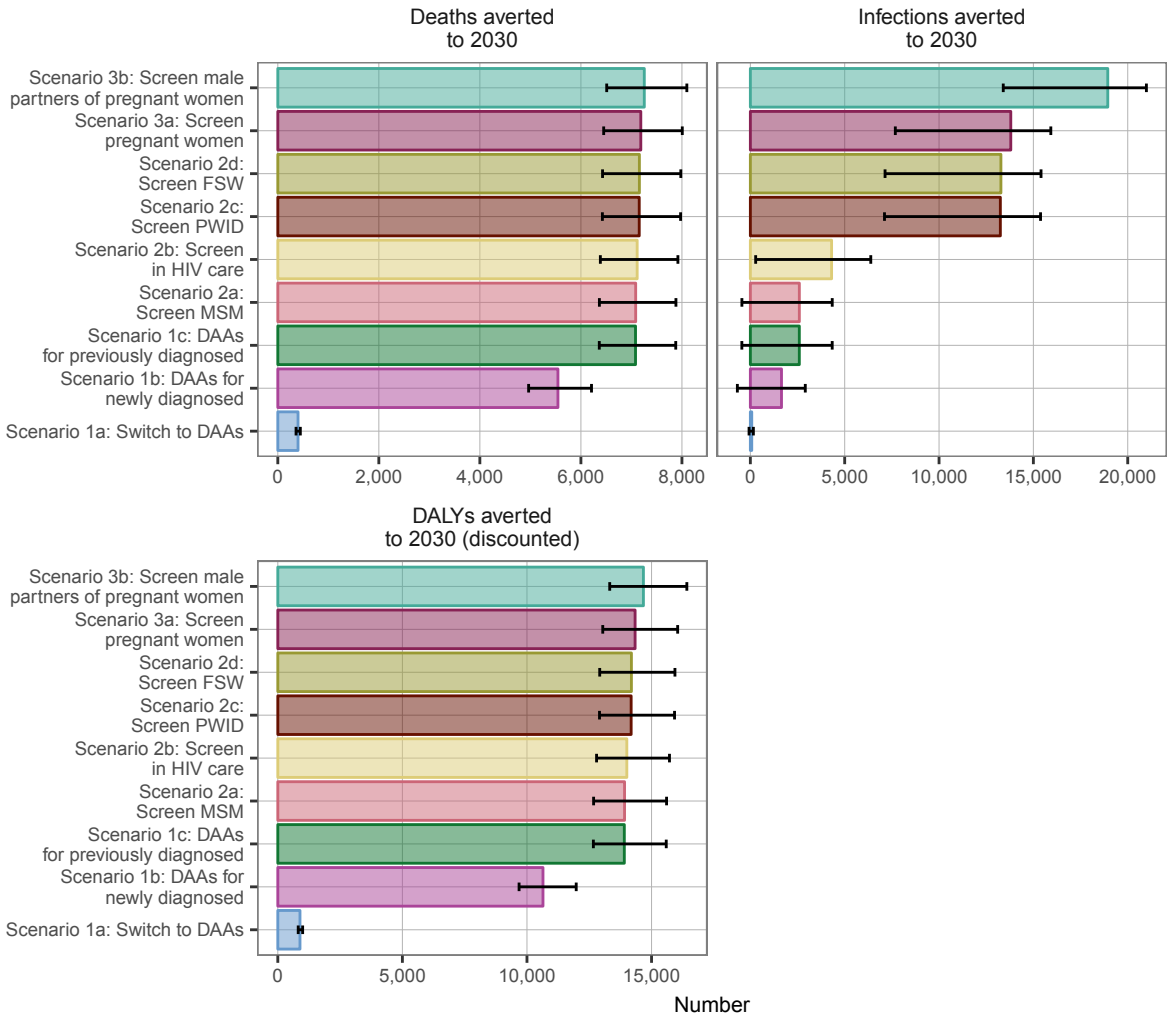


Figure 5.10 - Total death, infections and DALYs averted 2017-2030. Bars correspond to the total number of infections, deaths or DALYs averted in each intervention compared to status quo between 2017 (the intervention start date) and 2030. 95% Credible intervals are shown. Colours correspond to the colour of each intervention on the other figures and in table 5.1. DALYs are discounted by 3% per year.

5.3.3 Cost effectiveness of interventions and comparison of strategies

The changes in health care sector spending and the DALYs averted for each intervention compared to status quo are shown in figure 5.13; the CERs for all interventions are listed in table 5.6. CETs for China were estimated in 2015 at 369-1,150 USD/DALY averted (the range is due to the presentation of several methods in estimating the quantity), or adjusted for currency and inflation corresponds to a value of 2,400-7,000 CNY/DALY averted [626, 660]; both empirical estimates are much more conservative than a rule of thumb estimate that suggests 50% of per capita GDP is a suitable threshold [624], which would give a value of 25,000 CNY in 2015 if China's per capita GDP were used, or 15,000 CNY if Yunnan-specific per capita GDP were used[8] [661, 662]. Given this, we

[8]This is 25,000 CNY multiplied by the 2017 ratio of Yunnan to China per capita GDP of 0.58 [661, 662]

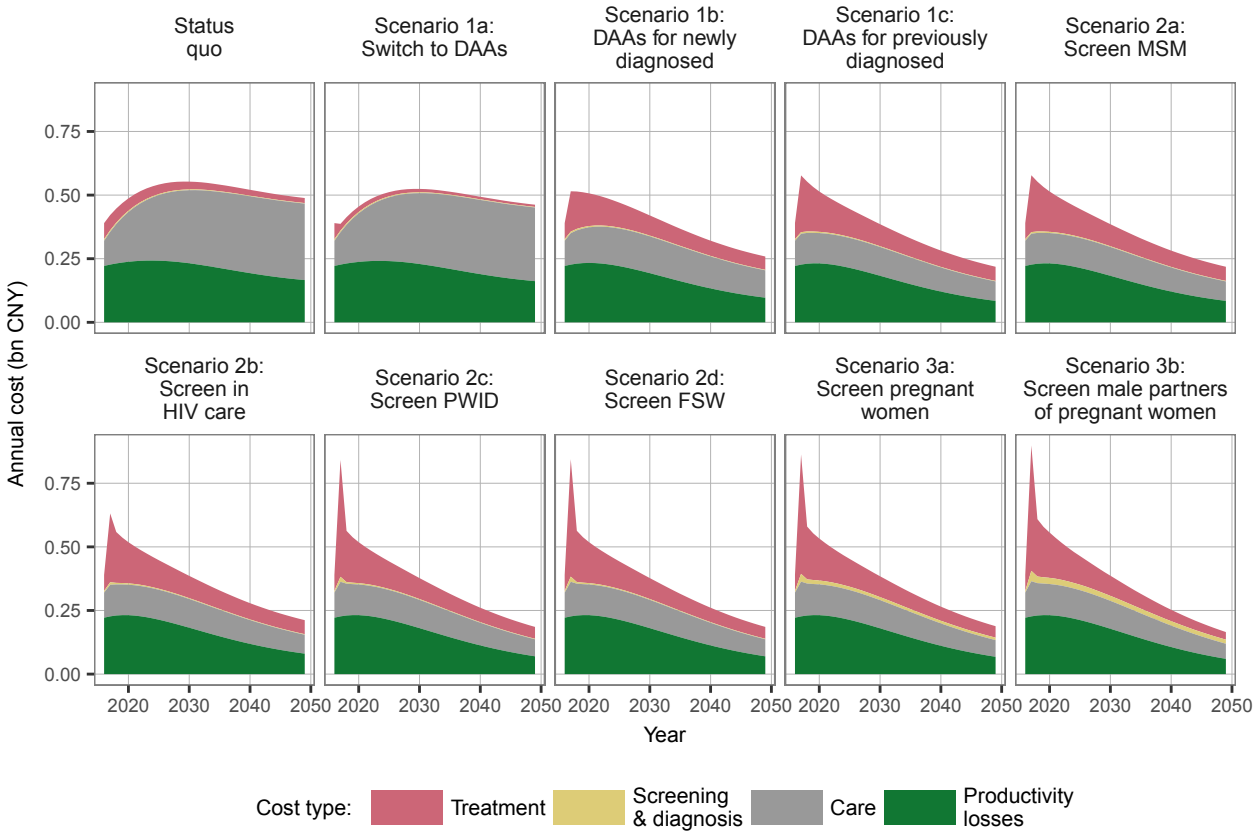


Figure 5.11 - Costs by intervention and component. Costs are subdivided by type. Care costs includes all care cost elements: direct medical, direct non-medical and indirect costs. HCV deaths denotes costs associated with productivity losses. Screening and diagnosis, and treatment costs are self-explanatory. All costs are median values; the height of the stack indicates the overall costs discussed in the text. Costs values are not discounted on this graph.

use the value of 7,000 CNY/DALY averted as an estimate of the opportunity costs of spending in the Chinese health care system.

Due to the price decrease of DAAs, scenario 1a is cost saving 100% of the time. The remaining interventions benefit from the automatic cost saving of switching to DAAs, but higher spending due to increased treatment volumes reduces cost savings (in the health care sector perspective) driving the CERs progressively upwards; scenarios 3a and 3b are the only interventions that are not cost saving in a majority of runs. Scenario 3a is the only scenario with a positive CER, though this is considerably lower than the CET range quoted above for China implying that it is cost effective; the upper credible intervals are marginally greater than the 7,000 CNY/DALY averted CET quoted above illustrating uncertainty as to whether interventions will be cost effective.

Figure 5.14 shows that CERs are most influenced by cost of DAAs and care. Figure 5.15 then explores further, how the cost of DAA and care costs affect the CER for different values of these particular variables (over expanded ranges from those used in the primary analysis). Figure 5.15

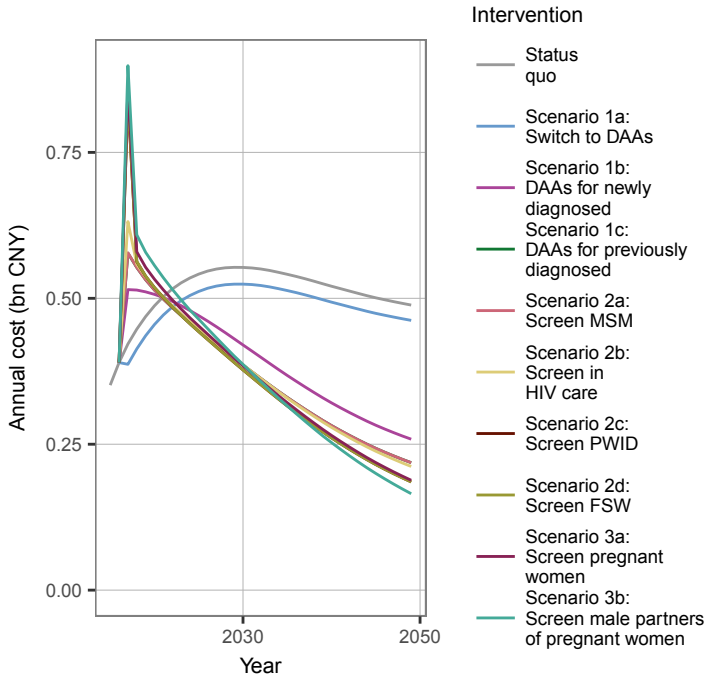


Figure 5.12 - Summed costs by intervention. Shown are the sum of all costs (every element in figure 5.11). Costs values are not discounted.

shows that, across all interventions and at the central estimate of care cost (one on the y-axis), the median CER may be lower than the CET even at DAA values of approximately 22,500 CNY, however, the CER becomes much higher than CET as values rise above this, indicating how, within the health care sector perspective, future cost effectiveness hinges upon DAA prices as would be expected.

Comparing intervention strategies. To further interpret these results, the CERs were calculated for interventions simulated independently compared to scenario 1a (as described above in sensitivity analyses). This removes the automatic cost saving that results from introducing DAAs (scenario 1a) and allows individual trends to be identified that are potentially masked by simulating the interventions incrementally to one another. The CERs for this analysis are shown in table 5.7. By definition there is no value for scenario 1a.

These results illustrate that removing the cost savings inherent in scenario 1a results in positive cost differences, that is the subsequent interventions mostly involve greater health care sector costs than scenario 1a (though a proportional number of runs in some interventions are cost saving, see table 5.7). Rolling out DAAs to those being diagnosed as part of routine screening or who are already diagnosed (scenarios 1b and 1c) is cost effective at a threshold of 7,000 CNY/DALY averted. These CERs are lower than the other interventions because scenarios 1b and 1c involve treating those in care who have been diagnosed as a result of routine testing. Such people are in later disease stages; expenditure on treatment for this group, therefore, will bring the greatest benefits because it will more quickly avert DALYs (in the form of YLDs) since this group are, or may soon

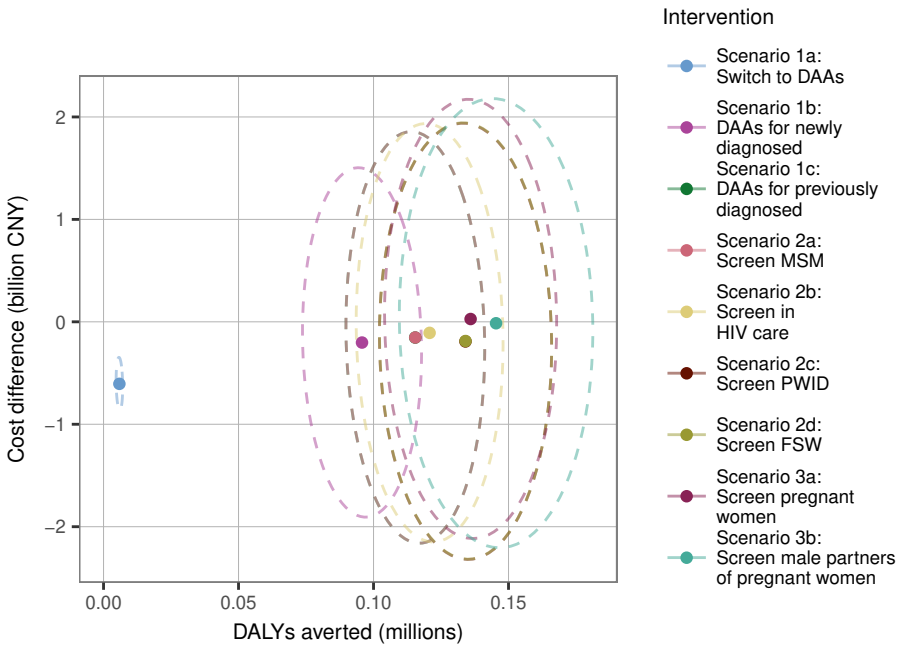


Figure 5.13 - Cost-effectiveness analysis. Shown are the cost savings and DALYs averted for each intervention relative to status quo.

be, in decompensated cirrhosis or HCC which have non-zero disability weights. Similarly, curing these individuals soon averts YLLs. The additional costs, therefore, more rapidly produce both health benefits (increasing the DALYs averted) and cost benefits (through reduced health sector costs) than scenarios 2a-3b.

The screening scenarios (scenarios 2a-3b) as a whole have lower CERs than the scenario set 1 interventions. This is because those cured as a result of such interventions will be cured at an early disease stage and so the direct benefits to those patients of such programmes will not be accounted for in the DALY or cost calculations until potentially decades later. This can be seen on figure 5.9, where additional YLLs averted in the scenario set 2 interventions do not begin to accrue noticeably until after around 2030. Such benefits add less to the CER calculation due to discounting, and so offset the initial expenditure on treatment less than scenario set 1 interventions.

Of the screening scenarios, only screening PWID (2c) falls below the threshold of 7,000 CNY/DALY averted, while the next two most cost-effective interventions are scenario 2b, (screening those in HIV care) and scenario 3b (screening male partners of pregnant women). These interventions have improved cost effectiveness as they drive considerable infections averted in contrast to screening FSW (2d), MSM (2a) or pregnant women (3a), see figure 5.10 above. Screening pregnant women in particular is associated with a high CER due to the large number of screenings offered which do not result in commensurate health benefits (since HCV prevalence among pregnant women is so low).

Sensitivity analyses. The variation in the CER by methodological parameters for the analysis in

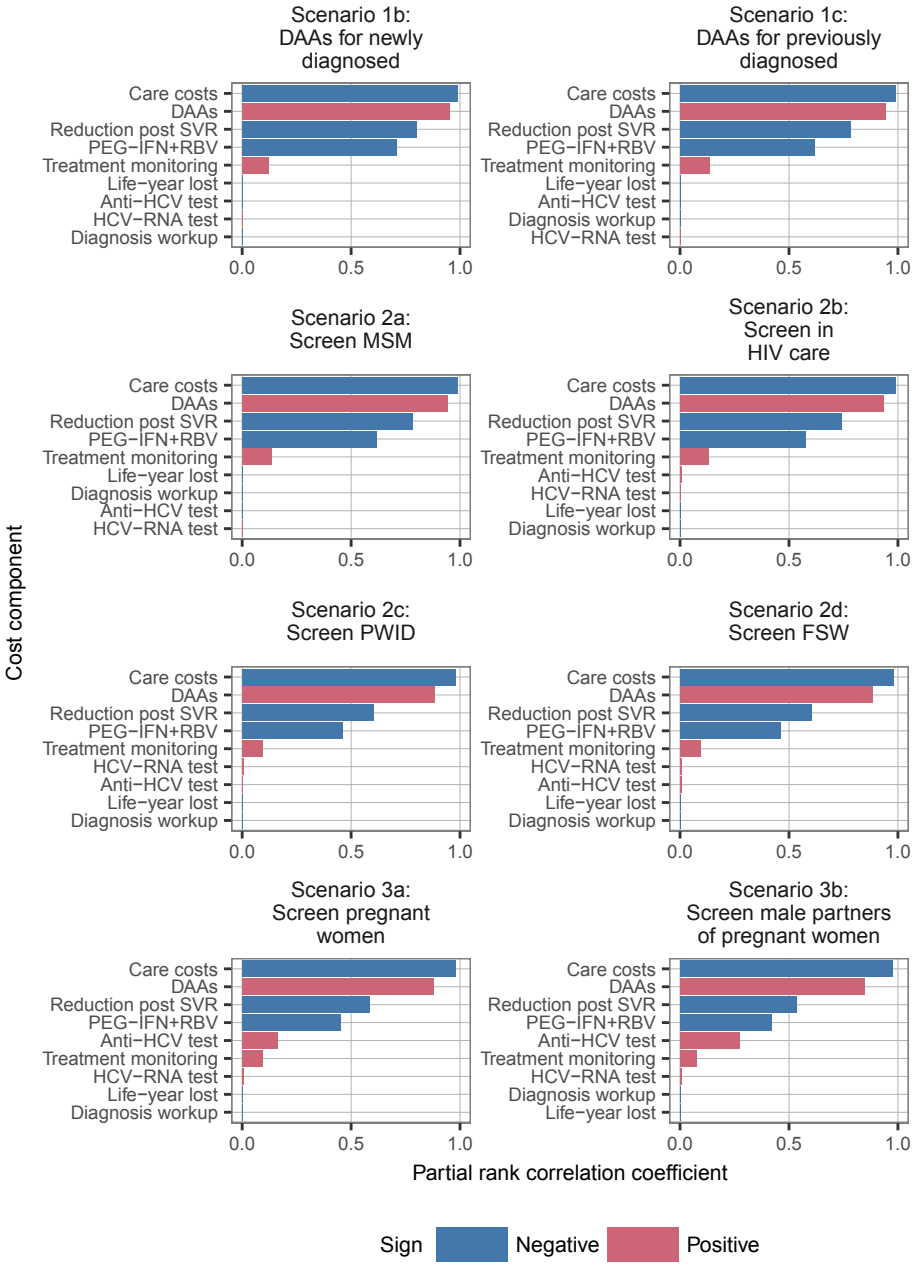


Figure 5.14 - Partial correlation coefficients relating cost variables to CER for cumulative interventions compared to status quo. Base CER values are those in table 5.6.

