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Abstract: See Exec Summary

Figure 1

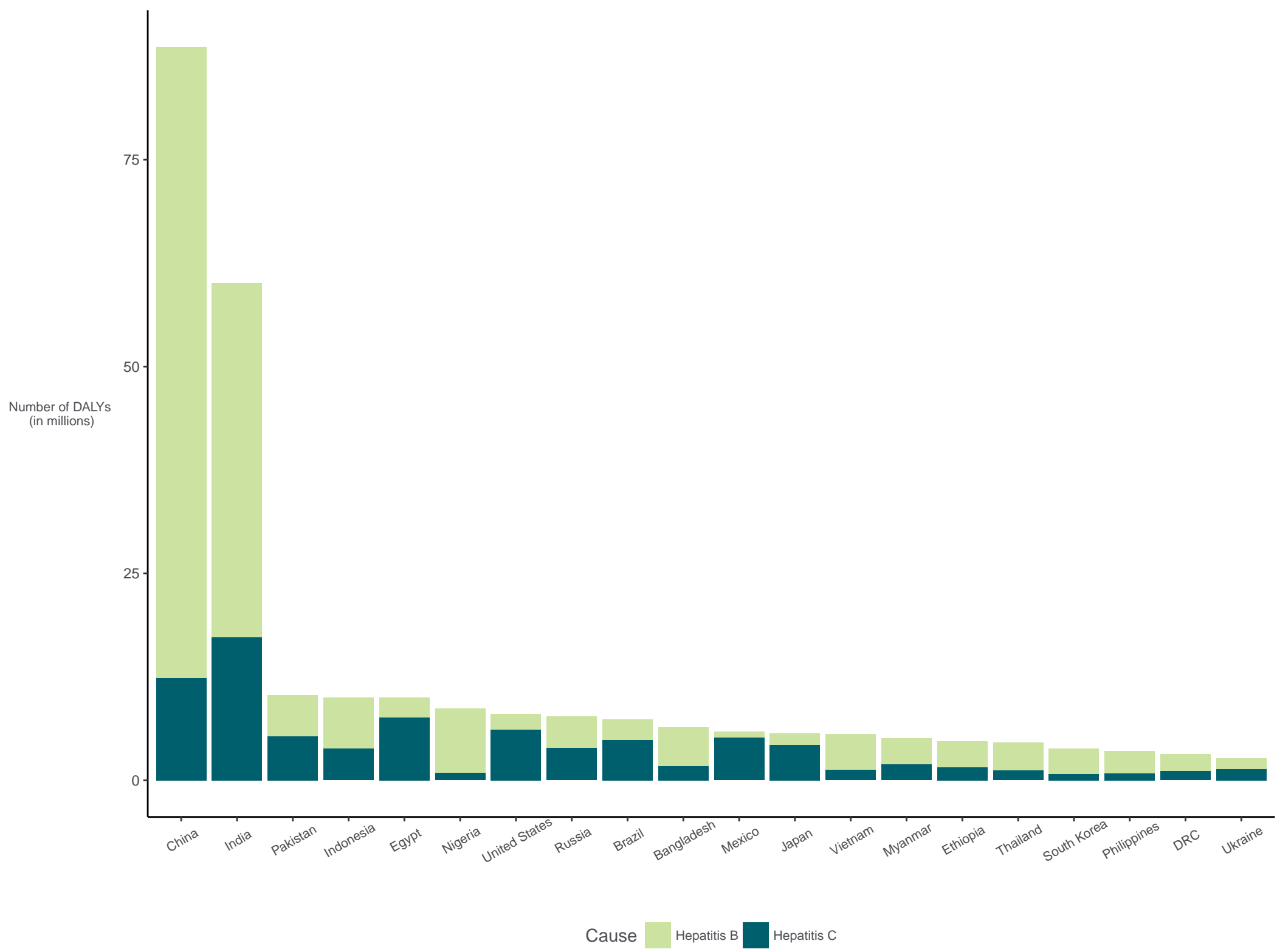






Figure 2 (top half)

WHO region									
	African	Americas	E Med	Euro	SEA	W Pacific	World	2020 target	2030 target
Population (mill)	1,000	989	654	914	1,945	1,867	7,369		
Prevalence chronic HBV (%)	6.1	0.7	3.3	1.6	2	6.2	3.5		
Prevalence chronic HCV (%)	1	0.7	2.3	1.5	0.5	0.7	1		

Figure 2 (bottom half)

Core Indicators									
Timely birth dose vaccine (%)	10	72	23	39	34	83	39	50	90
Third dose HBV vaccine(%)	76	89	80	81	87	90	84	90	90
Blood donations screened (%)	80	98	81	99.9	85	98	97	95	100
Needle/syringe distrubition (/100 IDU year)	6	22	25	59	29	57	27	200	300
Injection saftety (% resused needles)	3.7	3.4	14	4.6	5.2	3.2	5	0	0
Proportion of chronic HBV diagnosed (%)	0.3	9.1	1.8	14	2.6	2	9	30%	90%
Proportion of chronic HCV diagnosed (%)	5.7	36.3	17.7	31.2	8.7	21.5	20	30%	90%
Treatment coverage HBV (%)	<1*	13*	2*	7*	<1*	10*	5*	5 million	80%
Treatment coverage HCV (%)	2.2	11.1	12.1	4.9	7.1	4.8	7.4	3 million	80%

Incidence estimates												
Cumulative incidence of HBV in under 5s (%)		3	0.2	1.6	0.4	0.7	0.9		1.3		↓30%	↓90%
Incidence HCV (/100,000)		30.9	6.4	62.5	61.8	14.8	6		23.7		↓30%	↓90%

-  Routine reporting from countries
-  Estimates meeting standards defined by GATHER ([gather-statement.org](http://gather-statement.org))
-  Other estimates (incl modelling)
-  Extrapolation and inferences

Data from WHO Report 2017 unless stated

\* Polaris Observatory estimates for 2016 Lancet Gastro Hep (2018)

Figure 3

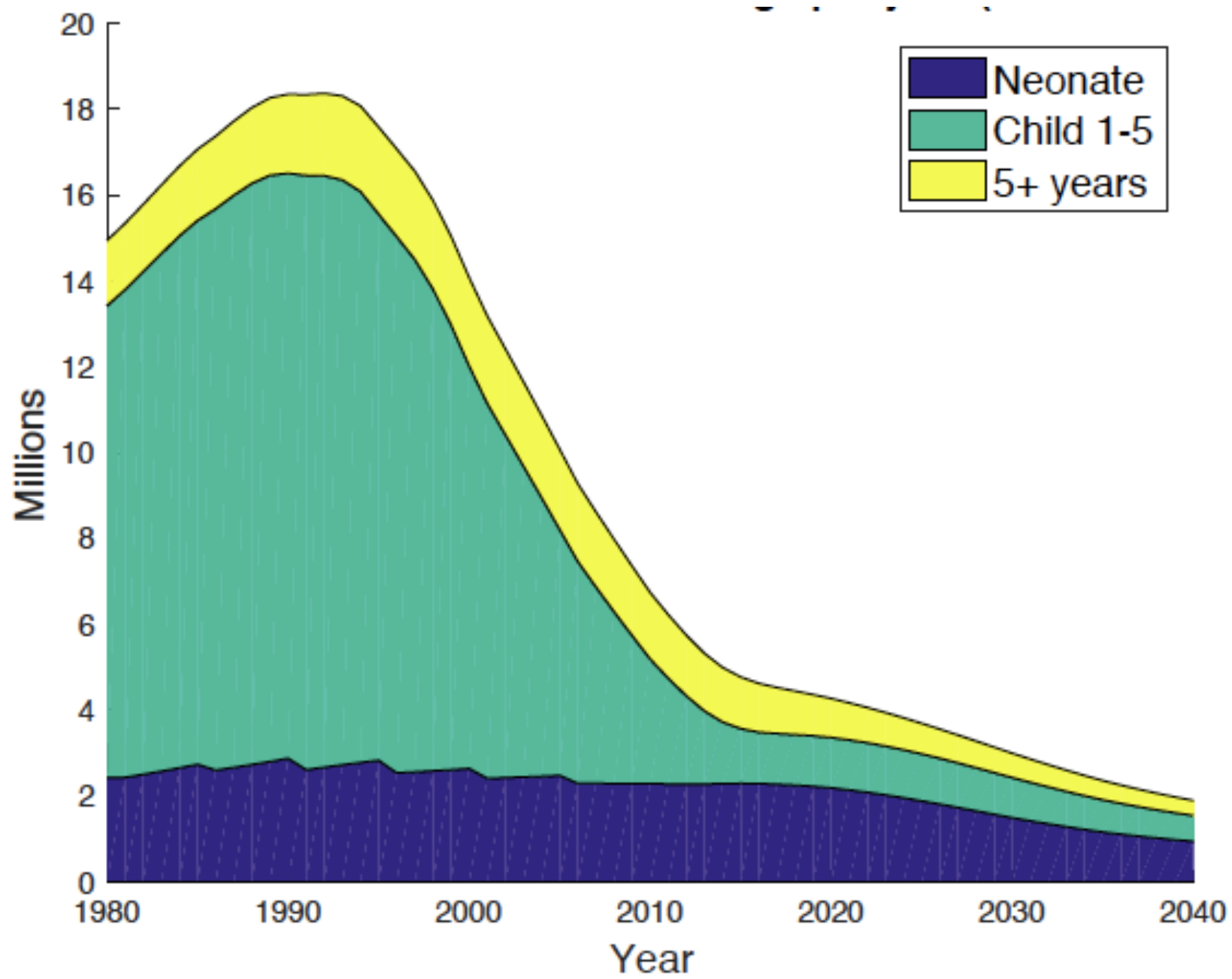


figure 6a

South, South-East, East Asia

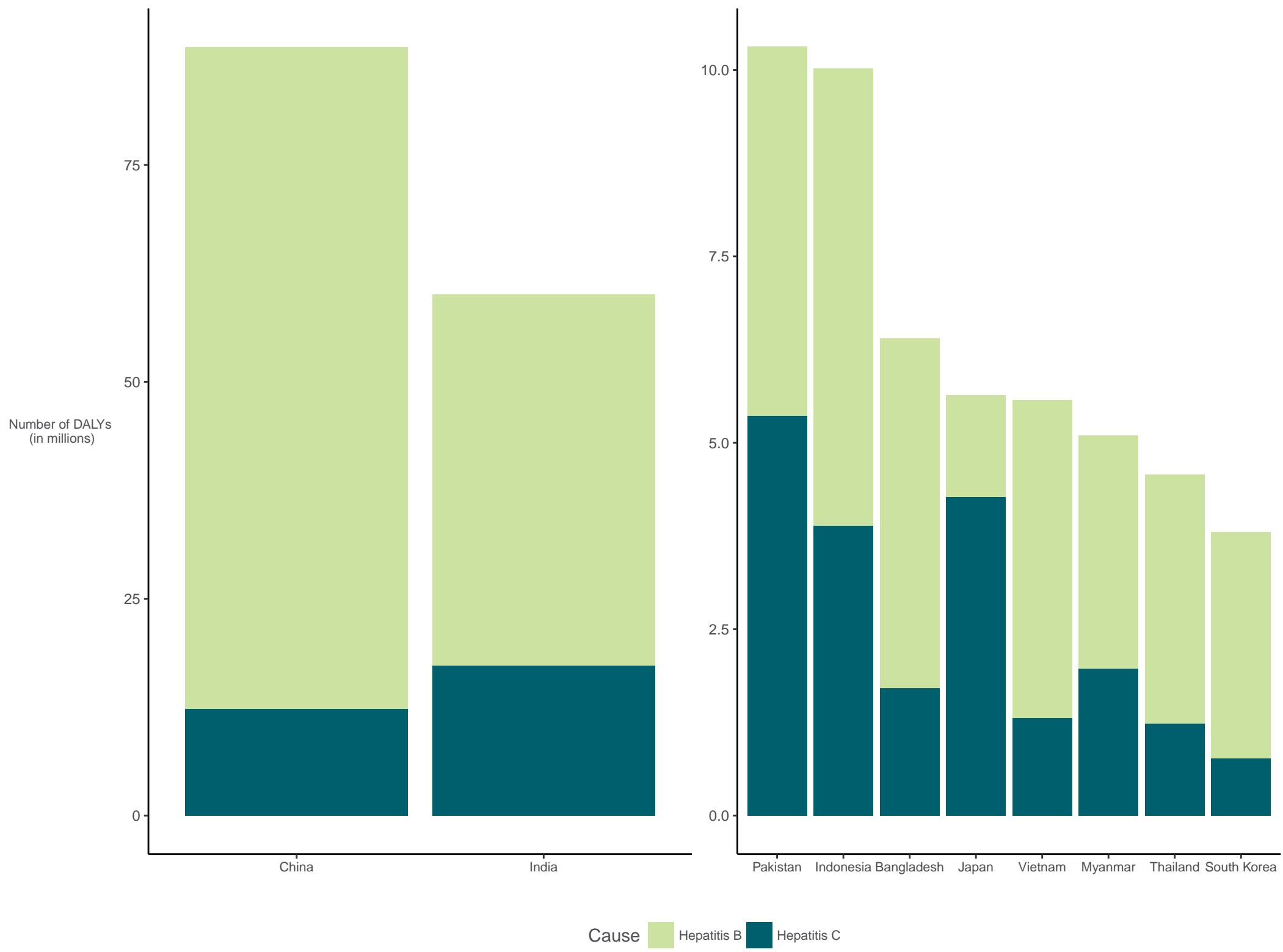


Figure 6b Progress towards WHO elimination targets in the most heavily burdened countries of Asia

Country	Policy & data		
	National plan/strategy	Reliable national epidemiological data	Estimate of economic burden
Bangladesh	●	○	○
China mainland	◐	●	◐
Hong Kong	○	○	○
Indonesia	●	◐	○
Japan	●	○	◐
Malaysia	◐	○	○
Myanmar	●	●	◐
Pakistan	◐	●	◐
Philippines	○	●	◐
Taiwan	●	●	◐
Thailand	◐	●	◐
Vietnam	◐	●	◐

- Denotes the existence of a policy
- ◐ Denotes a policy that is in development/not well applied or is in place for subpopulations
- Denotes the absence of a policy

<sup>1</sup>Shows coverage of infant immunization programmes including at least 3 doses of hepatitis B vaccine, where: ● ≥90% (2020)



figure 7a North Africa and Middle East

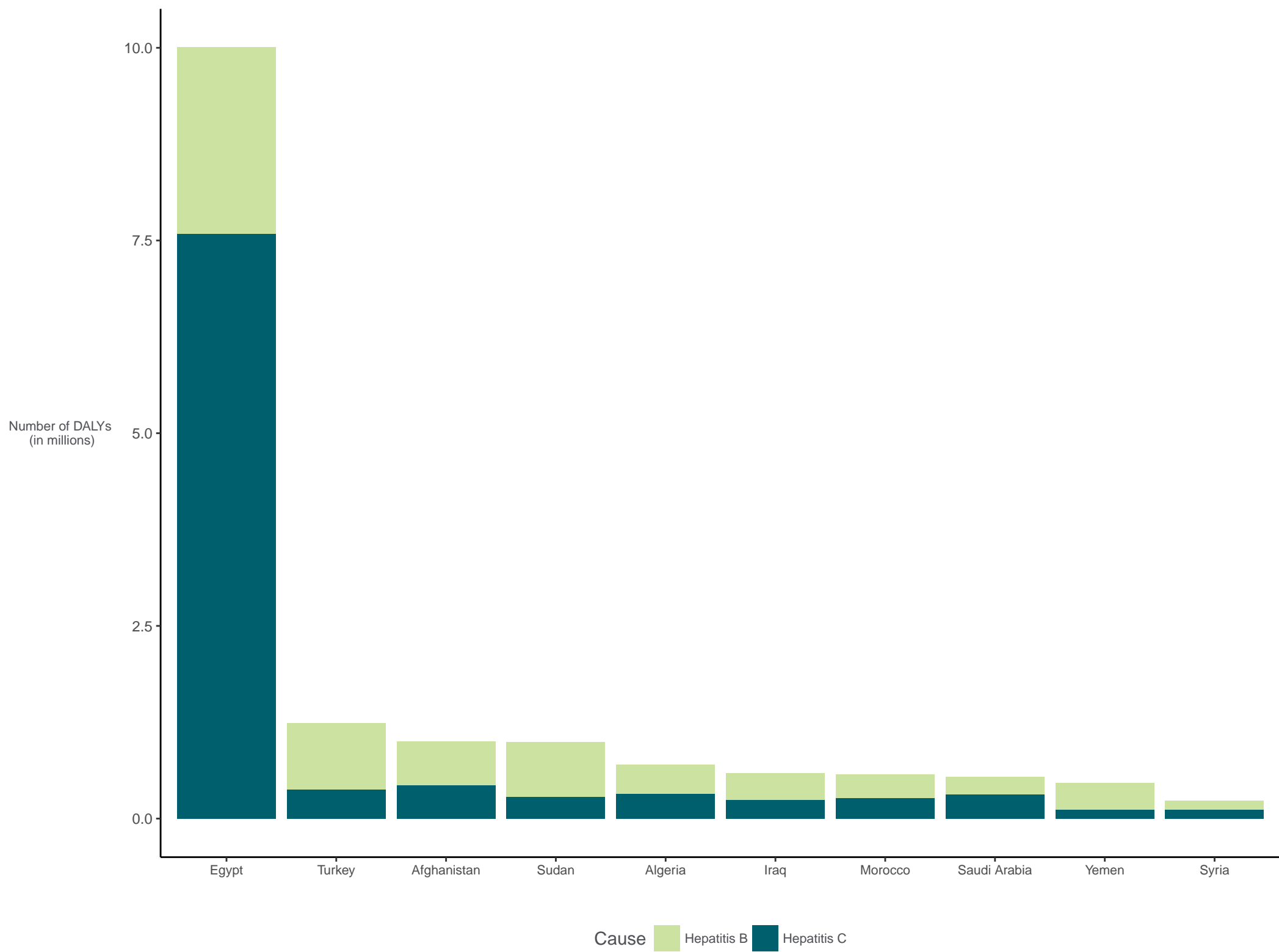


Table X.X Progress towards WHO elimination targets in the most heavily burdened countries of Mic

Country	Policy & data		
	National plan/strategy	Reliable national epidemiological data	Estimate of economic burden
Algeria	◐	○	○
Egypt	●	●	●
Iraq	●	●	○
Libya	○	○	○
Mauritania	○	○	○
Morocco	●	●	○
Saudi Arabia	●	●	○
Somalia	○	○	○
Sudan	○	○	○
Syria	○	◐	○
Yemen	○	○	○

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○ Denotes the absence of a policy

<sup>†</sup>Shows coverage of infant immunization programmes including at least 3 doses of hepatitis B vaccine, where: ● ≥90% (2021)

figure 8a

North & South America

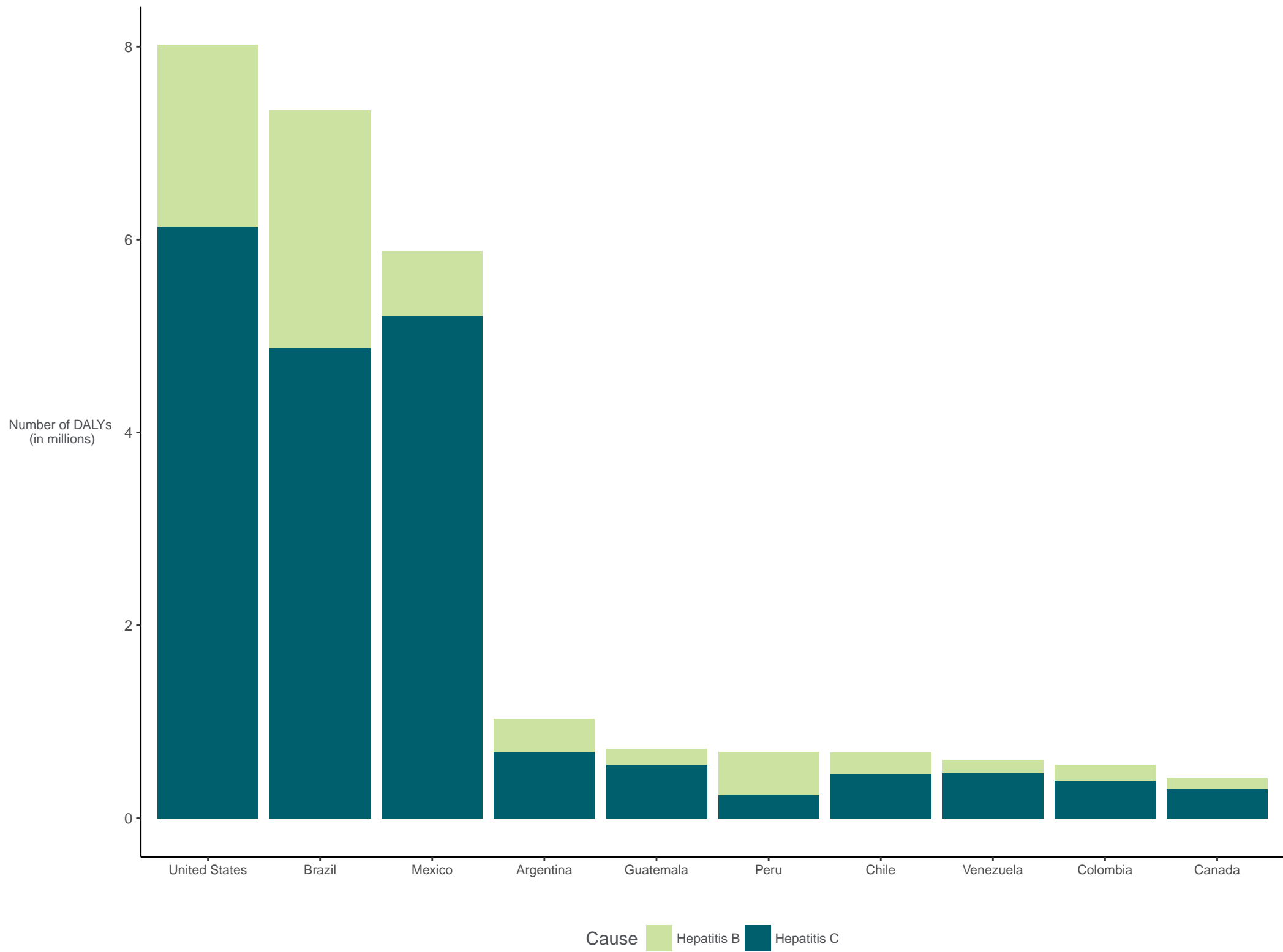


Table X.X Progress towards WHO elimination targets in the most heavily burdened countries of the

Country	Policy & data		
	National plan/strategy	Reliable national epidemiological data	Estimate of economic burden
Argentina	●	●	○
Brazil	●	●	◐
Canada	●	●	◐
Mexico	●	●	○
USA	●	●	◐

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○ Denotes the absence of a policy

<sup>1</sup>Shows coverage of infant immunization programmes including at least 3 doses of hepatitis B vaccine, where: ● ≥90% (2021)

figure 9a

Europe

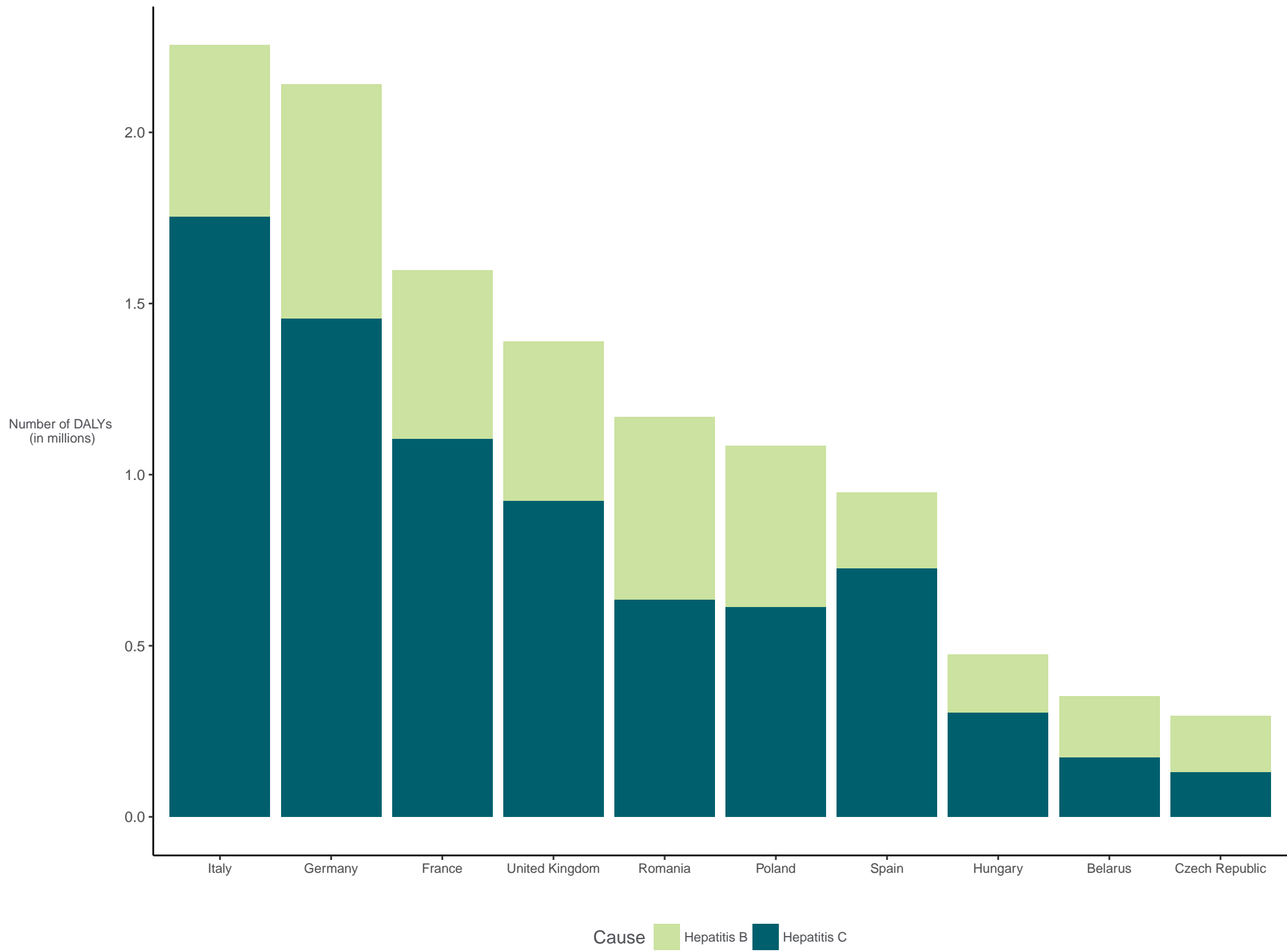


Figure 9b Progress towards WHO elimination targets in the most heavily burdened countries of Eur

