



Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission

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Viral hepatitis is a major public health threat and a leading cause of death worldwide. Annual mortality from viral hepatitis is similar to that of other major infectious diseases such as HIV and tuberculosis. Highly effective prevention measures and treatments have made the global elimination of viral hepatitis a realistic goal, endorsed by all WHO member states. Ambitious targets call for a global reduction in hepatitis-related mortality of 65% and a 90% reduction in new infections by 2030. This Commission draws together a wide range of expertise to appraise the current global situation and to identify priorities globally, regionally, and nationally needed to accelerate progress. We identify 20 heavily burdened countries that account for over 75% of the global burden of viral hepatitis. Key recommendations include a greater focus on national progress towards elimination with support given, if necessary, through innovative financing measures to ensure elimination programmes are fully funded by 2020. In addition to further measures to improve access to vaccination and treatment, greater attention needs to be paid to access to affordable, high-quality diagnostics if testing is to reach the levels needed to achieve elimination goals. Simplified, decentralised models of care removing requirements for specialised prescribing will be required to reach those in need, together with sustained efforts to tackle stigma and discrimination. We identify key examples of the progress that has already been made in many countries throughout the world, demonstrating that sustained and coordinated efforts can be successful in achieving the WHO elimination goals.

Executive summary

Viral hepatitis is a major public health threat and a leading cause of death worldwide. Every year viral hepatitis kills an estimated 1.34 million people, comparable to mortality from other major infectious diseases including HIV/AIDS, tuberculosis, or malaria. 96% of deaths are attributable to hepatitis B virus (HBV) and hepatitis C virus (HCV), which are the focus of this Commission. The 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 established, aiming for a global reduction in hepatitis-related mortality of 65% and a 90% reduction in new infections by 2030. 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 subnational levels, including the intensification of both prevention and treatment efforts. Some countries are advancing faster than others, typically those that have a national hepatitis strategy in place and strong political leadership.

Analysis for this Commission finds that 20 countries account for more than 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.

The Asian region is home to 11 of the 20 most heavily burdened countries and accounts for approximately 70% of viral hepatitis-related deaths globally; this 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 sensitive to and appropriate for the specific context. In this Commission we have sought expertise from all affected regions of the world, and we present examples of success and guidance on how to overcome barriers. Sharing these experiences will help all countries 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. Because of the success of HBV vaccination in preventing infection in later life, 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. The increasing proportion of new infections through mother-to-child transmission makes access to birth dose vaccine a key priority.

Elimination of viral hepatitis will require a shifting emphasis from a focus on individual patients to an emphasis on a coordinated public health approach to interruption of transmission and infection through prevention and treatment. In the short term, this will require simplified, standardised packages of interventions that can be delivered at scale. HBV and HCV share common

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See [Comment](#) pages 88, 90, 91, and 93

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routes of transmission, and tackling both together can produce improved 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 minimised, with greater emphasis placed on task-sharing approaches in which less specialised staff deliver treatment and care. A policy shift towards treating all individuals with HCV, irrespective of disease stage, and using pangenotypic regimens would greatly simplify care delivery and has the potential to decrease morbidity, mortality, and transmission. Where possible, services for managing viral hepatitis should be integrated with existing, related services, and many of the interventions required to prevent hepatitis infection should form part of broader efforts to strengthen health systems as a whole and to improve safety (eg, screening of transfusion, provision of clean needles, infection control in health-care facilities).

Perhaps the greatest challenge in achieving elimination targets is scaling up testing to all those at risk; as of 2015, an estimated 290 million individuals remained undiagnosed. As part of addressing this challenge, there is a need to improve access to appropriate diagnostics, which in some regions represents a greater financial barrier to scaling services than do drug costs. Inclusion of viral hepatitis in WHO's proposed Essential Diagnostics List is a welcome step forward, and prequalification 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 done in non-hospital settings.

In 2017, more people were infected with HCV than were cured. 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. Voluntary licensing schemes for lower-middle-income countries have already resulted in substantial price reductions in eligible countries, but many high-burden upper-middle-income countries are unable to access such schemes and cannot afford market prices. For these countries in the so-called squeezed middle, effective access policies must be developed or expanded for elimination goals to be achieved. The announcement in late 2018 that pibrentasvir and glecaprevir will be licensed to the Medicines Patent Pool means that generic versions of all key pangenotypic drugs for hepatitis C should become more widely accessible in many, but not all, low-income

countries. In the absence of voluntary licensing some countries might still need to consider compulsory licensing as an alternative option.