Table 5.6 - CER values for all interventions considered cumulatively compared to status quo.

Intervention	CER - CNY/DALY averted (95% CrI)	Percentage of runs cost saving
Scenario 1a: Switch to DAAs	Cost saving	100
Scenario 1b: DAAs for newly diagnosed	Cost saving (cost saving, 8,731)	63
Scenario 1c: DAAs for previously diagnosed	Cost saving (cost saving, 9,213)	58
Scenario 2a: Screen MSM	Cost saving (cost saving, 9,217)	58
Scenario 2b: Screen in HIV care	Cost saving (cost saving, 9,416)	56
Scenario 2c: Screen PWID	Cost saving (cost saving, 8,276)	60
Scenario 2d: Screen FSW	Cost saving (cost saving, 8,305)	59
Scenario 3a: Screen pregnant women	210 (cost saving, 9,860)	49
Scenario 3b: Screen male partners of pregnant women	Cost saving (cost saving, 9,030)	51

which interventions are incremental to each other and compared to status quo is shown in figure 5.16. This illustrates that variation in disability weights has minimal impact on CER. This is unsurprising given that the DALY calculation is dominated by YLLs (see figure 5.9 above). Reducing the time horizon greatly increases the CER (that is, increases the cost per DALY averted). The same is true for increasing the discount rate. Both effects illustrate how, as described above, benefits (both in the form of care costs or DALYs averted) can take decades to manifest; looking at a shorter horizon, or more heavily discounting, has the effect of reducing the benefits relative to the costs (which are mostly incurred upfront, see the sharp spikes in treatment costs on figure 5.11). Note the direction of effect is reversed for the always cost-saving scenario 1a, in which reducing the time horizon or increasing discounting decreases the DALY benefits, reducing the denominator of the CER and so making the CER more negative.

5.3.4 Return on investment and net benefit

The ROI was calculated by identifying the treatment, and screening and diagnosis costs as "intervention" costs and denoting the difference between such intervention costs between the intervention scenario and status quo as the "investment" cost. The cumulative values of each of these

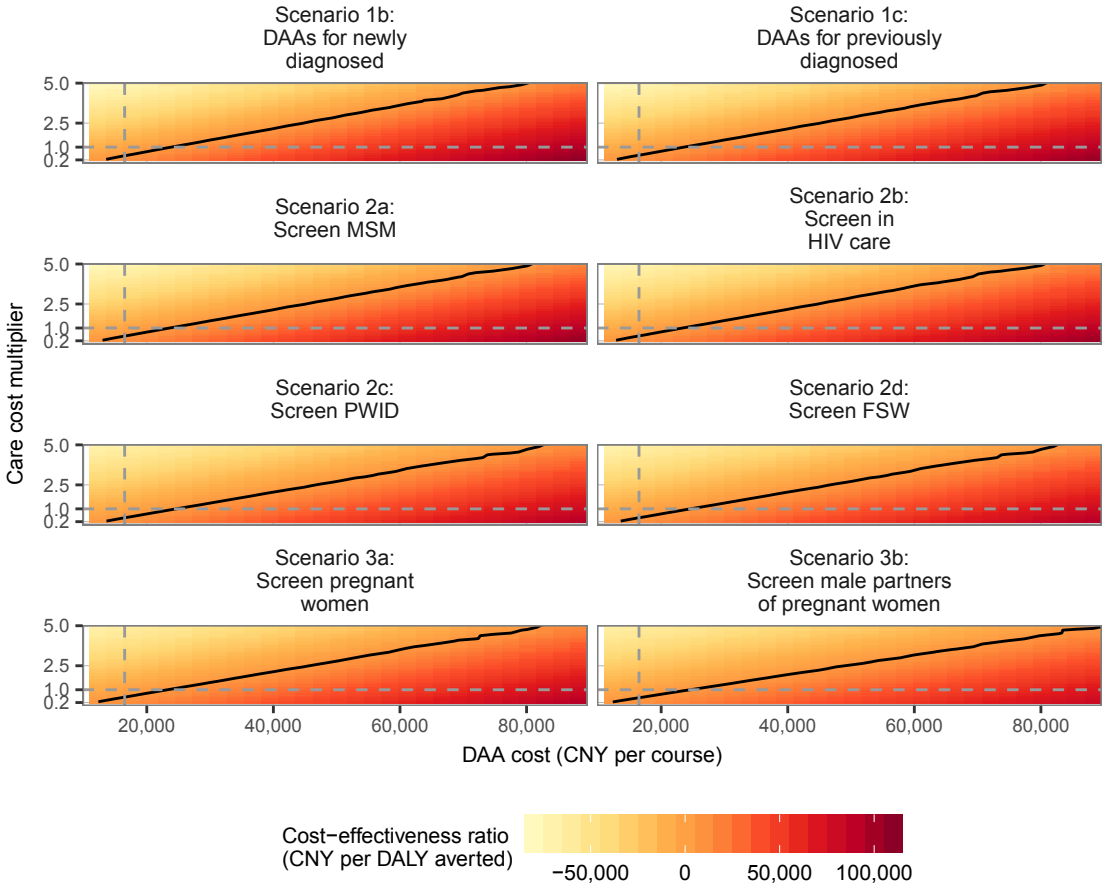


Figure 5.15 - Heat map of CER with varying care and treatment costs for cumulative interventions compared to status quo. The colour indicates the CER given varying care costs and DAA treatment costs. The black contour line on each graph indicates a separatrix, the boundary between cost effective and otherwise CERs, with a CET of 7,000 CNY/DALY averted adopted as described in the text: all points to the right and below the separatrices exceed this threshold. The horizontal and vertical dashed lines are the central values (care costs and DAA treatment course cost respectively) used in the primary analyses.

costs is illustrated in figure 5.17. As shown here, scenario 1a has a negative investment cost and so the ROI is not well defined (there is no net investment in a health care activity). As such, all subsequent graphs and results for ROI only show scenario 1b and beyond which incur positive investments. ROIs are shown in table 5.8 along with cumulative nominal investment and returns to 2050 that indicate the size of the outlay potentially required and the possible overall gains.

All investments in scenarios 1b to 3b have a positive return on investment, and indeed all ROIs are very high, declining from 330% ROI in scenario 1a to 280% in scenario 3b. This decline in ROI relates to the high upfront costs in the screening interventions and the feature whereby treating individuals with early infections has minimal immediate cost benefits; the benefits occur later with lower net present values and so contribute less to the ROI. The differences between ROI as each intervention element is added can be explained in similar ways as for the CEA above (such as the

Table 5.7 - CER values for all interventions simulated independently.

Intervention	Independent CER - single interventions versus scenario 1a CNY/DALY averted (95% CrI)	Percentage of runs cost saving
Scenario 1a: Switch to DAAs	-	-
Scenario 1b: DAAs for newly diagnosed	4,469 (cost saving, 15,070)	27
Scenario 1c: DAAs for previously diagnosed	4,397 (cost saving, 15,204)	27
Scenario 2a: Screen MSM	16,723 (10,401, 22,446)	0
Scenario 2b: Screen in HIV care	10,143 (cost saving, 18,576)	3
Scenario 2c: Screen PWID	6,929 (cost saving, 15,716)	10
Scenario 2d: Screen FSW	41,527 (17,064, 65,621)	0
Scenario 3a: Screen pregnant women	47,589 (33,015, 63,121)	0
Scenario 3b: Screen male partners of pregnant women	15,643 (5,999, 23,445)	0

Independent CERs are calculated by comparison to a counterfactual of scenario 1a (status quo + DAAs), as described in the text.

improvements in ROI when screening PWID, or screening male partners, compared to the previous interventions) and this is not repeated here as the explanations are broadly the same.

Nominal investment values give an indication of the money that will need to be found for the intervention packages simulated. Providing DAAs for those newly diagnosed, and those previously diagnosed, costs a nominal 2.1 billion CNY (95% CrI: 1.5-2.7 billion CNY), or approximately 0.3 billion USD. This represents a major part of the overall investment required when all interventions are considered together in scenario 3b (78%); the additional nominal cost of implementing all the screening elements comprising scenarios 2a-3b (to 2050) is a comparatively small 0.6 billion CNY (or 80 million USD).

Sensitivity analyses. The sensitivity of the ROI values above to all cost parameters is shown in figure 5.18. This demonstrates that care costs and DAA costs dominate the variation in ROI. The third most important contribution is PEG-IFN+RBV costs, illustrating that overall it is the cost of treatment that determines, in large part, the ROI.

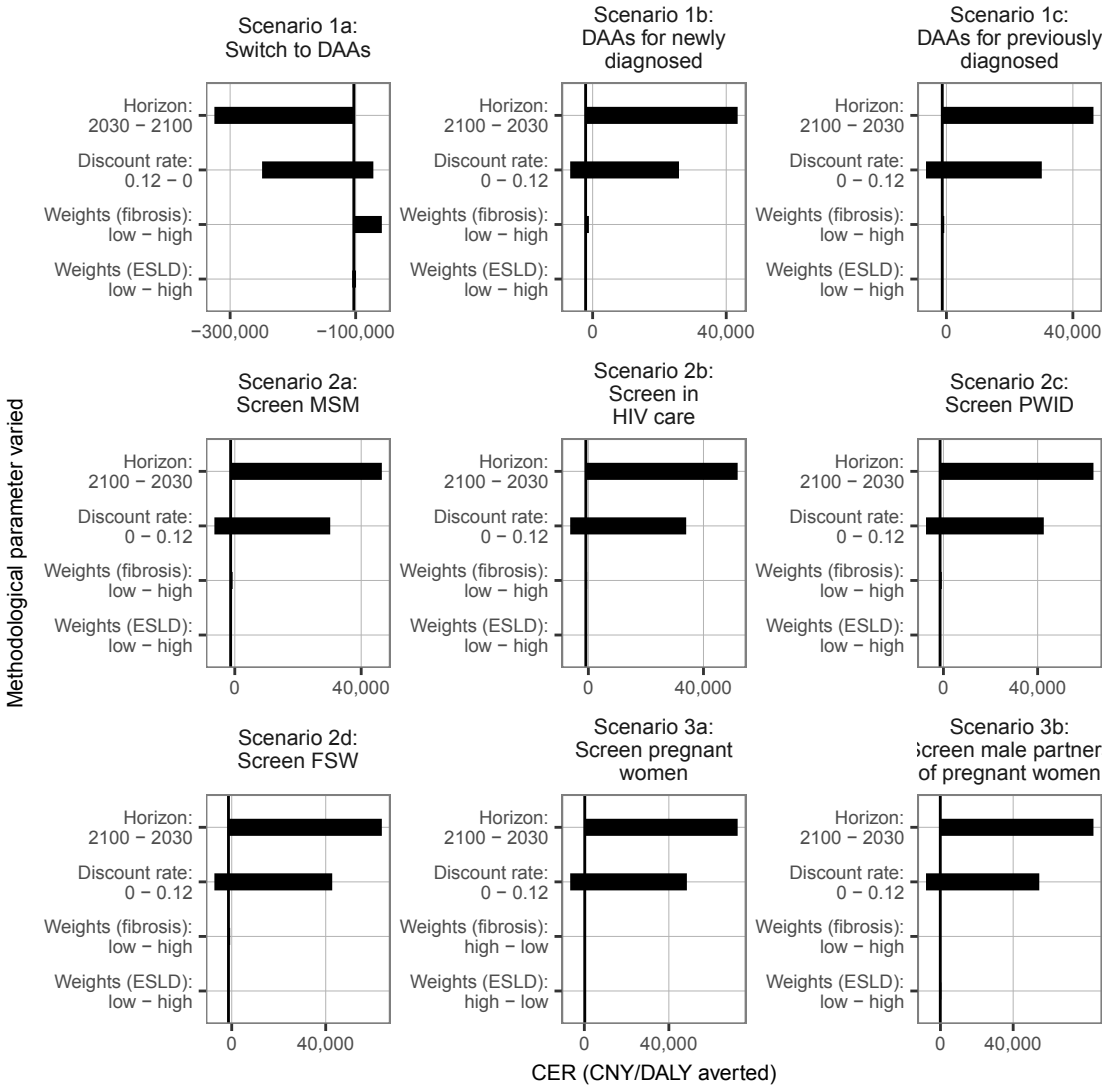


Figure 5.16 - Variation of CER by methodological parameters. Numbers indicate the range of values explored; the order indicates the direction in which the CER changes when changing the methodological variable. Low to high indicates values are altered between the values shown in table 5.5.

The impact of varying DAA cost (which is uncertain at present, see §5.1.4) and simultaneously varying care costs is shown in figure 5.19, on which is shown the separatrix between ROI>0 and ROI<0 (marking the point at which the investment in the intervention is greater than the overall cost savings it yields). At costs of care equal to the values used in the primary analysis above (care cost multiplier equals one), it would take a DAA cost of over 55,000 CNY per course to produce a negative ROI. Even were care costs reduced by a factor of five, it would still require DAA costs to be approximately 25,000 CNY for interventions to fail to provide a positive return, well above the upper bound used in the primary analysis of 20,000 CNY per DAA course. This indicates that when DAAs are made available in China, even if they cost considerably more than anticipated in

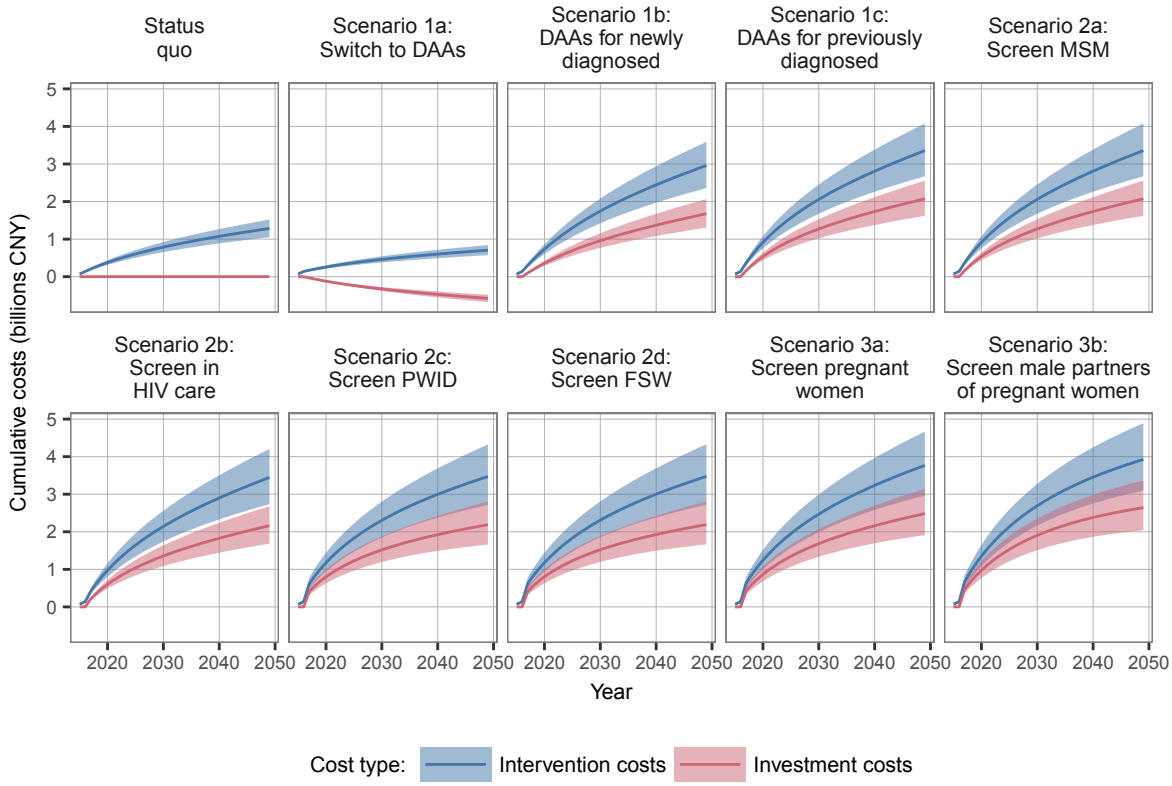


Figure 5.17 - Cumulative intervention and investment costs. The top line (and 95% CrI) show the total direct costs of each intervention (the summed treatment, and diagnosis and screening costs). The lower line shows the investment costs, that is the difference between each intervention and status quo (see definition of the ROI). For reference, 1 billion CNY is approximately 110 million GBP at September 2018 exchange rates [663].

the primary analysis used in this work, implementing the full set of interventions (scenario 3b) would still provide a positive return on investment.

Lastly, figure 5.20 shows the sensitivity of the ROI to changes in methodological parameters. The same explanations hold as for the variations in CER (see above): in short, reducing horizon length or increasing discount rate reduces benefits that accrue further in the future relative to interventions costs (the investment) so driving down the ROI.

5.4 Discussion

5.4.1 Summary

Epidemiological impact of interventions. The epidemiological impact of the different interventions varies with the particular element being added to that strategy. Introducing DAAs immediately reduces mortality as those treated have higher cure rates and benefit immediately in terms of reduced mortality. When screening high-risk groups, strategies that result in more PWID being

Table 5.8 - ROI values for all interventions.

Intervention	ROI (95% CrI)	Nominal investment to 2050 / billions CNY (95% CrI)	Nominal return to 2050 / billions CNY (95% CrI)
Scenario 1b: DAAs for newly diagnosed	3.26 (1.36, 7.30)	1.68 (1.12, 2.26)	4.21 (1.83, 8.72)
Scenario 1c: DAAs for previously diagnosed	3.10 (1.30, 6.83)	2.07 (1.44, 2.74)	5.04 (2.18, 10.46)
Scenario 2a: Screen MSM	3.10 (1.30, 6.83)	2.07 (1.44, 2.74)	5.04 (2.18, 10.46)
Scenario 2b: Screen in HIV care	3.01 (1.26, 6.61)	2.16 (1.51, 2.86)	5.01 (2.14, 10.45)
Scenario 2c: Screen PWID	3.20 (1.37, 6.97)	2.19 (1.50, 2.96)	5.18 (2.26, 10.69)
Scenario 2d: Screen FSW	3.19 (1.37, 6.95)	2.19 (1.51, 2.96)	5.18 (2.26, 10.69)
Scenario 3a: Screen pregnant women	2.76 (1.16, 5.97)	2.49 (1.79, 3.27)	4.94 (2.00, 10.46)
Scenario 3b: Screen male partners of pregnant women	2.85 (1.24, 6.05)	2.64 (1.95, 3.45)	4.94 (1.97, 10.53)

The investment and return values are nominal (undiscounted) values summed to 2050. The investment is the difference in intervention spending between the particular scenario and status quo. The return is the difference in non-intervention spending less the investment. The ROI is calculated from discounted (net present value) costs evaluated to 2100 and so the ratio of investment and return columns should not equal the ROI.

screened have the highest impact. This is because new infections are concentrated among PWID (as shown by the PAF for that group). Such interventions include the screen PWID intervention, screen HIV positive intervention (as HIV prevalence in PWID is higher than average) and screen male partners of pregnant women. Whether PWID will be equally represented among the male partners attending ANC clinics with pregnant partners is not known but we have assumed in this analysis that they will be, resulting in this intervention having a much larger intervention than the comparative strategy involving screening pregnant women alone. Implementing all available intervention strategies (scenario 3b), which comprises providing DAAs to recent and past diagnosed individuals, screening MSM, those in HIV care, PWID, FSW, pregnant women and their partners, will offer significant epidemiological gains: it can reduce mortality by 56% and incidence by 49% by 2030, averting 7,300 deaths and 19,000 new infections over that period.