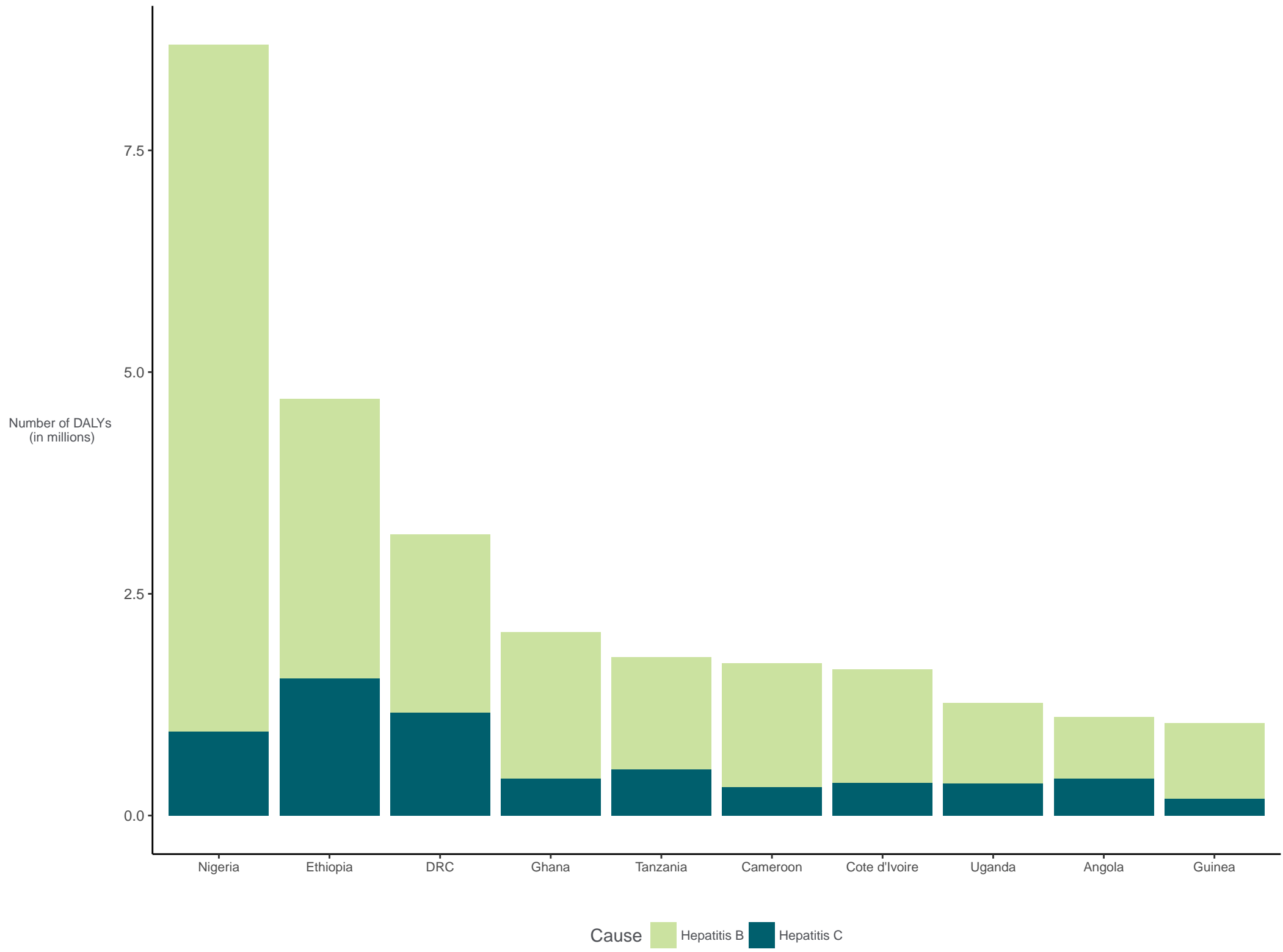
Country	Policy & data		
	National plan/strategy	Reliable national epidemiological data	Estimate of economic burden
France	●	●	◐
Germany	●	●	◐
Greece	◐	◐	◐
Hungary	○	○	○
Italy	●	●	◐
Poland	◐	◐	○
Romania	●	◐	○
Spain	●	●	◐
United Kingdom	●	●	◐

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- Denotes the absence of a policy

<sup>1</sup>Shows coverage of infant immunization programmes including at least 3 doses of hepatitis B vaccine, where: ● ≥90% (2020)

figure 10a

Sub-Saharan Africa



**Figure 10b**

Figure 10b Progress towards WHO elimination targets in the most heavily burdened countries of Si

Country	Policy & data		
	National plan/strategy	Reliable national epidemiological data	Estimate of economic burden
Nigeria	●	○	○
Ghana	●	○	○
Gambia	○	○	○
Cameroon	○	○	○
DR Congo	○	○	○
Uganda	●	○	○
Tanzania	○	●	○
Ethiopia	●	○	○
Rwanda	●	◐	○
South Africa	●	●	○

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○ Denotes the absence of a policy

<sup>1</sup>Shows coverage of infant immunization programmes including at least 3 doses of hepatitis B vaccine, where: ● ≥90% (2021)



figure 11a

Central Asia

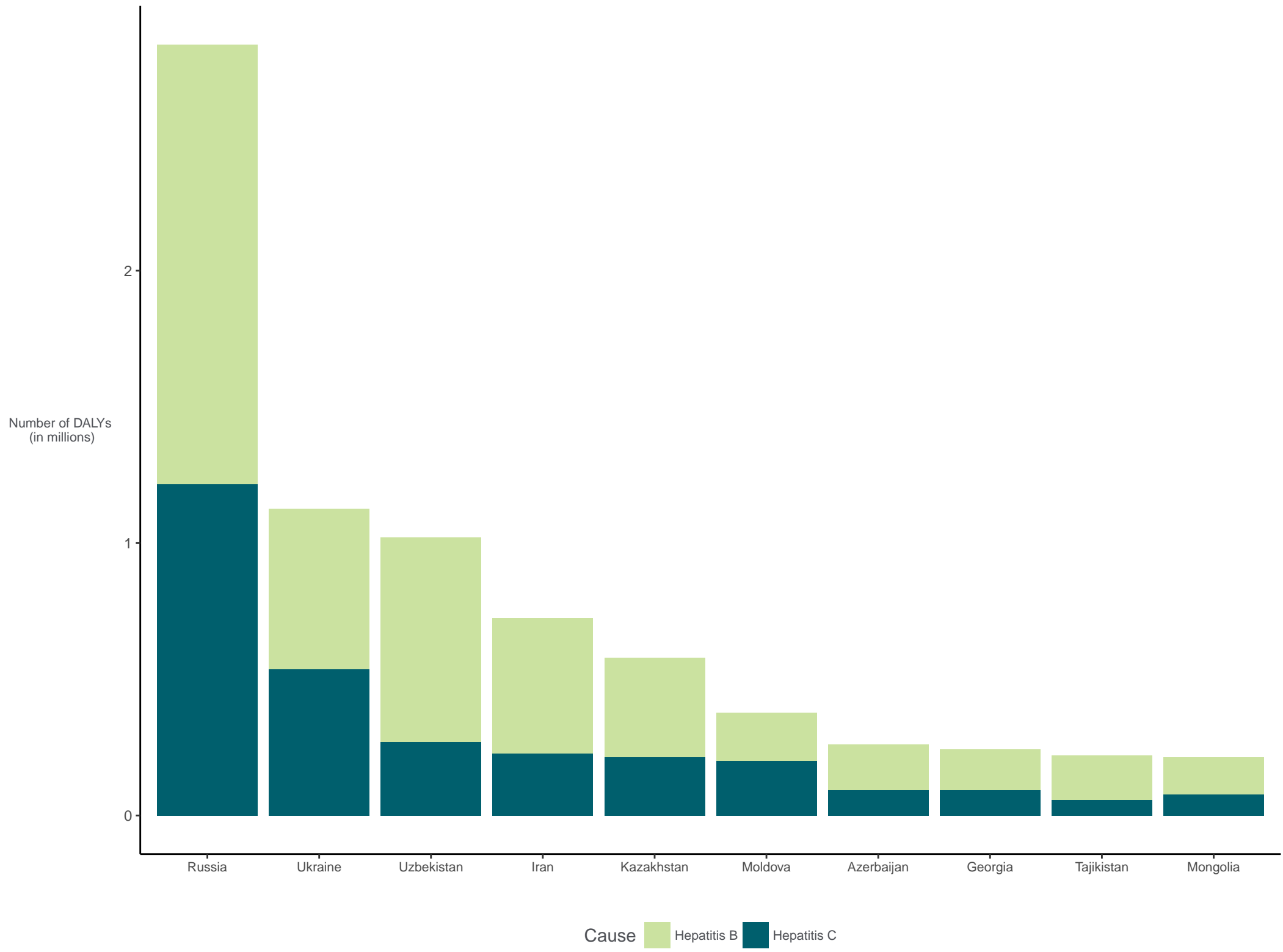


Figure 11b Progress towards WHO elimination targets in the most heavily burdened countries of Ea

Country	Policy & data		
	National plan/strategy	Reliable national epidemiological data	Estimate of economic burden
Armenia	○	○	○
Azerbaijan	◐	○	○
Belarus	○	○	○
Georgia	●	●	○
Kazakhstan	●	◐	○
Kyrgyzstan	○	○	○
Moldova	●	◐	○
Russia	○	○	○
Tajikistan	○	○	○
Ukraine	●	◐	○
Uzbekistan	◐	○	○

- Denotes the existence of a policy
- ◐ Denotes a policy that is in development/not well applied or is in place for subpopulations
- Denotes the absence of a policy

<sup>1</sup>Shows coverage of infant immunization programmes including at least 3 doses of hepatitis B vaccine, where: ● ≥90% (2020)

figure 12a

Oceania

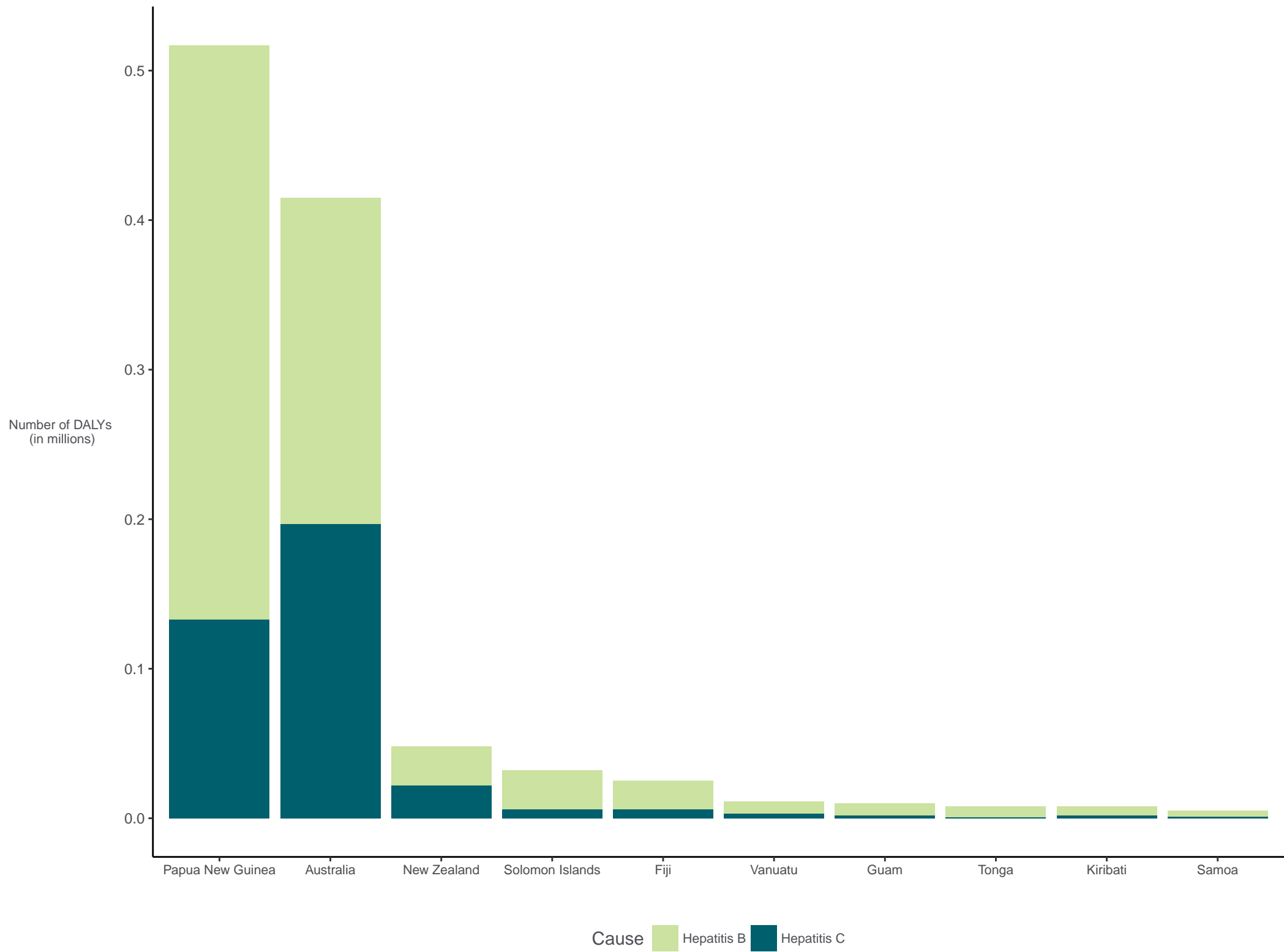


figure 12b

Country	Policy & data		
	National plan/strategy	Reliable national epidemiological data	Estimate of economic burden
Australia	●	●	●
New Zealand	●	●	●
Fiji	○	●	○
Kiribati	●	●	○
Papua New Guinea	○	◐	○
Tonga	●	●	○
Vanuatu	○	●	○
Solomon Islands	○	○	○

● Denotes the existence of a policy

◐ Denotes a policy that is in development/not well applied or is in place for subpopulations

○ Denotes the absence of a policy

<sup>1</sup>Shows coverage of infant immunization programmes including at least 3 doses of hepatitis B vaccine, where: ● ≥90% (2020)

Table 1

<b>Country ranked by viral hepatitis burden</b>	<b>GDP per capita in 2016 (current US\$) *</b>	<b>Health spend per capita (2014) (\$)</b>	<b>Health spend as % of GDP (2014) (%)</b>	<b>Government spending as % of total (2014) (%)</b>	<b>Prepaid private % of total (2014) (%)</b>	<b>Out-of-pocket spending as % total (2014)</b>	<b>Projected average Real GDP growth 2018-2022**</b>
1. China	8123.2	697	5.1	60.3	5	34.6	6.2
2. India	1709.6	253	4.5	31.3	2.4	65.6	7.9
3. Indonesia	3570.3	265	2.5	42.7	2.7	53.5	5.5
4. Pakistan	1443.6	132	2.7	32.1	6.1	55.4	5.8
5. Egypt	3477.9	581	5.4	39.9	1.5	58.3	5.5
6. USA	57638.2	9237	16.6	49.6	38.8	11.4	1.9
7. Bangladesh	1358.8	92	2.9	22.7	0	65.6	7.0
8. Russian Federation	8748.4	1877	7.1	51.8	2.8	45.5	1.5
9. Japan	38900.6	3816	10.2	83.6	2.4	13.9	1.9
10. Brazil	8649.9	1357	8.5	45.9	28.5	25.5	1.9

11. Vietnam	2214.4	398	7	53	6.9	37.5	6.2
12. Mexico	8208.6	1088	6.3	51.17	4.2	44	2.5
13. Thailand	5910.6	633	4.1	78.7	8.6	12.1	3.2
14. Myanmar	1195.5	121	2.5	36.2	0	45.6	7.5
15. Ethiopia	706.8	85	5.5	26.9	0	28.4	7.9
16. Nigeria	2175.7	225	3.7	22.1	0.8	70.1	1.7
17. DRC	405.5	46	4.5	21.3	0	37.4	3.8
18. Korea, Republic of	27538.8	2507	7.1	56	6.6	37.4	2.9
19. Italy	30674.8	3311	9	77.4	0.9	21.7	0.9
20. Philippines	2951.1	330	4.7	33.6	10.2	54.3	6.8

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## Executive Summary

Viral hepatitis is a major public health threat and a leading cause of death worldwide. Each year viral hepatitis kills an estimated 1.4 million people, comparable to other major infectious diseases including HIV, tuberculosis, or malaria. 96% of deaths are attributable to hepatitis B (HBV) and C (HCV), the focus of this commission. Availability of highly effective prevention measures and treatments has made the global elimination of viral hepatitis a realistic goal, endorsed by all WHO member states. Ambitious targets have been set out aiming for a global reduction in hepatitis related mortality of 65% by 2030 and reduction in new infections by 90%. Inclusion of viral hepatitis in the Sustainable Development Goals (SDGs) reflects a recognition of the importance of viral hepatitis to development.

This Commission was formed to take stock of the global situation as we embark on the journey to elimination and identifies key interventions needed to accelerate progress. Elimination will require comprehensive hepatitis strategies within affected countries and focused action at the national and sub-national levels including the intensification of both prevention and treatment efforts. Some countries are advancing faster than others. Typically, they have a national hepatitis strategy in place and strong political leadership.

Analysis for this commission finds that 20 countries account for over three quarters of the global burden of viral hepatitis. An effective response in these countries is crucial if global elimination targets are to be achieved. Home to 10 of the 20 most heavily burdened countries and accounting for approximately 70% of viral hepatitis related deaths, the Asian region stands out in terms of disease burden and the need for an invigorated response.

The nature of viral hepatitis epidemics differs significantly among countries and responses at country level must be context sensitive. In this commission we have sought expertise from all affected regions of the world with many examples of success and how to overcome barriers. Sharing these experiences will help all to make progress towards elimination.

Vaccination against HBV, which has been a major public health success, is projected to have prevented 310 million cases of hepatitis B between 1990 and 2020. Maintaining high childhood vaccination coverage rates remains crucial to all elimination plans. The success of HBV vaccination of preventing infection in later life means the proportion of new chronic HBV infections that arise through mother-to-child transmission is projected to rise from 16% in 1990 to 50% in 2030. This makes access to birth dose vaccine a key priority.

Elimination of viral hepatitis will require a shift from an individual patient focus to one that emphasizes a coordinated public health approach that includes interruption of transmission and infection through immunization, prevention, and treatment. In the short term, this requires designing simplified, standardized packages of interventions that can be delivered at scale. HBV and HCV share common transmission routes, and tackling both together can produce better

public health outcomes while yielding economic efficiencies. Not only will treating HBV and HCV interrupt transmission, it will also help prevent as many as one in 20 of all cancer-related deaths worldwide.

The development of public health programmes adapted to national settings is a priority for both HBV and HCV and will require education and training programmes, as well as a change in regulations, as part of a shift to more decentralised services. Requirements for specialist care will need to be minimized, with greater emphasis on less specialised staff delivering treatment and care through task sharing. A policy shift towards treating all individuals with HCV irrespective of disease stage, using pan-genotypic regimens, would greatly simplify care delivery and has the potential to impact on morbidity, mortality, and transmission. Where possible services for managing viral hepatitis should be integrated seamlessly with other related services in health systems and many of the interventions required to prevent hepatitis infection should form part of efforts to strengthen health systems as a whole and improve safety (e.g. screening of transfusion, provision of clean needles, infection control in healthcare facilities).

Perhaps the greatest challenge in achieving elimination targets is scaling up testing to all those at risk once treatment is available, as of 2015 an estimated 290 million individuals remained undiagnosed. As part of this, there is a need to improve access to appropriate diagnostics that, in some settings, are a greater financial barrier to scaling services than drug costs. Inclusion of viral hepatitis in WHO's proposed Essential Diagnostic List is a welcome step forward and pre-qualification of diagnostics will help with procurement. Research and development funding for more affordable, high quality diagnostics suitable for decentralised models of care should remain a research priority and health systems must allow for testing to be carried out in non-hospital settings.

In 2017, more people were infected with HCV than were cured. In order to reverse this, access to quality, affordable treatment needs to be greatly expanded. All originator companies of drugs recommended in the WHO Essential Medicines list should develop a clear access plan for lower-middle-income and upper-middle-income countries. This is not currently the case. Voluntary licensing schemes for lower-middle-income countries already achieved substantial price reductions in eligible countries, but high-burden upper-middle-income countries unable to access such schemes and unable to afford market prices, have become the "squeezed middle" until effective access policies are developed or expanded. Key pan-genotypic drugs, particularly pibrentasvir and glecaprevir, are not currently available through voluntary licensing. Collaboration with the Medicines Patent Pool (MPP) offers one potential avenue to improve access. However, in the absence of voluntary licensing, some countries may opt to consider compulsory licensing and as an alternatives option

Despite progress in drugs and diagnostics access, financing the elimination of viral hepatitis remains a critical challenge and lacks the major global support provided to HIV, TB or malaria.

With the current emphasis on achieving universal healthcare coverage, countries need to be supported in creating “fiscal space” to invest in programmes to eliminate hepatitis. Investment plans are needed to support national policies and to ensure evidence informed decision-making regarding which interventions will provide the greatest public health returns. In China, for example, investing in comprehensive HBV programming is estimated to bring savings of more than US \$1.5 for each \$1 spent, by 2030.

New innovative financing mechanisms may be required to support national programmes. A new international body is not essential. Existing international financing and development organisations like UNITAID (a leading organization in market shaping focused on HIV co-infection) are well placed to support expansion of access to prevention, diagnostics, treatment for eliminating viral hepatitis and , if domestic efforts to provide funding are unsuccessful, identify new streams of finance to support national programmes.

All those engaged with viral hepatitis elimination need quality data and simple, consistent targets to monitor progress and advocate for the national prioritisation of viral hepatitis prevention and treatment. NGOs and civil society have a key role to play in keeping viral hepatitis on the health agenda both nationally and internationally. Coupled with WHO monitoring and evaluation efforts and monitoring of the Sustainable Development Goals (SDGs), a new scorecard of national progress is needed to ascertain each country’s progress towards elimination of viral hepatitis, which is achievable

## Summary Table of Priority areas for action

Priority Area	National Priority Actions	International Priority Actions
Prioritize investments to support countries with greatest burden of viral hepatitis	All heavily burdened countries to have fully funded elimination plans by 2019	Recognition of need to focus on high burden countries and support for national policy development (All)
Funding for national elimination plans	Creation of fiscal space for new programmes with costed investment programmes  Adopt domestic innovative finance tools where appropriate	Support national policy makers in their activity (WHO, UNITAID, NGOs)  Provide international support for financing measures (UNITAID, GFATM, bilateral donors)
Prevention	Ensure all WHO elimination targets addressed in plans  Address operational challenges in delivery of birth dose HBV vaccine  Ensure provision of harm reduction services and engage with marginalised group (e.g. prisoners, PWIDs).  Ensure clear public health messages to encourage testing and treatment	Support countries to decriminalise injecting drug use and ensure equitable access to services for all (NGOs, WHO, civil society)  Ensure appropriate funding for HBV vaccine, including birth dose (GAVI, WHO)  Support R&D into HCV vaccine development (Research funders and pharma)
Testing and Models of Care	Focus on substantially scaling up testing for HBV and HCV  Create and evaluate simplified care pathways relevant to local setting, integrating with existing services.  Promote task sharing and decentralisation of care through capacity building, training and removal of	Support operational research into simplified pathways (Research funders, UNITAID)

	requirements for specialised prescribing	
Diagnostics	Ensure testing is integrated into the wider healthcare system, rather than centralised facilities	<p>Ensure access to quality diagnostics through Essential Diagnostic List and pre-qualification (WHO, funders)</p> <p>Support implementation science for models of care and R&amp;D into novel diagnostics suitable for decentralised settings. (Research funders, FIND, industry)</p>
Access to treatment	<p>Ensure all Essential Medicines for viral hepatitis are included in national programmes, with an emphasis on pan-genotypic regimens</p> <p>Apply comprehensive policy approach to promoting access, including compulsory licensing</p>	<p>Ensure all essential medicines are pre-qualified and either available through voluntary licensing or Medicines Patent Pool (WHO, NGOs, civil society, funders)</p> <p>Support shared procurement mechanisms for treatment (PAHO)</p>
Monitor Progress	<p>National plans need clearly defined, measurable objectives</p> <p>Develop new indices of national progress</p>	<p>Progress of individual countries needs to be closely monitored towards elimination goals (Polaris, WHO, Creation of Elimination Index)</p> <p>Develop greater capacity for advocacy in high burden regions (all)</p>

**Viral hepatitis is one of the leading causes of death in the world. 96% of those deaths are due to hepatitis B and C, which are the focus of this commission. Unlike many other major diseases, the tools exist to eliminate viral hepatitis. A highly effective vaccine is available to prevent hepatitis B, and a revolution in HCV treatment—namely direct-acting antiviral (DAA) drugs—means that therapies are now available that can be provided at scale in high-burden, low income countries. The potential to eliminate viral hepatitis has been recognised by recent World Health Assembly resolutions. In 2016, the WHO adopted its Global Health Sector Strategy setting out ambitious targets for elimination of viral hepatitis as a public health problem by 2030, including a 90% reduction in new infections and a 65% reduction in deaths attributable to viral hepatitis. At present, only a small number of countries are currently on track to meet these targets, but many countries are in the process of developing national strategies for the elimination of hepatitis. This commission draws together experts from, public health, clinical medicine, civil society, finance and policy to explore barriers to elimination and the means to overcome them. We have drawn on expertise from different regions to identify examples of best practice and key challenges ahead. We identify aspects of prevention that need to be more widely available and highlight the need for simplified models of care to facilitate the scale up of diagnosis and treatment that are required if the WHO targets are to be achieved. We also identify means of accessing new treatment and diagnostics and potential means to pay for them.**

## **Introduction [H2]**

Viral hepatitis is now recognized as a leading cause of death worldwide, causing an estimated 1.34 million deaths per year (nearly 4,000 per day), rivaling mortality caused by other major infectious diseases, including HIV/AIDS, malaria and tuberculosis<sup>1</sup>. In 2017, WHO released its first Global Hepatitis Report, which provided the first-ever baseline estimates of incidence, prevalence and mortality from viral hepatitis for the six WHO regions.<sup>2</sup> According to the report, an estimated 257 million people worldwide were living with HBV infection in 2015 and 71 million were living with HCV.

Until recently, however, there was a huge disparity between the global burden of disease and global policy on viral hepatitis. Viral hepatitis was omitted from the Millennium Development Goals;<sup>4</sup> before 2008, none of the 8000 WHO employees had ‘hepatitis’ in their job title;<sup>5</sup> and no non-governmental agencies existed that focused on the plight of people living with viral hepatitis worldwide. Thanks in part to data-driven advocacy efforts and the recognition that elimination is achievable, viral hepatitis has now cemented its place on the global health agenda and is included within the Sustainable Development Goals (SDG 3).

In 2016, WHO adopted its Global Health Sector Strategy (GHSS) for viral hepatitis,<sup>2</sup> which outlines an ambitious agenda for the global elimination of viral hepatitis as a public health threat by 2030, including a roadmap towards elimination and key prevention and treatment

interventions aimed to strengthen health systems within the context of the universal health coverage framework.

To achieve the WHO target for elimination of viral hepatitis—namely a 90% reduction in new infections and a 65% reduction in deaths attributable to viral hepatitis by 2030—efforts need to be sustained amidst a global health agenda that is increasingly focused on health systems approaches and non-communicable diseases rather than disease-specific programmes and communicable diseases. For this reason, a unified response to viral hepatitis is warranted, rather than siloed programmes for individual viruses. Viral hepatitis is infectious in nature, but with long-term sequelae including cirrhosis and hepatocellular cancer, it spans the divide between communicable and non-communicable diseases. HBV and HCV are responsible for more than 50% of all cases of liver cancer, which is the third biggest cancer killer globally and the second biggest in Africa<sup>3,4</sup>. Elimination of viral hepatitis has the potential to prevent more than one in 20 of all cancer deaths globally<sup>3</sup>.

The commission aims to identify the key challenges in achieving elimination when developing strategies for viral hepatitis elimination, and in doing so has drawn on a wide range of expertise. Our audience includes those involved in advocating for and developing those strategies. We also identify areas in which greater innovation—in technology, service delivery and finance—will help drive efforts towards elimination. In this section, we present an overview of current progress in tackling hepatitis B and C. In section 2 we review proven strategies for prevention of viral hepatitis and the priorities for implementation. Section 3 addresses some challenges of diagnosis, models of care and the need to improve access to affordable diagnostics. Access to medicines and the need for innovative financing strategies are outlined in Section 4. There is no large source of external funds for hepatitis, akin to the Global Fund for HIV, TB and malaria (GFATM), and unless the GFATM is able to extend its remit, hepatitis needs to be prioritised within domestic health funding. For many countries this is likely to require innovative means of financing.

This commission comes at a time when an increasing number of countries are beginning to develop viral hepatitis elimination strategies. Whilst there are shared issues among these countries, there are also issues of specific importance to different regions and different countries. In section 5, we have drawn together experts from different regions to identify examples of progress and regional barriers to elimination. In contrast to other work, we have taken a perspective of disease burden, drawing on analysis of the Global Burden of Disease programme to identify key priority countries.