Despite progress in access to drugs and diagnostics, viral hepatitis lacks the major global support provided to HIV, tuberculosis, or malaria, and insufficient financing remains a huge challenge for elimination efforts. With the current emphasis on universal health-care 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 that evidence-informed decisions are made regarding which interventions will provide the greatest public health returns. In China, for example, investing in comprehensive HBV programming is projected to result in savings of more than US\$1.5 for each \$1 spent by 2030.

New innovative financing mechanisms are likely to be required to support national programmes. A new international funding body is not essential. Instead, existing international financing and development organisations like Unitaid are well placed to support expansion of access to prevention, diagnostics, and treatment for viral hepatitis. If domestic efforts to provide funding are unsuccessful, new streams of finance to support national programmes must be identified.

All those engaged in viral hepatitis elimination efforts need high quality data and simple, consistent targets to monitor progress and advocate for the prioritisation of viral hepatitis prevention and treatment. Both non-governmental organisations and civil society have a key role to play in keeping viral hepatitis on the health agenda both nationally and internationally. Coupled with WHO evaluation efforts and monitoring of the SDGs, a new scorecard of national progress is needed to ascertain each country's progress towards elimination of viral hepatitis. The tools are available now to tackle viral hepatitis and there are many examples of them being used to good effect throughout the world. With sustained and coordinated effort, the WHO elimination targets are achievable.

Introduction

Viral hepatitis is now recognised as a leading cause of death worldwide, causing an estimated 1.34 million deaths per year (nearly 4000 per day), rivalling mortality caused by other major infectious diseases, including HIV/AIDS, malaria, and tuberculosis.¹ In 2017, WHO released its first Global Hepatitis Report,¹ which provided the first-ever baseline estimates of incidence, prevalence, and mortality from viral hepatitis for the six WHO regions. According to the report, an estimated 257 million people worldwide were living with hepatitis B virus (HBV) infection in 2015, and 71 million were living with hepatitis C virus (HCV).

Until recently, however, there was a huge disparity between the global burden of disease and global policy on viral hepatitis. Viral hepatitis was initially omitted