Economic cost of interventions. Economic costs were evaluated for all interventions. These are considerable, with treatment costs alone peaking at 490 million CNY in the first year in scenario 3b, but such costs are concentrated in the first few years of the intervention programmes: by 2023, the overall HCV costs (including productivity losses) upon implementation of this full package of intervention strategies will have dropped below the equivalent costs in status quo, while by

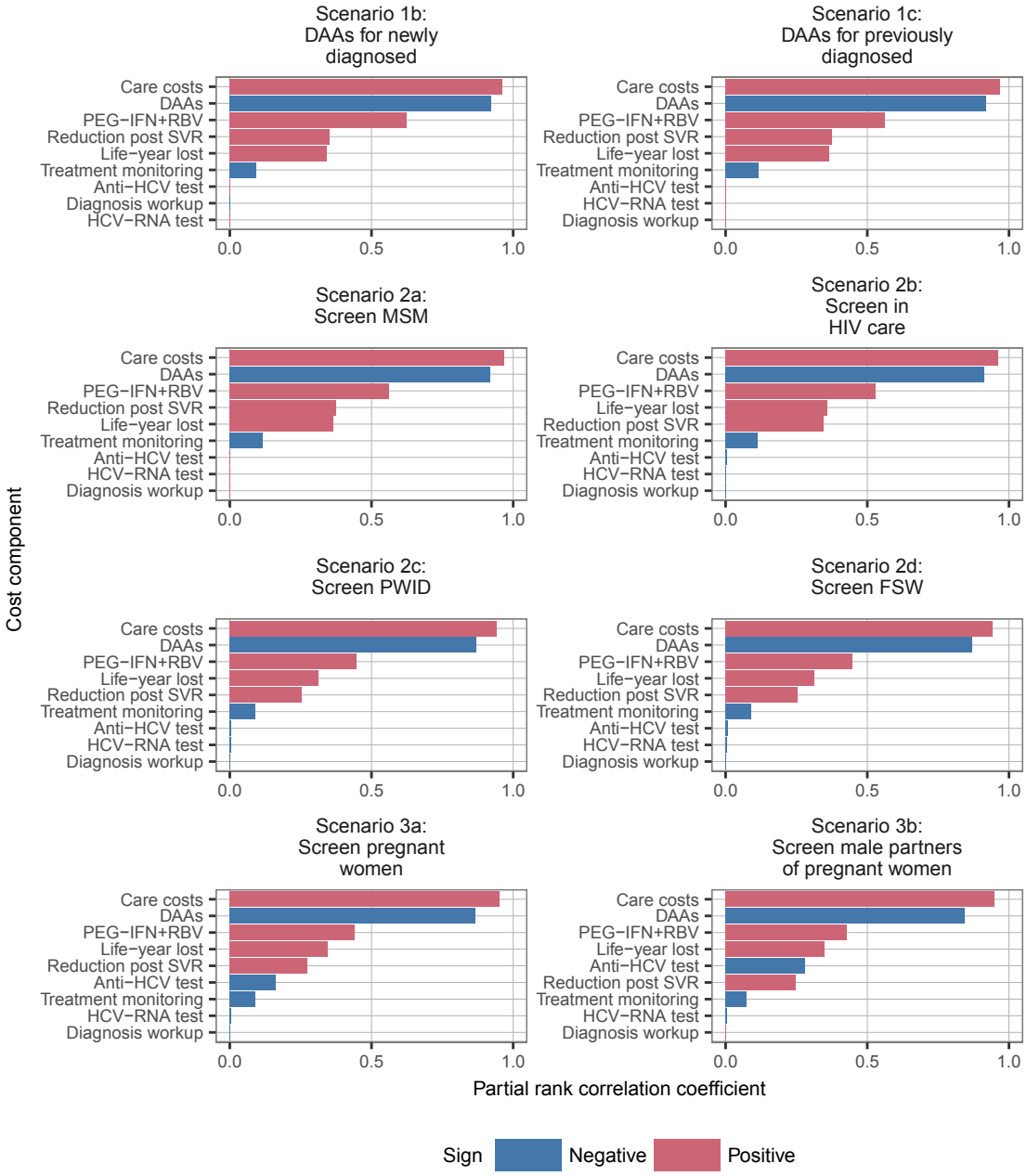


Figure 5.18 - Partial correlation coefficients relating cost variables to ROI.

2050 total costs due to HCV are 68% lower. Notably the overall long-term costs are lowest in the maximum impact strategy (with the full set of elements in scenario 3b), demonstrating the long term cost savings available as measured by including all costs identified in our costing model.

Cost effectiveness of interventions and comparison of different intervention elements. Cost-effectiveness analyses were carried out from a health care sector perspective and demonstrated that scenario 3b was a cost-saving intervention with a negative CER. This is driven by the automatic

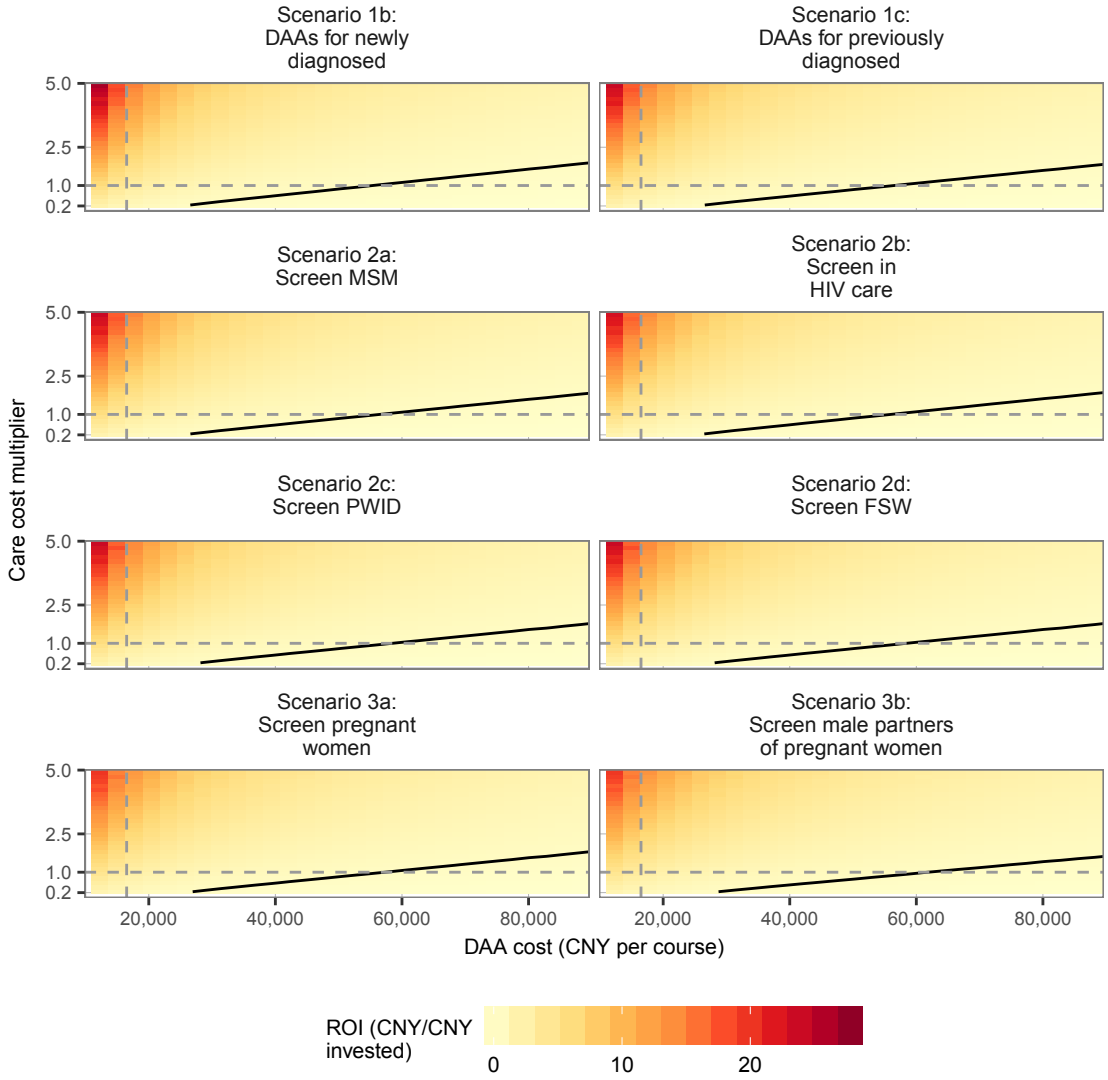


Figure 5.19 - Heat map of ROI with varying care and treatment costs. The colour indicates the return on investment achieved given varying care costs and DAA treatment costs. The black contour line on each graph indicates a separatrix, the boundary between positive and negative ROI: all points to the right and below the separatrices have negative ROI. The horizontal and vertical dashed lines are the central values (care costs and DAA treatment course cost respectively) used in the primary analyses.

cost savings provided by the switch to DAAs compared to the more expensive PEG-IFN+RBV and higher cure rates associated with DAAs, which both reduces DALYs along with future care costs. Cost savings are enhanced by the construction of screening interventions that avoid overhead costs by being implemented within other programmes that already exist. The possibilities of cost savings in even the most expansive intervention simulated here suggests that the current approach to screening and treating HCV carries avoidable opportunity costs, both in terms of lost health benefits and money that could be better utilised elsewhere in the health system. These costs are ultimately borne by individuals who are not treated and cured.

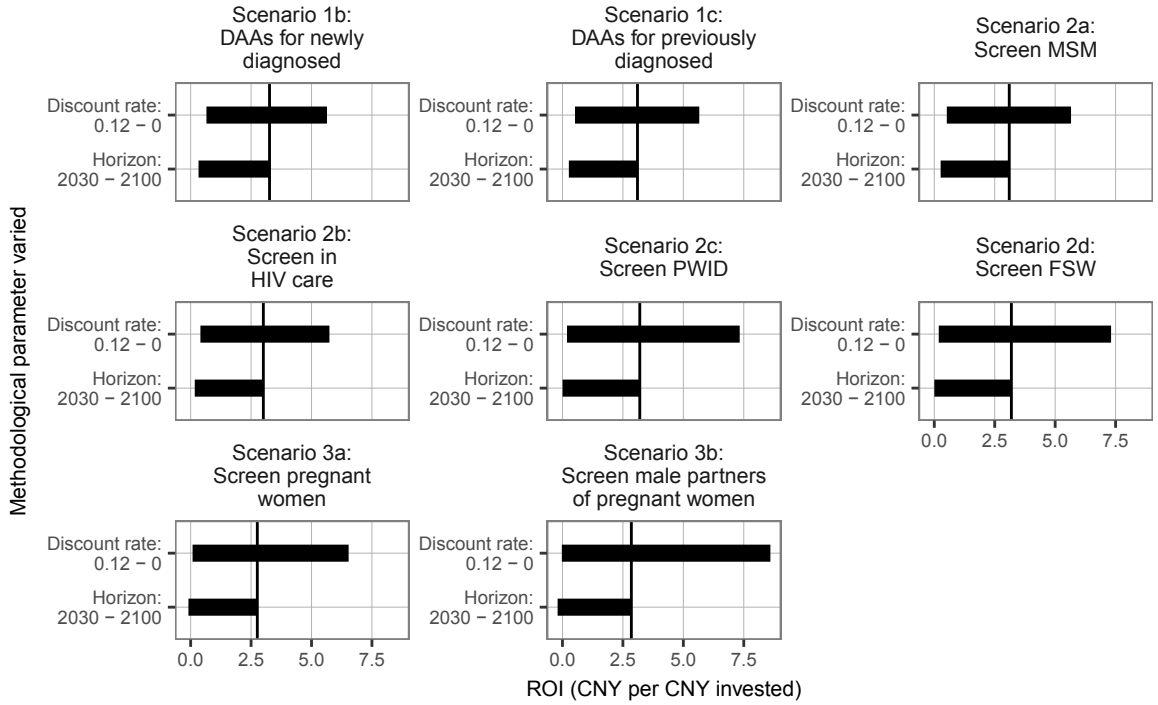


Figure 5.20 - Variation of ROI by methodological parameters. Only horizon and discount rate are shown as changing the DALY disability weights does not alter the calculation of the ROI. Numbers indicate the range of values explored; the order indicates the direction in which the ROI changes when varying the methodological parameter. Low to high indicates values are altered between the values shown in table 5.5.

Comparing the CERs of different interventions showed that screening interventions were generally less cost effective than introducing DAAs among those being diagnosed already as part of routine testing (scenario set 1 interventions), a consequence of the immediate health and economic benefits of treating those in the later stages of disease. The most cost-effective screening interventions were those associated with averting future infections (such as screening PWID), illustrating how long term benefits can improve the economic case for screening, even when considered from the health care sector perspective only and without building in broader measures of societal benefits. That screening PWID is so important is clear given the proportionally large number of future infections in this group alone. Efforts should focus, firstly, on ensuring access to DAAs for all those diagnosed as part of routine screening, and ensuring and promoting treatment for those who have been diagnosed but have delayed or not yet received treatment; secondly, on screening PWID through NGOs that work with this group; thirdly, on screening in HIV facilities; and lastly, on screening men presenting with partners for routine testing during pregnancy.

Net benefit to society. Investment costs in all interventions are considerable and these costs are not offset by future investment savings (as may occur if future testing and treatment, for example, decreased sufficiently) or by the immediate savings offered by switching to DAAs from the current status quo of PEG-IFN+RBV. Despite this, scenario 3b, with the highest investment costs, has a

positive ROI of 2.85 (a return of 285%), a value in line with estimates of ROI from other public health interventions suggesting a strong economic case for implementing these DAA intervention strategies [664].

5.4.2 Limitations

The model developed here has various data limitations. The prevalence estimates within specific risk groups are based on sentinel surveillance surveys carried out by groups who work with the various high-risk groups but these could suffer from sample bias; those who engage with such groups may not be representative of the group as a whole. Furthermore, group size estimates are derived from the grey literature and are liable to suffer from underreporting. One illustration of the possible weakness of the HCV prevalence data is the outlier in MSM prevalence points; the model ultimately fits to the remaining three points which appear to be consistent. In short, these estimates represent the best available data, and the model was designed to explore a range of epidemic scenarios suggesting conclusions are robust to a degree of uncertainty in these values.

No HIV-HCV coinfection estimates were available and we conservatively assumed equal prevalence as in the risk-group under consideration (for those risk groups in which HIV prevalence estimates were available). This would tend to underestimate the impact of scenario 2b (screening those in HIV care) since HIV infection is likely a predictor of HCV infection and so screening in this group should probably be more successful than we have projected.

Mortality estimates are based on sentinel surveillance surveys by the local CDC. These are viewed as having good coverage, however, cause of death is not provided in these estimates. Therefore, the HCV-attributable estimates are based on a review of surveys of the proportion of cirrhosis and HCC cases that are attributable to HCV in China. The ranges for HCV-attributable mortality chosen were deliberately broad, providing a wide range of possible models in respect of the mortality information to try and mitigate this uncertainty in the data.

Detailed population data were available for Yunnan specifically for most indicators, however, future projections are not made at the level of particular provinces. It was, therefore, necessary to utilise UN estimates of population projections for China as a whole to produce forward estimates of the population size in Yunnan. These estimates may not be reflective of Yunnan specifically and, as such, future population sizes (and so estimates of the number of active infections and deaths) may be under- or over-estimated accordingly.

With regards the economic modelling component, two perspectives were used and, as far as possible, recommendations relating to the reporting of this choice, and uncertainty to parameters like discount rate and time horizon were reported [646, 665]. Nevertheless, there were limitations to the methodology. Direct medical care costs available for Yunnan itself were utilised as they were directly relevant to the questions being asked and represent the best estimates available. Nevertheless, estimates made for these costs for other regions are heterogeneous and are often based on limited empirical data indicating that there may be uncertainty in these values [633, 634]. To

account for this we sampled care costs in our primary analysis over a wide range of values (0.5-2× the base costs) mitigating such concerns. Furthermore, we performed sensitivity analyses in which these care costs were varied over much wider ranges and explored the impact on our results of such an eventuality. A secondary assumption made here was that genotype testing would persist into the DAA era; this was to match the current approach to testing in Yunnan. In reality, however, once DAAs become widely available genotype testing will no longer be necessary. This assumption will only have a minor impact on the results; screening and diagnosis costs are negligible compared to other cost components and so removing genotype testing from the screening cost will only fractionally improve the case for DAAs compared to PEG-IFN+RBV.

Where Yunnan cost data were not available, we have had to make use of other potentially less appropriate sources, in particular utilising HBV disease estimates for the direct non-medical, and indirect medical costs [649]. The estimates were made almost ten years ago, suggesting that they could be out of date though they are China specific. The healthcare sector perspective analysis removes these costs from the calculation (as not pertaining directly to medical care): as the interventions were mostly cost saving, and all cost effective in this perspective, the results would not have been changed by reasonable changes to the values of these other care costs.

Intervention strategies were designed to make use of existing networks both as a means of reaching people as well as a means of reducing costs. Yet greater costs may be incurred by the "piggy backing" design of the interventions by the NGOs and health sector agencies now responsible for delivering HCV tests (either as initial overheads or through the need to contribute to running costs). The very small contribution screening and diagnosis costs make to the overall costs, and the minimal impact varying these costs has on CERs or ROI, suggests that only an exceptionally large increase in such costs would alter the conclusions drawn here. The point remains, however, that more operational research may be required to minimise the costs incurred through delivering HCV screening via other channels and to ensure that the strategies are sustainable in the long run.

We have made two further assumptions that may overstate the impact of intervention 3b. First, that 90% of partners of pregnant women will be available for testing (and of these 90% will accept testing, in line with the assumption for all screening groups). Whether men will be available in such high proportions remains to be seen; such an intervention has not been demonstrated in practice and further work on the feasibility and acceptability of this intervention will be required. Second, that PWID are present in the screened partner population in proportion to their presence in the adult population as a whole. Since PWID make up a considerable part of the epidemic (as demonstrated by the PAF for this group) and are mostly male, interventions that target 15-40 year old men could have a big impact as intervention 3b has demonstrated. Nevertheless, this relies on male PWID being equally represented in the partner population available for screening. Our simulation of intervention 3b here illustrates how screening of male partners could have a big impact on incidence and be a means of reaching more PWID than PWID screening alone, but the impact may be less if assumptions regarding partner screening are not met.

Finally, we have not incorporated the complex payment structure inherent in the Chinese medical system (see §5.1.3), as this was out of the scope of the current study. Such an analysis would be useful to carry out a formal budget impact analysis, for consideration of CEA from the patient's perspective and to determine cost sharing between patients, governments and insurance agencies. This would additionally allow the investment costs in the ROI analyses to be specified precisely as that met by the government and the ROI so arrived at would be directly comparable to that of other investments. As it stands, it is highly likely that some of the investment costs will be met OOP. Although the structure of copayment scenarios between patients, government agencies and insurers are uncertain and therefore are a limitation of the analysis, the Gates reference case suggests that amalgamating direct medical costs (even when they may be met OOP) is appropriate when such costs would ultimately fall on the health system [646].