## **The global burden of viral hepatitis and need for high quality data [H2]**

In 2016, more than 75% of the global burden of hepatitis and its related diseases was shouldered by only 20 countries (figure 1). To achieve meaningful progress towards the WHO targets for elimination will require a particular focus on progress within these countries, half of

which are in Asia, the region with by far the greatest burden of disease. Strikingly, only two of the most heavily burdened countries—USA and Japan—have made progress in reducing the burden of viral hepatitis in the last 20 years (supplemental figure 1). The majority of the 20 most heavily burdened countries are low-income or lower-middle-income, highlighting the need to help develop strategies that are achievable in healthcare systems with substantial financial and infrastructure constraints.

The WHO targets for progress towards elimination identify key areas in the coverage of services for those infected with hepatitis B and C (figure 2). Achieving progress in these areas requires further scale-up of interventions proven to be effective for both prevention, diagnosis and treatment, and of access to medicines.

Accurate surveillance data for new infections, chronic infections and mortality alongside programme monitoring indicators will be required not just to monitor progress toward elimination but to justify the investments required. In 2017, WHO released its first viral hepatitis report, which provided the first baseline estimates of the 10 core indicators of the Global Health Sector Strategy on viral hepatitis for the six WHO regions (figure 2)<sup>1</sup>. However, many gaps exist in data quantity and quality, and a critical review of the uncertainty of these estimates is required for countries to establish better systems for the generation of data that can guide elimination efforts.

### **Incidence, prevalence and mortality [H3]**

Estimates of the incidence of HBV and HCV infection come from different data sources. For HBV, the proportion of children aged five years who are chronically infected is used a surrogate indicator of the cumulative incidence of chronic HBV infection in the first five years of life, as a majority of infections are acquired in this time frame. It is also monitored as an indicator of progress towards the Sustainability Development Goals. For HCV, data are more limited, and most incidence estimates derive from mathematical models that are based on prevalence data. Generating better data, particularly on HCV incidence, will be increasingly important as efforts to scale up treatment progress.

Estimates of new infection with HBV have fallen steadily, from a peak of over 18m new infections per year in the early 1990s to an estimated 4.7m new infections in 2015, due to the introduction of the HBV vaccine<sup>5</sup>. New HBV infections are predicted to remain close to 3 million a year by 2030 without further scale up of prevention and treatment<sup>5</sup> (figure 3). In 2015, WHO estimated that 1.3% of children under five worldwide were positive for hepatitis B surface antigen (HBsAg), ranging from 4.7% in the African region and 0.3% in the Americas region. The prevalence of HBsAg in children is assessed with surveys to measure the impact of universal hepatitis B immunisation of infants. However, many countries have not conducted such surveys, and estimates require extrapolation from countries with better quality data. In the WHO Western Pacific region, where HBV prevalence was very high in the pre-vaccine era, a regional



initiative strongly encouraged countries to conduct surveys after vaccine introduction <sup>6</sup>. As a result, the uncertainty interval around the 0.9% prevalence estimate for this region is relatively narrow (95% uncertainty interval 0.6%—1.3%), whereas uncertainty intervals are wider in regions such as Africa (3% [2.0%—4.7%]), where fewer surveys have been conducted. Better data from Sub-Saharan Africa are needed to estimate the impact of the 76% coverage of the three-dose vaccine in the absence of a timely birth dose policy in most countries in this region.

Measuring the incidence of HCV infections is challenging in the absence of a test for recent HCV infection and in view of the high frequency of asymptomatic infections. Modelling estimates suggest that worldwide, in 2015, there were 1.75 million new HCV infections (global incidence rate of 23.7 per 100 000; uncertainty interval 1.6-2.1)<sup>1</sup>. The incidence of HCV infection may be estimated using several methods, including back-calculation from a curve with the age-specific prevalence of HCV infection, inference from sequential biomarkers surveys, and modelling based on estimates of the incidence of infection in various risk groups. Such modelling poses several methodological challenges, including difficulty in estimating incidence in regions where incidence is low or when input data on age-specific prevalence is of poor quality or is unavailable, and the necessity of assuming static prevalence data for inferring incidence estimates, which may not be appropriate in some countries, particularly as treatment and prevention are scaled up.

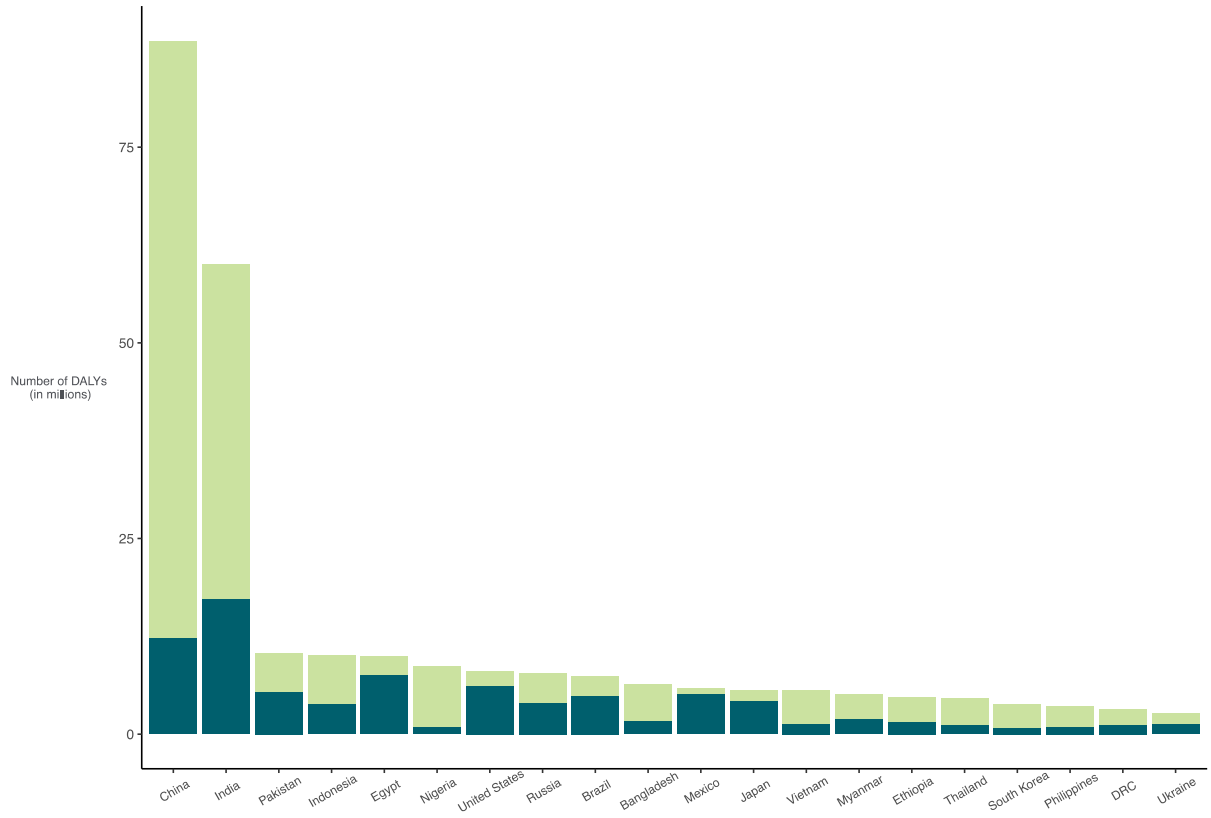
Trends in incidence identified by modelling studies can be verified using surveillance data, but these data also have limitations. Data on reported cases of acute HCV can provide information on time trends but are limited by substantial underreporting and a large proportion of asymptomatic infections. Data from longitudinal cohorts of at-risk populations, such as people who inject drugs (PWID), provide valuable information about changes in incidence over time and the impact of treatment scale up, but they can be difficult to obtain.

In 2015, WHO estimated that 257m people (3.5% of the population; uncertainty interval 199-368m) were living with HBV infection and that 71m people (1% of the population; uncertainty interval 62-79m) were living with HCV infection (figure 2, 4)<sup>1</sup>. The change from reporting prevalence based on individuals with detectable anti-HCV antibodies to only those with active HCV infection (based on detection of HCV RNA) is an important reflection of the high proportion of antibody-positive individuals who do not require treatment. HCV prevalence estimates are based on data from systematic reviews and extrapolations for areas of the world that do not have data. Biomarker surveys estimating the prevalence of HBsAg or antibodies to hepatitis C are the reference methods more commonly used to measure the prevalence of HBV and HCV infections. Countries that have a high burden of disease because of high prevalence, such as China,<sup>11</sup> tend to conduct such surveys to guide their policies. In countries that have lower endemicity, the costs of biomarker surveys are harder to justify and data are of lower quality, leading to more uncertainty. Even in countries in which biomarker surveys are conducted, the data are often limited by non-representative sampling strategies, issues with quality assurance of diagnostic assays, and absence of data disaggregated by age groups.

WHO estimated that viral hepatitis was responsible for 1.34 million deaths in 2015<sup>1</sup>. These estimates are based on a combination of data from vital registration databases (national data routinely collected on deaths), models that quantify the number of deaths from cirrhosis and hepatocellular carcinoma, and data from studies reporting the fraction of cirrhosis and hepatocellular carcinoma that are attributable to HBV and HCV infections<sup>7,8</sup>. As such, estimates of mortality attributable to HCV and HBV vary depending on the data source<sup>9</sup>. Improving and harmonising all estimates relevant to elimination is a priority for ongoing work which can be supported by all those involved in patient care, ensuring, for example, that causes of death are recorded and reported as accurately as possible. Increasing co-ordination between key organisations should continue improve the consistency and reliability of estimates, one important example being the announcement of greater collaboration between the Institute of Health Metrics and Evaluation, IHME and the WHO<sup>10</sup>.

**Figure 1** Total Disability Adjusted Life Years (DALYs) to hepatitis B and C in in 20 most heavily burdened countries, both sexes, all ages, derived for this commission from Global Burden of

# Disease dataset (2016)



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**Figure 2. Baseline estimates (2015) of progress towards elimination targets**

	WHO region							2020 target	2030 target
	African	Americas	E Med	Euro	SEA	W Pacific	World		
Population (mill)	1,000	989	654	914	1,945	1,867	7,369		
Prevalence chronic HBV (%)	6.1	0.7	3.3	1.6	2	6.2	3.5		
Prevalence chronic HCV (%)	1	0.7	2.3	1.5	0.5	0.7	1		
<b>Core Indicators</b>									
Timely birth dose vaccine (%)	10	72	23	39	34	83	39	50	90
Third dose HBV vaccine (%)	76	89	80	81	87	90	84	90	90
Blood donations screened (%)	80	98	81	99.9	85	98	97	95	100
Needle/syringe distribution (/100 IDU year)	6	22	25	59	29	57	27	200	300
Injection safety (% reused needles)	3.7	3.4	14	4.6	5.2	3.2	5	0	0
Proportion of chronic HBV diagnosed (%)	0.3	9.1	1.8	14	2.6	2	9	30%	90%
Proportion of chronic HCV diagnosed (%)	5.7	36.3	17.7	31.2	8.7	21.5	20	30%	90%
Treatment coverage HBV (%)	<1*	13*	2*	7*	<1*	10*	5*	5 million	80%
Treatment coverage HCV (%)	2.2	11.1	12.1	4.9	7.1	4.8	7.4	3 million	80%
<b>Incidence estimates</b>									
Cumulative incidence of HBV in under 5s (%)	3	0.2	1.6	0.4	0.7	0.9	1.3	↓30%	↓90%
Incidence HCV (/100,000)	30.9	6.4	62.5	61.8	14.8	6	23.7	↓30%	↓90%
<p> <span style="display: inline-block; width: 15px; height: 10px; background-color: #4F81BD; border: 1px solid black;"></span> Routine reporting from countries  <span style="display: inline-block; width: 15px; height: 10px; background-color: #A6C98A; border: 1px solid black;"></span> Estimates meeting standards defined by GATHER (<a href="http://gather-statement.org">gather-statement.org</a>)  <span style="display: inline-block; width: 15px; height: 10px; background-color: #F4A460; border: 1px solid black;"></span> Other estimates (incl modelling)  <span style="display: inline-block; width: 15px; height: 10px; background-color: #FFFF00; border: 1px solid black;"></span> Extrapolation and inferences                      Data from WHO Report 2017 unless stated                      * Polaris Observatory estimates for 2016 Lancet Gastro Hep (2018)                 </p>									



**Figure 3** Estimated total number of new chronic carriers of HBV infection annually with current levels of intervention (adapted from<sup>5</sup>)

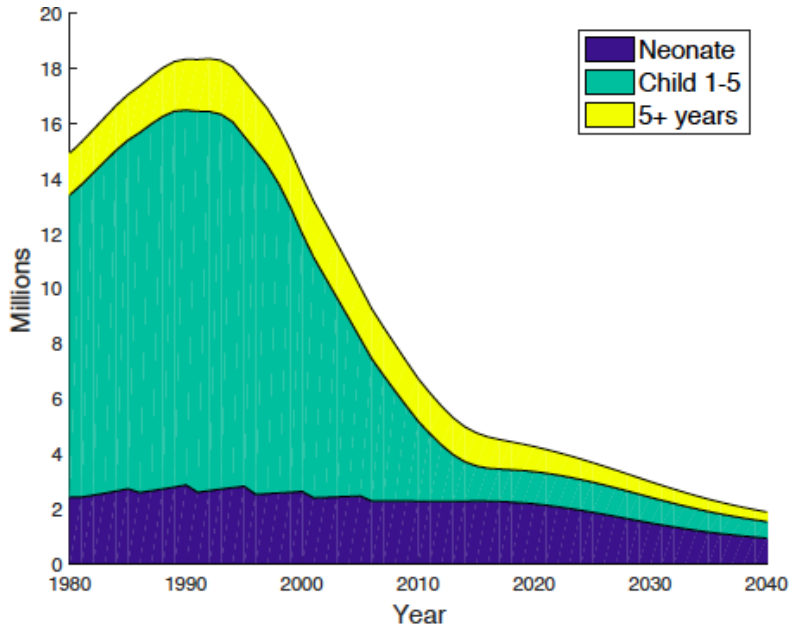
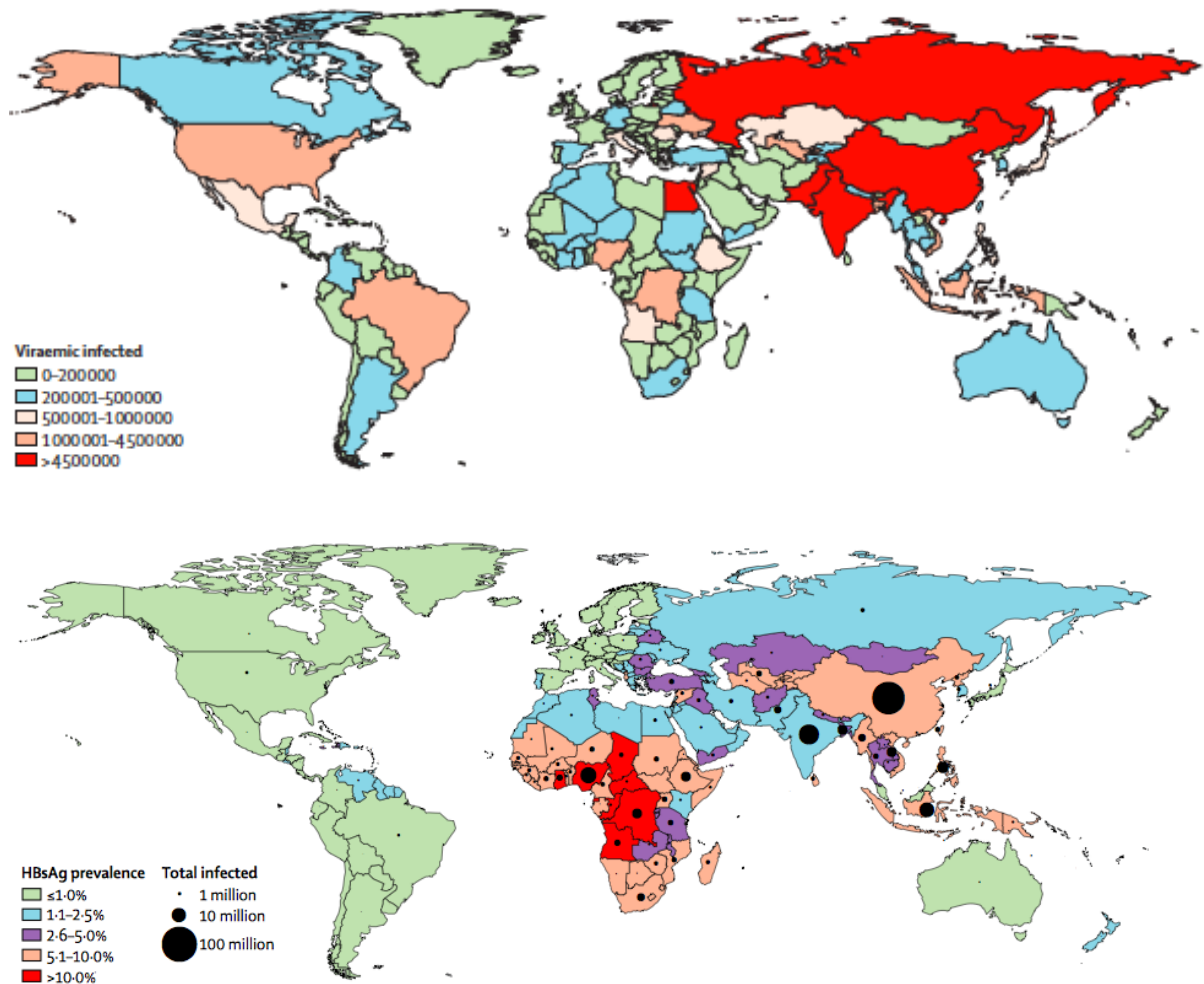


Figure 4 (a) Estimated numbers of viraemic HCV-infected individuals 2015 and (b) Estimates for HBsAg prevalence for countries with data and a model, or for which data were extrapolated from countries in the same GBD region with available data (all ages)<sup>11,12</sup>



## **Prevention of Viral Hepatitis [H2]**

The shared routes of transmission for hepatitis B and C viruses and HIV—through percutaneous or mucosal exposure to infected blood and bodily fluids—confers advantages in streamlining viral hepatitis prevention efforts, with a focus on integrated responses rather than vertical programmes.

The HBV and HCV epidemics vary considerably in different geographical settings, with different risk groups and risk factors for infection; thus, it is important that public health officials identify an appropriate mix of interventions that are adapted to the epidemiologic situation in a specific country. For example, in many high-prevalence countries, most HBV infections occur among children, whereas in low prevalence areas, more infections occur among adults, usually in defined populations<sup>13</sup>. Similarly, in high-income countries, most HCV transmission occurs among PWID, whereas in many middle and low-income countries, where infection prevention and control measures are weak, a large proportion of new infections occur in the health-care settings through unsafe injections and other invasive procedures<sup>14</sup>. Although there are substantial regional differences, globally the biggest gaps in service coverage relate to prevention of mother-to-child transmission of HBV and provision of harm reduction services among PWID.

### **Preventing early-life infection [H3]**

Globally, most hepatitis B infections occur around the time of birth through exposure to maternal blood and secretions, and in the first years of life through horizontal transmission among household contacts<sup>15</sup>. The risk of mother-to-child transmission ranges from 5% for women without detectable circulating concentrations of HBV E antigen (HBVeAg; a marker for high viral load) to 90% for women with detectable HBVeAg. The approaches to preventing early-life HBV infection can be broadly categorised as those administered to all children and those administered only to children born to mothers with chronic HBV infection (figure 3)

Horizontal transmission of HBV infection can be prevented by administration of HBV vaccine in early life, with three doses of vaccine shown to provide lifelong protection in more than 90% of individuals<sup>16</sup>. WHO recommends that all children be vaccinated against HBV within 24h of birth (a single antigen vaccine known as the birth dose vaccine), with two or three additional vaccinations with a heptavalent vaccine given starting at six weeks of age<sup>16</sup>. As of 2015, universal childhood vaccination has been implemented in 185 countries, and 84% of children born in 2015 were vaccinated with three doses of heptavalent HBV vaccine<sup>17</sup>. The global scale-up of hepatitis B vaccination has produced dramatic results, most notably in the Western Pacific region, where HBV immunisation has averted an estimated seven million deaths that would otherwise have occurred in the lifetime of children born between 1990 and 2014<sup>18</sup>. Globally, existing interventions are estimated to have reduced the incidence of new HBV infection by 83%, thus preventing 310 million chronic infections that would otherwise have occurred



between 1990 and 2020<sup>5</sup>. In Taiwan, universal HBV vaccination, which was implemented in 1984 and has high coverage rates, has reduced chronic liver disease and HCC-associated mortality by 90% among children and young adults who were vaccinated compared to those not vaccinated<sup>19</sup>.

The birth dose vaccine is the simplest and most effective means of preventing mother-to-child transmission of HBV infection and is the only strategy recommended by WHO. Progress in adopting the birth dose vaccine has been slower compared with childhood vaccination. Only 97 countries include it in their routine immunisation schedules, and only an estimated 39% of children received the birth dose in 2015<sup>17</sup>. Reasons for the low coverage of birth dose vaccination include lack of national policies, insufficient awareness among health care workers, high proportions of births occurring at home in some countries, and lack of coordination between vaccination and maternal-health programs. An additional barrier is financial, as donor agencies such as GAVI purchase the heptavalent childhood vaccine but not the single-antigen birth dose.

HBV transmission can still occur despite administration of the full vaccine schedule, particularly from women with high HBV viral loads. Therefore, in many countries with higher resource levels, additional measures are recommended for women at higher risk (figure 5), including administration of hyper-immune hepatitis B immunoglobulin (HBIG) in pregnant women who test positive for HBsAg, and treatment with antiviral drugs such as tenofovir for pregnant women with high HBV viral loads (ie, > 200,000 IU/mL), who are at particularly high risk of transmitting the virus<sup>20</sup>. Because of logistical challenges associated with HBIG administration and antiviral therapy, these interventions are not currently recommended by WHO.

A key question is what interventions should be prioritised and what additional measures are needed to eliminate early-life HBV infection (supplemental figure 2). Maintaining high rates of childhood vaccination is critical, but as the prevalence of HBV infection declines as a result, the proportion of perinatal infections will increase. Indeed, the proportion of new chronic infections that arise through mother-to-child transmission is estimated to increase from 16% in 1990 to 50% in 2030<sup>5</sup>. Therefore, in most regions, additional interventions will be required to further reduce infection rates. Scaling up childhood vaccination to 90% globally has been estimated to prevent 4.3 million HBV infections between 2015-2030 (figure 3) scaling up birth-dose vaccination coverage to 80% would prevent approximately 18.7 million HBV infections in the same time period<sup>5</sup>.

Progress in childhood HBV immunisation has slowed, and global vaccine coverage has increased by only 1% since 2010<sup>21,22</sup>. By 2015, only 126 of 194 countries had achieved the WHO target of 90% coverage of the third dose of HBV vaccine, and in only 52 of these countries did coverage exceed 80% in all districts<sup>22</sup>.

Clearly, the main priority to reaching elimination goals is to identify strategies to increase the administration of birth dose vaccine while also improve coverage rates of childhood vaccination. WHO's Strategic Advisory Group of Experts (SAGE) has made recommendations for strengthening national vaccine programs, including advocating for stronger national leadership and commitment, securing investments, and enhancing surveillance and accountability mechanisms <sup>22</sup>. For birth dose vaccination, international health agencies should continue to advocate alongside national governments for the inclusion of the birth dose vaccine in national vaccine schedules. In the absence of donor funding for the procurement of birth dose vaccine, it is important that national governments allocate sufficient funds to purchase the vaccine. As recommended by WHO, health-system interventions are also needed <sup>23</sup>. The most direct way to improve birth-dose coverage is to promote childbirth within health facility and strengthen linkages between immunisation and maternal-child health programs to ensure availability of vaccine and to promote awareness among health care workers. For children born at home, providing HBV birth dose to birth attendants and community health workers should be promoted as a way of reaching newborns who do not have contact with clinics around the time of birth. Structural interventions, such as simplified injection mechanisms and utilisation of vaccine that does not require cold-chain storage could also help improve birth-dose vaccine coverage <sup>23</sup>.

To fully minimise the risk of perinatal transmission, antenatal screening is important to identify women with chronic HBV infection, particularly those with high viral loads, provided the necessary resources (including appropriate diagnostics) are available. Many countries, including Africa, conduct universal antenatal HIV testing, and serologic testing for HBV could be incorporated into this testing with little additional cost. Since access to viral load testing is limited, a potential option is to administer antiviral drugs to all pregnant women who test positive for HBsAg, but the potential benefit and feasibility of this approach requires further study. Low-income countries should prioritise birth dose and routine childhood vaccination.

Mother-to-child transmission of HCV is not a major route of infection, with an estimated risk of 5.8% (95% CI, 4.2%–7.8%) among HIV-uninfected women and 10.8% (95% CI, 7.6%–15.2%) among women with HIV infection <sup>24</sup>. Nevertheless, as HCV infections through other routes of transmission are reduced, mother-to-child transmission might account for a higher proportion of new infections. DAAs, which rapidly reduce HCV viral load and cure HCV infection in a majority of people, are not yet approved for use in pregnant women, and studies are needed to determine their safety in this population. Since HCV therapy is curative, identifying and treating women with HCV infection before they become pregnant is currently the best approach to reduce this route of transmission and to improve the health status of these women.

### **Preventing infection amongst high risk adults [H3]**

#### **People who inject drugs [H4]**

PWIDs are at high risk of hepatitis infection, and increased efforts to prevent transmission in this

population will be essential to meet the global targets on elimination. Injection drug use has been reported in at least 179 of the world's countries and territories,<sup>25</sup> and according to the most recent estimates, there are currently 15.6 million (95% uncertainty interval 10.2–23.7 million) PWID aged 15–64 years globally<sup>26</sup>. However, these figures underestimate the true prevalence of injection drug use because this practice is often under-reported because it is stigmatised and often illegal<sup>27</sup>.

The sharing of injecting equipment (principally needles and syringes but also other paraphernalia) is a major risk factor for the transmission of viral hepatitis, particularly HCV<sup>28</sup>. As a consequence, 52.3% (95% UI 42.4–62.1) of PWID are HCV-antibody positive, and 9.1% (95%UI 5.1–13.2) are HBsAg positive<sup>26</sup>. Worldwide, the prevalence of HCV infection among PWID is 33-fold higher, and of HBV is 2.5-fold higher, than in the general population<sup>29,30</sup>. Further, PWID are estimated to contribute to nearly 40% of Disability- Adjusted Life-Years (DALYs) due to HCV and 1% of DALYs due to HBV<sup>31</sup>.

Implementation of a comprehensive package of harm reduction services for PWID is one of the priority actions outlined in the GHSS<sup>32</sup>. The package includes needle and syringe programmes (NSP), opioid substitution therapy (OST), hepatitis B vaccination, information, education and communication in risk reduction, and diagnosis and treatment of chronic hepatitis infection<sup>33</sup>. WHO also recommends the use of low-dead space syringes (to reduce the transmission of virus when needles are shared) and the offer of peer interventions among PWID<sup>34</sup>.

For HBV, targeted vaccination with the rapid schedule is recommended for PWID, including in countries that have the HBV vaccine incorporated into national childhood immunisation schedules<sup>35</sup>. However, vaccination rates have been poor in this population. Improving convenient access to vaccine (eg in prisons, NSP, and drug treatment centres) and offering incentives have been shown to increase HBV vaccine coverage among PWID<sup>35</sup>.

There is considerable evidence to support the effectiveness of both NSP and OST in reducing injecting risk behaviour and hepatitis virus transmission among PWID with the biggest individual risk reductions (70-80%) reported using a combination of NSP and OST<sup>36-39</sup>. However, despite multiple guidelines recommending NSP and OST, and widespread endorsement from international agencies, the global response continues to be woefully inadequate<sup>40,41</sup>. For example, there is still no provision of NSP and OST in 52% and 48%, respectively, of the 179 countries where injection drug use has been reported<sup>25</sup>. A major barrier to properly addressing the transmission of hepatitis viruses among PWID are national drug policies that prioritise criminalisation of drug use and drug suppression. Even in countries where harm-reduction services are authorised, police practices of harassment and arrest of PWID attending NSP and OST distribution centres limits their availability and effectiveness. As outlined in the Lancet commission on public health and international drug policy<sup>42</sup>, national drug policies should be modified to decriminalise minor drug offences, allow the possession of syringes, and ensure equitable access to harm-reduction services, including to marginalised groups such as prisoners

<sup>42</sup>. Once appropriate policies are in place, harm-reduction programs need to be sufficiently financed and designed so that they are accessible and acceptable to PWID, responsive to their needs, and free from the threat of harassment and arrest. Securing political commitment, investment in advocacy and, where necessary, revision of laws, legal policies and practices are critical to establish a more supportive environment <sup>33</sup>.

In addition to improving access to harm-reduction services, a comprehensive approach to hepatitis control must include access to HCV therapy for PWID who are infected. Accumulating evidence shows that PWID can achieve HCV cure rates similar to non-PWID, although re-infection rates are higher <sup>43-46</sup>. Treating PWID will also reduce risk of transmission, which would contribute to lowered prevalence <sup>47-49</sup>. Despite this, access to treatment is low among PWID, in part because HCV drug eligibility policies exclude active injectors in some countries. Furthermore, many health-care providers are reluctant to prescribe HCV therapy to PWID because of concerns of low adherence to treatment regimens. Educational efforts are needed among providers to highlight the importance of treating hepatitis among PWID. Economic evaluations suggest that, in many settings (where prevalence of chronic HCV infection is  $\leq 40\%$ ), treating PWID early with DAA regimens is more cost-effective than treating other patient groups because of the potential additional benefit of averted transmissions <sup>50</sup>. Further, national models of HCV elimination—such as that in Georgia—suggest that targeting and prioritising PWID for HCV therapy is critical for reducing transmission in the population as a whole. However, in many countries, HCV treatment is unavailable for people with mild disease or for PWID who are not in long term OST. Thus, empirical evidence demonstrating that treatment can indeed prevent transmission of HCV in PWID populations remains key to strengthening international guidelines and driving change in clinical practice <sup>51-53</sup>.

#### **Prison populations [H4]**

Incarcerated individuals are exposed to a unique environment in which various combinations of risk factors are ubiquitous, such as injection drug use, high-risk sexual activities, tattooing, and sharing of utensils, razors and nail clippers. The risk among inmates is further exacerbated by poor living conditions, such as overcrowding and poor hygiene <sup>54-56</sup>. The prevalence of HBV and HCV infections is higher in prisons compared with the general population, with the prevalence in the different regions of the world ranging from 1.4%-23.5% for HBV and 1.8%-20.6% for HCV <sup>57</sup>. Incidence of HCV among prisoners is also high, reported to be up to 30 cases per 100 prisoners per year <sup>58,59</sup>.

In most countries, enforcement of strict drug laws results in overrepresentation of PWID in penitentiary systems <sup>56</sup>. Approximately half of the prison population in the European Union has ever used illicit drugs. The time immediately following release from prison is also a period marked by increased sexual and drug use risk behaviours, which could lead to transmission of HBV, HCV, and HIV <sup>60</sup>.

Most prisoners do not have access to recommended intervention services aimed to reduce the risk of infection; for example, only eight countries have implemented NSPs in at least one prison<sup>61</sup>. This low level of services is due in large part to the fact that medical services in prisons are administered by the criminal justice system, whose priorities differ to that of the public health system. This is further exacerbated by low levels of investment in medical infrastructure and human resources for health in the prison systems.

Reducing the risk of hepatitis infection among prisoners will require high-level coordination between national health and criminal justice authorities, which would facilitate the development of prison-health policies and programs that were aligned with public-health priorities.

Promoting multi-stakeholder engagement with advocacy groups, peer-educators, academics and the general community would further help in the alignment of prison-health and community services. In addition to policies, greater investment is needed in the prison-health system to address insufficiencies in medical staffing and education as well as funding the provision of prevention and treatment services (including in the post-treatment phase).

In addition to enhancing prevention programs in prisons, treatment needs to be more widely accessible. With the duration of HCV treatment now as short as eight weeks, completion of HCV treatment is feasible in prison settings, even with short sentences. Because one of the obstacles for antiviral treatment in prisons is low awareness of infection status, the role screening for HBV and HCV upon entry and regular testing during the period of incarceration is something that needs greater evaluation to identify those needing antiviral treatment.

#### **Sexual transmission and men who have sex with men [H4]**

Sexual transmission occurs for both HBV and HCV and is thought to be the main route of transmission of HBV among adults; approximately one quarter of sexual partners of persons with acute HBV will become infected within six months<sup>62</sup>. Compared to the general population, sex workers, persons with multiple sex partners, and men who have sex with men (MSM) have increased prevalence of HBV infection<sup>63</sup>. The HBV vaccine effectively protects against sexually acquired HBV infection, and existing guidelines recommend that persons at increased risk of sexually transmitted infection be vaccinated<sup>16</sup>. Despite this, vaccine coverage remains low among adults in these populations<sup>64, 65</sup>, and health care providers often do not offer HBV vaccine to them<sup>66</sup>. Implementing strategies to improve coverage of HBV vaccination among individuals at increased risk of sexual transmission is a priority. This can be achieved by targeted vaccination, for example, at health facilities providing sexual health services or general-population approaches such as catch-up vaccination campaigns for school-age children to provide protection for those who were not vaccinated as infants. Strategies to address risky

behaviours, such as education efforts to promote condom use and partner reduction remain important interventions to prevent sexual transmission of hepatitis viruses.

Sexual transmission of HCV is less efficient than that of HBV. MSM with HIV infection are at the highest risk of sexual transmission of HCV; incidence of HCV is high in this population and has increased in recent years, particularly in Europe<sup>67</sup>. According to one review, MSM with HIV were at 4.1 time higher risk of acquiring HCV infection (6.08/1000 PY [95% CI 5.18-6.99]) than were MSM without HIV infection<sup>68</sup>. The strategies to reduce sexual transmission of HCV are the same as HBV transmission. Although a unique concern is the high rate of HCV reinfection in this population<sup>69</sup>, early empiric data from populations such as the Netherlands suggest a major impact on new infections once DAA treatment is widely available<sup>70</sup>.

### **Healthcare associated transmission [H3]**

Since HBV and HCV are transmitted through exposure to blood and bodily fluids, they are readily transmitted in health-care settings. Health-care associated HBV and HCV infections occur through blood transfusions, unsafe injections and other invasive medical procedures. There are no reliable estimates for the importance of transfusions as a source of hepatitis infections, but transfusion-associated infections are easily preventable by screening all blood donations in a quality-assured manner. According to WHO data, in 2013, 97% of 137 countries with available information were screening all blood donations using basic quality procedures, which included documented standard operating procedures and participation in an external quality assurance scheme<sup>71</sup>. However, screening of blood units is only one component of a well-functioning blood transfusion service. Other components include recruiting and retaining safe, voluntary, non-remunerated donors and appropriate clinical use of blood to reduce unnecessary blood transfusions. Reliable access to quality-assured test kits also remains a problem<sup>72</sup>. Improved program monitoring systems that collect data on testing practices in blood banks would provide useful information on how to strengthen national blood-safety systems.

According to modelling studies, in 2010, health care injections accounted for approximately 315,000 HCV and 1.7 million HBV infections<sup>73</sup>. Between 2000 and 2010, there was an 83% and 91% reduction in the number of injection-associated HBV and HCV infections, respectively, primarily as a result of increased use of single-use syringes and needles<sup>74</sup>. Despite this progress, unsafe injections remain an important source of hepatitis infection in certain parts countries, most notably the Eastern Mediterranean region where medical injections are overused and delivered in the informal health sector where it is difficult to enforce infection control practices.

National policies for the safe and appropriate use of injection must be based upon a three-prong approach<sup>75</sup> that includes a behaviour change strategy among patients and health care workers to reduce injection overuse and achieve safety; provision of sufficient quantities of injection devices and infection control supplies (include auto-disable syringes, reuse-prevention devices and sharps injury prevention devices); and safe sharps waste management. In 2015, WHO issued

guidelines recommending the exclusive use of re-use prevention devices<sup>76</sup>. Introduction of such devices will be key in countries where unsafe injections continue to fuel the HCV epidemic<sup>77</sup>. Injection safety activities must include interventions to prevent needle-stick injuries and implementation of universal precautions, routine HBV immunisation, provision of personal protective equipment and post-exposure management. A core component of an infection prevention and control (IPC) program is a reliable monitoring system that can assess the comprehensiveness, quality, and impact of IPC interventions. This can be challenging because of the wide range of recommended interventions and because some indicators require special surveys<sup>78</sup>

### **Hepatitis C vaccine**

A vaccine that could effectively prevent HCV infection would be an important tool to help control the HCV pandemic, particularly for groups experiencing high rates of HCV infection and re-infection. Even with high coverage of DAAs, a partially effective vaccine could have an impact in reducing HCV prevalence among PWID<sup>79</sup>. Unfortunately, the prospects for having such a vaccine remains distant. HCV vaccine development is made difficult by the number of distinct genotypes, the high mutation rate of HCV, the lack of an animal model and increasing challenges in undertaking efficacy studies<sup>80</sup>. Several candidate vaccines are in Phase I or II trial and although it will be many years before these vaccines could potentially be ready for use, they should remain a priority for the long-term elimination of infection.

### **Panel 1: Priorities for prevention for national and international policy makers**

- Early-life HBV infection
  - Promote global efforts to increase coverage of universal childhood vaccines (including HBV)
  - Promote introduction of birth-dose vaccination into national vaccine policies (and carry out operational research into how it is best delivered)
  - Advocate for budgeting and procurement of birth dose vaccine by international agencies, including Gavi, and national ministries of health
  - Evaluate novel vaccine technologies that support community based delivery of HBV birth dose vaccine and prenatal antiviral administration in resource limited settings
- Prevention among PWID
  - Promote decriminalisation of drug use and engagement of services with PWID
  - Increase coverage of harm reduction services through provision of OST and needle exchange
  - Expand provision of HCV treatment services among PWID
- Prevention among prisoners
  - Make health intervention in prisons a priority
  - Expand provision of hepatitis testing and treatment services among prisoners
- Prevention of infection in the general population
  - Promote hepatitis B vaccination and risk reduction interventions among persons at increased risk of sexual transmission of hepatitis
  - Increase awareness among health care workers and general population about overuse of medical injections
  - Introduce reuse prevention syringes
  - Strengthen infection prevention and control efforts
  - Strengthen blood-transfusion services to improve quality assured testing of blood donations



## Screening, diagnosis, cascade of care [H2]

### Screening and diagnosis [H3]

Timely testing is a critical public health intervention for disease prevention through early detection and treatment, particularly for chronic infections such as HBV or HCV that can have a long asymptomatic phase. For viral hepatitis, insufficient testing and linkage to care, rather than access to drugs, is an increasing barrier to elimination efforts. In 2017, only 9% of the estimated 257 million people with chronic HBV infection and 20% of the 71 million with chronic HCV infection were estimated to have been diagnosed<sup>1</sup>, illustrating the urgent need for improvement and scale up of testing strategies. There are wide disparities between regions in the reported proportion of infected individuals who are diagnosed (eg, for HBV, the proportion diagnosed is estimated at 83% for South Korea compared to 2% and 3% for India and Pakistan, respectively). However, it needs to be recognised that in many high burden countries, such as India and China, testing is common outside of the public health system where quality of tests is variable and data is not well captured in routine practice.

Achieving the high levels of diagnosis needed to reach elimination targets requires countries to incorporate testing and screening strategies into their national plans, with approaches tailored to the epidemiology, health priorities and health care resources of each region. The costs of testing receive less attention than drug costs, and work for this commission has demonstrated a strong correlation between gross national income (GNI) and proportion of individuals diagnosed with hepatitis C (supplemental figure 3). The main approaches are general population screening and a targeted risk-based screening of key populations. Targeted risk-based testing for HBV and HCV should be universally adopted given its higher yield and intuitive sense; however poor recognition of risk factors or identification of key at-risk populations in certain regions might necessitate the inclusion of general population screening approaches.

Compared to HIV infection or non-communicable diseases, HBV is particularly appealing for mass adult screening in highly endemic settings. A single screening in adulthood should be sufficient to identify infected individuals given that infection is usually acquired early in life and those not chronically infected are likely to have protective immunity due to childhood exposure. Few studies of the feasibility and cost-effectiveness of population-based screening for viral hepatitis have been done in high-burden, low-resource settings, but studies in The Gambia<sup>81,82</sup> suggest that population-based testing improves linkage to care and can be cost-effective. Community sensitisation and patient support groups are critical to the success of introducing viral hepatitis screening programmes either in the general population or at-risk groups.

For HCV, in countries where falling drug costs have allowed rapid scale up and cure of patients engaged in care, the focus has quickly turned to the challenge of identifying undiagnosed individuals. Broader testing approaches can be fruitful in this context. For example, Egypt has begun to screen army recruits, university students, and hospitalised inpatients, in an effort to

identify the still sizable population of undiagnosed individuals. In high-income countries, population screening has focused on specific populations, such as the 1945-65 birth cohort in the USA, and adult men up to age 60 and prenatal women in France<sup>83</sup>. While these approaches have been shown to be cost-effective, implementation has been challenging, and when used in isolation, these approaches may miss a significant proportion of those infected<sup>83</sup>.

Scaling up testing to achieve the diagnosis rates required for elimination may be possible without widespread population testing. Targeted screening approaches need to focus on high-risk groups, including PWID, individuals who are incarcerated and MSM, with universal screening offered in relevant settings such as prisons, supervised injecting centres, homeless or migrant centres, or opioid substitution centres. Modelling suggests that in a number of these high-risk populations, frequent (eg, annual) testing is required to reduce transmission and achieve WHO elimination targets<sup>84</sup>. However, there are relatively little data on the cost-effectiveness of different testing approaches, particularly in LICs<sup>85</sup> where such work needs to be given higher priority.

Facility-based screening of symptomatic individuals, including those with cirrhosis, offers an alternative approach. In Egypt, this strategy led to thousands of people with HCV being identified and treated over a short period of time.<sup>86</sup> However, whilst relatively simple to initiate, the economic considerations of such a strategy have been poorly assessed in LICs and LMICs. For HCV, such an approach is likely to have minimal impact on the on-going transmission of infection in the population, given that a large proportion of newly infected individuals have mild disease<sup>50</sup>. There has been a suggestion that testing strategies could be mandated by the state as a requirement for accessing services (eg, visas, driving licences and marriage licences). In theory, this approach could also be extended to provide evidence of successful treatment. However, adoption of such approaches has not been widespread due to human rights concerns.

The commissioners recognise that a staged, pragmatic, approach to screening may be necessary to achieve the high levels of diagnosis needed to achieve elimination. Countries may prioritise systematic screening in health facilities (eg, pregnant women and those attending liver services) and secure access to drugs and diagnostics initially. Screening can then be scaled up to at-risk groups and finally extended to population-based screening where required.

### **Cascade of care and models of care [H3]**

The cascade of care for the management of HBV and HCV has historically had major gaps, starting with low rates of diagnosis that ultimately lead to low treatment uptake and cure or control of disease. With the development of highly effective and safe therapies, many assumed that the cascade of care would rapidly improve and that a majority of infected individuals would be treated and, ideally, cured. However, many of the gaps in care occur long before treatment is considered (figure 7). As such, interventions to increase diagnosis rates, linkage to care and

retention in care will be required to make significant progress toward the elimination of viral hepatitis.

Scaling up of care services for both HBV and HCV in high burden, low-income settings can be accelerated by learning from the management of other infections. In particular, access to care will be limited if confined to speciality-based models of care (eg, requiring hepatologists, infection specialists or other skilled and expensive healthcare workers). Task sharing, in which a less specialised workforce is trained to deliver care, has not been widely adopted in high-income countries but has been an important part of treatment programs for HIV, TB and malaria in low-income settings, and could be equally beneficial in the context of viral hepatitis.

Models of care for HCV and HBV are different, primarily because of the lack of curative treatment strategies for HBV. As such, HBV care is focused on long-term disease monitoring and viral suppression (similar to HIV care), whereas HCV treatment is relatively short-term, particularly in those without advanced liver disease (similar to tuberculosis care). However, for individuals with HCV, longer-term care might be required to monitor for reinfection and complications of fibrosis. Innovative models of care will be needed to engage and maintain people in care, particularly for populations with less access to or engagement with the healthcare system.

#### **Cascade of care and improving care models for HCV [H4]**

There are many gaps in the cascade of care for individuals with HCV, including initiation of care (lack of diagnosis), retention in care, initiation of treatment after diagnosis, and screening for complications including liver fibrosis and HCC. Initiation of treatment is often hampered by restrictions on eligibility of DAA prescribers, which is often limited to specialist settings, and might particularly impact individuals in rural or remote areas with limited coverage by specialists.<sup>87</sup>

These restrictions also disproportionately affect high-risk individuals, such as PWID, who may be reluctant to attend specialty clinics to access treatment. Some regions in Europe and the USA also require documented abstinence from drugs and alcohol prior to accessing HCV therapy<sup>87,88</sup>. Creating barriers for entry to care is a major challenge to elimination, and these restrictions have not been supported by evidence. Indeed, there is accumulating evidence, for example, that treatment outcomes are equivalent in those with and without ongoing substance use, with high sustained viral response rates (94%) documented in individuals with ongoing active injection drug use<sup>89</sup>.

There is some evidence, albeit limited, that the use of case managers and peer outreach workers to schedule and accompany individuals to appointments, as well as the use of cash incentives, increases rates of attendance to specialist care<sup>90,91</sup>. There is also some evidence that integrating HCV care into drug, alcohol and psychiatric services can increase treatment uptake

<sup>92</sup>. Although it seems intuitive that management of HCV for PWID should be integrated into existing care models, controlled data showing the benefits of this approach, particularly in the interferon-free era, are limited, and data on screening and linkage to HCV care for PWID in low-income and middle-income countries are scant, despite an increasing burden of disease in many countries in this population.

Until recently, the requirement for liver biopsy to assess the extent of liver fibrosis was a major barrier for retention in care. Transient elastography (TE) and other non-invasive measures of liver fibrosis have now largely replaced liver biopsy, and the immediacy of TE results makes it particularly attractive. Use of TE was shown to increase engagement in follow-up care among people with recent injection drug use, particularly for those with high fibrosis scores<sup>93</sup>. In most low-income and middle-income countries, where access to both TE and liver biopsy is very limited, alternative measures such as APRI and FIB-4 may be useful. These biomarkers have excellent negative predictive value for cirrhosis (APRI < 1 93% NPV for cirrhosis) and are universally available; these test might also be useful in selecting patients who do not need follow-up for HCC screening after achieving SVR, as suggested by one US-based study<sup>94</sup>.

Restrictions on the eligibility of prescribers are not only a barrier to continuity of care, but also to implementation of task-sharing approaches. The simplicity, safety and finite duration of DAA-based HCV treatment allows for a shift away from specialised clinics and toward primary care. Relatively straightforward algorithms for diagnosis, pre-treatment work-up and selection of optimal therapy have been developed, allowing primary care providers, including nurses, physician-assistants and other allied health professionals, to oversee HCV care. Australia, for example, now permits a broad range of DAA prescribers—a shift from their initial policy of requiring specialists to approve prescriptions from primary care providers—resulting in improved HCV management in primary care settings<sup>95</sup>. High quality evidence is emerging to support care outside of specialised services<sup>96</sup> and no doubt much more will emerge. Nurse-led models have shown improved rates of patient satisfaction with overall care and higher rates of treatment completion compared to treatment in a hepatology clinic<sup>92,97</sup>. Task-sharing is particularly attractive to provide care in rural and remote communities as well as to serve particular populations, such as PWID. Task-sharing has worked well in LMIC for management of patients with HIV and TB and could be adopted for viral hepatitis care in this setting; however this strategy is being used in very few countries.

Historically, the largest drop-offs in the HCV cascade of care occur between antibody screening and confirmatory HCV RNA testing and then between diagnosis and attendance at first clinic appointments<sup>98,99</sup>. As such, approaches to minimise these gaps are a priority. Particularly for marginalised populations, outreach into the community to test and immediately engage people into care (test and treat) has been advocated. Offering patients treatment in familiar settings from trusted providers enhances treatment uptake and retention<sup>91,100</sup>. This type of approach has been particularly important for reaching populations with significant social challenges, such as those with on-going mental health and substance use issues or those in unstable housing.

Delivery of HCV treatment in OST clinics, community health centres and drug and alcohol support programs has demonstrated positive outcomes that extend beyond HCV cure rates,<sup>100</sup> including increased diagnosis rates. Modelling data suggest that a 'bring-a-friend' strategy of care amongst members of drug-using networks will be more effective at reducing prevalence and preventing reinfection than strategies targeting treatment randomly<sup>101</sup>. Studies formally evaluating this approach are ongoing. Numerous outreach programmes have been designed, particularly in large urban centres, with initial data supporting the use of peer navigators to assist with linkage to and retention in care, provision of care by nurses and primary care physicians rather than specialists, and integration of HCV treatment into multidisciplinary care to address other health and social issues<sup>102,103</sup>. Initial results suggest that such models are effective, with cure rates comparable to or better than those seen in clinical trials and real-world cohorts treated in hepatology and infectious disease clinics<sup>96</sup>. To reach the very 'hard-to-reach', more aggressive outreach programmes are being evaluated such as mobile vans equipped to screen for HCV, offer portable TE testing, and dispense and monitor therapy. Notably, these vans are staffed by trained nurses and peer outreach workers with no involvement of specialist physicians. It will be important to formally evaluate outcomes, acceptability and cost-effectiveness of various outreach programmes to develop best practices that can be broadly implemented.

Outreach programmes must take into account cultural-specific considerations that may impact how HCV is best managed in particular communities, such as PWID, Aboriginal communities, and Native American communities. As such, it is critical to involve community members in the design and implementation of screening and treatment strategies. Ensuring simplification of care is a key priority if rapid increases in diagnosis are to be achieved. The excellent safety profile of approved DAA therapies has reduced the need for on-treatment monitoring. While most treatment guidelines still advocate for on-treatment HCV RNA testing to confirm adherence, as well as periodic (usually monthly) laboratory testing to confirm safety, there is no evidence that such testing and monitoring is necessary to improve treatment outcomes. Studies of simplified monitoring strategies are underway (e.g. SMART-C, NCT03117569) and such approaches will ultimately need to be tailored to local settings and resources.

#### **Cascade of care and improving care models for HBV [H4]**

The natural history of HBV is more complex than for HCV, and differences in the disease course between geographical areas mean disease management algorithms are more complicated than for HCV infection. This complexity is a challenge for providing and evaluating continuity of care. Unlike HCV or HIV, where the presumption is that all infected individuals should be treated, this is not the case for HBV. For example, non-cirrhotic individuals who are HBsAg positive but do not have detectable HBV DNA (ie, who are not actively infected) may not require treatment. Assessing the proportion of HBV-infected individuals in need of treatment and determining what percentage of treatment-eligible individuals with HBV are currently receiving treatment is

challenging. There is also no consensus about which infected individuals require treatment, and the need for treatment may change over time, necessitating multiple follow-up visits<sup>104</sup>. There is a clear need for more studies in different settings to document the optimal continuum of care.

The complexity of many current HBV management guidelines, including those published by WHO, can be an obstacle to adopting simplified models of care, such as task sharing<sup>105</sup>. Developing locally relevant and robust algorithms must be a priority to help scale up HBV treatment in resource-limited settings. A recent study from West Africa<sup>162</sup> described and validated a scoring system (TREAT-B) based on serum HBeAg and ALT levels to identify patients who required therapy. As HBV treatment coverage increases with the availability of generic versions of the antiviral drugs entecavir and tenofovir, application of such simplified models of assessment will be a priority to support practitioners in resource-limited settings to appropriately manage patients with HBV. Similar to the situation with HCV, simplified non-invasive measures of fibrosis (APRI/FIB-4) may be adequate in most settings to identify patients requiring treatment, but their diagnostic performance need to be confirmed in specific populations<sup>106</sup>

In terms of management of individuals with HBV, it is attractive to link HBV care into existing models of HIV management. The mainstay of HBV therapy, tenofovir disoproxil fumarate (TDF) is also used to treat HIV, making many providers familiar with the drug's profile. In addition, many systems to manage HIV have the potential to be specifically tailored to be suitable for resource-limited settings, which can be easily adapted for follow-up of people with HBV.

### **Improving diagnostics [H3]**

Monitoring requirements for HBV are similar to those already in place for HIV, with stable asymptomatic patients generally attending care every 6 months. The introduction of direct-acting antiviral drugs for HCV, particularly those with pan-genotypic activity, that can be used without eligibility criteria based on fibrosis or a measurement of a log drop in viral load to track treatment response, now allows for the dramatic simplification of diagnostics to support HCV treatment programmes. For the first time, this offers countries a feasible path to implement and scale-up programmes. However, large technology and funding gaps exist across both HBV and HCV diagnostics, especially in terms of point-of-care technologies. With HIV, the limiting role of diagnostics and monitoring tests in scaling up therapy was not well recognised early in the strategic response to the disease. Only with the WHO/UNAIDS Treatment 2.0 strategy did diagnostics achieve prominence, resulting in increased efforts to roll out HIV viral load testing and to implement novel methodologies for point-of-care detection. It is important to note that progress in improving access to HIV rapid diagnostics has been underpinned by strict quality approval of tests and large donor support; similar efforts are needed for hepatitis. The first WHO Guidelines for Hepatitis B and Hepatitis C testing highlight the need for such a response<sup>107</sup>. Elimination of viral hepatitis cannot be achieved without comprehensive access to affordable,

feasible and quality diagnostics, in order to define the epidemic, focus programmatic resources, and allow simplified pathways for diagnosis and care.

#### **Rapid-detection tests and point-of-care diagnostics [H4]**

Advances in rapid diagnostic technologies have created new opportunities for enhancing access to testing and care, as well as monitoring treatment response, a number of which were recently reviewed<sup>108</sup>. These alternative sampling methods (use of dried blood spots, oral fluids, self-testing) and combination of rapid diagnostic tests for simultaneous detection of HIV, HBV and HCV infection. More affordable options are also being explored for confirmation of active infection (HBV DNA and HCV RNA), such as point-of-care molecular assays, HCV core antigen and multi-disease polyvalent molecular platforms that make use of existing centralised laboratory-based or decentralised TB and HIV instrumentation. Health system improvements, such as integration of laboratory services for procurement and sample transportation and enhanced data connectivity, can be used to support quality assurance and supply chain management.

Most traditional serological methods for the detection of HBV and HCV are laboratory-based and, although rapid diagnostics tests are available (see supplemental tables 1-3), there is significant variability in their performance as alternatives to laboratory-based immunoassays. Recent systematic reviews of 33 rapid detection tests for HBsAg and of 30 rapid detection tests for HCV-specific antibody reported high pooled sensitivity and specificity values respectively, but with a lower sensitivity of the HBsAg tests in HIV-positive patients (72%).<sup>109,110</sup>

Oral tests for detection of HCV-specific antibodies have slightly lower pooled sensitivity but comparable sensitivity compared to blood-based tests, and may be particularly useful in contexts where venepuncture may be difficult, such as subsets of PWID. Among the existing rapid detection tests for HCV, OraQuick HCV Rapid Antibody Test (OraSure Technologies, Bethlehem, Pennsylvania) is the best-performing and the only US-FDA approved rapid detection test for HCV. However, given the current pricing of the OraQuick test at roughly USD10 per test<sup>111</sup>, it is unlikely to be widely adopted in resource-limited settings, and more affordable tests with comparable performance as the OraQuick and documented accuracy in both in HCV-monoinfected and HIV-HCV co-infected people, are urgently needed.