5.4.3 Conclusions and implications for public health policy

This analysis, quantifying the impacts, cost effectiveness and ROI of HCV screening and treatment interventions, is the first analysis we are aware of that investigates such questions within the context of a fully dynamic model and that considers both a health care sector perspective and a broader societal perspective. As such, this work offers new insights that are of direct relevance to the creation of concrete HCV intervention strategies, both in Yunnan itself and in China more broadly (though further analysis would be required to make the extrapolation to China as a whole or to other provinces). Our analysis is timely as more countries (potentially including China as early as next year) are likely to gain access to cheaper DAAs and so will begin to consider how to scale up HCV interventions. Several broad conclusions can be drawn from this work that will be of relevance to such programmes more generally.

Firstly, the value used for DAA cost in this analysis is based on local estimates of the price that might be paid in the near future (and corresponds to around 150-450 USD per course) and at this price interventions are cost saving. A positive ROI was maintained even when simulating increased DAA costs of around 8,400 USD per course[9]. Nevertheless, it remains the case that quoted values for DAAs in China are closer to 13,000 USD and DAA prices are similar in other upper-middle-income countries like South Africa and Brazil [494]. 'High' costs have been used as a reason for not implementing DAAs since they became available in 2014 [666] and DAA prices are still central in our analysis: reaping the economic rewards of HCV intervention programmes will rely on achieving price reductions. This is particularly true in countries like China that still do not have agreements to produce or purchase generics and are not offered DAAs from originator companies at the low prices at which they have been made available in lower-income countries [494]. The developments described in the introduction indicate that this situation may change soon and our analysis suggests (at least from the perspective of Yunnan) that DAA price reductions are required that bring costs down at least below 8,400 USD per course. A related concern is also the price at which such drugs are made available to patients. Our analysis builds in the assumption that OOP payments

[9] Assuming a 12 week supply of daclatasvir [494] and sofosbuvir [612].

will be sufficiently low that all those offered treatment are able to afford it but this will only be the case by engaging all stakeholders and focussing attentions on the need to provide DAAs with minimal copayments [494].

Secondly, several of the above analyses have suggested that differences in the economic and epidemiological impacts of interventions are driven by a discrepancy between the time at which the cost is incurred and the benefit gained. This leads to a set of "low lying fruit" interventions in which treatment courses are offered to those at advanced stages of the disease, resulting in immediate benefits that offset the costs. Screening interventions, by contrast, result in treating often healthy individuals, a fact that dilutes the economic argument by introducing extra costs for deferred benefits. It is important, therefore, to make use of all available "free" channels to reach individuals and offer HCV screening. This is required both practically (as a means to reach people at all) and to support the economic argument for such programmes. Focussing on higher risk groups, in particular PWID, also maximises the relative cost effectiveness of such screening programmes compared to broader schemes that pick up fewer infections (and avert fewer infections) such as screening pregnant women.

Thirdly, once such available screening channels are exhausted, it remains to be seen what methods are available to continue to improve screening and get into care those who will not be reached by the methods suggested above. Targeted screening by age group (such as of those over 40 years old) is one possibility that could ensure continued progress is made towards the mortality elimination target in particular. While the full suite of interventions (scenario 3b) does reduce the overall number of active infections considerably, it is highly likely that finding the remaining HCV infections will be increasingly challenging. Even extremely dedicated outreach programmes can struggle to find additional infections, as has been demonstrated in Egypt for example (Mark Thursz, Imperial College London, personal communication, 31st January 2018), while interventions to identify the remaining "hard to reach" individuals are likely to be expensive. These additional expenses will potentially offset the economic benefits as described in the previous paragraph.

Lastly, even in the most ambitious scenario (3b) simulated here, incidence is only reduced by 52% which falls well short of WHO elimination targets. The above discussion describes the challenges of achieving positive returns when adopting well designed, cheap screening interventions, let alone the much more expensive interventions potentially required to reach all HCV-positive individuals. Given this, it is worth noting that HCV prevention strategies were suggested by us during consultation meetings but Yunnan CDC wanted to focus on treatment interventions alone. This suggests a somewhat one-sided view of HCV interventions which focus only on treatment; prevention initiatives are not considered an integral part of the HCV burden reduction toolkit. As the previous chapter has shown, this represents a missed opportunity and, from the economic perspective taken in this chapter, could weaken the economic case for the screening and treatment interventions being evaluated.

Chapter 6

Conclusion

Chapter 6 gives an overview of what has been achieved by the work in this thesis and contributions are detailed. Two meta-limitations of the work are discussed. Lastly, possible future research directions are described.

6.1 Summary and contributions of this work

This thesis has employed mathematical modelling tools to investigate the public health impact of interventions intended to reduce the burden of HCV infection at the global and local levels. This section will summarise how the aims of this thesis were met and highlight the contributions (publications and presentations) made by this work to the field.

Chapter 1 introduced the work by describing the burden of liver disease globally and the key role HCV infection plays within this. The development of highly effective drugs in 2014 and modelling of the HBV epidemic led to the establishment of formal viral hepatitis targets by WHO, which were subsequently enshrined in the UN sustainable development goals. We identified a lack of published evidence regarding the attainability of HCV elimination targets or quantification of how such targets could be met either on the global or local scales; this led us to carry out the work laid out in this thesis.

Chapter 2 provided an up-to-date overview of the epidemic in the manner of past summaries [216, 238, 245, 277–279, 667, 668]. The review of the modelling literature was the first critical analysis to take a broad look at previous HCV modelling work, going beyond past reviews that focussed solely on the health-economic literature [326, 327]. The models we analysed were found to fall into two broad categories: firstly, there were those that investigated disease

within the context of specific high-risk populations and focussed primarily on prevalence reducing interventions within this group alone. Such analyses did not require a consideration of the wider population and did not analyse how treatment or prevention interventions might affect mortality. The second group of models, by contrast, focussed on the question of how to reduce mortality. These analyses, by contrast, did not incorporate models of incidence and could not determine how the treatment interventions they considered could ultimately reduce incidence, neglecting the benefits this brings. The two strands of modelling, it was observed, were complementary and would need to be brought together to produce a model that could probe the impact of interventions upon the HCV epidemic considered both in terms of the burden of new infections and in terms of the burden of premature death.

Elements of this chapter formed part of a paper (Heffernan et al. "Aiming at the global elimination of viral hepatitis: challenges along the care continuum". Open Forum Infectious Diseases. 1st January 2018) that is reproduced in appendix C [142]; this was developed out of work at the first "Chronic Viral Hepatitis in Africa" workshop (10th-13th October 2016, Egypt). Details on the role of modelling in public health and its relationship to tackling the global burden of viral hepatitis were part of a talk given to physicians at University College London ("Tackling the global burden of hepatitis", University College London Clinical Research Group Science Day, 7th December 2017).

Chapter 3 described the model developed to answer our research aims. We synthesise the two key facets of previous work identified in chapter 2, allowing an investigation of mortality and incidence targets within one framework, along with facilitating the investigation of prevention and treatment strategies. We also built a model that could be calibrated to 190 countries allowing a global analysis to be carried out. This is the first such model that has been developed that can simulate HCV prevention and treatment interventions for any given country and allows projections of the global HCV epidemic to be made under a range of intervention scenarios described in this chapter.

Published contributions arising from chapter 3 are described in relation to chapter 4 below. A talk was also given on the methods developed in this chapter ("Calibrating a global model of hepatitis C", Imperial College London PhD Away Day, 3rd July 2017).

Chapter 4 applied the model to answer the question of whether or not WHO global elimination targets could be met. This quantified the extent to which the key indicators of general population risk reduction, PWID harm reduction coverage and diagnosis coverage had to be improved in order to reach elimination targets. A comprehensive package of prevention, screening and treatment interventions could avert 15 million new infections, 1.5 million cirrhosis and liver cancer deaths, corresponding to an 81% reduction in incidence and a 61% reduction in mortality compared to the 2015 baseline. This reaches the WHO incidence reduction target of 80% but is just short of the mortality reduction target of 65% (which would be reached in 2032).

Such an analysis relied on assuming all countries simultaneously scaled up general population risk reduction interventions to produce a further 80% reduction in risk from 2015 levels, rolled out OST and NSP programmes to 40% of the PWID population, and diagnosed 90% of those infected with HCV by 2030. These high values, and the sensitivity of the results to them, demonstrated the magnitude of the public health response that will be required to come close to elimination.

The incorporation of prevention interventions into this analysis, and the identification of these as critical in reaching elimination, is a key result that redresses the often treatment-centric focus of policy makers. Showing the importance of just a handful of countries including China to global elimination progress indicates not only the potential to miss elimination targets (if only one country "falls behind") but equivalently demonstrates that significant progress can be made with intervention scale up in a handful of countries.

The model of chapter 3 and results of chapter 4 have been published (Heffernan et al. "Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model". The Lancet. 28th January 2019) see appendix C [669], and is the first such published analysis of the WHO targets, fulfilling the first research question set out in chapter 1.

In addition, a talk summarising this paper was given at the World Hepatitis Summit ("Modelling the global elimination of hepatitis C", World Hepatitis Summit São Paulo, 2nd November 2017) and the same talk won first prize in the Imperial College London PhD Symposium ("Modelling the global elimination of hepatitis C", Imperial College London, 26th October 2017).

Chapter 5 used an adapted version of the model to investigate the epidemiological and economic impact of interventions implemented in a specific HCV epidemic, that of Yunnan Province, China. Working closely with local partners at the Yunnan CDC we designed a range of screening and treatment programmes, including providing DAAs to new and past HCV diagnosed individuals and screening a range of groups. When implemented in unison, these could reduce incidence by 49%, mortality by 56% and the number with active infection by 64% compared to 2015 baseline values. The cost of treatment alone in this scenario peaked at 492 million CNY (approximately 54 million GBP), however, by 2050 overall costs associated with HCV are 68% lower than in a status quo scenario with no intervention scale up. The full suite of interventions was cost saving in a majority of simulations when considering costs only from a health care sector perspective. Interventions that tackled mortality burden immediately were most cost effective. Of screening interventions, those that screened PWID and so averted future infections were shown to be more cost effective than other screening initiatives. Despite large increases in the number screened and treated compared to status quo, there was a positive net benefit from all interventions, driven by future cost savings, reductions in productivity losses associated with premature death and the lower cost of DAAs than PEG-IFN+RBV.

Additional analyses illustrated that DAA costs are still a key factor in ensuring economic benefits are attained indicating that recent Chinese national government efforts to reduce prices are critical. Other key conclusions drawn in this work were that screening interventions were less cost effective, particularly when they did not target the highest risk groups; and beyond the set of strategies considered, it is not clear how progress might be made, particularly given that focus remained on treatment alone over prevention strategies.

This work will form part of the material used by the Yunnan CDC to advocate for implementing DAAs in general in their dealings with the national government. It will guide local policy with regards the integration of HCV screening into the appropriate NGOs and existing healthcare programmes as we simulated in our analysis. I expect to present the analysis in meetings to national government officials and to continue the collaboration in future. This set of analyses fulfilled the second of our research goals, to examine concrete interventions in a specific setting and provide useful programme policy guidance to a health decision maker.

6.2 Limitations

The epidemiological results presented in this thesis have been generated by a bespoke mathematical model. All modelling analyses bring with them a range of limitations and assumptions that have to be addressed or acknowledged and these have been discussed already in the preceding chapters. Here two broad sets of limitations (data limitations and the strong assumptions regarding intervention impact) are highlighted. These are believed to be of particular significance to this work and the ways in which we mitigate these are discussed.

Firstly, HCV prevalence and HCV-attributable mortality data were required to calibrate the model, yet the values used for these quantities have a variety of drawbacks. Mortality estimates were produced within the somewhat opaque modelling framework of IHME [9]. The starting point for these calculations are cancer registries and other mortality databases on the country level. Often these do not exist; where they do there are a variety of issues that can be present, not least of which are underreporting of, in particular, HCC deaths since this cause of death is difficult to ascertain. The scarcity of information regarding the proportion of cirrhosis or HCC deaths due to viral hepatitis adds additional uncertainty (the subsequent division to HCV-specific viral hepatitis mortality presents a second layer of complication as was observed in the specific case of Yunnan in chapter 5) [6].

The data we adopted for overall HCV prevalence derive, ultimately, from a systematic review of heterogeneous country-level studies in which prevalence estimates in a particular group (such as pregnant women only, or blood donors) end up being used for the country as a whole [278, 280]. HCV prevalence among PWID data come from another systematic review [256] in which country-level estimates are, in some cases, based on studies involving small sample sizes and from only one location (often a city) indicating the possibility of systematic bias. In both cases, prevalence values were only available for a single point in time, preventing calibration to longitudinal data that

would otherwise have informed modelled disease trends. The even greater lack of incidence data [28] prevented this being used in either a model fitting capacity or for formal model validation, and indeed the overall lack of data precluded the adoption of more sophisticated model validation techniques (such as out-of-sample validation) that would complement the Bayesian calibration technique adopted here to ensure adequate model fit.

The spur to proceed with the analysis in spite of such data limitations was, in the end, the considerable political interest in HCV elimination sparked by the development of DAAs and cemented by the creation of WHO targets. In short, the world is moving towards the implementation of elimination strategies with or without such data. We, accordingly, sought to answer the questions not answered by the establishment of these targets: can they be reached and how? We, therefore, used the above values to align our work with the WHO targets [28] and designed the model with a view to mitigating these limitations (such as by encouraging a broad array of fits to mortality estimates). Furthermore, by publishing the results and presenting the full methods we will have provided the first transparent global analysis of the elimination targets. This can form the basis for further research and the work can be refined as and when better data become available.

The second limitation considered here is the assumption that outreach screening, improvements in blood and infection control, and the creation and extension of PWID harm reduction strategies can proceed in all countries and reach comprehensive coverages in the medium term (to 2030). This is a limitation because projections regarding reaching (or coming near to reaching) elimination targets rely, in our analysis, on the intervention strategies considered being effective. From a modelling standpoint this limitation was acknowledged and a range of sensitivity analyses were performed; these quantified how critical these indicators are to making progress.

Yet it is not practically known how the targets suggested in the global analysis can be met in all settings. Blood safety and infection control scenarios were designed in the global analysis with deliberate vagueness because of the uncertainty regarding the ultimate provenance of these infections (discussed previously) and it requires detailed data and country-level planning to make progress in minimising infections from such sources [670]. Progress relies on a will to take action which has been assumed in the intervention strategies modelled in our analysis.

A related concern is the misinterpretation of the analysis we have carried out (particularly in its published form). Our work suggests what can be achieved (effectively whether the framework of the targets is consistent) with regards reducing global burden of disease. This is, therefore, a projection of a possible outcome under an optimistic comprehensive package of interventions. There is a risk, however, that our work will be interpreted predictively ('this is what will happen'). By design, global targets are ambitious and the intervention coverage targets we have modelled have, accordingly, been equally ambitious. This is a point we hope will not be lost. In our discussion here and in published work we stress the challenge of meeting these targets in all settings, in addition to showing the benefits of meeting them, to try and mitigate the risk of misinterpretation. We have also drawn on a range of specific country examples in our discussions to show what can be

achieved in order to illustrate how progress could be made toward reaching these highly ambitious intervention coverage aims.

Perhaps even more significantly, the costs of improving the indicators required in the global analysis could well preclude implementation; additionally, political will (and the funding that goes with it) may be lacking for certain interventions. Most notably, harm reduction programmes often struggle to retain funding in even high-income countries such as Scotland, are seldom politically popular and are routinely defunded in many different settings. Improving diagnosis is another challenge that must be met but whose ultimate cost could be prohibitive. These all represent limitations to implementation and not limitations of the analysis. It is not, ultimately, the choice of modellers what to spend money on. All this analysis can and should do is demonstrate what can be achieved, with issues of cost or political unfavourability of interventions questions to be raised by policy makers.

One way in which modelling can be brought to bear more precisely on these sorts of questions is through working closely with local health agencies and analysing the costs as well as impacts of interventions within a specific setting. This motivated our work in Yunnan which allowed us to take part in this step of the process of developing HCV interventions. Such local analyses are a key next step in moving beyond global ambitions to concrete strategy. It is to considerations of the interplay of global targets and local implementation and the role of future modelling work within this dialogue that we now turn.

6.3 Global ambition, local reality and future research directions

This work began by posing two questions: the first question asked whether global elimination targets could be met. No work to date had looked critically at the elimination targets and so we developed a comprehensive analysis of HCV interventions at the global scale and produced an evidence-based analysis of the attainability of the high-profile WHO elimination targets. This demonstrated the challenges of reaching these targets. The second question asked what the impact of interventions delivered in a specific setting would be. Our work in Yunnan represents one of the first combined epidemiological and economic analyses investigating HCV interventions in a local setting. This analysis showed that there is a need to adopt pragmatic implementation strategies with regards screening to keep costs down so ensuring net benefit to society and also suggested that prevention programmes may not be a focus for policy makers.

We have made progress by answering these questions and in so doing are following in a long line of analyses that apply mathematical modelling to questions of public health policy (as illustrated by our discussion in chapter 2). Yet there remains much more that should be done and many more uses to which the many forms of modelling can be put beyond what we have done here.

Firstly, with regards the global model we developed, we have presented our results in a transparent way in publication, marking the first such analysis of the WHO targets. It is hoped that our

work marks a starting point from which further analyses will be carried out. These could investigate the global targets utilising new models with different assumptions against which our model's projections can be compared and contrasted. For instance, our results for the impact of prevention interventions could be compared against suitably extended versions of the VMH models (see chapter 2) which simulate PWID harm reduction in a different way to the approach we have taken. This would mirror pioneering model comparison analyses in the field of HIV modelling [671]. Results could also be aggregated to produce ensemble models, a relatively recent development within epidemiology, which have been developed to produce ensemble forecasts for diseases as diverse as influenza and malaria [672, 673]. The model developed here could also be used to investigate different interventions such as examining the global impact of targeted testing and treatment for PWID, an intervention previously considered in modelling analyses focusing on high-risk groups specifically [674]. This strategy is of interest as it may offer enhanced treatment-as-prevention benefits.

Secondly, an extension of the global analysis to add an economic component is envisaged that would allow us to put a value on the cost of implementing the interventions we have considered. Such global "price tags" can focus attention on where costs must be reduced as well as identifying low cost opportunities to make gains in the push towards elimination. These global economic estimates could also be compared to pharmaceutical companies' forecasts of DAA demand and revenue projections, with possible consequences for their pricing models.

Thirdly, the economic modelling we have carried out in Yunnan should be an integral part of local HCV intervention analysis since it allows for formal comparisons to be made between competing investments in the context of limited resources. Extensions of this work could be carried out which examined overall budget impact. Collaborations with local bodies offer a means of producing such highly specific analyses, but data limitations even at this level were still significant. This suggests a role for more in-country work in future analyses to furnish models with, in particular, more primary costing data.

Fourthly, regions or countries engaged in scaling up interventions must collect more data on disease burden and the treatment cascade. These data allow progress to be measured which can be used to justify expenditure; this can then promote further investments in successful programmes. Future modelling analyses would benefit, accordingly, from richer epidemiological and programme data, and the availability of such data will be instrumental in delivering insightful policy in the future. Modelling will play a role here in collating data and making inferences (such as to infer epidemic size) as well. There is, in other words, a role for modelling in disease and programme monitoring; such analysis will feed back into policy decisions, ideally, in a virtuous cycle: better data leads to better decisions which spurs collection of better data, all elements of which can be mediated by modelling.

Lastly, the work in Yunnan has suggested that the current scale of ambitions is not sufficient to reach global elimination targets. This was revealed not only through the focus on treatment over

prevention, but also in the cautiousness with which programmes such as screening pregnant women and their partners were met, while the full set of intervention strategies fell well short of meeting elimination targets. A vital future research direction is, therefore, in operational research that will investigate optimal intervention strategies. As was discussed in chapter 2, this could include significant mathematical modelling components (in contrast to most applications of operational research in public health today). These modelling extensions could study how to maximise the efficiency of HCV programmes and improve outcomes. Operational research is being carried out with regards improving the HCV treatment cascade [158, 675]; but incorporation of modelling could support these efforts both in terms of the design of the interventions trialled and, more importantly, by extrapolating the results of trials to suggest what the impact of successful interventions could be if implemented more broadly.

The move in this thesis has, ultimately, been from answering questions concerning global elimination targets to answering questions about local interventions. We have tackled issues of both large and small scale, implementing models accordingly. The above discussion illustrates how our modelling, and other forms of models besides those which we have designed and applied here, can continue to inform the HCV policy debate. At the global level, further analyses in a similar vein to our global work can be performed that critique or confirm the conclusions we have drawn and extend upon them. At the local level, analyses like our Yunnan work can make the case for specific policy decisions, rooting these decisions in health economics backed up by richer data and local understanding of pragmatic intervention strategies than are available in a global analysis. Through this progression from the large to the small scale a new question has emerged regarding the elimination of hepatitis C as a public health threat: how can global targets, aimed for with specifically designed local interventions, be effectively implemented? Only through further work (like that described in the previous paragraph) which hones in on the issues of operations and implementation can this necessary question be answered. This future research direction, within which modelling can play a key role, represents a critical next step in tackling the HCV epidemic, ensuring that global ambitions are converted into local reality, to the benefit of all those living with, or at risk from, HCV.

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COUNTRY-LEVEL TREATMENT CASCADE VALUES

Table A.1 - Percentage diagnosed and treated in 2015.

Country	Percentage diagnosed	Percentage treated of diagnosed
Country-specific values [226]		
Austria	33	29
Belgium	44	5
Bulgaria	19	4
Croatia	24	2
Cyprus	10	7
Czech Republic	31	7
Denmark	63	5
Estonia	50	5
Finland	77	2
France	74	14
Germany	57	20
Greece	29	6
Hungary	48	5
Ireland	40	7
Italy	42	10
Latvia	45	5

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Table A.1 – *Continued from previous page*

Country	Percentage diagnosed	Percentage treated of diagnosed
Lithuania	13	23
Luxembourg	54	7
Malta	92	1
Netherlands	60	20
Poland	18	12
Portugal	34	17
Slovakia	9	11
Slovenia	52	5
Spain	34	29
Sweden	85	7
United Kingdom	39	12
Country-specific values [394]		
Bahrain	17	2
Cameroon	4	8
Colombia	13	2
Dominican Republic	10	7
Ethiopia	3	10
Ghana	7	0
Hong Kong	23	6
Jordan	21	3
Kazakhstan	17	3
Malaysia	8	2
Morocco	10	10
Nigeria	4	0
Oman	19	3
Qatar	46	28
Taiwan	43	4
Country-specific values [393]		
Iceland	83	3
Indonesia	11	0

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Table A.1 – *Continued from previous page*

Country	**Percentage diagnosed**	**Percentage treated of diagnosed**
Iran	35	7
Japan	74	4
Lebanon	22	11
Pakistan	16	14
Romania	17	4
Saudi Arabia	23	2
South Korea	42	5
United Arab Emirates	42	3
Country-specific values [395]		
Argentina	37	1
India	6	12
Israel	28	4
Mexico	35	2
Mongolia	30	1
New Zealand	42	5
Norway	63	5
Russia	38	0
South Africa	15	0
Country-specific values [392]		
Australia	88	1
Brazil	16	6
Canada	73	2
Egypt	18	17
Switzerland	41	3
Turkey	18	5
Adjusted regional values used for remaining countries [28]		
African region - AFRO	6	3
Region of the Americas – PAHO	45	14
Eastern Mediterranean Region - EMRO	21	0

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Table A.1 – *Continued from previous page*

Country	Percentage diagnosed	Percentage treated of diagnosed
European Region - EURO	13	2
South-East Asia Region - SEARO	9	7
Western Pacific Region - WPRO	16	6
Global	20	7

Countries with treatment cascade estimates reported for 2013 or 2014 had estimates of 2015 treatment cascade values produced using available information in the relevant papers regarding new diagnosis and treatments combined with estimates of new infections and mortality. In the case of India, Pakistan and Egypt, significant treatment expansion was reported in 2015. Treatment numbers were altered by adding 100 000 extra treatments for Egypt [494], 65 000 for Pakistan [494], and 42 000 for India [483] when producing updated 2015 percentage treated values; not doing this led to extremely high estimates for the adjusted regional SEARO and EMRO percentage treated values. Regional values calculated such that, in combination with country-specific values above, the global diagnosed and treated percentages match WHO global estimates [28].

Table A.2 - Number of DAAs in countries with DAAs introduced in 2016.

Country	Number of DAA courses
Argentina	1,200
Australia	40,000
Brazil	41,200
China	133,000
Egypt	700,000
France	45,000
Georgia	21,700
Indonesia	400
Mongolia	6,500
Morocco	6,500
Pakistan	161,000
Romania	6,000
Rwanda	1,000
South Africa	160
Spain	72,000

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Table A.2 – *Continued from previous page*

Country	Number of DAA courses
Ukraine	2,500
United Kingdom	12,000

Where data on DAA uptake include treatment courses delivered in 2017, the values are adjusted on the assumption of constant access to produce 2016 estimates (for example, 200,000 DAA courses are estimated for China to mid-2017; this is adjusted to a 2016 only value by multiplying by 2/3). In addition to the above countries, DAAs are implemented in countries noted as introducing DAAs in the WHO progress report [494] or in a recent study of DAA expansion in the European Union but for which precise 2016 figures were not given. The proportion treated in 2015 is assumed to be equal to the 2016 value and these numbers are used for the number of DAA treatment courses in 2016. The countries modelled as offering DAAs in 2016 that are not listed in the above table are: Austria, Belgium, Bulgaria, Canada, Croatia, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Slovakia, Slovenia, Sweden, Switzerland and USA. As noted above, this prescription results in approximately 1.8 million treatment courses being delivered (in line with stated numbers [494]) of which around 86% (1.5 million) are with DAAs.

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APPENDIX B

List of countries by region

Countries by GBD study region

190 countries and territories were simulated. The only regions with populations greater than 100,000 not modelled were French and Dutch overseas territories. These were not simulated because there are no GBD study mortality estimates for these regions. GBD study mortality numbers for China include Macao SAR and Hong Kong SAR; to simulate mainland China independently the China mortality rates were combined with population sizes to produce mortality numbers for the Chinese mainland only. Mortality information from the 2013 GBD update was used for Hong Kong SAR and Macao SAR, since this update included mortality estimates specific to these regions (the 2016 update does not).

- *Central Asia:* Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan and Uzbekistan.
- *Central Europe:* Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Macedonia, Montenegro, Poland, Romania, Serbia, Slovakia and Slovenia.
- *Eastern Europe:* Belarus, Estonia, Latvia, Lithuania, Moldova, Russia and Ukraine.
- *Australasia:* Australia and New Zealand.
- *High-income Asia Pacific:* Brunei, Japan, Singapore and South Korea.
- *High-income North America:* USA and Canada.
- *Southern Latin America:* Argentina, Chile and Uruguay.
- *Western Europe:* Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and United Kingdom.
- *Andean Latin America:* Bolivia, Ecuador and Peru.

- *Caribbean:* Antigua and Barbuda, The Bahamas, Barbados, Belize, Cuba, Dominican Republic, Grenada, Guyana, Haiti, Jamaica, Puerto Rico, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago and US Virgin Islands.
- *Central Latin America:* Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama and Venezuela.
- *Tropical Latin America:* Brazil and Paraguay.
- *North Africa and Middle East:* Afghanistan, Algeria, Bahrain, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Palestine, Oman, Qatar, Saudi Arabia, Sudan, Syria, Tunisia, Turkey, United Arab Emirates and Yemen.
- *South Asia:* Bangladesh, Bhutan, India, Nepal and Pakistan.
- *Southeast Asia:* Cambodia, Indonesia, Laos, Malaysia, Maldives, Mauritius, Myanmar, Philippines, Sri Lanka, Seychelles, Thailand, Timor-Leste and Viet Nam.
- *East Asia:* China, Hong Kong SAR, Macao SAR, Taiwan and North Korea.
- *Oceania:* Federated States of Micronesia, Fiji, Guam, Kiribati, Papua New Guinea, Samoa, Solomon Islands, Tonga and Vanuatu.
- *Central Sub-Saharan Africa:* Angola, Central African Republic, Congo, Democratic Republic of the Congo, Equatorial Guinea and Gabon.
- *Eastern Sub-Saharan Africa:* Burundi, Comoros, Djibouti, Eritrea, Ethiopia, Kenya, Madagascar, Malawi, Mozambique, Rwanda, Somalia, South Sudan, Tanzania, Uganda and Zambia.
- *Southern Sub-Saharan Africa:* Botswana, Lesotho, Namibia, South Africa, Swaziland and Zimbabwe.
- *Western Sub-Saharan Africa:* Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Côte d'Ivoire, The Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, São Tomé and Príncipe, Senegal, Sierra Leone and Togo.

Countries in the European Union

- *EU:* Austria, Italy, Belgium, Latvia, Bulgaria, Lithuania, Croatia, Luxembourg, Cyprus, Malta, Czech Republic, Netherlands, Denmark, Poland, Estonia, Portugal, Finland, Romania, France, Slovakia, Germany, Slovenia, Greece, Spain, Hungary, Sweden, Ireland and United Kingdom.

Countries by WHO regional office

- *African Region – AFRO:* Algeria, Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, São Tomé' and Príncipe, Senegal, Seychelles, Sierra Leone, South Africa, Swaziland, Tanzania, Togo, Uganda, Zambia and Zimbabwe.

- *Region of the Americas – PAHO:* Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Puerto Rico, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, USA, Uruguay, Venezuela and US Virgin Islands.
- *Eastern Mediterranean Region – EMRO:* Afghanistan, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, South Sudan, Sudan, Syria, Tunisia, United Arab Emirates and Yemen.
- *European Region – EURO:* Albania, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Macedonia, Malta, Moldova, Montenegro, Netherlands, Norway, Palestine, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, Turkey, Turkmenistan, Ukraine, United Kingdom and Uzbekistan.
- *South-East Asia Region – SEARO:* Bangladesh, Bhutan, North Korea, Hong Kong SAR, India, Indonesia, Macao SAR, Maldives, Myanmar, Nepal, Sri Lanka, Taiwan, Thailand and Timor-Leste.
- *Western Pacific Region – WPRO:* Australia, Brunei Darussalam, Cambodia, China, Fiji, Guam, Japan, Kiribati, Laos, Malaysia, Micronesia, Mongolia, New Zealand, Papua New Guinea, Philippines, Samoa, Singapore, Solomon Islands, South Korea, Tonga, Vanuatu and Viet Nam.

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APPENDIX C

PUBLICATIONS

Accepted and published articles

The following papers have been published during this PhD. The two first author publications are reproduced below.

- Cremin Í, Watson O, Heffernan A et al. *An infectious way to teach students about outbreaks*. Epidemics. 5th December 2017
- Heffernan A, Barber E, Cook N et al. *Aiming at the global elimination of viral hepatitis: challenges along the care continuum*. Open Forum Infectious Diseases. 1st January 2018
- Heffernan A, Cooke G, Nayagam S et al. *Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model*. The Lancet. 28th January 2019

Open Forum Infectious Diseases

MAJOR ARTICLE

Aiming at the Global Elimination of Viral Hepatitis: Challenges Along the Care Continuum

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A recent international workshop, organized by the authors, analyzed the obstacles facing the ambitious goal of eliminating viral hepatitis globally. We identified several policy areas critical to reaching elimination targets. These include providing hepatitis B birth-dose vaccination to all infants within 24 hours of birth, preventing the transmission of blood-borne viruses through the expansion of national hemovigilance schemes, implementing the lessons learned from the HIV epidemic regarding safe medical practices to eliminate iatrogenic infection, adopting point-of-care testing to improve coverage of diagnosis, and providing free or affordable hepatitis C treatment to all. We introduce Egypt as a case study for rapid testing and treatment scale-up: this country offers valuable insights to policy makers internationally, not only regarding how hepatitis C interventions can be expeditiously scaled-up, but also as a guide for how to tackle the problems encountered with such ambitious testing and treatment programs.

Keywords. elimination; hepatitis care continuum; policy; viral hepatitis.

Viral hepatitis was responsible for 1.3 million deaths globally in 2015 and is now the seventh leading cause of mortality, rising from the 10th cause in 1990 [1, 2]. The full burden of disease encompasses not only mortality, but also reduced quality of life for patients (through cirrhosis and associated complications), financial costs of care for individuals and health care systems alike, and economic costs to society as a whole. Despite this burden, viral hepatitis has only in recent years received the attention it merits. Now, with a World Health Organization (WHO) elimination strategy published [1], the international community is at last focused on tackling the twin epidemics of hepatitis B virus (HBV) and hepatitis C virus (HCV).

At a recent conference (the first "Chronic Viral Hepatitis in Africa" conference, Egypt), clinicians and researchers from across the globe discussed the challenges of reaching WHO elimination targets. Considering the hepatitis care continuum (Figure 1) [3, 4], we identified several key areas in which progress must be made before elimination will be reached. We focused on those areas in which improvements are possible (using tools currently available) and on those aspects of treatment and care where the impact of changes in policy or strategy is potentially greatest. This viewpoint is a distillation of these discussions and is written with the aim of informing policy at this critical moment in the formation of national and international viral hepatitis programs.

HBV BIRTH-DOSE VACCINATION: CONFRONTING LOST OPPORTUNITIES

Scaling-up of infant vaccination has already had demonstrable impacts on global HBV prevalence [5]. Infant vaccination alone, however, does not prevent mother-to-child transmission (PMTCT). As the risk of chronic hepatitis B (CHB) infection is as high as 90% if infected perinatally [6], effective PMTCT is crucial to reducing incidence.

A key component of a comprehensive PMTCT strategy is birth-dose vaccination. Modeling studies have suggested that an 80% global scale-up of birth-dose vaccination plus infant vaccination, compared with scaling-up of infant vaccination alone, could avert 18.7 million new chronic infections over the next 15 years, highlighting its importance as a PMTCT tool [7]. Monovalent HBV vaccine is inexpensive (US$0.20 per dose), and birth-dose vaccination is likely to be cost-effective [8].

Despite such evidence, global HBV birth-dose vaccine coverage remains low, at 39% [9]. Moreover, vaccines are often administered beyond 24 hours of birth [10], when they are less effective in

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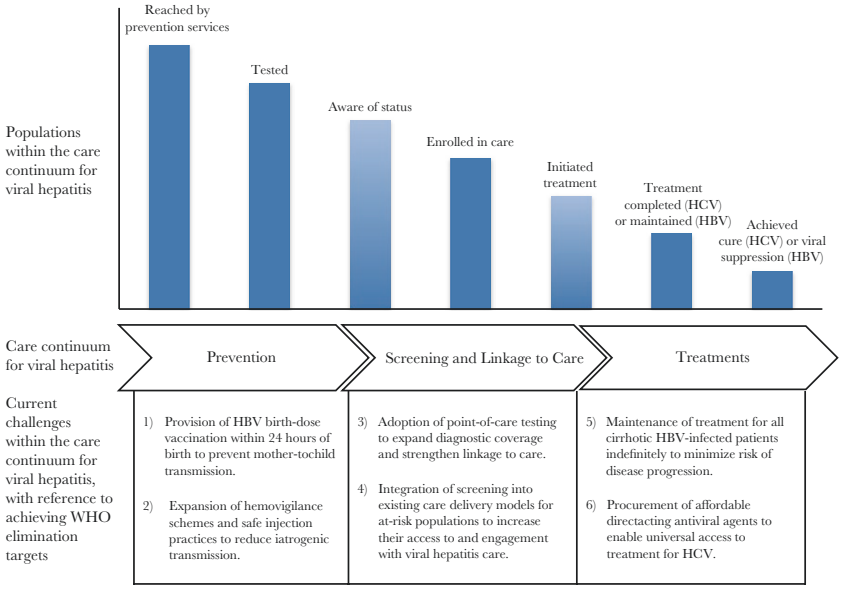


Figure 1. Overview of the WHO care continuum for viral hepatitis and the associated challenges encountered when aiming toward WHO elimination targets, adapted fromn Zhou et al. [3]. Populations within the care continuum for viral hepatitis are as defined within the Global Health Sector Strategy on Viral Hepatitis [4]. Abbreviations: HBV = hepatitis B virus; HCV = hepatitis C virus; WHO = World Health Organization.

PMTCT [11, 12]. There are several reasons for this low coverage: the monovalent vaccine is not funded by agencies like GAVI, as the cost of the vaccine falls below their funding threshold [13]; there are significant costs for vaccine delivery [14]; cultural factors may reduce access to health care by women in the postpartum period [15]; and hepatitis B interventions are rarely a public health priority [16], with only 9 countries in sub-Saharan Africa, for example, incorporating birth-dose vaccination into their national policies by 2015 [10, 17].

Innovative approaches exist to improve timely birth-dose vaccination administration, including increasing the number of health staff–attended births [18], ensuring coordination between immunization and maternal health services [19], expanding vaccine management systems [19], using prefilled injectable vaccines for home births [20], promoting awareness of the need for timely HBV vaccination [21], and simplifying the supply chain by, for example, using heat-sensitive labels to allow storage of vaccine outside the cold chain [22, 23].

A substantial scale-up in birth-dose vaccination coverage is pivotal to reaching WHO 2030 elimination targets [1]. This is long overdue, and acceleration of efforts requires a combination of political engagement by governments, financial commitment, and strategic planning to help countries reach these goals.

IATROGENIC TRANSMISSION: A COST-EFFECTIVE APPROACH TO CURBING TRANSMISSION

Blood and injection safety are fundamental to national viral hepatitis programs [1]. In Africa, for example, the risk of acquiring HCV from blood is 2.5 per 1000 units transfused, compared with 1 per 2–3 million units in high-income countries [24]. In addition, the reuse of injection equipment, inadequate sterilization procedures, lack of universal precautions, sharps injuries, and inadequate medical waste management systems all contribute to the burden of viral hepatitis. To reach WHO targets by 2030, all blood donations should be screened for HIV, HCV, HBV, and syphilis in a quality-assured manner, and 90% of injections should be administered using a safety-engineered device [25].