One antibody-based rapid detection test for HBV and two for HCV have received WHO prequalification. Several CE-mark assays are commercially available but not have not been pre-qualified<sup>170</sup>. The WHO Prequalification Programme assesses the performance of in-vitro diagnostics using samples from diverse geographic regions and their suitability for use in resource-limited settings. More prequalified diagnostics are needed to ensure that test quality remains at the centre of procurement processes. However, in many low-income and middle-income countries procurement tenders are often based solely on price and therefore many companies are not incentivised to seek pre-qualifications. Countries should ensure that have a

competent regulatory body that follows guidance of the International Medical Device Regulators Forum (formerly GHTF)<sup>112</sup>.

The WHO recently launched a model Essential Diagnostics List (EDLs) to satisfy the priority health care needs of the population. This should help strengthen quality assurance, human resource training and supply chain management. The inclusion of viral hepatitis diagnostics in this list will help to galvanise programmes to offer tests and facilitate mechanisms to improve affordability.

Detection of virus is important not only for diagnosing active infection, but also for screening in blood transfusion services, which is a priority area for scale up. The majority of low-income and middle-income countries use serological assays for blood screening, because they are usually simpler and more affordable than molecular testing<sup>113</sup>. However, these tests often suffer from high rates of false-positivity, resulting in unnecessary discarding of blood<sup>114</sup>. As blood safety tests are subject to stricter regulatory requirements compared to diagnostic tests, few options exist for low-income and middle-income countries, and no options are available for point-of-care or emergency settings. Rapid detection tests may be used in these situations, although they are not designed for blood safety testing and may be less sensitive than enzyme-based immunoassays, leading to transfusion of potentially infectious blood<sup>113,114</sup>. The implementation of better quality control and assessment and more feasible product solutions are therefore urgently needed<sup>63</sup>.

Access to tests that directly detect virus remains essential for both HBV and HCV, particularly as test-and-treat strategies are rolled out. For HBV, like HIV, assessment of viral load remains the preferred means of monitoring treatment efficacy, and for HCV, increasing availability of treatment will result in increasing proportions of individuals with detectable HCV-specific antibodies but no detectable virus.

There are few options for HBV DNA testing in resource-limited settings, and there are currently no WHO prequalified HBV DNA tests, although a number of polyvalent laboratory-based platforms have stringent regulatory authority (SRA)-approved assays. Although laboratory-based options exist for HBV DNA testing, sample acquisition and transport can be challenging, costs are high, and availability is limited. There are only two near point-of-care test cartridges in development for HBV DNA detection in serum of plasma (from Cepheid and Mobio diagnostics).

SRA-approved assays for active HCV infection exist, including several laboratory-based and one near patient option (suitable for use in or adjacent to clinical areas) from Cepheid (the CE-marked HCV Viral Load cartridge and instrument, Cepheid AB) that requires serum or plasma.<sup>111,115</sup> The Cepheid AB test is also the only WHO prequalified test available, but only two studies have been conducted to date in resource-limited settings of India<sup>116</sup> and Cambodia<sup>117</sup>. Additionally, Cepheid has recently developed a redesigned cartridge to allow the use of whole blood from finger pricks with high accuracy,<sup>118</sup> which will help overcome challenges associated



with venepuncture in certain patient groups and will simplify sample processing and accelerate results. Another near-point-of-care assay that has been recently CE-marked is the Genedrive HCV ID Kit (Epistem Ltd, UK)<sup>119</sup>; however, this system requires serum or plasma and an interrupted power supply, therefore being most suitable for decentralised testing at the district healthcare level<sup>119</sup>.

Detection of HCV core antigen, may be an alternative strategy to HCV RNA testing<sup>120,121</sup> for detecting active viral replication, and a one-step HCV diagnostic strategy may be a solution for some high prevalence settings. The current guidelines recommend antibody screening followed by confirmation of active infection using a test for the virus itself, whether via HCV core antigen or RNA testing; however if a cheaper, highly sensitive, point-of-care version of the core antigen test could be developed, it could replace the two-step antibody plus viral confirmation approach. A one-step core antigen testing strategy would also help to overcome the low sensitivity of antibody screening tests in immunosuppressed individuals that lead to false negative results. To date, only one highly sensitive core antigen test exists, the Abbott ARCHITECT HCV antigen assay, which requires the use of a large, high-throughput, laboratory-based, multi-analyte analyser and is not widely available in LMICs. At least one point-of-care HCV core antigen test is in development.

Where on-site access to nucleic acid tests is not possible and sample transport systems for whole blood, plasma or serum are limited, dried blood spots provide an alternative approach that is potentially suitable for a wide range of resource-limited settings<sup>29,30</sup>. Dried blood spots are stable for long periods and at high temperatures and can be prepared from capillary whole blood, thus obviating the need for phlebotomy. This sampling approach has been successfully implemented in Scotland<sup>122,123</sup>. Systematic reviews and meta-analyses have demonstrated acceptable performance and accuracy of dried blood spots for the detection of HBsAg, HBV DNA, HCV antibody and HCV RNA<sup>120</sup>.

#### **Financing diagnostics [H4]**

There is limited information available on the extent of HBV and HCV country guidelines, policies and extent of implementation on the ground with regard to HBV and HCV diagnostics. This information is essential to ensure that relative comparisons can be made between products, countries, and public and private sectors, and will also help to identify the cost drivers that are most in need of intervention. A similar approach for DAA pricing has been helpful in advocating for price reductions<sup>124</sup>. For the moment, only manufacturer-provided ex-works or free carrier pricing exists for virological HCV tests, along with the technical, implementation and procurement information<sup>111</sup>. Even when manufacturers offer bundled pricing (ie, volume-based ceiling prices across a range of polyvalent tests rather than vertical pricing alone), most HCV tests are significantly more expensive than their HIV counterparts. Bundled pricing is also generally limited to virological tests (ie, excluding tuberculosis, for example, where common

instrumentation could be valuable), and preferential pricing may be restricted to high burden and/or low-income countries rather than including all low-income and middle-income countries.

A lack of donor commitment to hepatitis and a reliance on domestic funding have not only delayed the scale-up of hepatitis programmes but have also prevented the development of market shaping strategies, such as pooled procurement and increased competition. Manufacturers perceive the developing world market as small and fragmented, and lack a strong business incentive to invest in hepatitis diagnostics that are better adapted to resource-limited settings. Available funding is generally limited to diagnostics and treatment for HCV-HIV co-infection, and HBV is omitted altogether. Additionally, more detailed policy information on out-of-pocket expenses to expose policies and practices that limit access would be useful, as diagnostic tests may not be free under public hepatitis programmes. Countries can take advantage of the infrastructure already put in place for HIV, especially where manufacturers offer bundled pricing across their tests for polyvalent platforms<sup>18</sup>.

## **Panel 2: Priority steps for countries scaling up testing and diagnosis**

### **Governments and implementing partners:**

- Implementation of in-country hepatitis programmes consistent with WHO guidelines (leveraging existing infrastructure from other programmes, such as HIV).
- Scale-up of patient-centric hepatitis programmes to meet the needs of all those affected, including high-risk groups, without necessitating unaffordable, out-of-pocket expenses that prevent linkage or access to treatment.
- Access to a competent regulatory body to assess the quality of diagnostics
- Access to transparent and disaggregated pricing on the full and total costs of diagnostics. Price decreases should be facilitated through increased volumes, competition, bundled pricing and pooled procurement.

### **Ministries of Health:**

- Use of pan-genotypic, DAAs for HCV treatment to enable diagnostic and monitoring simplification for increased programmatic feasibility and access to care.
- Ensure integration of vertical disease programmes and opportunistic cross-disease screening, even in vertical disease programmes.
- Secure access to appropriate diagnostic tests
- Consider renewing serosurveys if previously carried out with older, less specific tests
- Define priority groups at risk of transmission and patients with severe liver disease.
- Develop local capacity, evidence and guidance to inform scale up of services and simplified protocols suitable for task sharing
- Engage healthcare workers, civil society and governments by raising awareness and education and reduce discrimination.
- Ensure collection of data on progress towards targets to monitor impact and inform the need for changes to testing strategies.

### **Diagnostic manufacturers:**

- More comprehensive, manufacturer-led testing of specimen and product stability to better understand the limits of transport and storage conditions, including alternative sample types, such as DBS. This will help to ensure feasibility and that products aren't used off-label or under research use only.
- Validation and filing for regulatory approval, by manufacturers, of DBS for serology and virology.
- Manufacturer-led dual claim for virological tests for diagnosis and monitoring of cure.
- Together with funders, additional investment into development of point-of-care tests adapted to RLS, including for serology, virology, blood safety and staging.

### **International organisations, governments, implementing partners and other stakeholders:**

- The involvement of civil society as a powerful advocacy tool and important voice in designing and ensuring patient-centric approaches and access to care.



## Access to Medicines for viral hepatitis [H2]

There are different challenges to ensuring widespread access to HBV and HCV treatment. Access, to HCV treatment has been a major focus of attention since the marketing of sofosbuvir and will be discussed further below, but it is also a crucial time to look at improving access to HBV treatment. Two key long-term HBV treatments are recommended in international guidelines, tenofovir disoproxil fumarate (TDF) and entecavir, which are sufficient for the management of most patients. As of 2018, both drugs are off-patent in most major markets (excepting Russia and China<sup>125</sup>). The cost of TDF and entecavir is not a barrier to access in most developed economies, but in some markets the potential efficiencies of generic competition are yet to be realised. For example, in 2015, generic entecavir retailed in the US for close to the same price as the branded drug in Europe (US \$6000/year), despite the potential for it be sold for under 50 USD /year<sup>126</sup>.

TDF is now widely available in low-income countries, following its licensing to the Medicines Patent Pool in 2006 and voluntary licensing schemes from Gilead,. The key role of TDF in HIV combination therapies has meant active competition amongst generics manufacturers, with the drug now widely available for under US\$50 a year. Despite great progress in HBV drug pricing, only an estimated 1.7 million of those infected are on treatment<sup>125</sup>. In many low-income countries there remains a key paradox: funding is often only available for those with HIV co-infection, not those with HBV infection alone, and prices may be different for each indication<sup>127</sup>.

Affordability of HCV treatment as a key barrier to elimination has been well documented in both the richest and poorest health economies. Both high prices and large numbers of patients in need of immediate treatment have created a daunting budgetary challenge to health systems. Recent treatment coverage estimates for HCV suggest that few countries are on target to achieve elimination of HCV as a public health problem by 2030<sup>128</sup>. Of the 71 million people globally who are chronically infected, only 1.1 and 1.76 million initiated treatment in 2015 and 2016, respectively; 86% of treated patients are on DAA-based therapies<sup>125,129</sup>. The lack of access to affordable treatments is one of the key reasons why many HCV-infected patients are undiagnosed, as widespread screening and testing needs to be linked to, and justified by, treatment access.

Intellectual property remains a major factor limiting the availability of generic DAAs. Gilead, BMS, Merck, and AbbVie have filed several types of patents on each DAA, with patent protection status varying by country<sup>130</sup>. The voluntary license agreements signed by some originator companies have enabled generic producers to manufacture and sell versions of sofosbuvir, ledipasvir, velpatasvir (Gilead)<sup>131</sup>, and daclatasvir (BMS-MPP)<sup>132</sup> to countries listed in the licensed territory. Consequently, countries included in these agreements should be able to procure generic DAAs from multiple licensees at generally affordable prices due to generic competition. The “access” prices for countries in the Gilead license territory who procure from the originator are approximately 250 USD per bottle of sofosbuvir, and 300 USD per bottle of sofosbuvir/ledipasvir or sofosbuvir/velpatasvir<sup>133</sup>. Where multiple generic sources have registered and made their DAAs available, prices can be much lower. The minimum cost of production of DAAs, a guide to target generic prices, can be estimated based on the cost of the active pharmaceutical ingredients along with the average costs of the manufacturing process for tablet formulations, and the profit margin for the generic supplier. The basic minimum cost of a

12-week course of sofosbuvir and daclatasvir could be as little as approximately 48-81 USD per person, including an estimated profit range of 10-50%<sup>134</sup>.

Some countries have benefitted from a significant reduction in the prices, with resulting improvements in access, while others have not yet been so successful. The most significant price decreases were seen in India, Pakistan, and Egypt, countries included in voluntary licenses that have dynamic generic industries, where 3 months of sofosbuvir plus daclatasvir could be procured in local markets at US\$423, \$240, and \$95 respectively in 2017<sup>129</sup>. In June 2018, the Ukrainian Ministry of Health, supported by United Nations Development Programme, completed a tender whereby they secured a price of US\$20 per bottle of generic sofosbuvir, quality assured by WHOPQ, and US\$6 per bottle of generic daclatasvir.

Outside of the Gilead and BMS-MPP license territories, countries with a strong negotiating capacity and relatively high procurement volumes that allow savings based on economies of scale have achieved DAA price reductions with originator companies and have set up ambitious HCV elimination targets, as is the case for Australia<sup>135</sup>. More generally, in countries where DAA patents have been granted, competition between branded products has started to bring prices down. The 2017 US FDA and EMA approval of Abbvie's pan-genotypic eight-week glecaprevir/pibrentasvir treatment is expected to influence the price of sofosbuvir-containing combinations, most notably in countries with a political commitment to universal access to HCV treatment.

Price reductions have been less marked to date in upper-middle income countries, which are excluded from voluntary licenses. In Brazil, where the Ministry of Health proposes extending treatment to all patients with HCV, negotiation with originator companies has resulted in more modest price reductions (e.g., 43% vs. 93% in Brazil vs. Egypt for sofosbuvir plus daclatasvir between 2015 and 2017)<sup>136</sup>. The modest nature of the price reduction has widespread implications given that Brazil is considered to be a benchmark for the establishment of DAA prices in Latin America. Patent applications on sofosbuvir are still pending examination at the Brazilian patent office; however, most applications have received a technical opinion favouring rejection; recently a generic sofosbuvir was approved by the Brazilian Health Regulatory Agency (ANVISA)<sup>137</sup>.

In Malaysia, another upper-middle-income country, efforts by the Ministry of Health to negotiate a voluntary license and an affordable price for sofosbuvir were unsuccessful. The Cabinet issued a government-use license<sup>138</sup> to gain access to generic sofosbuvir at a 97% price reduction and initiate treatment scale-up<sup>129</sup>. This resulted in the addition of Malaysia and 3 other middle-income countries (Thailand, Belarus, and Ukraine) to Gilead's license territory.

The continuous pressure of over-priced medicines on public health budgets in high-income countries has led some of these countries to consider making use of TRIPS agreement flexibilities. For example, the Italian Medicines Agency has refused to pay more than US\$4,000 per treatment, and threatened to issue a compulsory license to allow local production if they were not able to negotiate a better price with Gilead<sup>139</sup>. Chile has also taken the first step towards issuing a compulsory license to allow importation of less expensive generic drugs<sup>140</sup>.

Although Abbvie's pangenotypic HCV combination, glecaprevir/pibrentasvir was approved in March 2017, by mid-2018 there was no information available on plans to allow for access outside of high-income countries. Ensuring access to glecaprevir/pibrentasvir in low-income and middle-income countries might help to scale up therapy given the shorter 8-week duration in first-line treatment, but perhaps more importantly, might play a role for re-treatment of patients who have failed treatment with other DAA regimens. Currently, the only licensed retreatment option for patients failing sofosbuvir-based treatment is the combination of sofosbuvir/velpatasvir/voxilaprevir. While this triple combination is included in Gilead's voluntary license, generic companies have not yet started to develop this combination, leaving countries who can procure via Gilead's "access program" to pay US\$600 per bottle.

The Drugs for Neglected Diseases initiative, (DNDi) partners with access-oriented pharmaceutical companies, middle-income countries, and other treatment providers and organisations to provide affordable tools to meet public health needs. As part of an ongoing program of development, interim results of a phase II/III clinical trial of sofosbuvir plus the new NS5A inhibitor ravidasvir carried out in Malaysia and Thailand showed good efficacy (97% SVR12)<sup>141</sup>. This combination may offer an affordable alternative for countries, such as Argentina and Brazil, that are excluded from the originators' licenses and where patent applications on sofosbuvir are still pending examination or are under legal challenge<sup>142</sup>. These countries should carefully analyse whether these patent applications deserve to be granted according to their own patent law and the flexibilities of the WTO TRIPS agreement. Countries that have granted patents on DAAs and remain confronted with expensive prices could issue a compulsory license on sofosbuvir, following the lead of Malaysia, in order to access the more affordable sofosbuvir/ravidasvir regimen.

Registration is an important consideration in access to medicines, as both originator and generic companies have regulatory strategies to prioritise countries where they will file their products and, for some countries, registration is a requirement to take part in national tenders. The time to register a product varies by country, taking as long as several years in some. The WHO pre-qualification program evaluates the quality of generic medicines for HCV, HIV, TB, and malaria, and includes a collaborative registration process whereby approved medicines can be registered in less than 90 days in participating countries, reducing the workload involved in drug registration for the national drug regulatory authorities and facilitating access to quality assured generic sources of DAAs. As of June 2018, three generic formulations of sofosbuvir have been prequalified by the WHO (Mylan, Hetero, and Cipla)<sup>143</sup>. Two additional versions of sofosbuvir (Pharco and Strides) and one for daclatasvir (Hetero) are quality assured via the Global Fund Expert Review Panel's risk-benefit analysis process<sup>144</sup>; additional dossiers for generic DAAs have been submitted for WHO-PQ quality assessment. Generic DAAs are not assessed by the U.S. FDA (as is done for generic antiretroviral drugs) as PEPFAR has yet to fund treatment for HCV or finance quality assessment via the US FDA for generics. With the exception of voxilaprevir, glecaprevir, and pibrentasvir, all approved DAAs (including tenofovir and entecavir) are included in the 20<sup>th</sup> WHO Essential Medicines List<sup>145</sup>.

Both low-income countries and middle-income countries remain underserved in terms of access to HBV and HCV medicines. A substantial number of upper-middle-income countries—often referred to as the squeezed middle—that have a high prevalence of HBV and HCV but remain

excluded from voluntary licenses and are faced with expensive prices from originator companies. All originator companies with treatments included in the WHO HCV guidelines should have access policies that not only allow generic manufacture of the drugs for low-income settings, but also ensure equitable access across all middle-income settings. Even in countries included in the voluntary licenses, where intellectual property is not seen as a barrier, the major issue of financing both HCV and HBV programmes lies ahead.

## **Innovative Financing for Viral Hepatitis [H2]**

Achievement of elimination will depend less on technical capabilities and more on leadership, political will and financial considerations. Even when there is strong leadership and political will, availability of finances, the application of funds and health system capabilities will determine the magnitude and the speed of response.

A relatively modest amount of the new funding for the global response to viral hepatitis will be channelled to global development and health agencies to be used for global R&D, surveillance, harmonising norms and standards (eg, WHO vaccination schedules for HBV and treatment guidelines for HCV), global data and information for shared learning, and generation of comparative analyses and evidence<sup>146</sup>. By contrast, domestic sources currently account for most of the funding for developing a country-level response to viral hepatitis. These include both private sources (eg, private insurance and out-of-pocket payments) and public financing (ie, government budget allocated to health). In many of the countries most heavily burdened with infection, a majority of health spending is out-of-pocket (see Table 1 )

At the country level, public financing for health (as for any sector) is determined by the fiscal space available to the government,<sup>147</sup> which depends on the sources of finance available from improved economic growth creating favourable macroeconomic conditions: generation of revenues from new taxation or strengthening of tax administration; borrowing from domestic and international sources; reprioritisation of health within the existing government budget; more effective and efficient allocation of available health resources; and innovative domestic and international financing.<sup>148 149</sup>

With regard to economic growth, all 20 of the countries most affected by viral hepatitis are projected to achieve economic growth in the next 5 years according to the International Monetary Fund (IMF) . However, while improvements in economic circumstances typically help countries to gradually increase domestic financing for health in line with real growth in the GDP, these increases do not tend to be rapid or large. Increases in general taxation, from income tax or value added tax, are not politically popular. Improvements in collection of taxes takes time and when these revenues are realised, they are rarely earmarked for health. Borrowing from domestic or international sources for funding health budgets is unlikely, as the expenditures funded by borrowing should lead to improvements in economic growth and help generate revenues to service the debt. Reprioritisation of government budgets to allocate a greater proportion to health is potentially attractive but requires political leadership and consensus to redirect funds from other sectors. Perhaps more promising is more effective and efficient allocation of health resources, which could potentially release funds to be reinvested. Indeed, WHO estimates that around 20-40% of all health spending is wasted.<sup>150</sup> However, even if feasible, realising these efficiency gains and reallocating them to viral hepatitis would take time.



The most potentially fruitful source of new and additional funding for health, and in particular to catalyse a response to viral hepatitis, is innovative domestic and international financing, which was identified as a promising source of new and additional financing for global health to help meet the MDGs at The International Conference on Financing for Development held in Monterrey, Mexico, in 2002<sup>151,152</sup>. Many countries have successfully used domestic and international innovative financing to mobilise new and additional resources for health. Domestically, for example, countries such as Egypt, the Philippines, and Thailand have used targeted taxes on tobacco to provide earmarked funding for the health sector.<sup>153</sup> Financing from international innovative financing has been more promising than domestic sources to catalyse and accelerate response to epidemics such as HIV, tuberculosis and malaria. As such, a brief analysis of the international innovative financing landscape—in particular innovative financing mechanisms<sup>154</sup> and innovative financing instruments<sup>155</sup>—is instructive to learn lessons and to explore how such mechanisms and instruments could be used for viral hepatitis.

To date three innovative financing mechanisms<sup>154</sup> have reached global scale, namely the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund, established in 2002)<sup>156</sup>, GAVI (established in 2000)<sup>157</sup> and UNITAID (established in 2006)<sup>158</sup>. These innovative financing mechanisms link different elements of the financing value chain to mobilise funding from multiple sources (such as governments, private foundations, and the private sector), pool finances, channel and allocate funds to health programmes through implementing organisations and governments in low-income and middle-income countries. By 2017, the Global Fund had disbursed US\$ 33.8 billion<sup>159</sup> for HIV/AIDS, tuberculosis, malaria and health systems; GAVI had disbursed US\$11.2 billion<sup>160</sup> for vaccines; and UNITAID had invested more than US\$2 billion<sup>161</sup> in medicines, diagnostics and health products for HIV/AIDS, drug resistant tuberculosis, malaria, and HCV.

These financing mechanisms have innovated to improve each step of the finance value chain and enhance linkages between and integration among steps, to create additional value in financing. This has allowed for additional funding to be rapidly channelled to health programmes and has created incentives to improve implementation and performance of these programmes to achieve better health outcomes at a large scale<sup>154</sup>. While the Global Fund and GAVI mobilised and disbursed large amounts of new funding, UNITAID was able to strategically leverage its funds by focusing on improved market dynamics for new medicines, diagnostic and health products to substantially lower prices and to improve access.

In addition to innovative financing mechanisms, several innovative financing instruments have been developed,<sup>155</sup> ten of which have reached scale to mobilise around US\$8.9 billion in 2002–15. The funds generated by innovative instruments were channelled mostly through GAVI and the Global Fund, and used for programmes for new and underused vaccines, HIV/AIDS, malaria, tuberculosis, and maternal and child health.<sup>235</sup> These instruments have different characteristics in relation to the nature of funding, amount of funding raised, the mechanism used to raise funds, the flexibility by which the funds raised could be used, and the timing of application of funds relative to when the funds were mobilised.

### **Global Health Bonds**

The International Finance Facility for Immunisation, IFFIM<sup>162</sup>, uses donor funds or future pledges as security to issue bonds in capital markets, thereby monetizing the pledges. The proceeds

from the bond are then channelled to GAVI, the Vaccine Alliance, and made available to countries to invest in immunizations programmes. The monetization of future pledges through bond issuance enables funding to be made available immediately for immunization programmes, to 'front-load' funding and to accelerate uptake of new and existing vaccines.

### **Debt conversion Instruments**

Instruments such as Debt2Health<sup>163</sup>, the World Bank Investment Partnership for Polio International Development Assistance Buy-Back Program (IDA Buy-Back)<sup>164</sup>, the Japan International Cooperation Agency Overseas Development Assistance Loan Conversion Program for Polio (ODA Loan Conversion), are debt conversion instruments, which convert credits/loans to grants, often with conditions of meeting a health or social target such as achieving immunization coverage.

With Debt2Health, another debt conversion instrument, the debt swap agreement is executed between a creditor and a debtor country (the beneficiary), whereby the creditor forgoes a portion of a debt on the condition that the debtor country invests an agreed counterpart amount on national health programs. The investment is made by contribution to the Global Fund according to a schedule established as a part of a debt swap agreement.

Buy-downs, such as IDA Buy-Back or ODA Loan Conversion, allow a third party to buy-down all or a part of a loan, either by softening the loan terms or by paying down interest and/or principal amount. The buy-down releases the loan recipient (the debtor country) from all or part of future obligations for repayment of principal or interest, thereby allowing those resources to be earmarked for health or social programs. The strength in buy-down arrangements stems from the third party mandating that the borrower invest the repayment resources in health and social programmes, often with terms are tied to performance objectives, such as reaching immunization or treatment coverage targets.

### **Market Commitment Instruments**

The Affordable Medicines Facility for Malaria (AMFm)<sup>165,166</sup> has been used to make available affordable effective malaria treatments (artemisinin based combination treatments – ACTs) through the public and private sector institutions and non-governmental organisations (NGOs) and to displace less effective treatments from the market. The funds for AMFm, which came from donor countries, were pooled at an innovative financing mechanism (in this case the Global Fund), were then used to negotiate with manufacturers of ACTs, which met quality criteria, to achieve a price reduction in return for predictable and increased volumes of medicines supplied by the manufacturers. The price of ACTs are further reduced through a subsidy from the host financing mechanism to the public or private sector buyer, via a co-payment at the top of the global supply chain.

The Advanced Market Commitments Pilot for Pneumococcal Disease<sup>167</sup>, used donor funding or pledges to establish legally binding long-term purchase commitments for new vaccines. The availability of long-term commitments enabled encouraged vaccine manufacturers to invest in new vaccines with pre-negotiated prices subsidized by donors and recipient countries and predictable volumes.

### **Social and Development Impact Bonds**

An alternative and promising funding instrument, which is new to health, is a Social Impact Bond, which is constructed by a government agency that wishes to achieve a desired social or health outcome.<sup>168</sup> An external organization or contractor is then engaged to achieve the outcome. A third-party investor provides upfront working capital as an at-risk investment. With working capital, the external organization then sets up programmes or interventions to achieve this outcome, either through direct service provision or through intermediary service providers. If the desired social outcome is achieved, the government releases payment to the external organization, based on terms specified in an upfront contract. Levels of payment are typically based on the amount of savings that accrue to the government due to the success of the programme. If the outcome is not met, the government disburses no payment. The external organization then repays its investors their principal plus a return on the investment.

Development impact bonds are a variation on the social impact bonds, with the main distinction that the payment to third-party implementers upon successful achievement of pre-specified outcomes comes from an external funder (e.g. a development agency or a charitable foundation), rather than a government<sup>169</sup>. Social and development bonds enable private investors to invest in social problems by taking a risk but with an opportunity to generate a return on investment with successful outcomes that also generate savings for the government or the development agency.

### **Global solidarity taxes and levies**

Financial transaction taxes, especially those that can help reduce excessive speculation in financial markets, is another possible and potentially very large source of new funding for health in general and viral hepatitis in particular. Several countries, such as South Korea, Hong Kong, India, Brazil, Taiwan, South Africa and Switzerland have already introduced financial transaction tax to generate general tax revenues.

A further potential innovative financing instrument, modeled on the successful Airline Solidarity Levy<sup>10</sup>, is a micro tax on data transmission, applied to mobile phone usage. With the airline solidarity levy, participating countries implement a tax (levy) on airline tickets for flights originating from local destinations. Each country determines the amount, nature and collection mechanism of the levy. Resulting proceeds are donated to UNITAID either as a companion to budgetary contributions or as an independent contribution.<sup>10</sup>

Innovative financing holds much promise to provide catalytic funding to augment funding from domestic sources in order to rapidly scale up treatment access to diagnostics and medicines for viral hepatitis. There is enough evidence on the success of innovative financing instruments in mobilizing funds and innovative financing mechanism to channel them to countries to provide a rapid access to novel diagnostics and treatments. There is an opportunity to utilise a combination of innovative financing instruments, by replicating those with a record of success, to mobilise and 'frontload' funding to augment domestic funds in order to rapidly invest in diagnosis and treatment of viral hepatitis. Frontloading of funds to rapidly expand access to treatment will enable, beyond the individual health benefits and cure, realization of beneficial effects of 'treatment as prevention' to interrupt then halt transmission to achieve elimination. Several steps are needed to make this a reality, **however**.