There are several options for reducing risk of transfusion-transmissible infections (TTIs). Centralized blood transfusion services targeting low-risk, regular, voluntary blood donors should be developed and integrated into health care systems [26]. Although more expensive than replacement donor systems [27], voluntary blood donors represent a safer, more sustainable approach [28] and should contribute at least 80% of all donations to transfusion services [29]. All donations should be screened for TTIs, with external quality assurance, using highly sensitive and specific assays [30, 31]. National hemovigilance systems supported by local transfusion committees enable ongoing surveillance for transfusion-related complications [32], but in low- and middle-income countries (LMICs), only 28% operate hemovigilance systems [33]. Blood safety programs can be cost-effective [34], but cost-effectiveness varies, and this should inform program design: adding antigen-antibody combination tests to reduce the serologically negative window period can be cost-effective [35], whereas TTI predonation

screening using rapid diagnostic tests (RDTs) is not considered to be cost-effective [36].

Improving injection safety is also key to reducing iatrogenic transmission: in 2010, approximately 1.7 million new cases of HBV and up to 315 000 new cases of HCV were attributable to unsafe injections [37]. Such infections can be avoided through the use of safety-engineered devices that protect health care workers from hazardous occupational exposures to bodily fluids [38], needle/sharps hygiene and safe disposal, and a ban on needle reuse [39]. Such measures must be delivered alongside education of health care workers in universal precautions and safe waste management systems. National policies for safe and appropriate use of injections are, furthermore, highly cost-effective [40]. Global bodies must take the lead in promoting and financing blood screening and injection safety initiatives to ensure that these cheap and effective interventions are implemented worldwide.

DIAGNOSTICS FOR HCV: TACKLING THE BOTTLENECK

The advent of highly efficacious direct-acting antiviral (DAA) treatment has revolutionized the therapeutic landscape for chronic HCV infection, but less attention has been paid to screening and diagnosis. Given the nature of the infection, asymptomatic HCV-infected individuals are unlikely to seek health care [41]. Consequently, WHO targets of 90% of active infections diagnosed by 2030 [1] are aspirational, outstripping the diagnosis coverage achieved even in those countries that have been most successful in identifying infected individuals, such as France, Australia, and Sweden [42]. Currently, a 2-step process for diagnosing active HCV infection is usually required: a serological test to screen for exposure, followed by an HCV RNA nucleic acid test (NAT) to confirm viremia [43]. This 2-step process inevitably leads to patient loss to follow-up (LTFU) [44–46]. Furthermore, in LMIC, NAT is economically challenging, and the specialized laboratory staff and equipment are often not available [47, 48].

Alternatively, serum HCV core antigen quantification (HCVcAg) can be used as a surrogate marker for HCV viremia. Testing HCVcAg is a relatively low cost (as low as US$10 per sample [49]), fully automated, and a commercially available assay that can be performed on the Abbott ARCHITECT platform, making it an attractive test for resource-limited settings [49, 50]. Employing HCVcAg testing while still dependent on a centralized testing facility can "uncouple" the sample collection from the testing site through the use of dried blood spot (DBS) samples [51, 52]: While whole blood and plasma samples require prompt transport to the laboratory or refrigeration, DBS samples can be stored at room temperature for several weeks [53]. The robustness of this sample storage technique makes it ideal for decentralizing testing, which is attractive for resource-limited settings [43]. Though testing DBS samples for HCVcAg has been shown to have reduced sensitivity compared with using serum samples [52, 54], the low cost and uncoupling of sample and testing site suggest a role for DBS testing in marginalized populations unlikely to present at centralized testing facilities [54].

The development and validation of RDTs has become a research priority. The WHO has prequalified 2 HCV RDTs: SDBioline (SDBioline, Gyeonggi-do, Republic of Korea) and Oraquick (OraSure Technologies Inc., Bethlehem, PA) [55, 56], an oral fluid-based point-of-care (POC) test with a comparable performance to third-generation enzyme immunoassays (EIAs) [57]. POC testing has been shown to improve HIV linkage to care in LMIC and to be cost-effective [58-60, S61]. Combination RDTs for HIV, HBV, and HCV have also been shown to increase uptake and receipt of results relative to laboratory testing [S62].

Finally, the adoption of pangenotypic DAA regimens may eliminate the requirement for genotype testing entirely [53]. All such developments can simplify and strengthen the diagnosis and treatment cascade, removing potential causes of LTFU, and will be crucial in reaching diagnosis and treatment targets. Active implementation of affordable POC testing at the primary care level will be essential to upscale identification and linkage to care of infected individuals.

PROVIDING CARE: ACCESSING HARD-TO-REACH HCV-INFECTED POPULATIONS

In most countries, anti-HCV prevalence is well below 10% in the general population [S63] but significantly greater in high-risk populations. The most studied population is PWID, in which anti-HCV prevalence can exceed 90% [S64], but men who have sex with men (MSM) and other recreational drug users are increasingly being recognized as significant at-risk populations [S65, S66]. Such populations are often difficult to reach for a variety of reasons, including stigma and the possibility of prosecution [S67, S68]. Programs specifically designed to address epidemics within these populations are critical to the success of disease burden reduction efforts.

Qualitative [S69, S70] and quantitative [S71–S73] research has shown that PWID are interested in engaging with health care services for HCV testing and treatment; there is clear evidence of successful treatment outcomes in this group [S74], yet treatment in PWID remains suboptimal [S75,S76]. Health care provider concerns can act as barriers to HCV treatment. Such concerns may include the presence of comorbidities, the belief that there will be adherence issues, and difficulties managing side effects [S77]. From a patient perspective, there are several factors that may reduce the likelihood of accessing HCV treatment, including negative experiences within health care systems [S78, S79], low literacy rates [S80, S81], inadequate communication with health care providers regarding the nature of the disease and treatment options [S79], and social factors such as discrimination, the threat of stigmatization, and criminalization [S81].

Reviews of treatment models in high-income countries suggest that effective approaches to improving rates of HCV diagnosis and treatment integrate HCV services into addiction care units [S82]. Focusing on treatment of addiction [S83] and encouraging

positive feedback between health care staff and PWID [S84] improve outcomes. Such multidisciplinary approaches reduce noncompliance even among homeless or active illicit drug users [S85]. Similar approaches can be utilized in general practitioner services; a study in the United Kingdom demonstrated how specialist nurses seconded to primary care facilities can offer screening to at-risk individuals, considerably improving HCV detection [S86]. An alternative approach may be treatment as prevention: Modeling suggests that it may be effective at curbing transmission in both PWID [S87] and MSM [S88].

In LMIC, many patients, in addition to those discussed above, are hard to reach through lack of health care services. In such scenarios, HCV screening could be integrated into existing care delivery models for HIV and tuberculosis (TB) [S89, S90]. Success of HIV treatment roll-out offers valuable lessons [43]: Community-based testing improves uptake among high–CD4 count individuals compared with facility-based approaches [S91], and we propose that the impressive improvements in HIV case finding could be replicated for HCV using similar methods.

TREATING HBV INFECTION: SETTING GLOBAL STANDARDS TO SIMPLIFY CARE

Achieving ambitious WHO testing and treatment targets for HBV requires careful consideration of the challenges of scale-up; discussion should focus on simplified models of care and methods of wide-scale testing and treatment, particularly in LMICs.

Treatment for CHB targets individuals with, or at risk for, advanced liver disease, and aims to suppress virus replication, halt disease progression, prevent complications, and avert HBV-related deaths [S92–S94]. Several antiviral agents approved for the treatment of CHB are available in developed countries, with regional guidelines outlining a continuum of care and recommendations on who to treat, how to treat, and when to stop treatment [S95–S96]. These documents, while based on evidence of drug efficacy and benefits of treatment, are not adapted for use in countries where CHB is endemic and HBV-related mortality is highest [2]. WHO guidelines for the prevention and treatment of CHB attempt to address this unmet need [S94]. Tenofovir is the recommended antiviral in resource-limited settings, with entecavir recommended in children aged 2–11 years. The guidelines encourage the use of clinical parameters (clinical diagnosis of cirrhosis) and/or noninvasive tests (APRI score > 2) to assess severity of liver disease.

WHO guidelines suggest that treatment should be targeted at those with the highest risk of disease progression, based on the detection of persistently raised alanine aminotransferase (ALT), and HBV DNA levels greater than 20 000 IU/mL in those older than age 30 years [S94]. All cirrhotics should be treated regardless of ALT levels, HBeAg status, or HBV DNA levels. The simplicity of administration of these antivirals, their tolerability and safety profiles, and their high barrier to resistance make them ideal for long-term use in regions where close monitoring and management of adverse effects may not be feasible.

While there is consensus that cirrhotics require lifelong treatment, the safety of stopping therapy in noncirrhotic patients remains less clear. Most international guidelines recommend discontinuation of therapy for noncirrhotic HBeAg-positive individuals who show evidence of HBeAg loss and seroconversion to antibody to HBeAg (anti-HBe), undetectable HBV DNA, and who complete at least 12 months of consolidation therapy [S94]. Discontinuation is only recommended when ALT and HBV DNA levels can be monitored, as a high proportion relapse after stopping treatment [S94, S97], placing an additional financial strain on health care systems. Antiviral therapy can be stopped in noncirrhotic HBeAg-negative individuals at least 12 months following loss of HBsAg and achieving anti-HBs status [S98]. This needs to be accompanied by sustained virological suppression and normalization of ALT, with off-treatment monitoring for relapse. With only a small proportion of patients achieving HBsAg loss, and with the need for regular monitoring for reactivation and flares after cessation of antiviral therapy in both HBeAg-positive and -negative individuals, we believe it is advisable at present to treat all patients indefinitely [S98]. The additional financial burden that such lifelong treatment imposes, however, as well as challenges to maintaining people in the cascade of care, must be acknowledged when adopting this approach.

An additional complication is access to treatment in LMICs: despite generic tenofovir costing less than US$50 per annum and being accessible to HIV-HBV co-infected individuals as part of antiretroviral therapy, many HBV-monoinfected individuals cannot access antiviral therapy or have to pay out of pocket. National health care systems need to ensure funded, sustainable access to antiviral therapy for HBV-mono-infected individuals, implemented in concert with diagnosis scale-up strategies.

Treatment programs need to be accompanied by wide-scale HBV testing, particularly in LMICs, where screening rates are low. Community-based testing and treatment for chronic HBV infection has been shown to be feasible: In The Gambia, the Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) study showed that POC HBV tests perform well in African community settings [S99], and subsequently demonstrated that community-based screening could achieve high coverage and good linkage to care [S100] while remaining cost-effective [S101].

THE COST OF DIRECT-ACTING ANTIVIRALS FOR HCV: HOW PROGRESS CAN BE MADE

A 12-week DAA course costs in excess of US$70 000 in the United States today [S102]. With an estimated 71 million active HCV infections globally [1], such prices render any program aimed at global HCV elimination unrealistic. In 2016, the WHO reported a range of approaches adopted by several countries to demonstrate how barriers to treatment can be overcome [S103].

In LMICs where patents have not been filed or remain under examination, a market for low-cost, generic versions of patented

drugs can be created. Sofosbuvir is not patented in Egypt, and a 28-day supply currently costs under US$30 [S104]. India has used this approach to facilitate production of generics, but a recent decision to grant a patent to Gilead for Sofosbuvir may damage India's role as an HCV generics producer [S105]. Pharmaceutical companies have, in places, awarded voluntary license agreements to permit local companies to produce generics. As of August 2015, Gilead had 11 such agreements with Indian companies [S106]. Additionally, the originator company of Daclatasvir has signed an agreement with the Medicines Patent Pool to enable sublicensing to multiple generic manufacturers in 112 LMICs [S103]. Many middle-income countries are viewed as having market potential and are excluded from these agreements, including China, Brazil, and Thailand [S106]. More generally, complexities of voluntary licensing fragment the market, ensuring that pricing power remains in the hands of pharmaceutical companies [S107]. This problem can be circumvented by development of new therapies: The Drugs for Neglected Diseases Initiative (DNDi) has obtained the license for a new HCV DAA, ravidasvir. This has allowed it to begin production of the drug through an Egyptian firm, Pharco Pharmaceuticals, without the need to maximize profit [S108].

High-income countries can bulk purchase to reduce costs; no country has attempted this more ambitiously than Australia. The government agreed to a AU$1 billion (US$0.73 billion) program to treat 62 000 individuals, corresponding to per-treatment costs of around US$12 000 [S109]. The true novelty of the Australian approach is that if expenditure exceeds up-front cost, the price of drugs decreases, potentially to 0 [S109]. Australia has, in effect, created a subscription system, paying a fixed amount and treating as many Australians as it can.

What ultimately unites these approaches is their customized nature; some countries have had success in reducing prices, but others risk being left behind. A unified approach must be taken to ensure that high-quality, low-cost drugs are available regardless of location. Pooled procurement is one method for achieving this, an approach pioneered by the Global Fund to tackle the HIV, malaria, and TB epidemics [S110], and attempts are underway to apply this approach to viral hepatitis [S111]. Such schemes could be transformative; however, they will rely on capital and political will to achieve the scale required for the program to be a success.

Egypt as a Case Study

Egypt serves as a model for HCV diagnosis and treatment scale-up [S104, S112]. This country, with the world's highest HCV prevalence, has increased HCV treatment numbers to the hundreds of thousands [S103] and intends to treat 5 million patients by 2030 [S104]. It has achieved this by slashing HCV treatment costs and empowering dozens of diagnostic facilities. Furthermore, by simplifying the diagnostic process through implementing the first universal test and treat strategy, it has reduced the time from initial diagnosis to treatment to as little as one week in some centers [104]. Egypt offers an invaluable example to policy makers, not only as an exemplar of how viral hepatitis interventions can be scaled-up quickly and intensively, but also as a guide for how to tackle the problems that may be faced with such ambitious interventions.

Recommendations

Egypt demonstrates what can be accomplished with regards to HCV diagnosis and treatment, given sufficient political will, state coordination, and investment. Across the world, efforts to address viral hepatitis, both HBV and HCV, should focus on providing universal HBV birth-dose vaccination within 24 hours of birth, establishing hemovigilance schemes to prevent transmission of blood-borne viruses, providing nonreusable syringes and educating health staff in injection safety, adopting new diagnostic technologies to expand access to screening, specializing intervention efforts for vulnerable high-risk groups to reduce transmission where it is highest, treating all HBV-infected patients indefinitely to minimize potential harm caused by discontinuation, and collaborating across the continent to drive down HCV drug costs to ensure that, once treatment has been accessed, it is affordable.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Articles

Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model

Alastair Heffernan, Graham S Cooke, Shevanthi Nayagam, Mark Thursz, Timothy B Hallett

Summary

Background The revolution in hepatitis C virus (HCV) treatment through the development of direct-acting antivirals (DAAs) has generated international interest in the global elimination of the disease as a public health threat. In 2017, this led WHO to establish elimination targets for 2030. We evaluated the impact of public health interventions on the global HCV epidemic and investigated whether WHO's elimination targets could be met.

Methods We developed a dynamic transmission model of the global HCV epidemic, calibrated to 190 countries, which incorporates data on demography, people who inject drugs (PWID), current coverage of treatment and prevention programmes, natural history of the disease, HCV prevalence, and HCV-attributable mortality. We estimated the worldwide impact of scaling up interventions that reduce risk of transmission, improve access to treatment, and increase screening for HCV infection by considering six scenarios: no change made to existing levels of diagnosis or treatment; sequentially adding the following interventions: blood safety and infection control, PWID harm reduction, offering of DAAs at diagnosis, and outreach screening to increase the number diagnosed; and a scenario in which DAAs are not introduced (ie, treatment is only with pegylated interferon and oral ribavirin) to investigate the effect of DAA use. We explored the effect of varying the coverage or impact of these interventions in sensitivity analyses and also assessed the impact on the global epidemic of removing certain key countries from the package of interventions.

Findings By 2030, interventions that reduce risk of transmission in the non-PWID population by 80% and increase coverage of harm reduction services to 40% of PWID could avert 14·1 million (95% credible interval 13·0–15·2) new infections. Offering DAAs at time of diagnosis in all countries could prevent 640 000 deaths (620 000–670 000) from cirrhosis and liver cancer. A comprehensive package of prevention, screening, and treatment interventions could avert 15·1 million (13·8–16·1) new infections and 1·5 million (1·4–1·6) cirrhosis and liver cancer deaths, corresponding to an 81% (78–82) reduction in incidence and a 61% (60–62) reduction in mortality compared with 2015 baseline. This reaches the WHO HCV incidence reduction target of 80% but is just short of the mortality reduction target of 65%, which could be reached by 2032. Reducing global burden depends upon success of prevention interventions, implemention of outreach screening, and progress made in key high-burden countries including China, India, and Pakistan.

Interpretation Further improvements in blood safety and infection control, expansion or creation of PWID harm reduction services, and extensive screening for HCV with concomitant treatment for all are necessary to reduce the burden of HCV. These findings should inform the ongoing global action to eliminate the HCV epidemic.

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Introduction

Globally, it is estimated that 71·1 million (95% uncertainty interval 62·5–79·4) individuals are chronically infected with hepatitis C virus (HCV),[1] of whom 10–20% will develop liver complications including decompensated cirrhosis and hepatocellular carcinoma.[2,3] These complications were responsible for more than 475 000 deaths in 2015 and, in contrast with the malaria, tuberculosis, and HIV epidemics, the number of deaths from viral hepatitis infection has risen in recent years.[1,4] HCV transmission is most commonly associated with blood transfusions, healthcare-related injections, and injection drug use.[5] Transfusion transmissible infections and infections associated with lapses in injection safety have declined globally,[6,7] although these remain key risk factors in lower-income countries.[8] Infection associated with injection drug use is the primary transmission route in countries where other transmission routes have mostly been eliminated.[8,9] Treatment for HCV infection used to comprise weekly subcutaneous injections of pegylated interferon and oral ribavirin,[10] which had low success rates and was associated with a range of side-effects.[11,12] A watershed moment came in 2014 with the development of highly efficacious direct-acting antivirals (DAAs),[13,14] which allow interferon-free

Research in context

Evidence before this study

In 2017, WHO set targets to eliminate hepatitis C virus (HCV) infection globally as a public health threat. We searched PubMed on Feb 23, 2018, for studies published in English that modelled the epidemiological impact of HCV interventions or modelled the global HCV epidemic, using the following search strategy: "(hepatitis C AND model* AND (global OR intervention*))". We found 33 relevant studies. Mathematical models have been developed to investigate the effectiveness of harm reduction strategies in high-risk groups but these have not examined impact at the population level. Models of the population impact of screening and treatment have been developed and used to investigate WHO mortality targets at both the national and regional levels. These studies, however, could not investigate incidence targets because they did not utilise dynamic transmission models that would allow the impact of prevention interventions and the effect of treatment on incidence to be captured. A recent study used a dynamic transmission model to estimate the population-level impact of both prevention and treatment interventions in Pakistan. This work found that only with extremely high coverage of interventions can elimination targets be met. No study has modelled HCV interventions at the global scale.

Added value of this study

To our knowledge, our study is the first to estimate the impact of interventions on the global HCV epidemic and to address WHO HCV elimination targets. We explicitly model the transmission process within and between population groups, allowing us to model prevention as well as screening and treatment interventions. The model is calibrated to all global epidemiological and programme data in a statistically principled way. We quantify the extent to which prevention, screening, and treatment could reduce the burden of HCV globally. Our results highlight the key role prevention has in reducing the burden of disease, the bottleneck screening places on the impact of HCV interventions, and the importance of expanding access to direct-acting antivirals.

Implications of all the available evidence

Across the globe, coverage of key prevention, screening, and treatment interventions is currently well below the levels we estimate are needed to have a major impact on the HCV epidemic. Operations research into how to improve coverage in all settings, as well as increased funding for effective strategies, will be required to make progress towards HCV elimination targets.

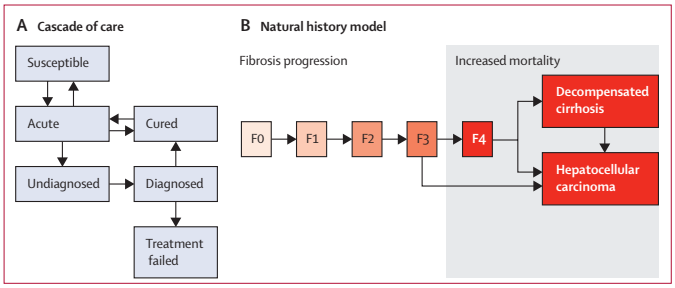


Figure 1: **Model structure**

Boxes represent compartments of the model and arrows denote annual transition rates that can depend upon age, sex, risk group, or duration of infection that can vary over time. At any given point, every person is in one compartment of the cascade of care (A). These compartments are further subdivided by age, sex, and risk group. Spontaneous clearance occurs in a fraction of those acutely infected who return to the susceptible population. Treatment can result in cure and reinfection can occur after successful treatment. Infection results in people entering the natural history model (B): HCV disease progresses through five METAVIR[18] fibrosis stages, from F0 (no fibrosis) to F4 (compensated cirrhosis). The potential effects of age and male sex on progression and mortality rates are accounted for in calibration. People in the cured compartment of the treatment cascade have reduced or zero disease progression rates depending on disease stage. See appendix for full details, including a list of parameter values with dependencies and the complete model structure diagram. HCV=hepatitis C virus.

treatment, greatly improved cure rates, better side-effect profiles, and shorter duration of therapy more amenable to widespread use.[15,16]

Advances in HCV therapeutics have led to a commitment from all 194 member states of WHO to eliminate viral hepatitis as a public health threat.[1,17] WHO HCV elimination targets are defined as a 65% reduction in mortality and an 80% reduction in incidence by 2030 from 2015 baseline (the HCV incidence reduction target combines with a 95% reduction target for viral hepatitis B incidence to produce the overall viral hepatitis incidence reduction target of 90%).[17] This is to be achieved through a combination of preventing transmission by improving blood safety and infection control measures, extending harm reduction services aimed at reducing transmission among people who inject drugs (PWID), and expanding testing and DAA treatment for those already infected.[1]

Although these targets were formulated by WHO through extensive consultations,[17] the feasibility of achieving WHO targets globally is not known. Given the current focus on these targets, it is imperative we understand the full effect of HCV interventions at the global scale. We sought, therefore, to use mathematical modelling to provide the first estimates of the impact of combined prevention, diagnosis, and treatment programmes on the global HCV epidemic and to determine the achievability of WHO elimination targets.

Methods

Model structure

We developed a mathematical model to project the future course of the HCV epidemic country by country. We analysed the impact of a set of intervention packages at the global scale by combining the results for 190 individual countries. Our compartmental model simulates the population of a country from 1950 to 2100, grouped according to infection and treatment status (see the treatment

cascade in figure 1). Compartments are further stratified by age, sex, and risk group (PWID and non-PWID). Infection (the transition from susceptible to acute compartments) is specified according to HCV prevalence and a risk group-dependent, age-dependent, and time-dependent risk of transmission that is calibrated in model fitting; perinatal infection can also occur. Background age-specific, sex-specific, and time-specific mortality is simulated according to UN projections.[19] PWID experience an additional mortality risk compared with other groups.[20,21] HCV infection results in additional risk of liver-related mortality (denoted HCV-related mortality); increased non-liver-related mortality in those infected with HCV is not simulated because it is a much less substantial cause of death in HCV-positive individuals than is liver-related mortality[22,23] and WHO viral hepatitis targets focus on liver-related mortality.[24] It should be noted that neglecting non-liver-related mortality will tend to underestimate the impact of interventions.[25,26]

Past treatment and diagnosis is modelled as follows: we increase rates of diagnosis and treatment such that the proportion who are diagnosed, and the proportion treated, match WHO estimates for these quantities in 2015.[1] DAAs are implemented from 2016 in countries where their use is reported.[27,28] In these countries, the rate of treatment is calculated in the model such that the reported number of DAA treatment courses is matched by the model.[27,28] All other countries continue to implement treatment with pegylated interferon and ribavirin after 2015. This approach results in 1·76 million HCV treatment courses being delivered in 2016, of which 86% consist of DAAs.[28] After 2016 (or 2015 for countries without 2016 data), the future rates of both diagnosis and treatment are fixed unless altered through an intervention. Treatment success depends on the type of treatment used (ie, pegylated interferon and ribavirin or DAAs). Reinfection following cure is also simulated: as a conservative assumption, reinfection risk is set to be equal to primary infection risk.[29]

Following infection with HCV, disease progression occurs according to a widely recognised natural history (figure 1B).[2,30,31] Progression occurs through the five METAVIR[18] fibrosis stages. Increased HCV-related mortality occurs from compensated cirrhosis (stage F4), decompensated cirrhosis, and hepatocellular carcinoma. Disease progression and mortality rates are reduced (to zero, in some cases) following cure. All parameters in the natural history model are taken from the literature (appendix); where values are uncertain, parameters are drawn from prior distributions informed by the literature.

Model calibration

All uncertain parameters were allowed to vary in calibration. These parameters include those of the natural history model and the risk group-dependent, age-dependent, and time-dependent risks of infection. These risks of infection are modelled as flexible splines, where the knot values are drawn from suitable prior distributions; for full details of the modelling of transmission and a complete list of parameter values and prior distributions, see the appendix.

We calibrated the model, in a Bayesian framework, to three sets of information: overall HCV prevalence,[1,32] PWID HCV prevalence,[33] and HCV-attributable mortality (according to age, time, and sex).[4,34] 1000 samples were drawn from the parameter posterior distributions using incremental mixture importance sampling.[35] This self-monitoring approach to approximating the posterior distribution proceeds by calculating the importance weight for a given parameter set and then drawing new parameter values until the expected fraction of unique parameter sets in the final resample corresponds to the case where all parameter weights are equal—ie, such that no one parameter set dominates the resampled values (appendix).[35] The parameter sets drawn from the posterior distribution were used to make forward projections of the epidemic under a range of intervention scenarios.

Intervention scenarios

Six scenarios were constructed to assess the impact of differing levels of prevention, screening, and treatment intervention scale-up (table). The status quo scenario, which represents our best estimate of what the HCV epidemic will look like with no changes made to diagnosis or treatment, maintains diagnosis and treatment rates at their 2016 (or 2015 where 2016 data were not available) values and assumes no reduction in general or PWID population risk. We inferred diagnosis and treatment rates by scaling up these quantities to match the proportion diagnosed or treated where data were available,[40–43] or using regional averages where data were lacking, with DAAs introduced in relevant countries in 2016 (appendix);[28] at the global scale, this results in 20% of people diagnosed in 2015, of whom 7% are treated.[1]

Four intervention strategies were sequentially added to the status quo scenario, starting in 2017: (1) blood safety and infection control, leading to an 80% reduction in HCV infection risk in the non-PWID population by 2020; (2) PWID harm reduction, whereby 40%[38] of the PWID population are reached with a combined package of opioid substitution therapy (OST) and needle and syringe programmes (NSP), leading to a 75% reduction in infection risk in those covered;[36,37] (3) offering DAAs at diagnosis (regardless of disease stage), with status quo rates of diagnosis maintained (90% accept treatment); and (4) outreach screening, resulting in 90% of the HCV-infected population being diagnosed by 2030 (table). Each intervention builds in the features of the previous strategies; intervention 4 comprises all interventions and is referred to as the comprehensive intervention package.

Finally, a no-DAA scenario, which is equivalent to status quo but incorporates only treatment with pegylated

See Online for appendix

	Risk of infection in non-PWID population	Risk of infection in PWID population	Treatment	Treatment coverage	Diagnosis coverage
No-DAA scenario	As per 2015 risk	As per 2015 risk	Pegylated interferon and oral ribavirin	Treatment rate fixed at 2015 or 2016 value	Diagnosis rate fixed at 2015 or 2016 value
Status quo	As per 2015 risk	As per 2015 risk	DAAs from 2016	Treatment rate fixed at 2015 or 2016 value	Diagnosis rate fixed at 2015 or 2016 value
Interventions added cumulatively to the status quo scenario					
(1) Blood safety and infection control	80% reduction by 2020*	As per 2015 risk	DAAs from 2016	Treatment rate fixed at 2015 or 2016 value	Diagnosis rate fixed at 2015 or 2016 value
(2) PWID harm reduction	80% reduction by 2020*	75% reduction at 40% coverage by 2020†	DAAs from 2016	Treatment rate fixed at 2015 or 2016 value	Diagnosis rate fixed at 2015 or 2016 value
(3) Offer DAAs at diagnosis	80% reduction by 2020*	75% reduction at 40% coverage by 2020†	DAAs from 2016 and in all countries from 2017	Treatment offered within 1 year of diagnosis; those previously diagnosed are treated at original treatment rates	Diagnosis rate fixed at 2015 or 2016 value
(4) Outreach screening	80% reduction by 2020*	75% reduction at 40% coverage by 2020†	DAAs from 2016 and in all countries from 2017	Treatment offered within 1 year of diagnosis; those previously diagnosed are linked back into care for treatment‡	Rate increased linearly such that 90% of people infected are diagnosed by 2030

PWID=people who inject drugs. DAA=direct-acting antiviral. OST=opioid substitution therapy. NSP=needle and syringe programmes. *General population risk reduced linearly from 2016 to 2020. †PWID risk reduction simulated as combined OST and NSP, the method of harm reduction with the strongest evidence of reducing HCV transmission among PWID.[36,37] A suitable coverage for this intervention, therefore, is the so-called WHO high target for OST of 40%,[38] beyond that reached in most countries to date.[39] PWID intervention coverage is increased linearly from 2017 to 2020. Coverage only includes opioid-dependent PWID as suitable for OST.[33] ‡Outreach diagnosis campaign facilitates return to care for those already diagnosed, leading to 10% returning annually for treatment.

Table: **Details of intervention scenarios modelled**

interferon and ribavirin, was included to analyse the scope of the epidemic if the recent adoption[44] of DAA treatment is not maintained.

Sensitivity analysis

Uncertainty in the natural history model is accounted for in calibration by drawing 1000 samples from the parameter posterior distributions. The model is run 1000 times with these parameter sets and medians and credible intervals (CrIs; 2·5th and 97·5th percentiles) for all quantities of interest are evaluated. The effects of other notable model assumptions (ie, reinfection rate, effectiveness of PWID harm reduction interventions, and delay in possible retreatment after reinfection) are investigated through one-way sensitivity analyses (appendix). We investigated the sensitivity of the outcomes in the comprehensive package of interventions by doing one-way sensitivity analyses on the three key intervention parameters: risk reduction in the non-PWID population, coverage of harm reduction in the PWID population, and proportion diagnosed by 2030. For each of these parameters, we explored the range from no improvement to 95% (the upper limit is chosen to represent a highly ambitious increase).[45] We did another set of sensitivity analyses in the same manner as this but using the status quo as our starting point (as opposed to the comprehensive package of interventions) to explore the effects of each programme element. Finally, we evaluated which countries contributed most to infections and deaths averted under the comprehensive package of interventions and then re-ran the model without these countries included in the intervention package, with all values set to the status quo scenario, to quantify the sensitivity of our global results to progress made in key countries.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study, and all authors had final responsibility for the decision to submit for publication.

Results

We found 69 million (95% CrI 67–71) active viraemic infections and 512 000 deaths (497 000–533 000) in 2015, with 277 incident infections (262–294) per 1 million people, in line with WHO estimates for that year (figure 2).[1] The projected proportion of new infections expected in PWID between 2016 and 2030 was 29% (95% CrI 27–32) in our model, in keeping with WHO estimates in 2015 that 22% of new infections were in PWID.[1] Projecting the epidemic forwards in the status quo scenario, we find that the number of active infections will slowly decrease to 58 million (54–62) by 2050 but could rise by the end of the century. Likewise, incidence would gradually decrease to 198 infections (179–218) per 1 million people by 2060 but might increase thereafter. Mortality from HCV gradually decreases for more than three decades but can increase thereafter in line with the possible increasing numbers of active infections (figure 3). These results reflect our assumptions in the status quo scenario that risk of infection does not decrease in any group after 2015 and that numbers of PWID will not change. Not implementing DAAs at all results in worse outcomes than in the status quo scenario, with considerably higher mortality and incidence (figure 3).

Programmes aimed at curbing the spread of blood-borne infections among the non-PWID population (intervention 1) can dramatically reduce incidence (figure 3).

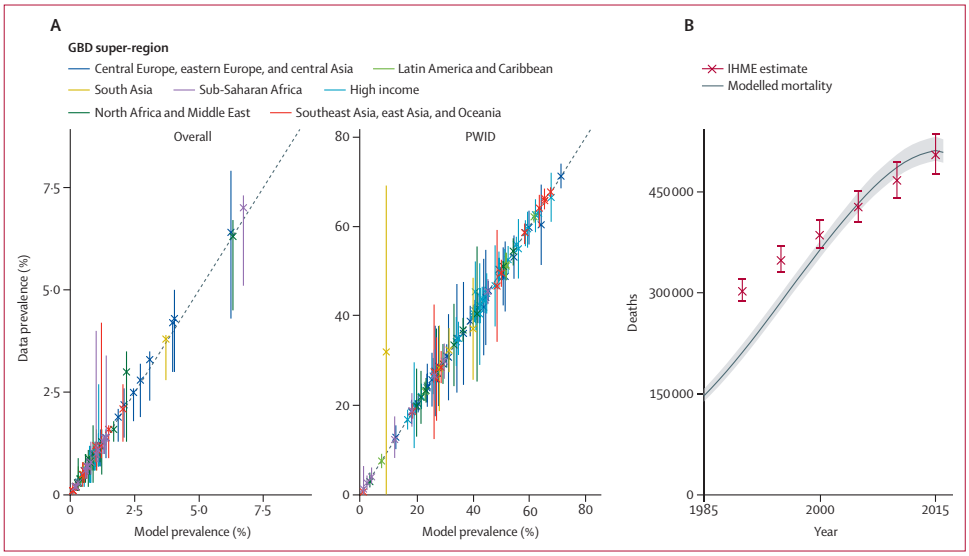


Figure 2: **Calibration results**
(A) Comparison of the model's simulated prevalence of HCV with prevalence data for all 190 countries simulated,[40–43] colour-coded by GBD super-region (see appendix for the full list of regions). Overall prevalence values are from 2015 whereas PWID values come from a range of years.[18] The diagonal lines mark equivalent estimates. (B) Comparison of modelled HCV mortality numbers with IHME HCV mortality estimates.[4,34] Countries were calibrated to age-stratified and sex-stratified mortality estimates; modelled outputs were summed into overall cirrhosis and hepatocellular carcinoma mortality numbers and compared with aggregated IHME estimates for the years 1990, 1995, 2000, 2005, 2010, and 2015. GBD=Global Burden of Disease Study. HCV=hepatitis C virus. IHME=Institute for Health Metrics and Evaluation. PWID=people who inject drugs.

Global improvements in blood safety and infection control (lowering the general population risk of HCV infection by 80%) reduce the annual number of new infections in 2030 by 58% (95% CrI 56–60) compared with the status quo scenario in the same year. Along with these improvements in blood and infection safety, extending OST and NSP harm reduction services to 40% of the opioid-dependent PWID population (intervention 2) will reduce the number of new infections in 2030 by a further 7 percentage points (figure 3). Taken together, these prevention interventions could avert 14·1 million (95% CrI 13·0–15·2) cumulative infections by 2030. Due to the long incubation period of HCV infection, however, such reductions in incidence will not immediately translate into reductions in mortality: by 2030, the decrease in mortality will be small in either scenario (figure 3) and the combination of both interventions will only reduce mortality in 2050 by 18% (17–19).

Expanding access to DAAs, in addition to the prevention interventions, is projected to cut future mortality more substantially. Replacing pegylated interferon and ribavirin with DAAs in all countries where they have not been rolled out, and offering these at time of diagnosis (intervention 3), has substantial short-term impact: we estimate 640 000 fewer deaths (95% CrI 620 000–670 000) from liver cancer and cirrhosis by 2030. However, compared with intervention 2, there is no additional effect on incidence (figure 3). This scenario illustrates that improvements in outcomes can be attained by ensuring access to DAAs without otherwise changing diagnosis or treatment programmes. However, such gains fall well short of WHO mortality targets (figure 3) and these programmes also offer only minimal prevention benefits.

Adding outreach screening (intervention 4), such that the proportion diagnosed reaches 90% by 2030, further reduces mortality and incidence (figure 3). This scenario incorporates all prevention, screening, and treatment elements of the previous strategies. With this comprehensive package of interventions, there would be a 61% (95% CrI 60–62) reduction in mortality by 2030 compared with the baseline 2015 value—corresponding to 1·5 million (95% CrI 1·4–1·6) deaths prevented. Our estimates show a treatment-as-prevention benefit: compared with prevention interventions alone (intervention 2), the comprehensive package of interventions averts an average of 950 000 additional infections by 2030, resulting in 15·1 million (13·8–16·1) new infections averted in total. Achieving such reductions requires a massive screening programme and demands a rapid increase in new treatment courses in the short term—namely, 51·8 million (50·5–53·3) courses of DAA treatment by 2030 (appendix). In the following 20 years, by contrast, the total number required is a much more modest 12·0 million (11·5–12·7) courses. The reduced

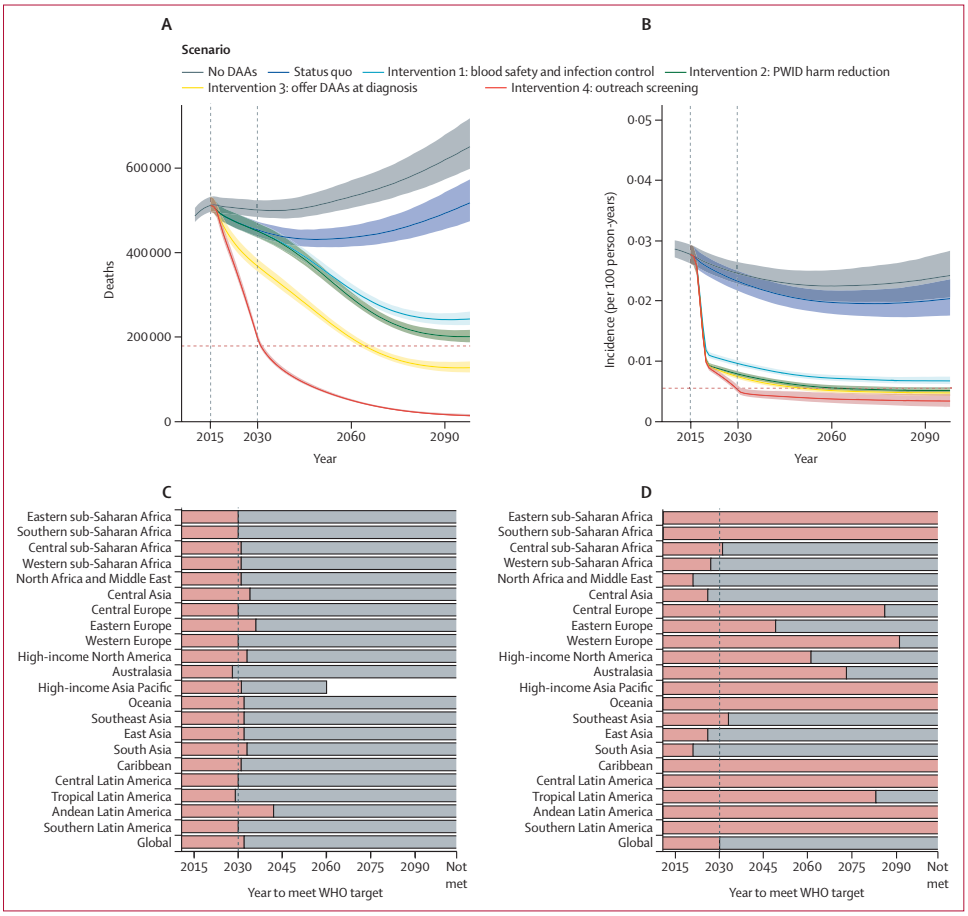


Figure 3: **Global intervention results**

(A) Number of deaths due to HCV by scenario. Note that due to the high impact of the comprehensive package of interventions (intervention 4) on reducing the number of deaths, the credible intervals are extremely narrow around the median. (B) Incidence of viraemic HCV infection (number of incident chronic infections divided by number of people susceptible) by scenario. Note that the incidence curves for interventions 2 and 3 are almost coincident. Vertical dashed lines indicate baseline (2015) and the year for targeted elimination (2030). Horizontal dashed lines indicate elimination targets: 65% reduction of mortality and 80% reduction in incidence. In panels (C) and (D), data are shown by GBD region. The end of each bar represents the median year of mortality (C) or incidence (D) elimination. Grey bars show the status quo scenario; the red portion of each bar shows the comprehensive package of interventions (intervention 4). Where a red bar extends to the edge of the graph, elimination was not achieved in any scenario before 2100. The dashed vertical line indicates the WHO elimination year target of 2030. DAA=direct-acting antivirals. GBD=Global Burden of Disease Study. HCV=hepatitis C virus. PWID=people who inject drugs.

treatment requirement after 2030 indicates that rapid testing and treatment scale-up is a means to control the epidemic in the long term.