As a first step, with the support of donors, political leaders, civil society and affected countries, consideration should be given to launching a global coalition of stakeholders to create an innovative financing initiative for viral hepatitis. The involvement of civil society is critical in mobilising global and national support and to create a movement to secure a commitment to viral hepatitis elimination. Civil society has the legitimacy to act as independent champions of patients' rights to achieve equity and hold governments to account. Visible leadership from senior politicians is also critical to generate country and global level responses.

The second step should involve the development of an investment case for viral hepatitis, to demonstrate the feasibility of elimination and quantify health and economic benefits of potential investments, to demonstrate the substantial health, social and economic returns to investment. For example, a recent analysis on HCV in Egypt has estimated the economic impact of the HCV epidemic on Egypt to show that as of 2015, HCV epidemic reduced GDP by 0.3% and by \$1 billion each year, and additionally led to a drop in living standards equal to 1.5% of GDP and GDP per capita and \$5 billion each year. The study estimated that the spending on demand-driven treatment would be re-financed by savings in costs of within 6 years, and carried a financial rate of return of 24 percent, even before taking into account the values of any health gains. The study showed that elimination was cost effective, and treatment and screening policies would achieve considerable health gains largely cost-free and reduced mortality results in a gain in living standards equivalent to 0.6 to 0.8 percent of GDP<sup>170</sup>.

The third step is to identify and secure commitment from an innovative financing mechanism to pool, channel, allocate and monitor effects of financing. The evidence suggests that establishing a new financing mechanism is challenging, with only three reaching global scale to date.<sup>3</sup> Further, in addition to inherent risk of failure, establishment of a new funding mechanism in an already crowded global architecture would not be timely nor is it likely to be welcomed by the donor community. UNITAID, which is already a funder of HCV programmes, and has collaborated with GAVI, a funder of HBV vaccine programs worldwide, to introduce new vaccines, appears to be the most promising innovative financing mechanism for viral hepatitis elimination. As an innovative and lean institution, UNITAID has had demonstrable success in shaping market dynamics to achieve substantial reductions in prices of innovative diagnostics and medicines and to expand access. UNITAID would be well positioned to house a new innovative financing facility for viral hepatitis elimination, which could be funded from multiple sources, such as from donors, philanthropic agencies, private sector and innovative financing instruments (such as solidarity levies). In addition, UNITAID has successfully established and hosts the Medicines Patent Pool, which negotiates with pharmaceutical companies that hold patents to obtain licences for the production and distribution of generic versions of patented medicines for hepatitis C in low-income and middle-income countries.

As a fourth step, several innovative financing instruments with successful track records could be replicated to mobilise new and additional funding for the innovative financing facility for viral hepatitis elimination. Four innovative financing instruments could be created or used to this end. First is a global health bond, similar to The International Finance Facility for Immunisation, which can be used to mobilise funds and pledges from donors and countries to create a bond, which then enables frontloading of investments for rapid scale up of treatment. Second, a market commitment instrument that combines the experiences of Advance Market Commitment and The Affordable Medicines Facility for Malaria, could be used to generate agreements between existing and potentially new producers of diagnostics and medicines for

viral hepatitis to commit to future volumes of diagnostics and advance market in return for lower prices. Third, a debt conversion instrument akin to Debt2Health or Buy-Downs for Polio Elimination, could be used by creditor nations to encourage affected debtor countries to invest in viral hepatitis elimination and achieve elimination targets, in return for debt forgiveness, or buy-down of debt or interest payments. Finally, a social or development impact bond, which brings together donors, affected countries, private investors and innovative organizations, could produce impactful results to eliminate viral hepatitis. Depending on the setting and the need, each of these instruments could be utilized. For example, an advance market commitment instrument could be used to 'frontload' screening, diagnosis and treatment to accelerate elimination in countries with high prevalence of HBV and HCV, or a social impact bond could be used to expand a programme in countries where programmes exist but are not well-established or impactful. Debt conversion instruments would be useful in countries where domestic financing is low and where programmes do not exist to stimulate investment and programme development

The presence of highly effective interventions to prevent and treat viral hepatitis and to interrupt and halt transmission, offers the promise of rapid elimination to prevent unnecessary deaths, as well as adverse social and economic impact. There is an urgent need for global collective action to accelerate expansion of worldwide access to prevention and treatment of viral hepatitis treatment. Innovative financing, with its untapped potential, holds the promise of being the catalyst for elimination of viral hepatitis.

### **Panel 3: Key recommendations – access to medicines and financing**

#### **Access to Medicines**

- Access to HBV treatment should remain a priority at a time when there is greater focus on HCV treatment
- Intellectual Property Rights remain a barrier to accessing treatment, particularly in upper-middle income countries. Countries need to consider compulsory licensing if affordable prices cannot be achieved
- All originator companies need to ensure there is an access policy for low/low-middle income settings for drugs approved on WHO Essential Medicines List
- Countries should take advantage of the collaborative registration process available through WHO pre-qualification

#### **Financing**

- Consideration should be given to launching a coalition of stakeholders to create innovative financing for viral hepatitis elimination, particularly focussed on high burden/ low income countries
- Innovative financing tools developed for HIV, TB, malaria and vaccination programmes can be adapted for viral hepatitis e.g. advanced marketing commitments, global health bonds and debt conversion instruments
- Greater emphasis needs to be placed on developing investment cases for viral hepatitis, demonstrating the returns on investment in elimination

- **Table 1 20 countries GDP and health spend per capita, including out-of-pocket expenditure for 20 countries with greatest burden of viral hepatitis**

## 5.1 Viral hepatitis in Asia [H2]

Asia experiences a greater challenge from HBV and HCV infections than any other region of the world,<sup>9</sup> with half of the 20 most heavily burdened countries residing in this region. The region accounts for 74% of deaths from liver cancer globally, mainly attributable to HBV and HCV<sup>171</sup>. Countries in Asia with a high burden of viral hepatitis span the economic spectrum from high income (Japan, South Korea), to upper-middle income (China, Thailand), lower middle income (Bangladesh, Indonesia, India, Pakistan, Myanmar, Philippines, Vietnam) and low-income countries (Nepal, North Korea). There is a negative correlation between GNI and prevalence of both HBV and HCV in the region, with a greater burden in lower income countries<sup>172</sup>

Deaths from viral hepatitis-related cirrhosis and liver cancer increased between 1990 and 2013 in all 13 Asian countries and territories included in an analysis of GBD data by the Coalition to Eradicate Viral Hepatitis in Asia Pacific (CEVHAP)<sup>270</sup>. Deaths from HBV-associated liver cancer increased from 1990 to 2013 in many countries/regions, most dramatically so in Myanmar, Taiwan, Vietnam and Thailand, whereas deaths due to HBV-related cirrhosis declined in Bangladesh, China mainland and Vietnam. Whether the decline in cirrhosis in these countries is real or a consequence of challenges in recording cirrhosis cases is unclear, particularly in view of the concurrent rise in cancer deaths. China dominates the regional burden of viral hepatitis and is particularly challenged by HBV (figure 5.1a), with more than around 80 million people estimated to be chronically infected<sup>12</sup>.

### Success stories and ongoing challenges [H3]

Major success stories in the region relate to implementation of highly successful programs of hepatitis B vaccination, inclusion of hepatitis B treatments in social health insurance programs and the wide spread availability effective generic DAAs for treatment of HBV and HCV infection. However significant challenges remain, including ongoing mother to child transmission of HBV, unsafe injection practises and still-limited access to DAAs despite availability of generics.

Several high-income countries and territories within Asia—including Japan, South Korea and Hong Kong—have demonstrated what can be achieved by scaling up HBV vaccination. All three countries or territories have long-standing vaccination programs, but they have differed in their success to date. Vaccination was introduced in Hong Kong in 1983, with universal implementation in 1988<sup>173</sup>. As a result, a marked decrease in the prevalence of HBV in Hong Kong was reported in pregnant women born after 1984 compared to those born before 1984, with the former up to 68% less likely to be infected by HBV<sup>174</sup>. Vaccination of healthcare workers in Hong Kong was also prioritised in 1983 and is now a key method of maintaining immunity in medical workplaces<sup>175</sup>. Japan similarly prioritises vaccination of healthcare workers, but only recommends vaccination of newborns of HBV-infected mothers<sup>176</sup>. Neonates in Japan are also treated with HBIG. Of all high burden countries, Japan has shown the greatest relative decline in mortality from viral hepatitis since the GBD programme began in 1990, falling from a ranking 8<sup>th</sup> to 16<sup>th</sup> in terms of mortality from hepatitis. Among lower income countries, Bangladesh was one of the first to introduce HBV vaccination in 2003 and as a result, HBV prevalence in Bangladesh had declined from 8% in 1984 to 5.4% in 2007<sup>177</sup>.



China has met and exceeded the WPRO target for HBV vaccination and reduction of HBsAg prevalence among those under 5 years old. In mainland China, universal HBV vaccination in newborns started in 1992 and the vaccine has been free of charge since 2002 and vaccination service for newborns has also been free since 2005<sup>178</sup>. High coverage of infant vaccination in China, resulting in part from the 2002 Expanded Programme on Immunisation, has reduced HBsAg prevalence from 9.8% in 1992 to 7.2% in 2006 among individuals aged 1-59 years, from 10.7% in 1992 to <1 % in 2014 among those aged less than 15 years, and from 9.7% in 1992 to an estimated 0.32% in 2014 in those aged less than 5 years<sup>179</sup>. The enormous effort and great success in prevention and control of HBV by universal vaccination in China have been highly praised by WHO and awarded by WPRO.

Timely birth dose of HBV vaccine is a key to preventing mother-to-child transmission of HBV in China<sup>180</sup>, where the prevalence of HBsAg in women aged 20-49 years in rural China was around 6% (approximately a third of them were also positive for HBeAg) in 2014.<sup>181</sup> To increase the timely provision of birth-dose vaccine in China, institutional delivery of babies is encouraged and is subsidised for women who live in remote areas. Since 2010, the government has also offered free prenatal testing for HBV, HIV, and syphilis, as well as free HBIG for babies born to mothers who are HBsAg-positive. Clinical studies have shown that antiviral therapy with TDF, telbivudine or lamivudine in mid-late pregnancy virtually eliminates mother-to-child transmission of HBV in mothers with high viral load<sup>182</sup>. In addition, the Hepatitis B Shield Project, initiated in 2015, aims to reduce or eliminate mother-to-child transmission of HBV via standardised management including timely administration of birth dose of HBV vaccine and HBIG for newborns of mothers with HBsAg positivity, and antiviral therapy during the third trimester for mothers with high viral load. By March 2017, 106 project hospitals have been recruited into the project, more than 2,000 doctors have been trained and 4,502 pregnant women infected with HBV have been treated under the scheme.

In terms of access to medicine, basic social health insurance programmes are now estimated to cover 95% of the population of mainland China, and antiviral drugs for HBV—including conventional interferons, pegylated interferons, entecavir, lamivudine, adefovir and telbivudine—have been included in the national list of reimbursement for the insured since 2010<sup>178</sup>. Due to the advocacy of all stakeholders, the price of TDF for treating HBV has been dramatically reduced in China mainland through government negotiation, and the price of entecavir has been reduced by generic manufacturing. As a result, the proportion of individuals with access to the recommended entecavir or TDF<sup>183</sup> has steadily increased in the past years (from less than 20% in 2003 to more than 70% in 2016). To promote standardisation of clinical management of chronic HBV, a 2-year continuing medical education program has been offered to more than 9000 local doctors who work at hospitals in 60 small or intermediated size cities which are home to most of the population who are chronically infected with HBV in mainland China (Jia, personal communication).

To reduce HBV transmission associated with blood transfusion or blood product use, the Chinese Ministry of Health mandated screening of blood donors for HBsAg in the early 1980s and for HCV-specific antibodies since 1993. In 1998 monetary compensation for blood donation was outlawed and donated blood has been tested for HBV DNA and HCV RNA since 2015. As a result, infection with HBV or HCV caused by unsafe blood transfusion is now very rare. These policies have also contributed in a dramatic decline in the prevalence of anti-HCV antibodies from 3.2% in 1992 to 0.43% in 2006<sup>178</sup>.

Unsafe medical injection remains a major challenge in the region. In 2015, WHO launched new injection safety guidelines<sup>184</sup>, which included a recommendation that by 2020 all Member States should switch to exclusive use of safety engineered injection devices. Motivated by this recommendation, a study based in a large district in rural Pakistan showed that a community-based intervention designed to improve knowledge and practice of safe medical injections could substantially improve both awareness of the association between unsafe injections and viral hepatitis and clinical practice (eg, an increase in reported use of new needles from 15% to 29% between 2011 and 2012)<sup>185</sup>. In India, high-level political engagement has led to initiatives within the State of Punjab, including establishment of 40 model injection safety centres at district-level health facilities and medical and nursing institutes throughout the State, which also serve as a training resource for health workers on injection safety and reuse-prevention measures.

Although access to treatment with DAAs is still limited within the region (see table 5.1), India and Bangladesh have become global powerhouses for the manufacturing of generic antiviral therapy for HCV. Voluntary licenses for sofosbuvir, daclatasvir, velpatasvir and volixaprevir have the potential to bring DAA costs into an affordable range, and DAA costs have already fallen substantially in many high-burden, low income countries such as Pakistan and India. There is still a risk that heavily burdened upper-middle income countries in the region (eg, China, Malaysia, Thailand) may be unable to benefit from generic competition but also are unable to afford higher prices. The extension of Gilead's voluntary license to Malaysia, which might have been accelerated by the threat of a compulsory license, is a positive move toward addressing the problem of accessibility and affordability. However, in China mainland, only a few DAAs have been recently approved and are available, and their high cost has precluded them from wide coverage in the basic social health insurance program. So far only a few provinces have included the DAAs in their list of medications for reimbursement.

Where available, provision of DAA regimens will likely require task shifting of treatment from specialised facilities to primary care. One example of expanded access to primary care has been in Bangladesh, where the Directorate General of Health Services has developed a module to train government physicians in the management of viral hepatitis. To date more than 3,000 physicians have been trained.

NGOs have an important role to play in advocacy for patients with hepatitis throughout the region. Notable achievements include those of the CFHPC, which is a national level public welfare foundation with strong social influence that has been working for 20 years to improve the general level of health in China by raising funds, acquiring supplies, and organising public welfare activities. Yiyou Liver Center, an NGO founded in 2013 by Chuang Lei, who has hepatitis B, aims to safeguard equal rights for those infected with HBV, and has been instrumental in achieving changes in policy by uniting with other stakeholders and utilising social media. Their advocacy efforts toward reducing drug prices and inclusion of TDF for HBV and DAAs for HCV in medication reimbursement lists have been successful at the national (TDF) level and regional (DAAs) level. NGOs and civil society will need to play a bigger role with respect to elimination efforts in the future.

### **Barriers to elimination [H3]**

Despite the overall high burden of disease, there are great disparities in the Asian governmental responses to the viral hepatitis epidemic. Common challenges to elimination include insufficient public awareness of risk factors and modes of transmission, leading to under diagnosis; high rates of transmission through medical exposures; limited access to care for PWID; prevailing stigma and discrimination against people infected with hepatitis viruses; and financial barriers to treatment and care<sup>285</sup>. The CEVHAP<sup>186</sup> analysis of national policies on chronic viral hepatitis identified areas requiring focus, including a need for strategic policy, availability of routine data, prevention strategies, clinical management and cost or availability of effective treatment. All countries and territories, with the exception of Hong Kong, have or are in the process of developing national strategic plans to eliminate viral hepatitis in line with WHO targets (table xx). However, budget allocation towards implementation of these plans is still to be confirmed in a majority of countries and territories.

Stigma around a diagnosis of viral hepatitis is prevalent in Asia and needs to be overcome. In many countries and cultures, HBV and HCV infections are considered death sentences due to a lack of awareness among the public and, in many cases, health care workers. Many countries or territories in Asia lack legislation to protect against discrimination among people with chronic viral hepatitis, and many countries criminalise drug use (Table 5.1). Only Japan, Hong Kong or Taiwan have some legal framework to protect those diagnosed with hepatitis against discrimination. Japan has a Basic Act on Measures against Hepatitis, which outlines how to protect people with chronic viral hepatitis from discrimination, and Hong Kong and Taiwan have general laws to protect citizens with hepatitis against discrimination<sup>186</sup>. Discrimination against people with chronic HBV infection still exists, particularly among less well-educated individuals<sup>187</sup>. To protect rights to education and employment, since 2010, tests for HBV infection at recruitment of students and employees have been banned in mainland China.

There are fewer success stories among PWID, which comprises a population of at least 2.8m in Asia<sup>188 189</sup>. For example, Malaysia and China are among the few countries in Asia to implement a methadone substitution programme for PWID<sup>190</sup>.

Despite recent initiatives, many countries in Asia have high rates of unsafe medical injections, with 75% of injections considered unsafe based on re-use of needles and syringes<sup>191,192</sup>. Pakistan is estimated to have the highest use of therapeutic injections in the world at 13-14 injections per person per year (compared to the WHO standard of 1-2 injections per person per year<sup>193</sup>). The high rate of medical injections, alongside other risk factors such as blood transfusions, dental treatments and individual risk behaviours like tattooing<sup>191</sup>, has contributed to an estimated 150,000-200,000 new HCV infections each year in Pakistan<sup>191</sup>. These challenges are shared in many other countries in the region<sup>194</sup>.

Access to treatment is also a major issue in Asia, as the cost of drugs and diagnostics are often not covered by government programmes and remain largely out-of-pocket expense for many individuals, particularly in high-burden, low-income countries<sup>195,196</sup>. Moreover, in many countries there is a disparity between urban and rural populations in terms of access to diagnostics and treatment<sup>197</sup>.

### **Key priorities for action**

Despite the diversity of the region in terms of both the burden of viral hepatitis and economics, there are common challenges that could affect many country's efforts to eliminate HBV and HCV by 2030.

Although many countries have shown a clear commitment to seriously engage in elimination efforts, much work is needed to achieve political engagement, particularly in high-burden, low-income countries. So far, no lower-middle income countries in Asia have embarked on treatment programmes similar to that developed in Egypt. Several possible reasons for political inaction include a poor understanding of the disease burden (due in part to lack of high-quality sero-surveillance data), and of the health and economic repercussions of inaction (due to lack of investment case analyses). Although national action plans exist or are being developed in many countries, the budgetary commitments for their implementation often lag behind.

Clearer investment cases are needed for governments to embark on ambitious elimination programmes. Studies on return on public sector investment in HBV prevention and treatment have been done in China and demonstrate that money spent on HBV will save money over the 15-year horizon<sup>198</sup>. Such estimates have been instrumental in helping China develop a policy for viral hepatitis control, and similar analyses need to be done more widely (including for HCV).

Despite strong progress in HBV vaccine coverage, continued efforts are required to maintain and expand coverage. In South Korea, for example, declines in HBV prevalence have been slow despite implementation of universal vaccination in 1992 (only 32.5% of males received all three recommended doses of the vaccine in 2006-8, primarily because of a lack of public awareness about the necessity of vaccination<sup>199</sup>). Provision of the birth dose vaccine has also been problematic for various reasons, including a high proportion (nearly 40%) of home deliveries in some countries, GAVI's insistence on providing only the pentavalent (childhood) vaccine to countries whose immunisation programmes it supports, and lack of HBV testing among pregnant women<sup>200</sup>. Continued investment is also required to ensure safe injection practices, which could prevent an estimated 2.7% of new HBV and 6% of new HCV infections each year<sup>289</sup>.

With regard to access to DAAs, immediate steps should be taken in Malaysia to facilitate extension of voluntary licensing agreements for generic manufacturers and, if possible, to extend this to other high burden upper-middle income countries in the region. In addition, voluntary licenses for shorter duration, pan-genotypic DAA regimens would be beneficial alongside greater efforts to ensure drugs are registered rapidly once available.

In conclusion, Asia has the highest burden of viral hepatitis than any other region of the world and yet most infected individuals remain undiagnosed. The battle for elimination of viral hepatitis by 2030 will be won or lost in this region. Although there are already stories of significant success based on highly effective vaccinations campaigns against hepatitis B in some countries and availability of oral generic medications to treat both hepatitis B and C, challenges remain particularly in areas of nosocomial transmission of these infections on the one hand and wide access to medications on the other. Many governments of the region are still not fully engaged in the elimination effort and this requires substantially enhanced advocacy in the region.

**Panel 4: Key priority areas for action for Asia**

- **Increase political engagement in the elimination effort, particularly lower-middle income countries within the region.**
- **Support development of investment cases for governments that wish to embark on ambitious elimination programmes**
- **Continue efforts to maintain and expand HBV vaccine coverage, with particular emphasis on maximising birth dose vaccination and prevention of mother-to-child transmission.**
- **Control the spread of viral hepatitis through nosocomial means, particularly unsafe injection practices.**
- **Capitalize on the availability of cheap generic medications in the region for treatment of both HBV and HCV and develop strategies to increase access significantly.**

**Figure 6a The 10 countries with the greatest burden from viral hepatitis in Asia (data from Global Burden of Disease, 2016)**

**Figure 6b Progress towards WHO elimination targets in the most heavily burdened countries of Asia (2017)**



## **Viral hepatitis in the Middle East and North Africa [H2]**

An estimated 15.5 million people in the Middle East and North Africa (MENA) are chronically infected with HBV, and 8.5 million with HCV<sup>201,202</sup>. Prevalence of HBV and HCV varies across the 22 countries in the region; HBV prevalence ranges from 16%-19% in Mauritania and Somalia to 0.5% in Bahrain (supplemental Table 4). HCV prevalence in Egypt exceeds 6% (4.4% in those aged less than 60 years), which is higher than in any other country in the world<sup>203,204-209 201,210-213</sup>. Egypt also dominates the region with respect to DALYs attributable to viral hepatitis (figure 7a). Of the estimated 6.6 million HCV-viraemic below the age of 15 globally,<sup>214</sup> 820,000 (12.5%) live in the MENA region (supplemental table 5).<sup>214</sup> More than 90% of people living with HBV and HCV infection live in low-income and middle-income countries in the region, including the North African countries (Algeria, Egypt, Libya, Mauritania, Morocco, Somalia and Sudan), Iraq, Syria, Turkey and Yemen. In these countries, folk practices and substandard health facilities remain the main causes of transmission.

Programs to manage viral hepatitis and action plans for disease control and elimination vary widely between countries in the MENA region; most countries have a low prevalence of HBV and HCV, and viral hepatitis is not a top healthcare priority. Many countries have no quality epidemiological data, an essential step to identify needs and formulate a management plan, and most countries do not have a national plan or infrastructure in place for management. However, several countries in the region have made substantial progression path to elimination of viral hepatitis (Figure7b).

### **Success stories and ongoing challenges [H3]**

The huge burden of HCV in Egypt and HBV in Saudi Arabia, and the efforts undertaken to control the epidemic and eliminate viral hepatitis are exemplary and illustrate how a well-planned and executed national program can make a difference in population health and wellbeing.

The high prevalence of HCV in Egypt has been attributed to mass treatment of schistosomiasis from the 1950s to the 1980s, in which shared, unsterile syringes and needles were used<sup>215,216</sup>. This represents the largest ever iatrogenic spread of blood-borne infection, with millions of people exposed to HCV, generating the high prevalence of HCV infection that remains today<sup>217,218</sup>. In 2006, the government of Egypt set up the National Committee for Control of Viral Hepatitis (NCCVH) to oversee the management of the HCV epidemic<sup>219,220</sup>. The NCCVH set a national strategy and established specialised treatment centres managed by qualified hepatologists. Through the program, treatment is paid for by the state, including full reimbursement for laboratory tests and treatment. In 2014, an action plan was developed aimed at reducing the national prevalence of HCV to <2% by 2025 and <1% by 2030, potentially preventing more than 250,000 deaths between 2015 and 2030 (Supplemental figure 5)<sup>221</sup>. As part of this plan, the NCCVH negotiated the price of DAAs down to 1% of the US price,<sup>222</sup> without



precluding local production of generics. The introduction of locally produced generics in late 2015 reduced the cost of 12 weeks' treatment with sofosbuvir and daclatasvir to about US\$80, resulting in a massive treatment uptake of about 1m patients in 2016 and 2017<sup>219,223</sup>. As a result, Egypt is on the path to meet elimination targets for HCV by 2030 or even earlier. By May 2018, close to 2m patients with chronic hepatitis C had been treated with DAAs; the treatment rate has now exceeded 25% of the infected population.

The program had to overcome several un-anticipated challenges during the first phases of its initiation, which serve as lessons for other countries in the region and elsewhere<sup>86 240</sup>. The initial challenge was management of the number of patients to be treated upon initiation of the program, estimated at 750,000 diagnosed patients, which required a web-based national patient management system. Given that supplies of medication were initially limited, patients had to be prioritised for treatment, starting with patients with advanced fibrosis or cirrhosis, which caused administrative and moral problems, and resulted in a backlog of hundreds of thousands of patients. With increased supply of medication and the introduction of generics, prioritisation ended. An ongoing challenge going forward is the identification of a sufficient number of patients needing treatment to achieve HCV elimination goals. Registration of new patients needing treatment has decreased from 300,000 during the first week of the program to less than 10,000 patients per month in 2017. To address this, the Ministry of Health started a national screening program, initially targeted to individuals aged 16-25 years as a requirement for national identification cards and driver's license, enrolment in university, and military service (for males). However, as HCV prevalence is lowest in this age group (<2%),<sup>203</sup> more than 15m individuals would have to be screened to reach the number needed to be treated each year in the national plan (350,000), and identifying each patient will cost more than USD\$50. As such, screening should be focused on populations with higher prevalence and risk, such as adults over age 40 years, PWID, and people who are incarcerated.

Several factors contributed to the initial success of Egypt's national HCV treatment program, including the availability of large scale epidemiological data, which defined the epidemic and drove sustained societal pressure for state-sponsored treatment. The availability of effective DAAs with excellent safety and tolerability profiles, the decreasing costs of brand medications at the outset of the program, and the approval and use of effective cheap local generic medications facilitated the escalation of the program. Although Egypt remains the country with the highest prevalence of HCV in children (1.08%), a dedicated paediatric program for treatment of HCV sets it apart from other countries in the region. To date, more than one thousand children aged 3 to 18 years have been treated with pegylated interferon through an NGO sponsored program. DAAs approved for children are currently being used in some centres but are yet to be introduced into the national treatment program. The NCCVH action plan also included guidelines for ensuring blood safety, injection safety, and strict infection control,<sup>224</sup> which were applied to a few model dialysis centres and were instrumental in reducing incidence and prevalence of HCV<sup>225</sup>, but they still need to be applied nationally.

Saudi Arabia established a national committee in the 1980s, when the prevalence of HBsAg-positive individuals neared one-quarter of adult males, more than 10% of females<sup>246</sup>, and 7% of children<sup>226</sup>. As part of the national plan, a vaccine program was launched in 1989<sup>227</sup>, with a catch-up program to vaccinate all children at school entry, and vaccination of all healthcare workers and haemodialysis patients. As of October 2007, all people age 24 years or younger (~60% of the population<sup>28</sup>) had been vaccinated<sup>228</sup>, and vaccination coverage is now close to 100%. The vaccination programs were coupled with strict national blood safety and healthcare infection control policies, including mandatory testing for HBV, HCV, and HIV as part of a compulsory premarital screening program, as well as recommended screening for HBsAg among pregnant women<sup>229</sup>, resulting in almost complete blood safety. As a result, the prevalence of HBV in Saudi Arabia has dropped substantially over the last two decades, with the virtual elimination of HBsAg among vaccinated children aged 1-12 years<sup>230,231</sup>. Saudi Arabia has already met and exceeded most of the WHO targets for elimination of hepatitis B for 2020 and 2030. Pivotal to this success were the establishment of a highly empowered steering committee that included all concerned parties: researchers, clinicians, and ministry of health officials; epidemiology studies, and public and governmental acknowledgement of the problem.