Interventions do not have a uniform impact across different countries; projections by country are presented in the appendix. Upon all countries rolling out DAAs and offering these at diagnosis (intervention 3), most countries in Africa, along with south Asia, east Asia, and southeast Asia, experience smaller reductions in mortality than do countries in other regions (appendix). This reflects the lower existing diagnosis coverage in these countries. The effect of prevention interventions on incidence is also dependent on local epidemiology. Certain countries, such as Egypt, Mongolia, and Pakistan, benefit greatly from improvements in blood safety and infection control (intervention 1) because these reduce risk of infection in the entire population (appendix). Countries that have a large proportion of the HCV epidemic concentrated in PWID—eg, the USA, Australia, and Spain—show more improvement upon expansion of PWID harm reduction services (intervention 2; appendix). All countries experience reductions in both mortality and

incidence upon implementation of the comprehensive package of interventions (appendix), reflecting the high impact a multifaceted approach to tackling the epidemic can have.

WHO mortality and incidence elimination targets are narrowly missed in 2030 with the comprehensive package of interventions: the WHO-defined mortality elimination target occurs in this model by 2032, whereas the incidence elimination target is met by 2030 (figure 3). The comprehensive package of interventions does, however, lead to a 61% (95% CrI 60–62) reduction in mortality in 2030 compared with the status quo scenario (figure 3). The mortality elimination targets could be reached by 2030 if the coverage of diagnosis were increased to 95% rather than the 90% assumed above (appendix). Further incidence reduction is possible, but this is primarily achieved by increasing PWID harm reduction coverage: if coverage is increased to more than 80%, incidence rates can be reduced by nearly 90% compared with 2015 baseline values (appendix).

We also examined year of elimination by Global Burden of Disease Study (GBD) regions. All regions reach the mortality elimination target at similar times after implementing the comprehensive package of interventions (figure 3). Although global incidence targets are met, eight regions do not reach the incidence elimination target before 2100. A key determinant of whether incidence elimination is achieved is the proportion of infections by risk group: the regions that reach incidence elimination before 2030 are characterised by low numbers of infections in PWID relative to the rest of the population (appendix).

Reducing the global burden of hepatitis C depends on the progress made in just a few countries. Most infections and deaths averted, after implementation of the comprehensive package of interventions, are concentrated in a small number of countries, in particular China, India, Pakistan, and Egypt, which are the countries that contribute most to projected new infections by 2030 (figure 4). If China, India, or Pakistan do not implement

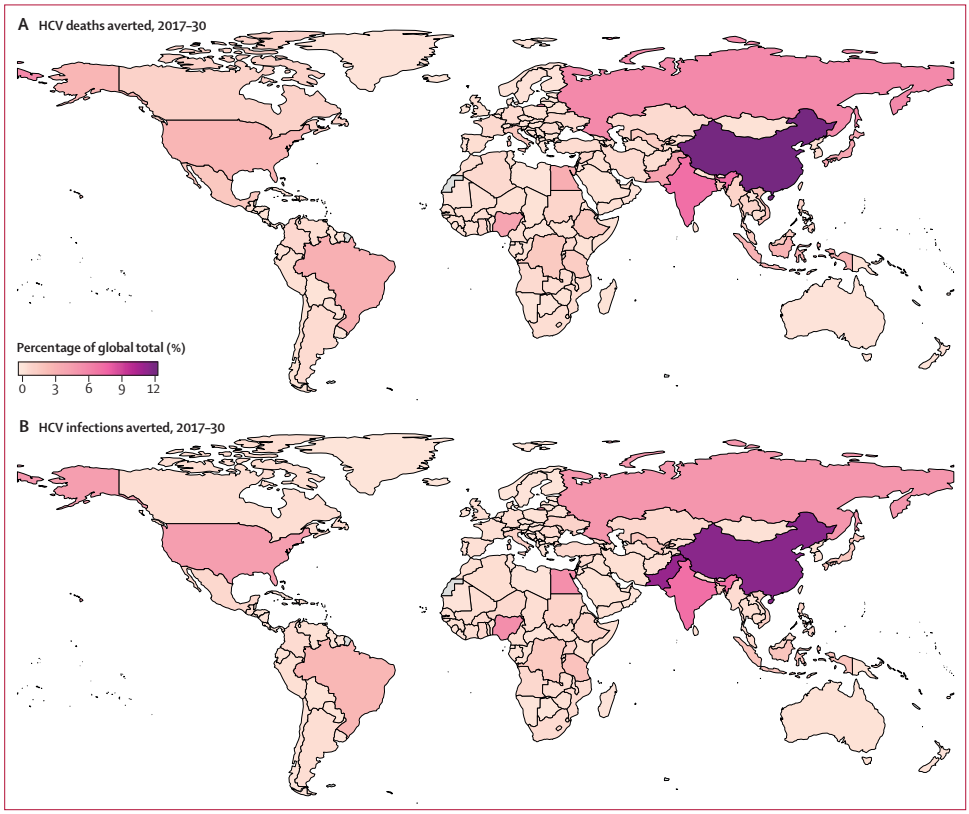


Figure 4: **Distribution of global deaths averted and infections averted when implementing the comprehensive package of interventions compared with the status quo scenario**
Cumulative deaths and infections averted in 2017–30 are shown by country as percentages of the total global number averted.

the comprehensive package of interventions, the year in which global incidence elimination is reached is pushed back to at least 2047 (appendix), whereas not implementing the comprehensive package of interventions in these countries would result in global incidence reductions in 2030 of 69% (95% CrI 66–74), as opposed to an 81% (78–82) reduction when all countries implement the interventions (appendix).

We found that improving blood safety and infection control alone (ie, starting from the status quo scenario), such that the risk of infection in the general population decreases by 95%, can reduce incidence in 2030 by 72% (95% CrI 70–73; figure 5). Although HCV-positive PWID comprise only a minority of global HCV-positive individuals, programmes that can reduce PWID transmission have a global impact upon incidence: expanding PWID harm reduction coverage to 95% (in the absence of any other intervention scale-up) could reduce global incidence by 33% (31–36) in 2030 (figure 5). Screening and treatment interventions carry a double benefit: increasing the proportion diagnosed and treated (without scaling up the prevention interventions) reduces both mortality and incidence through a treatment-as-prevention effect (figure 5). Yet, treatment alone has less impact than when combined with prevention interventions: the comprehensive package of interventions reduces incidence in 2030 by 81% (78–82) compared with 60% (57–62) when prevention interventions are not implemented.

Because the degree of effectiveness of PWID harm-reduction programmes is more uncertain than that of DAA treatment, and the effectiveness of such programmes probably varies substantially between settings, we did sensitivity analyses to investigate the dependence of the results on this aspect of the model. Reducing the effectiveness of OST and NSP interventions from 75% to 20% (within the context of the comprehensive package of interventions, scenario 4) pushed back the year of incidence elimination to 2052 (appendix). As shown by the regional breakdown, this is driven by delays in elimination in regions in which HCV-positive PWID comprise a large proportion of the HCV epidemic (such as western Europe, high-income North America, and Australasia; appendix). By contrast, simulations in which PWID harm reduction effectiveness is taken to be 90% resulted in a median estimate of 470 000 fewer courses of treatment being delivered by 2030 in intervention 4 than when the effectiveness is assumed to be 75% (appendix).

Year of incidence elimination is sensitive to the extent of intervention scale-up (appendix). Reducing coverage of any intervention, within the context of the comprehensive package, predictably pushes elimination further into the future. However, the relationship between the level of diagnosis and impact on incidence (and year of achieving the elimination target) is found to be parabolic; that is, intermediate levels of diagnosis led to lesser reductions in incidence than either no increase or enormous increases in diagnosis rates. This is because we have assumed that cured people are at risk of reinfection and, at lower levels of diagnosis coverage, infection risk for PWID remains high and so there can be more infections than with no intervention. At high levels of diagnosis, this effect is overwhelmed by the reduction in infection risk that is brought about by the reduction in the numbers of infectious people. The risk of reinfection is, however, not known, and if it were lower than the risk of initial infection then the year of elimination could be sooner than we have estimated and thus the non-linear, parabolic effect described disappears (appendix). Further sensitivity analyses showed that the delay in accessing retreatment after reinfection had no impact on the results (appendix).

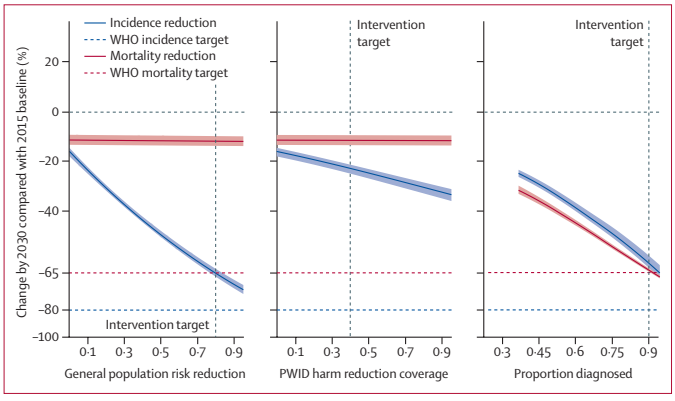


Figure 5: **Reduction in mortality and incidence in the status quo scenario upon improving prevention or screening intervention coverage**

Changes in mortality and incidence by 2030 upon increasing the reduction in general population (ie, non-PWID) risk, the coverage of PWID harm reduction interventions, and the proportion diagnosed by 2030, from status quo values. The vertical dashed lines show the values targeted in the intervention scenarios (see table).

Discussion

A dramatic decrease in both mortality and incidence in HCV could be possible through implementation of a comprehensive package of prevention, screening, and treatment interventions. Even though it narrowly falls short of the WHO targets for 2030, such an impact would be a tremendous stride forwards, averting 15·1 million new infections and 1·5 million HCV-related deaths by 2030.

Several important challenges must be met and this analysis raises points of direct relevance to policy and programme development. First, the benefits of DAAs will only be fully reaped with an exceptional increase in diagnosis coverage to 90% by 2030. The treatment of only those already in care will not translate into substantial reductions in HCV deaths or incidence. However, Malta is the only country in which the diagnosis coverage is estimated to be at such a high level.[27] Progress could be made in different ways in the coming years:

innovative means of increasing awareness and encouraging HCV testing in a range of settings are being explored[46] and new technologies, such as point-of-care viral load finger-stick tests,[47] should soon be available.[48] Both awareness raising and simpler diagnostics could facilitate large increases in knowledge of HCV status as has occurred in the HIV arena.

Second, the HCV epidemic among PWID has a deciding role in determining whether incidence elimination targets are met. The modelled strategy that resulted in incidence elimination being met by 2032 relied upon coverage of OST with NSP increasing to 40%: however, only 1% of PWID live in countries with such high coverage of these harm reduction services.[39] If the effectiveness of those programmes is lower than has been estimated in some settings,[36,37] then elimination becomes a much more remote prospect, with elimination not being reached until after 2050, even with high coverage of other interventions. This result, along with the finding that reinfection plays a key role in delaying the year of incidence elimination, highlights that PWID prevention must be central to HCV policy. Targeted treatment-as-prevention approaches among PWID might reduce incidence,[49] although this must be done in the context of enhanced harm reduction interventions and community involvement.[50] Eliminating structural and systemic barriers such as the criminalisation of PWID or treatment restrictions on active drug users can improve access to health services.[51,52] A Hepatitis C Action Plan programme in Scotland has shown that national reductions in incidence are possible through an integrated approach involving scaling up of OST with NSP along with increasing awareness and provision of HCV testing for PWID (including ever-PWID).[53] Such progress relies on political will and reliable sources of funding that, in low-income and middle-income countries in particular, are often lacking—this is a serious challenge HCV programmes often face.[54]

Third, continued improvements in blood safety and infection control are key components of the global elimination intervention package and drive a large reduction in new infections. Although proven safety and control measures exist and have played a major part in reducing incidence in many settings,[55,56] only 39% of countries worldwide operate haemovigilance systems,[55] and unsafe (often unnecessary) injections continue to be a major source of HCV infection.[7,57] The reasons for the persistence of unsafe injections as a transmission route are complex,[58] and context-specific management methods are necessary if there are to be continued reductions in the risk of HCV transmission via these routes.[59]

Finally, the global HCV epidemic is concentrated in a set of countries that could face myriad challenges in implementing the PWID harm reduction, infection control, and outreach screening initiatives required. This hurdle might make talk of elimination seem more tenuous but should also focus attention while illustrating that major progress can be made with policy changes in just a few places. In terms of global HCV epidemiology, and given the stated aims of WHO and the Sustainable Development Goals to "combat hepatitis",[60] progress made in these settings should be of primary concern.

These policy points reinforce and augment the conclusions drawn by other studies. Several modelling analyses have highlighted the challenge of reducing transmission among PWID and have advocated simultaneously scaling up prevention and treatment interventions to reduce prevalence.[61,62] Our work extends this to show that, even on the global scale where incidence is dominated by non-PWID transmission, reducing incidence among PWID plays a key part in determining whether elimination targets are met. A recent study[63] has incorporated dynamic modelling of PWID into a full population model of the HCV epidemic in Pakistan. The authors find that only with extremely high coverage of interventions can elimination targets be met. This result agrees with what we have shown on a global scale that even with exceptionally high intervention coverage, elimination targets are difficult to meet. An EU modelling study[27] has suggested that mortality elimination targets can be met in this region. Similarly, we find that, provided there are ambitious increases in screening and treatment, mortality elimination targets are met in most regions by around 2030. The EU study did not, however, model incidence dynamically and could not draw conclusions regarding incidence targets. Our analysis has shown that even with extensive scale-up of prevention interventions, several regions do not meet incidence elimination targets before 2100, driven in large part by ongoing PWID transmission.

To produce a global analysis, we have had to manage a variety of data and modelling limitations. We used modelled estimates of mortality from the GBD project;[4,34] these have been produced for most countries and allow basic epidemic trends to be inferred even where other data are lacking. To manage the uncertainty this introduces, we built the model to be flexible when calibrating to these inputs because they are estimates rather than data. To simulate the treatment cascade, we used regional estimates to extrapolate to countries without data. This process necessarily smooths out country-level differences in diagnosis and treatment coverage, introducing error in some individual country projections. Country-level cascade information is, however, available for countries that account for about 60% of the global viraemic population, giving good resolution on the treatment cascade for most of the globally infected population. Furthermore, low overall treatment numbers compared with the size of the epidemic mean that error introduced through extrapolating to the remaining 40% of the viraemic population will have only a small impact on projections.

There is considerable uncertainty about the source of infections among the general population, which makes it impossible to be sure about the extent to which this route

of transmission is being, and can be, reduced. Although WHO calls for no unsafe injections and 100% of blood donations screened with quality assurance,[1] both the difficulty in reaching these targets and the many ways of being infected with HCV beyond these two routes (appendix) led us to specify only an 80% risk reduction among the general population in intervention 1; this is to be conservative regarding what is a necessarily vague intervention strategy. We varied this in sensitivity analysis to explore the impact this programme parameter had on outcomes. Similarly, the impact of PWID harm reduction interventions is uncertain outside of the primarily North American and European settings in which OST and NSP initiatives have been studied.[36,37] We varied this quantity in sensitivity analysis to account for this limitation, but in implementing PWID harm reduction globally we are assuming that such programmes can have equal success in all regions. Lastly, we did not model changes in the proportion of the population who are PWID. There is growing concern about potential increases in the number of PWID in the USA,[64] for instance, yet the relationship between non-medical use of prescription opioids and initiation of injection drug use is not well understood.[65] Conversely, in other regions such as Europe, the proportion of the population who are PWID might have decreased,[66] such as in Scotland, which has reported a decline in injecting drug use over the past decade.[67] With such uncertainty regarding possible changes in the proportion of the population who are PWID, we kept this quantity fixed and did not simulate possible increases or decreases in the future. Nevertheless, future structural interventions could reduce the number of PWID[68] and so potentially limit the ongoing spread of HCV.

In conclusion, reaching WHO elimination targets is an extremely challenging aim that requires a multifaceted approach combining screening, prevention, and treatment with a focus on those countries in which burden is greatest. Such efforts will entail considerable practical challenges and have large cost implications—running into the tens of billions of US dollars by 2030 for a complete viral hepatitis strategy[17]—but many countries have made substantial progress despite this: Egypt empowered local facilities, created numerous opportunities for HCV screening, and treated 700 000 HCV-infected individuals with DAAs in 2016;[28,69] Australia has negotiated a volume-based pricing model for DAAs that encourages, rather than rations, the prescription of expensive DAA treatment courses;[70] and Scotland has successfully coordinated national expansion of harm reduction services with HCV testing and treatment provision resulting in a sharp increase in people achieving sustained virological response.[71] By using new tools and the examples of relevant countries to devise ambitious, integrated interventions, this modelling work has shown that substantial progress towards global elimination can be made while greatly reducing the burden of new infections and premature deaths.

Contributors
AH, GSC, SN, MT, and TBH all jointly conceived of the study. AH reviewed the literature; devised, programmed, and ran the model; and wrote the initial draft. GSC, SN, MT, and TBH all reviewed and revised subsequent drafts.

Declaration of interests
AH declares no competing interests. GSC has acted in advisory or educational roles for Gilead and Merck Sharpe & Dohme. SN and TBH have received personal fees from WHO for work related to this topic; TBH has also received fees from the Bill & Melinda Gates Foundation, Anansi Health, and Avenir Health for unrelated work. MT has acted in advisory or educational roles for Abbvie, Gilead, and Merck Sharpe & Dohme.

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