### **Limitations and Barriers to Elimination**

Most countries in the MENA region are low-income or middle-income countries that cannot afford to treat HCV-infected patients with DAAs or HBV patients with second generation nucleos(t)ide analogues if cheap generics are not available. This problem is magnified in countries with a relatively large disease burden (Mauritania, Somalia, Sudan, Syria and Yemen). Most other countries either can afford originator drugs or have access programs or affordable generics. The cost of HCV diagnostic tests is also increasing (the cost of diagnostic tests in Egypt's national program now exceeds the cost of treatment), and there are no generic or locally produced diagnostic tests. Furthermore, multiple baseline and follow-up tests for HCV (as required in Egypt's national plan) adds considerably to costs. Simplifying monitoring and follow-up strategies, replacing RNA testing with HCV-cAg testing, and developing local diagnostic tests, could result in major cost savings.

In countries with national plans in place, identification of a sufficient number of HCV-infected patients needing treatment is an ongoing challenge. Pro-active intervention to prevent transmission and new infection are also be required. Most ongoing transmission of HCV is in healthcare settings, and strict infection control standards must be enforced throughout government and private healthcare settings. The growing size of the youth population in the MENA region (160 million people aged 14 years or less) represents another potential barrier to HCV elimination, and prevention, diagnosis and management of HCV at an early age is essential.

**Panel 5: Key priorities for action in the MENA region**

- Conduct epidemiology studies to identify the burden of viral hepatitis in countries lacking data.
- Establish national plans for HBV and HCV elimination where needed.
- Ensure HBV birth dose vaccine implementation in all countries, and increase coverage in countries without universal coverage. Improve third-dose vaccine coverage in countries with <95% coverage
- Restore vaccine programs that have been disrupted due to conflict.
- Implement maternal screening for HBV in all countries.
- Implement vaccination programs for refugees and migrant children.
- Implement and monitor strict infection control policies.
- Improve access to affordable antiviral drugs, including provision of generics.
- Improve identification of individuals with HCV in Egypt needing treatment through targeted screening.

**Figure 7a The 10 countries with the greatest burden from viral hepatitis in MENA region (data from Global Burden of Disease, 2016)**

**Figure 7b Progress towards WHO elimination targets in the most heavily burdened countries of MENA region (2017)**

### 5.3 Elimination in the Americas

The Americas account for just under 10% of both deaths and DALYs attributed to viral hepatitis globally. In contrast to Asia, HCV is the greatest challenge to public health in the region, accounting for 70-80% of hepatitis related deaths (figure 10a). The USA, Brazil and Mexico account for approximately half of the regional disease burden (figure 10a). An estimated 2.7-3.5 million people live with chronic HCV in the USA alone<sup>232</sup>. In 2007, the number of HCV-related deaths exceeded those of HIV/AIDS-related for the first time, with most new HCV infections linked to injection drug use. In Brazil, 1.5-2 million people are infected with HCV<sup>201,233 234</sup>, which remains the leading cause of cirrhosis and hepatocellular carcinoma in the country<sup>235</sup>. The USA and Brazil, which have similar burdens of disease but very different economic resources (per capita income of USA is approximately 6 times higher), have both made important steps towards elimination that serve as an example for other countries in the region.

#### Successes and ongoing challenges

All countries in the region have included HBV vaccination in their official immunisation schedules, and many countries have adopted nationwide birth-dose HBV vaccination<sup>236</sup>, representing over 90% of births within the region, although this is not yet widely implemented in Canada. The USA and Brazil have achieved high coverage of HBV vaccination; coverage in Mexico appears to have fallen slightly in recent years (82% in 2015), but the coverage of birth-dose vaccination is consistently high (98% in 2015, compared to 72% in USA). A number of countries including Argentina, Brazil, Peru and the USA, have extended vaccination to older groups and have implemented catch up vaccination campaigns<sup>236</sup>.

The impact of HBV vaccination has been seen throughout the region. There has been a marked drop in the incidence of acute HBV in the general US population, now estimated at 0.9/100,000 persons, and among underserved communities. For example, HBV was endemic in the 1970s among the Alaska Native People (HBsAg prevalence of 3-8%)<sup>237</sup>, but a comprehensive screening and vaccination programme in the 1980s reduced transmission from over 200 symptomatic cases/100,000 to nil. Annual incidence in this population is now <1/100,000, and no child under 20 is known to have chronic HBV<sup>238</sup>. Substantial declines in childhood HBsAg prevalence have also been documented in Peru<sup>239</sup>, Colombia<sup>240</sup>, and Canada<sup>241</sup>. Vaccination efforts in Brazil have resulted in a change in the country's HBV endemicity status from intermediate to low<sup>242</sup>. However, there remain marked regional differences<sup>4,6</sup> with particularly high HBsAg prevalences (up to 6.2%) in areas of the Amazon<sup>243</sup>. In the USA, 84%-88% of pregnant women are tested for HBsAg. Despite this, an estimated 800-1000 infants are infected at birth<sup>244</sup>. As many of these infections constitute a failure to vaccinate infants born to mothers with high viral load, US guidelines now suggest maternal antiviral treatment for those with HBV levels above 200,000 IU/ml<sup>245</sup>.

Brazil has shown strong political leadership in tackling hepatitis C. Brazil integrated the Viral Hepatitis National Program with the National STD/AIDS Department in 2009, has sought to include viral hepatitis in the public health program (Sistema Unico de Saude), and periodically publishes

guidelines for viral hepatitis management in the country<sup>246-248</sup>. In 2015, DAA therapy was made available, although as of early 2018, DAA therapy was limited to those with significant fibrosis or high risk of complications<sup>248</sup>. In 2011, the government implemented rapid HCV testing, with around 3 million tests done annually in the last few years<sup>249</sup>, as compared to estimates of 20,000 HCV infected patients diagnosed annually and as few as 10,000 treated each year **in 2013**<sup>234 250</sup>. Falling drug prices are expected to make treatment more widely available, with over 60,000 patients already receiving DAA treatment between 2015-7.

In the USA, one-time HCV testing is recommended for people born between 1945 and 1965, as an estimated 75% of all HCV infected people in the USA were born during those years. Such birth cohort testing is cost effective and identifies relatively high proportions of HCV-infected individuals; however, implementation of this strategy has been limited and requires increased professional education and technologies to integrate testing into routine health care<sup>251,25238</sup>. Advocacy for this approach is emerging elsewhere in the region, including Canada and Brazil<sup>253</sup>. Monitoring the success of this testing programme and promoting similar programmes is vital for progress.

### **Barriers to Elimination**

Injection drug use is a major barrier to elimination efforts in the USA. New HCV infections in the USA doubled from 2010 to 2015, most dramatically among young adults with a history of injection drug and opioid agonist (eg, oxycodone) use. Injection drug use is also responsible for a 21% increase in HBV incidence in the USA in 2015. Reductions of HCV incidence have been documented among PWID<sup>254</sup>, and this population is an ongoing focus of prevention efforts. The US prison population is another major barrier to elimination efforts. Over one million persons are incarcerated in the USA at any given time with limited access to healthcare, including hepatitis testing and treatment.<sup>255</sup> Testing and treatment for HCV in corrections facilities represents an enormous opportunity to achieve elimination goals<sup>256,257</sup>.

The USA, Brazil and Canada share the challenge of providing equitable access to health across extensive, varied geographical regions, with rural populations often living long distances from health care services. In the USA, this creates a particular problem in tackling the rural opioid epidemic, with an estimated 80% of all HCV-infected people aged less than 30 years living more than 10 miles from a syringe service program<sup>258</sup>. This situation underscores the importance of combating the rural opioid epidemic using diverse strategies, including integration of HCV testing and treatment services into syringe services programs, and designating pharmacies as sources of safe injection equipment.

In Brazil, major geographical, social and economical disparities exist among the different regions of the country, creating inequities in access to care, especially for subpopulations residing in underserved areas of the North, Northeast and Midwest areas such as the Amazon basin. These inequities include limited access to a specialist who can provide DAA therapy (currently available in only a few centres in Brazil), often resulting in long delays between diagnosis and initiation of therapy. The paucity of specialist care is also a challenge for retention in care; a study conducted in Southeast Brazil found that 22.1% of anti-HCV-positive patients in the region were lost to follow-up

(lapse of more than 1-year since the last clinical appointment)<sup>259</sup>. And despite increased HCV testing in Brazil, the proportion of those diagnosed remains low<sup>234,250</sup>.

In the USA, disparities in health insurance coverage constitutes a substantial barrier to care and treatment for viral hepatitis, despite improvements associated with implementation of the US Affordable Care Act. In states that have expanded Medicaid, access to prevention, screening and care services has improved for low-income individuals<sup>260</sup>. Even for individuals who have health insurance, national HCV testing recommendations have not been incorporated into primary care and other settings in which at-risk patients could be offered HCV testing<sup>33</sup>. This gap is reflected by the low (~50-60%) awareness of HCV infection in USA<sup>261</sup>. Furthermore, many primary care clinicians in the USA remain unprepared to provide DAA treatment, a problem that can be rectified through increased education (including for pharmacists and other mid-level providers) and development of simplified care algorithms.

As in other regions, migration from countries with high HBV endemicity poses a challenge to elimination in the USA and Canada, with an estimated 54,000 persons with chronic HBV migrating to the USA in 2004-8<sup>262</sup>, roughly half of whom were born in Asia. As a result, the USA recommends (but does not mandate) HBV testing for those born in countries with a >2% HBsAg prevalence.

Incomplete epidemiological and surveillance data is another major impediment to achieving elimination goals in the USA. At present there are insufficient resources to provide the case surveillance data needed to monitor the number of HBV infected people. As most states that have adopted requirements for reporting HCV test results lack the capacity to investigate acute cases, develop case registries, and collect longitudinal data to monitor the cascade of care. A panel recently commissioned by the US National Academies of Science, Engineering, and Medicine recommended that the Centers for Disease Control (CDC) work with state and local health departments to support monitoring of all HCV cases reported to public health surveillance, and that the CDC conduct serologic surveys of high risk populations<sup>263</sup>, an endeavour that could be facilitated by leveraging existing HIV/HCV and cancer registries<sup>264</sup> and electronic clinical care data<sup>99</sup>. However, additional funding is sorely needed to measure the effect of these initiatives in term of progress toward elimination goals, and to identify the areas on which to focus the limited public health resources

Costs of testing and therapy remain a barrier to access throughout Latin America; in 2017 only 12 of 20 countries reported offering free testing for HCV, and a majority of countries did lacked access to DAAs<sup>265</sup>. The Pan American Health Organisation's strategic fund has incorporated DAAs as of 2017, which allows pooled procurement of essential medicines and strategic health supplies. The fund is able to supply interest free credit lines to countries, Colombia being among those who have used them<sup>265</sup>.

**Figure 8a The 10 countries with the greatest burden from viral hepatitis in the Americas (data from Global Burden of Disease, 2016)**

**Figure 8b Progress towards WHO elimination targets in the most heavily burdened countries of the Americas (2017)**

**Panel 6: Key priorities for action in the Americas region**

- Ensuring adequate resources for surveillance and data collection systems to monitor and evaluate progress towards elimination goals
- Elimination targets in for HBV in the US need to take account of the significant contribution to new infections from migration
- Ensure a greater focus on access to care and treatment for incarcerated populations, particularly in US
- Support the development of decentralised services and prescribing by non-specialist services will be particularly important in reaching underserved populations far from large urban centres
- Ensure countries throughout the region can use existing mechanisms to ensure procurement of affordable medicines (e.g. using PAHO)

## Viral hepatitis in the European Union [H2]

The burden of viral hepatitis in the 28 member states of the European Union (EU) varies significantly from country to country, but is greatest in Italy and Germany (figure 11a). A relatively high prevalence of viral hepatitis in new member states have added to the overall regional disease burden.

In 2016, the prevalence of chronic hepatitis B in the EU was estimated at 0.89% (4.5m individuals), with country level HBsAg prevalence ranging from 0.1% to 5.5%<sup>266</sup>. HBV vaccination in the EU countries started in the 1990s, although Denmark, Finland, Hungary, and Slovenia do not provide universal infant vaccination nor do they report vaccination data. The UK added the HBV vaccine to infant vaccination schedules in 2017. The prevalence of HBsAg among children aged 5 years was 0.11% in 2016<sup>12</sup>; over two-thirds of these cases are in Italy, Poland, UK, Romania, Germany, and Greece. Only 11 countries in the EU (of 23 that provided data) reported three-dose vaccination coverage levels of 95% or higher in 2015 (supplemental figure 6)<sup>125</sup>.

In 2015, the prevalence of HCV in the EU was estimated at 0.64% (95% uncertainty interval 41-74%) corresponding to 3,238,000 (2,106,000-3,795,000) RNA positive infections<sup>267</sup>. The highest burden of the disease in the EU is found in Italy, Spain, Germany, Romania, France and the UK. Nine countries (Italy, Romania, Spain, Germany, France, the UK, Poland, Greece, and Bulgaria) account for more than 80% of the total viraemic HCV infections in the region.

In Europe, as in other regions, HCV is now transmitted primarily among PWID<sup>31</sup> and there is a higher prevalence amongst prisoners, migrants and the homeless compared with the general population<sup>268</sup>. The pooled estimates of the percentage of PWID who are young (age <25 years), have unstable housing or were homeless, a history of police arrest or incarceration, and engage in sex work highlight the patterns and prevalence of drug use and the underlying socio-demographic factors, all of which contribute to higher risk of HCV infection<sup>26</sup>. Historical use of improperly sterilised needles with subsequent transmission might account for the higher burden of disease in Southern Europe particularly Italy, Spain and Romania. Most of the patients infected in Europe are age 45 to 60 years old, suggesting a possible target birth-cohort group for screening programmes.

In the WHO Euro region, an estimated 14% of all HBV infections are diagnosed<sup>125</sup>, but current estimates on the percentage of those who are treated are inconclusive. Over a third of HCV infections in the EU have been diagnosed, but there is considerable variability; more than 70% of infections in Sweden, Malta, Finland and France are diagnosed compared to less than 20% in Bulgaria, Lithuania, Poland, and Slovakia. In a 2013 WHO survey in 25 EU and European Economic Area (EEA) Member States, all countries reported having a national surveillance system for acute HBV and 23 reported having a surveillance system for acute HCV. National surveillance systems for chronic HBV and HCV infection were reported by 18 countries and 17 countries, respectively<sup>269</sup>.

Europe has well characterised cohorts with HCV-HIV co-infection<sup>270</sup>. Data from the EuroSIDA HIV infected observational cohorts show that the prevalence of anti-HCV varies: in Eastern and Southern Europe (where HIV is frequently acquired via injection drug use), 58% and 29% of patients are anti-HCV antibody positive, respectively, and modelling suggests that eliminating HCV from HIV-positive



populations will be possible<sup>271</sup>. In Northern and Western Europe (where sexual transmission among MSM is the major route of HIV transmission), 17% and 20% are anti-HCV antibody positive respectively<sup>272</sup>. In both settings, HIV-positive MSM appear to be accessible and motivated to receive HCV treatment. Thus engagement with well-established HIV services presents a key opportunity for microelimination<sup>70,273</sup>. However, it remains to be seen whether changes in sexual behaviour as a consequence of more widespread access to HIV pre-exposure prophylaxis will alter HCV transmission<sup>274</sup>.

### **Success stories and ongoing challenges [H3]**

The EU is strategically placed to work toward elimination of HBV and HCV, given the existence of relatively strong public health systems and, in some countries such as Spain, Portugal, Iceland, and Scotland, strong political commitment towards elimination. Notable success has been obtained in implementing HBV vaccination, and treatment of individuals diagnosed with HBV. Western European regions have shown small declines in HCV prevalence<sup>128</sup>; in Spain and Portugal, more than five times more people reached SVR than there were new infections in 2016<sup>128</sup>. In Portugal, the efforts of civil society and academic stakeholders have resulted in a consensus on the need for an overall focus on policies for HCV elimination and prevention, financing, access models, a national action plan and a central patient registry. In addition, programs that ensure access to clean injection equipment, and changes in social and political attitudes that eschew punitive measures for drug users have increased treatment rates. Access to treatment remains unequal across the EU, however; approximately 146,000 (4%) of 3.4 million people with chronic HCV in the EU were treated in 2015, with Spain, Italy, Germany, France, and the UK accounting for more than 80% of those treated whereas less than one percent 1% were treated in Bulgaria, Croatia, Malta, and Romania.

Scotland serves as a model EU country with well-developed linked data systems providing comprehensive epidemiological information on HCV to support policy initiatives, with funding for diagnosis and implementation. For example, using the nationwide Scottish registry of HCV treated patients, examined those achieving SVR between 1997 and 2016 and found that the apparently higher incidence of HCC after DAA therapy might be explained in part by differences in clinical characteristics of groups receiving different treatments<sup>275</sup>. The UK clinical and public health systems are providing some of the strongest evidence of the success of DAAs on the clinical burden challenge of HCV<sup>276-278</sup>.

### **Barriers to elimination [H3]**

Immigration represents a particular challenge for elimination efforts in the EU. In 2010, 47.3 million people living in the EU were born outside their resident countries. Limited data indicates that prevalence of HBV and HCV is higher in migrants to the EU and the European Economic Area (EEA) countries (the EU plus Iceland, Liechtenstein and Norway) compared to the population as a whole, reflecting prevalence rates in their countries of birth<sup>279</sup>. The number of new HCV infections in the EU is estimated at 57,900 (43,900-67,300) per year, with another 30,400 (26,600-42,500) new infections diagnosed amongst migrant populations<sup>201</sup>. An estimated 1-2 million migrants to Europe have chronic hepatitis B.<sup>280</sup> Migrants therefore are a key group for case finding and treatment and constitute an important relative contribution to prevalence of viral hepatitis, although the

proportion varies from country to country. For example, there were an estimated 480 new chronic HBV infections within Germany in 2015, with an additional 17,800 new cases through immigration in the same year<sup>279</sup>.

Most newly acquired chronic HBV infections are perinatal<sup>266,281</sup>, and the prevalence of HBV among women of child bearing age is highest among immigrant populations<sup>280</sup>. There is no uniform policy for antiviral prophylaxis for highly viraemic mothers to reduce the risk of mother to infant transmission in the EU, an area that needs to be addressed in guidelines.

Injection drug use remains central to the epidemic in the EU<sup>282</sup>. In 2016, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) estimated the percentage of high-risk opioid users receiving opioid substitution therapy in 23 EU/EEA countries, which ranged from 8% in both Latvia and Slovakia to more than 75% in France and Luxembourg. Only 10 countries had high intervention coverage as defined by the threshold of greater than 50% of the target population, and only six of the 15 EU/EEA countries with available data could be categorised as high-coverage countries, defined as more than 200 syringes per PWID distributed per year<sup>283</sup>. In seven countries, less than 30% of the target population was estimated to be receiving OST<sup>283</sup>. As in other parts of the world, OST and (particularly) NSP are reported to be less available in prisons in EU/EEA countries. Access to community testing, psychiatric or addiction services, harm reduction assistance and social care resources are variable, as are policy responses<sup>284</sup>.

Differences between the autonomous health care systems of the EU prevent harmonised policies and the EU has not sought to align national laws and policies for the management of viral hepatitis. Although Joint Procurement Agreements for pandemic vaccines are in place, supranational procurement or price convergence of tests, devices and antiviral therapies have not materialised because of divergent national policies and budgets.

The Action plan for the health sector response to viral hepatitis in the WHO European Region, endorsed by the WHO European Regional Committee in September 2016, adopts the WHO global viral hepatitis elimination targets regarding HBV and HCV transmission and mortality<sup>285</sup>. Though several countries have developed strategies, not all have and regional targets will be much more achievable when this national policy infrastructure is in place throughout the EU.

**Panel 7: Key priorities for action in the EU**

- A cohesive regional European strategy for coordination of data, context-based screening and drug procurement should be adopted
- Countries should develop costed elimination delivery plans, and ensure that appropriate resources are in place to provide access.
- HCV screening, treatment, and harm reduction programmes among high-risk groups, including PWID, incarcerated individuals, and MSM should be strengthened
- Migrant populations should have access to national health and insurance services, with efforts to remove stigmatising inferences.
- More widespread adoption of decentralized care and implement point-of-care

testing in high-prevalence environments (prisons, addiction centres, and regions with particularly high disease prevalence)

**Figure 9a The 10 countries with the greatest burden from viral hepatitis in the EU (data from Global Burden of Disease, 2016)**

**Figure 9b Progress towards WHO elimination targets in the most heavily burdened countries of the EU (2017)**

## **Viral hepatitis in Sub-Saharan Africa [H2]**

HBV is endemic in Sub-Saharan Africa with approximately 60 million people chronically infected, of which 1.96 million are HIV co-infected<sup>270,286</sup>. WHO estimates the prevalence of HBsAg at 6.1% to 8.8%<sup>287</sup>. The burden of HCV is also significant, with approximately 10 million infected. In West and Central Africa, 5.7% are coinfecting with HCV and HIV<sup>288,289</sup>. HBV and HCV infection in the 10 most heavily burdened SSA countries account for approximately 200 000 deaths annually, equating to just under one-fifth of the global mortality<sup>9</sup>. HBV alone is implicated in more than half of liver cirrhosis and three-quarters of hepatocellular carcinoma cases<sup>290</sup>.

New highly effective treatments, innovative diagnostics and the new global political landscape focused on hepatitis, make elimination of viral hepatitis in SSA feasible. Many countries are developing national viral hepatitis plans, and some countries already have such plans (figure 10b). Nonetheless, WHO targets are formidable in a region comprising 47 countries with a mean per capita GNI of less than \$1657 USD and a total health expenditure of only 5.5% of GDP<sup>291</sup>. Many countries in SSA share healthcare challenges related to large rural populations, poor health infrastructure, shortages of healthcare personnel, and endemic infectious diseases including malaria, tuberculosis and HIV/AIDS.

The establishment of robust national viral hepatitis plans to guide implementation strategies is the first major step towards demonstrating political commitment at a country level. In 2016, only 1.1 million HBV-infected individuals had been diagnosed (0.1% to 4% with the highest rate in the Eastern SSA) and 33,000 were estimated to be treated, which equates to less than 1% of those eligible. Almost no countries have initiated large scale screening programmes for HCV and most infected individuals remain undiagnosed. Apart from Rwanda, access to therapy is limited. As of December 2017, only seven countries in SSA had developed a costed hepatitis plan (Ghana, Nigeria, Ethiopia, Cote d'Ivoire, Senegal, South Africa and Mauritania) whereas 15 other countries (including Cameroon, Tanzania, Democratic Republic of Congo and Tanzania) had drafts in various phases of development. The lack of detailed and reliable HBV and HCV sero-epidemiological data in many parts of sub-Saharan Africa despite existing data suggesting considerable burden. This hampers planning but must not be used as an excuse to retard implementation.

## **Success stories and ongoing challenges [H3]**

Rwanda was one of the first countries in SSA to establish a national viral hepatitis control programme, initiated in 2012 and built on the existing HIV infrastructure. The Rwandan comprehensive community health system offers near universal (>90%) health insurance coverage, and government partnerships have enabled access to subsidised therapy for HCV and HBV. By the end of 2017, over 2000 people had started curative HCV treatment using a simplified DAA regimen approach<sup>292</sup>. In 2017, the Rwandan Biomedical Centre embarked on a campaign of vaccination, screening and confirmation, identifying an estimated 9,000 HCV-infected individuals and 722 HBV-infected individuals that needed to be linked to care and treatment. As of early 2018, free HBV and HCV treatment and assessment of viral load is now offered to all Rwandan citizens, whereas free treatment was previously offered only to certain Rwandans depending on social stratification category. Rwanda illustrates that the incorporation of viral hepatitis and HIV into the package of essential health services can be successful provided governmental commitment to strengthening of health infrastructure and provision of adequate financing for compulsory health insurance.

The testing of blood products for transmissible infection has improved significantly in SSA. 40 WHO Africa countries in SSA, now report testing 100% of all blood donations for all transfusion-transmitted infections<sup>293</sup>, although overall coverage is still lower than other regions.

### Barriers to elimination [H3]

Horizontal transmission in childhood is the predominant route of HBV transmission in SSA, responsible for ~ 90% of chronic HBV infections. The annual number of HBV perinatal infections is estimated to be twice that of HIV perinatal infections, indicating that identifying women at risk of transmitting the infection to their infants is crucial to preventing mother-to-child transmission<sup>294,295</sup>.

By 2017, only nine countries in SSA had implemented the birth dose vaccine, and HBV vaccine coverage is only 77%. Implementation is a challenge in a region where many births occur outside health facilities (40-50% of deliveries in Uganda and Nigeria). Additional barriers to providing the birth-dose vaccine in SSA include cost, because funding from Gavi was not available for the monovalent HBV birth-dose vaccine; vaccine stock-outs; transporting and administering the vaccine in the setting of home-births; concerns about vaccine storage outside the cold chain; and cultural factors such as waiting until after a child's naming day (around 7 days) to bring him/her to a healthcare facility for vaccination.<sup>296</sup>

Strategies ensuring universal coverage and timely administration of HBV birth dose vaccines, such as pregnancy tracking, using pre-filled auto-disposable devices (eg, Uniject™) and use of community healthcare workers to administer the vaccine have been successfully used in Vietnam, Indonesia and China<sup>297-299</sup> and require evaluation in SSA. Integration of the birth dose vaccine into an early postnatal care package that includes home visits within one day of home birth, as recommended by WHO and UNICEF, would have the dual benefit of improving newborn survival and reducing long-term HBV mortality<sup>300</sup>. Introduction of monovalent HBV birth-dose vaccine within 24 hours of delivery, coupled with the identification and treatment of HBV infected mothers, are critical to elimination of HBV, and should be a priority for the region<sup>73 301</sup>.

Injection drug use is a barrier to elimination efforts in SSA, as elsewhere. 8% of PWID globally are estimated to live in SSA<sup>302</sup>. However, few countries have government supported NSP or OSP<sup>303</sup>, and discrimination against and stigma amongst these high-risk individuals is not challenged. Furthermore, vulnerable or marginalised groups, such as MSM and PWID, risk criminal prosecution given that homosexuality is illegal in several SSA countries.

Another major barrier to elimination in SSA is the lack of awareness about viral hepatitis among both patients and healthcare workers. Data from West Africa reported that <1% of participants knew of their hepatitis B status<sup>81</sup>, and healthcare workers often lack adequate knowledge of viral hepatitis, in stark contrast with their HIV knowledge<sup>304</sup>. Screening efforts in this region should focus on a targeted approach, for example by testing for HBV at antenatal visits. For HCV, screening should focus on individuals who have received blood or blood products, PWID, MSM, healthcare workers, recipients of intramuscular antimony injections (due to unsafe injections) and recipients of traditional practices involving parenteral inoculation, such as scarification and adult circumcision.

Due to the poor government healthcare infrastructure and financing, out-of-pocket expenditure in both public and private health facilities constitutes over 60% of total health expenditure in most of Western Africa<sup>305</sup>, as compared to less than 20% in Southern African countries such as South Africa, Namibia, Mozambique and Botswana, where government healthcare financing is greater<sup>306</sup>. Even with falling prices for viral hepatitis therapy, treatment and diagnostics remains unaffordable for many people in the region.

Only 3% of the global healthcare workforce resides in SSA and this shortage hinders the equitable delivery of healthcare, including for viral hepatitis. International migration, attrition, training shortfalls relative to population growth, and poor remuneration and working conditions contribute to these shortages<sup>307</sup>. WHO estimates that 4.3 million healthcare workers are needed

to fill this gap in 57 countries in Africa and Asia<sup>308</sup>. Expedited training of middle-level healthcare medical, nursing and laboratory personnel is required for healthcare in general. With the development of new rapid diagnostics and mobile health technologies, community healthcare workers are increasingly providing services in rural and underserved communities, especially in maternal health and HIV services. Evaluating simplified models of care that can be delivered through community healthcare workers is a high priority in SSA<sup>309,310</sup>.

A public health approach has been successful in managing the HIV/AIDS pandemic, and this should now be adopted for viral hepatitis. HIV treatment programmes are established in many countries and provide universal free HIV care for persons in peri-urban and urban areas. These treatment programmes provide disease specific infrastructure, operate their own supply chain, provide subsidised medication and have established monitoring, evaluation and national surveillance systems specific for HIV with substantive funding from PEPFAR, Global Fund and other global donors. With the decline in donor funding, the establishment of viral hepatitis programmes within the context of universal healthcare is currently being advocated by WHO, is supported by many countries within SSA and is essential to achieve the viral hepatitis elimination targets<sup>311</sup>.

<b>Panel 8: Key priorities for action in SSA</b>
<ul style="list-style-type: none"> <li>• Efforts should continue to ensure full vaccine coverage and ensure universal implementation of HBV birth dose vaccine within 24 hours of delivery</li> <li>• Universal antenatal screening for HBsAg needs to be prioritized</li> <li>• Affordable quality nucleic acid tests (NAT) need to be widely available , for both HBV and HCV</li> <li>• There needs to be sustainable access to treatment for HBV mono-infected individuals, not just those with HBV/HIV co-infection</li> <li>• There is a need for education programmes around HBV and HCV to decrease public stigma around viral hepatitis</li> <li>• Community based activist or support groups need to mobilise to support viral hepatitis programmes</li> <li>• Decriminalise high risk groups e.g. MSM, PWI(U)D</li> </ul>

**Figure 10a The 10 countries with the greatest burden from viral hepatitis in sub-Saharan Africa (data from Global Burden of Disease, 2016)**

**Figure 10b Progress towards WHO elimination targets in the most heavily burdened countries of the SSA (2017)**

## 5.6 Viral hepatitis in Eastern Europe and Central Asia [H2]

The Eastern Europe and Central Asia (EECA) region is one of the most heavily affected by viral hepatitis and HIV. The HCV epidemic is growing, with an estimated 11.3 million HCV seropositive individuals in the region<sup>1</sup> and a particularly high prevalence of viral hepatitis-HIV co-infection among PWID<sup>270</sup>.

As in SSA, there is a lack of reliable epidemiological data on viral hepatitis in a majority of EECA countries due to an absence of national registers and large-scale testing campaigns or studies.<sup>312</sup> HCV prevalence estimates among the general population range from 1.2% (Kazakhstan) to 8-12% (Ukraine). HBV prevalence estimates range from 0.04% (Tajikistan) to 8% (Uzbekistan), although the low reported prevalence in Tajikistan likely reflects low quality surveillance data. HBV vaccination is supported by governments and/or international organisations (eg, GAVI, UNICEF) in a majority of surveyed countries, and average coverage is 89%. However, vaccine coverage ranges widely, with some regions having very low coverage (eg, 28.8% in Ukraine). Available data about annual HBV-related and HCV-related mortality rates are thought to be underestimates due to their widespread under-documentation on death certificates. Very few data are available on viral hepatitis related mortality, but a study in Russia estimated that PWID aged less than 30 years account for 80% of all HBV-related deaths<sup>2</sup>.

An estimated 3.1 million PWID live in the region (1.8 million in Russia alone), and there is limited or no access to prevention services for PWID in this region. Injecting drug use remains the primary driving force for both HIV and HCV epidemics. HCV prevalence among PWID ranges from 20.9% (Uzbekistan) to 70-95% (Belarus), a high proportion of whom are also infected with HIV (as high as 98% in some areas of Russian Federation). HBV prevalence among PWID ranges from 0.1% (Belarus) to 56% (Kyrgyzstan). For HCV, PWID are specified as a key population in national plans and guidelines in all countries. MSM, healthcare workers, and patients undergoing invasive/hospital-level procedures are specified in national plans of 10 countries. The EECA region has low coverage of antiretroviral therapy (ART), estimated at 21%, meaning those living with HIV are particularly vulnerable to accelerated liver disease progression.

### Success stories and ongoing challenges [H3]

Georgia has become a regional and international leader in HCV national elimination efforts, with an implemented strategy resulting from the joint efforts of civil society and NGOs, strong political will of the state authorities, and financial and technical support of international donors (CDC) and industry (Gilead). HCV RNA prevalence in Georgia is estimated at 5.4% (approximately 150,000 individuals), and the majority (57%) of infected individuals acquired infection from injection drug use, although there are also a substantial number of infections amongst MSM (7.1-18.9%) and healthcare workers (5%). Treatment for HCV is freely available within the National HCV Elimination Programme. Civil

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society organisations in Georgia have significantly improved hepatitis awareness amongst stakeholders and the general population, mobilising and involving communities in the policy-making process. Separate national treatment programs are available in Georgia, Azerbaijan and Moldova. Treatment for viral hepatitis is offered as part of state programs in Armenia, Belarus, Kazakhstan, Kyrgyzstan, Russia and Ukraine.

Mongolia provides an example for other high burden countries. According to a population based nationwide study done in 2008, the prevalence of viremic HCV infection was 11% and that of HBsAg was 11.8%, of whom 60% were also positive for hepatitis Delta antibody. According to 2016 national statistics of Mongolia, liver cancer is the most prevalent malignancy, at 44.0% of all cancers in Mongolia. The Mongolian Parliament recently approved implementation of the Hepatitis Prevention, Control and Elimination Program 2016 to 2020, with the mission to eliminate HCV in Mongolia by 2020 and to significantly decrease the incidence of viral hepatitis, liver cirrhosis and HCC. The government allocated 232 billion Mongolian tugrug (96 million USD) for the program through 2020. By end of 2016, the Mongolian Government has included HBV and HCV medicines in the national health insurance, which covers 98% of the population. Therefore, the health insurance will provide 75\$ for branded Harvoni and 65\$ for generic Harvoni. As of 2018, approximately 20,000 people have been treated by the new DAAs. The cure rate for treatment of HCV infection is 98-99%.

In 2015, Alliance for Public Health with support of Global Fund, launched treatment programme in Ukraine specially targeted at PWIDs providing DAA-based HCV treatment free of charge for over 1900 people. Donor-supported programmes are also being implemented in Armenia and Belarus (by the Government of Georgia and Gilead), Uzbekistan (MSF), Kazakhstan (Abbvie), and Kyrgyzstan (Global Fund).

### **Barriers to elimination [H3]**

Among the most vulnerable populations, particularly PWID, access to HCV services remains extremely limited due to stigma, discrimination and criminalisation. Viral hepatitis programmes targeted at PWIDs have been implemented only in Ukraine (by the Alliance for Public Health) and Georgia. Criminal responsibility for personal drug use (without intent to sell) is applied in all surveyed countries, and punitive drug laws and policies lead to levels of incarceration above the global average in Russia, Belarus, Georgia, Azerbaijan, Kazakhstan, and Moldova. PWID reportedly represent about one third of prisoners in the region, although they could make up between 50-80% of the prison population in some countries<sup>313</sup>.

In countries where possession of micro-doses of drugs (eg >0.005g opium extract in Ukraine) classifies as a drug violation, harm reduction programmes face serious barriers, including the detainment and prosecution of outreach workers in possession of used (exchanged) syringes. As a result, drug users often refuse to participate in NSP, which are available in all surveyed countries but to widely varying degrees (eg, >1600 NSP sites in Ukraine, but only 4 sites in Russia). NSP services in prisons and criminal executive institutions are provided only in Armenia, Kyrgyzstan, Moldova, Ukraine and Tajikistan. Access to OST is also limited, with no programme in Uzbekistan and OST prohibited in Russia. Almost 900 patients from non-government-controlled areas of Donetsk and Luhansk oblasts were deprived of their OST since the beginning of the armed conflict between Russia and Ukraine, and the OST programme in Crimea was discontinued. In Georgia, prisoners can



receive OST only for detoxification in some pre-trial detention facilities. HCV treatment for individuals undergoing OST also occurs in prisons in Moldova.

In April 2016, during the United Nations General Assembly Special Session, Ukraine, Moldova and Georgia, signed a statement<sup>314</sup> that harm reduction should be further promoted and implemented. It is important to note that these expressions of international support have not yet been matched by financial or political commitments. Some of the countries face a risk of breakdown in prevention and harm reduction services after decreasing of Global Fund support, as happened in Albania, Macedonia, Romania, Serbia, Montenegro and Russia. Despite some progress in Georgia, Kyrgyzstan, Ukraine, and Moldova, the state authorities in other countries, including Kazakhstan, Belarus, Russia and Azerbaijan, have not implemented prevention and harm reduction, noting lack of funding sources in majority of cases.

Despite some progress in region, recent estimations indicate only 1% of people with HCV have access to treatment<sup>312</sup>. Three countries (Azerbaijan, Georgia, Uzbekistan) can access generic daclatasvir (from Bristol Myers Squibb, BMS) thanks to the BMS agreement with the Medicine Patent Pool (MPP). Most others can potentially procure daclatasvir from the MPP licencees if there is no patent infringement. The bilateral Gilead voluntary licensing agreement for sofosbuvir covers Belarus, Kyrgyzstan, Tajikistan, Ukraine and Uzbekistan.

In 2015-6, legal objections to patents for sofosbuvir were filed in Russia and Ukraine. In January 2017, Ukraine approved an out-of-court settlement between Gilead and the state regarding the circumstances of registration. In Russia, the patent for sofosbuvir was opposed by NGO Humanitarian Action, which resulted in exclusion of pro-drug formula from the patent. Starting from January 2017, the drug manufacturer Nativa Ltd. is conducting generic sofosbuvir clinical trials in Russia. In Belarus, two versions of generic sofosbuvir were registered, and Belorussian and Egyptian drug manufacturers agreed to primary and secondary packaging of Egyptian generic sofosbuvir (Hepasoft) in Belarus.

Whilst access remains limited, patients and carers have sought alternative ways to provide treatment. Procurement of generic DAAs through buyers' clubs<sup>315</sup> is documented in four countries: Belarus, Kazakhstan, Russia, Ukraine. In Belarus, a buyers' club is reportedly the main procurement source for treatment.

**Panel 9: Key priorities for action in EECA**

- Develop reliable national surveillance system both for hepatitis B and C, including key populations
- Development and inclusion of antidiscrimination policy in national strategies with decriminalization of personal drug use without intention to sell
- Ensure state funding to scale up harm reduction services including OST and NSP.
- Integrate HCV services into harm reduction (simple service delivery model, peer support).
- Continue raising awareness among the stakeholders and populations (both general

population at those most-at-risk)

- Advocate for accelerated registration of DAAs and application of different strategies including the use of TRIPS flexibilities for scaling up access to generics
- Strengthen cooperation between CSOs and government and ensure community involvement at all levels of response to the epidemics

**Figure 11a The 10 countries with the greatest burden from viral hepatitis in Eastern Europe and Central Asia (data from Global Burden of Disease, 2016)**

**Figure 11b Progress towards WHO elimination targets in the most heavily burdened countries of EECA (2017)**

## Viral hepatitis in Oceania [H2]

Australia, New Zealand, and Pacific Island Countries and Territories form part of the WHO Western Pacific Region, which has high viral hepatitis prevalence, particularly HBV, which causes a similar burden of mortality as for tuberculosis, HIV, and malaria combined<sup>316</sup>. The region provides an illustration of the contrast between high and low-resource approaches to achieving global elimination targets for HBV and HCV infection.

Australia and New Zealand are urbanised, high-income countries with universal free healthcare, heavily subsidised medications, and surveillance systems for notifiable infectious diseases, including viral hepatitis<sup>376</sup>. The estimated prevalence of HBsAg in 2015 was 1.0% in Australia and 4.1% in New Zealand, differences due in part to the size of the indigenous and migrant populations in the two countries. The prevalence of HCV is relatively low (1.0%)<sup>29,317-319</sup>, with most new infections occurring in PWID as in many other regions<sup>376</sup>. HBV and HCV cause significant morbidity and mortality in Australia and New Zealand<sup>320,321</sup>, accounting for 1.4% and 1% of deaths, respectively, in 2013<sup>321</sup>, and the burden of viral hepatitis-related liver cirrhosis and HCC is rising. HCV accounts for 41% of annual cases of HCC, whereas HBV accounts for 22% of cases<sup>322,323</sup>. HCV is the commonest and HBV the third-commonest indication for liver transplantation in Australia and New Zealand, accounting for 23% and 6% of all adult cases respectively<sup>324</sup>. Indigenous populations (eg, Aboriginal and Torres Strait Islanders in Australia, Māori in New Zealand) experience worse health outcomes and higher prevalences of disease compared with the population as a whole<sup>319</sup>. Indigenous populations have lower HBV vaccination rates, higher rates of injection drug use, and a higher prevalence of cofactors for liver fibrosis and carcinogenesis, including alcohol misuse and the metabolic syndrome<sup>154,325,326</sup>. Australia and New Zealand also have high levels of immigration, resulting in an increased prevalence of HBV and viral hepatitis as a whole<sup>327</sup>.

The Pacific Island Countries and Territories are geographically, culturally, and socioeconomically diverse. Most are low-middle income countries, and an estimated 25% of the population lives in poverty<sup>328</sup>. The prevalence of HBV in the Pacific Island Countries and Territories ranges from 3% to 23%<sup>329,330</sup> (supplemental figure 8), and vertical HBV transmission of HBV persists despite timely birth-dose vaccination, with 3–5% of infants born to HBsAg-positive mothers becoming HBsAg positive after vaccination<sup>331</sup>. This is attributed to high viral loads at time of delivery, lack of access to additional prevention strategies such as HBIg and nucleoside analogue therapy, and incomplete delivery of timely full vaccination schedule in some settings<sup>329</sup>. Data on HCV in this region are scarce (supplemental figure 8), but prevalence estimates are generally low (<0.5%)<sup>329,332-352</sup>. The prevalence of liver cirrhosis and liver cancer in this region is poorly characterised<sup>329,353,354</sup>, but 2016 estimates from the Global Burden of Disease Study show that mortality from viral hepatitis (predominantly HBV) exceeds that from malaria, HIV and TB combined for all of the Pacific Island Countries and Territories except Vanuatu and Solomon Islands<sup>329</sup>. Additionally, obesity and type 2 diabetes are highly prevalent in the region and are important cofactors for non-alcoholic fatty liver disease, cirrhosis progression and liver cancer<sup>355,356</sup>.

## Success stories and ongoing challenges [H3]

Australia and New Zealand have invested in strategies to increase access to testing and treatment for HBV and HCV, spearheaded by strong community advocacy, health research, health service and political leadership, and a commitment to the WHO 2030 elimination targets.

Australia leads the world in some areas of its response to HCV, including having one of the world's highest proportions of diagnosed individuals (~80%) among those infected<sup>318,357</sup>. Australia has also led the way in making HCV treatment universally accessible through an initial 5-year investment of over AUD\$1 billion (approximately USD\$720 million) in a risk-sharing arrangement with pharmaceutical companies. This arrangement enabled provision of DAA treatment for all chronically infected patients<sup>358-360</sup>, and boosted treatment uptake substantially, with over 30,000 people receiving DAAs in 2016<sup>361</sup>. Modelling studies suggests this approach is cost-effective and will be vital for achieving the 2030 targets (supplemental figure 9)<sup>362-364</sup>. Australia's HCV program includes health promotion and education, GP-initiated treatment and nurse-led care, treatment in prisons, NSPs and OST for PWID, and prevention programs for sexual partners of infected individuals<sup>101,365</sup>. The governmental response to HCV in New Zealand is less advanced, but the country has made progress in improving access to treatment, reducing transmission via harm reduction strategies<sup>366-370,473</sup> and screen-and-treat outreach programmes<sup>371</sup>.

Universal infant HBV vaccination and catch-up programmes have been in place in New Zealand and Australia for nearly two decades<sup>324,372,373</sup> (supplemental figure 10), with resulting declines in HBV notifications, as documented in many other regions<sup>319,374</sup>. In New Zealand, universal vaccination has eliminated HBsAg prevalence in Māori children living in the eastern Bay of Plenty as of 1992<sup>375</sup>. New Zealand also has a successful community-based program of national HBV screening and surveillance—one of the largest in the world—and the Hepatitis Foundation of New Zealand has conducted national HBV screening and surveillance since 1998 as part of the Treaty of Waitangi initiative to close the gaps in health outcomes for Māori. The surveillance program has identified around 30,000 HBsAg carriers among adult Māori, Pacific and Asian New Zealanders (Ed Gane, May 2018, personal communication). However, in both Australia and New Zealand, indigenous communities have lower timely immunisation coverage, contributing to higher prevalence of HBV and related sequelae<sup>319,376,377</sup>.

The HBV vaccination program in the Pacific Island Countries and Territories is one of the most effective globally. By 1997, all countries and territories had adopted a regionally coordinated HBV vaccination program<sup>331,378</sup>, with coverage in 2010 exceeding 80% everywhere except the Solomon Islands and Palau. 13 countries achieved the 2017 WHO milestones of less than 1% HBsAg prevalence among 5-year-olds (as well as the interim 2012 milestone of <2% prevalence<sup>379-381</sup>), despite being ineligible for Gavi-supported vaccination programs and without 100% government funding<sup>382</sup>. The few countries with HBsAg prevalence above 2% in 2017, including Papua New Guinea, Solomon Islands, Kiribati, Samoa and Vanuatu, also had the highest HBsAg prevalence before 2012<sup>379,383</sup>. Novel strategies to improve hepatitis B vaccine birth dose delivery include use of vaccines outside of cold chain in Kiribati in geographically remote areas<sup>384</sup>.

### **Barriers to elimination[H3]**

Despite subsidised HBV screening in Australia and New Zealand and specialist management and treatment for infected individuals, there are major barriers with regard to linkage to care. In 2012, 57% of Australians with HBV were diagnosed, 13% were linked into care following diagnosis and only 5% had received antiviral therapy<sup>385</sup>. Barriers to treatment include lack of awareness of the risks of HBV infection among patient populations, general practitioners, and health care workers<sup>386-392</sup>; inadequate guidelines for diagnosis by general practitioners and referral to specialist services; and underdeveloped shared care pathways between specialists, primary care physicians and nurses for patients with HBV<sup>393</sup>.

Major challenges also remain in the Pacific Island Countries and Territories. Although this region has had great successes in HBV vaccination, coverage fell in some countries between 2010 and 2015, perhaps reflecting improved vaccination surveillance data but also loss of momentum, limited stocks and inadequate resources. Furthermore, catch-up vaccination programs for adults are inadequate<sup>331</sup>, and birth-dose vaccination delivery varies significantly across the region<sup>382,394-398</sup>. Many factors contribute to low vaccine uptake, including geographical isolation, limited access to antenatal screening, births outside health care facilities, inadequate vaccine supplies and cold chain systems, lack of Gavi funding for the monovalent vaccine, lack of skilled medical staff, and higher obstetric complication rates, the latter because health workers often withhold birth-dose vaccine when the infant is unwell, despite guidelines<sup>329,399-402</sup>. Neither HBsAg nor antiviral therapy in the third trimester are routinely provided in most Pacific Island Countries and Territories due to prohibitive cost and limited supply<sup>329</sup>. HBsAg testing is provided free of charge in Fiji, Kiribati, Papua New Guinea, the Solomon Islands and Tonga, but only Kiribati has an HBsAg screening and linkage-to-care policy<sup>329</sup>.

Key barriers to HCV screening include cost and the high false-positive rate for detection of anti-HCV antibodies due to cross-reactivity with malaria and dengue antibodies—an important issue for tropical countries with low HCV prevalence<sup>342,346,403,404</sup>.

Lack of treatment access is another major constraint for both HBV and HCV elimination. Across the region, tenofovir is licensed only for HIV infection, not HBV mono-infection, and entecavir is not available. Moreover, tenofovir purchased outside of the Global Fund to Fight Aids, Tuberculosis and Malaria mechanism for HIV is several-times higher in price. Very few countries have state-funded treatment for either HBV or HCV (tenofovir is now licensed for use in Kiribati and this is in progress in Fiji), although pooled procurement options are being considered.

The Pacific Island Countries and Territories remain hampered by insufficient resources to implement interventions, weak health infrastructure and weak disease surveillance programs, and few countries and territories can afford the cost of universal access to HCV and HBV therapy. Improved surveillance and data collection are also urgently needed. Australia and New Zealand are well placed to support universal access to antiviral treatment in the Pacific Islands and Territories by supporting negotiations with pharmaceutical companies, considering pooled procurement options to overcome the price negotiation barrier of small national populations, and funding for regional treatment initiatives. Plans to extend New Zealand's HBV screening and surveillance into Samoa and Tonga in development (Ed Gane, Auckland City Hospital, May 2018, personal communication) is a positive step.

**Figure 12a The 10 countries with the greatest burden from viral hepatitis in Eastern Europe and Central Asia (data from Global Burden of Disease, 2016)**

**Figure 12b Progress towards WHO elimination targets in the most heavily burdened countries of EECA (2017)**

**Panel 10: Key priorities for action in Australasia and the Pacific Islands & Territories**

- Healthcare worker and community education to increase awareness and demand for testing
- National government and advocacy group-led public health campaigns to reduce stigma associated with viral hepatitis
- Investment in improved HBV vaccine birth dose delivery
- Improved surveillance and data collection systems to outline, monitor and evaluate progress towards elimination goals
- Investment in health workforce and health system infrastructure
- Government subsidised, quality-controlled diagnostic testing for HBV and HCV
- Universal access to HBV and HCV treatment through initiatives such as pooled procurement and use of generics

## **Sustaining Progress towards Hepatitis Elimination [H2]**

There is no doubt that the once-in-a-generation transformation of HCV treatment has energised the movement towards elimination of not just HCV, but also HBV – with scalable treatment options now available for both these major infections. The last 3 years have seen substantial progress towards elimination, including the universal adoption by countries of the WHO Global Health Sector Strategy in 2016 and adoption of more detailed regional action plans; the specific inclusion of viral hepatitis in the Sustainable Development Goals; the emergence of next-generation pan-genotypic DAA treatment options for HCV treatment; the singular success in the Western Pacific Region of reducing MTCT; the highly publicised HCV elimination plans in Georgia and Egypt; and the launch of NOhep, the global hepatitis elimination movement. These achievements deserve to be celebrated, but the challenge now is sustaining this momentum, in order that the ambitious WHO elimination goals can be achieved.

In this commission we have emphasized the different pace of progress in different regions of the world. This presents an important opportunity to share learning, from both successes and mistakes and identify those approaches which will best suit individual countries. Of the 20 highest burden countries (figure 1xx), some (e.g. India, Nigeria, Russia and Bangladesh) have yet to make significant progress towards elimination, particularly for hepatitis C. There are still countries, especially in the Eastern Mediterranean and African regions that are struggling to implement the HBV birth dose vaccine, but most have now committed to action. Yet others, like Egypt and Australia are moving faster.

International organisations have a key role in supporting national progress and they need to ensure that viral hepatitis is part of their remit, on a par with other major infectious diseases like TB and HIV. Some organisations have been leaders in this regard, notably the WHO, UNITAID and CHAI, but more can be done. There are several areas these and other organisations can prioritise to support hepatitis elimination efforts (see Table of Priority areas). Some are specific to hepatitis, for example the need to support the scale up of birth dose vaccination which should fall within the Gavi remit for support (see section 2). Several others can leverage existing mechanisms supporting other disease responses, notably HIV, to improve access to care and treatment.

Ensuring good quality data on the burden of disease is crucial to inform global policy. This commission has emphasized data from the Global Burden of Disease programme which combines data on mortality with years of healthy lives lost estimate the burden of viral hepatitis (DALYs). This provides additional information to most estimates (including WHO) which focus on the numbers of those affected and annual deaths. The distinction is important as it places hepatitis within the context of other disease when prioritizing finite health resources. It has to be hoped that the recent announcement of a partnership between IHME (who produce the Global Burden Estimates) and WHO will allow both to be presented together more regularly.

There has been real progress in to improving access to generic medications. Whilst drug access remains a global priority, particularly in relation to access to pan-genotypic regimens (notably glecaprevir/pibrentasvir, see section 4), this commission also emphasises the importance of diagnostics. Greater innovation is required to develop new diagnostics that are suitable for high

burden/low resource countries, to ensure high quality care. The recent establishment of a WHO Essential Diagnostic List is a welcome recognition of this importance. This now needs to be matched by greater focus on pre-qualification to ensure provision of high quality diagnostics and providing clinical evidence for simplified management algorithms where diagnostics are not available.

Despite the burden of disease and existence of cost-effective interventions, there is currently no sign that a new global mechanism for funding viral hepatitis will be implemented to support the expansion of testing and treatment, nor is the Global Fund likely to expand its remit in the short term. This places an onus on countries to develop new fiscal space to accelerate elimination, which may require innovative means of financing. Financing the scale up of testing is the key challenge to elimination, and sustaining progress will require not only financing but also strong political will and unrelenting advocacy.

Supporting countries to finance their hepatitis programs as part of universal healthcare coverage is vital, and potential approaches have been outlined within the commission (section 4). The costs of drugs and diagnostics remain a concern, but falling drug costs for both HBV and HCV, mean that investment in hepatitis has the potential to be not only cost-effective, but cost-saving. As such, greater emphasis will need to be placed on returns on investment in hepatitis programmes.<sup>198</sup> Benefits of national hepatitis plans go beyond elimination of viral hepatitis, as many of the required prevention measures will help to strengthen the health system as a whole. Infection control, blood safety, safe and rational injecting practices, and harm reduction are key examples. These added benefits need to continue to be defined and articulated for national programs<sup>198</sup>.

Whereas most countries have had active HBV vaccination programmes for many years, broadening these efforts to include HCV requires a significant change in thinking for some governments, given the broader social issues involved and the absence of an effective HCV vaccine. Governments serious about developing actionable national plans will need to ensure wide engagement with stakeholders to include individuals and organisations representing at-risk groups (eg PWID, prisoners and individuals with HIV). Nowhere is this more challenging, and more important, than in parts of the world where risk behaviours remain criminalised and the health and criminal justice systems are poorly integrated. Sustaining progress will require political will and continued advocacy.

Political will is complex and can be driven by a variety of factors, often in combination. It can be driven by personal factors, or it can be motivated by the sheer scale of a public health problem (as in Mongolia, where the death toll from viral hepatitis is so high that it automatically becomes a national priority). Political will can also be generated by advocacy or by patiently engaging policy-makers in a way that allows them to feel they can make a difference. To support this, more initiatives are needed to foster the development of regional champions within civil society, professional bodies and policy circles. In writing this Commission we have sought wherever possible to draw on expertise within high burden countries, but there is still a need for a wider range of voices advocating change. This requires support with similar investment in advocacy for hepatitis to that seen for HIV.

It is likely that a select number of smaller countries, e.g. Iceland and Georgia will be able to achieve the WHO elimination goals well ahead of schedule, and possibly even eradicate infection. For larger,



more heavily-burdened countries, aiming to eliminate HBV or HCV infection in key sub-populations (microelimination) offers achievable intermediate steps towards elimination. Examples of successful microelimination efforts already exist such as the efforts achieving elimination of HBV in those under 20 in Alaska discussed in section 5.3. This will become particularly important as countries make progress towards nationwide elimination, and provide success stories to maintain political will if progress itself reduces the immediate imperative for action as mortality and prevalence rates fall.

Unless significant progress is made in the highest burden countries with some of the greatest challenges, elimination targets will not be achieved. Governments should expect to be held accountable for their progress toward national hepatitis elimination strategies, and it is reasonable for those providing funds to ask for evidence of the impact of that funding. Data on progress to achieve elimination targets will be regularly reported by WHO and others, but more attention needs to be paid to national performance relative to other countries. The structure of the WHO, reporting as it does to its member states, makes it harder for WHO alone to identify those countries lagging behind and other measures of progress.

The development of the first health-related index measuring progress towards the sustainability development goals (SDG) <sup>405</sup> is a helpful example, but has its limitations. The SDGs monitor the prevalence of HBsAg in those under 5 as a good indication of progress in vaccination and preventing mother-to-child transmission, but this doesn't account for those with chronic infection in need of treatment. The absence of any single measure of progress for HCV within the SDGs is more concerning. A Hepatitis Elimination Index needs to be developed to assess progress towards national elimination targets. Some early work on this has begun within the Polaris Observatory. However, such initiatives are costly and need to be funded as a priority to ensure momentum is maintained towards elimination.

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