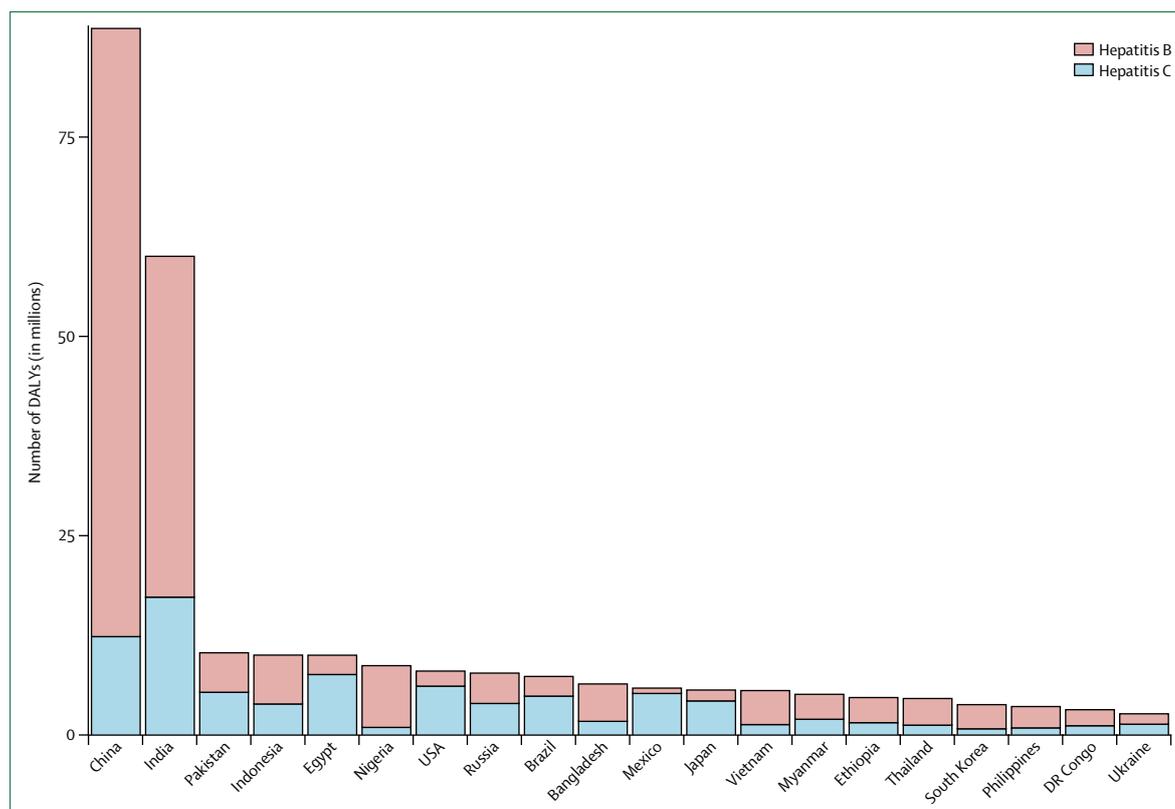


Figure 1: Total disability-adjusted life-years (DALYs) to hepatitis B and C in 20 most heavily burdened countries, both sexes, all ages, derived for this Commission from Global Burden of Disease dataset (2016)

from the Millennium Development Goals; before 2008, none of the 8000 WHO employees had hepatitis in their job title; and no non-governmental agencies existed that focused on 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 in the Sustainable Development Goals (SDG 3).

In 2016, WHO adopted its Global Health Sector Strategy (GHSS) for viral hepatitis,² which outlines an ambitious agenda for the global elimination of viral hepatitis as a public health threat by 2030, including a roadmap toward elimination and key prevention and treatment interventions aimed at strengthening health systems within the context of the universal health coverage framework.

To achieve the WHO targets 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 carcinoma, 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^{3,4} Elimination of viral hepatitis has the potential to prevent more than one in 20 of all cancer deaths globally.³

This Commission aims to identify the key challenges when developing strategies for viral hepatitis elimination, and in doing so has drawn on a wide range of expertise. Our intended 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. We first present an overview of current progress in tackling hepatitis B and C, followed by a discussion of proven strategies for prevention of viral hepatitis and the priorities for implementation. We then address challenges related to diagnosis and models of care, including the need to improve access to affordable diagnostics and medicines, and the need for innovative financing strategies. There is no large source of external funds for hepatitis, akin to the Global Fund to fight AIDS, Tuberculosis, and Malaria, and unless the Global Fund can extend its remit, hepatitis needs to be prioritised

	WHO region						World	2020 target	2030 target
	African	Americas	E Med	Euro	SEA	W Pacific			
Population (million)	1000	989	654	914	1945	1867	7369		
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%		
Indicators									
Timely birth dose vaccine (%)	10%	72%	23%	39%	34%	84%	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%
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)
■ Other estimates (including modelling)
 ■ Extrapolation and inferences

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

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. While there are shared issues among these countries, there are also issues of specific importance to different regions and different countries. As such, 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 relative disease burden, drawing on analysis of data from the Global Burden of Disease (GBD) programme to identify key priority countries.

The global burden of viral hepatitis and need for high quality data

In 2016, more than 75% of the global burden of hepatitis and its related diseases was shouldered by only 20 countries (figure 1). Meaningful progress towards the WHO targets for elimination will require a focus on progress within these countries, half of which are in Asia, the region with by far the greatest burden of disease.³ Strikingly, only two of the most heavily burdened countries—USA and Japan—have made progress in reducing the burden of viral hepatitis in the past 20 years (appendix p 3). Most of the 20 most heavily burdened countries are low-income countries or lower-middle-income countries, highlighting the need to help develop strategies that are achievable

in health-care systems with substantial financial and infrastructure constraints.

The WHO targets for progress towards elimination identify core indicators related to coverage of services for those infected with HBV and HCV (figure 2). Achieving progress in these areas requires further scale-up of interventions proven to be effective for prevention, diagnosis and treatment, and scale-up of access to medicines.

Accurate surveillance data for new infections, chronic infections, and mortality alongside programme monitoring indicators will be required not only to monitor progress toward elimination but to justify the investments required. The WHO viral hepatitis report¹ provided the first baseline estimates of the core indicators of the GHSS on viral hepatitis for the six WHO regions (figure 2). However, many gaps exist in data quantity and quality, and a thorough 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

Estimates of the incidence of HBV and HCV infection come from different data sources. For HBV, the proportion of children aged 5 years who are chronically infected is used as a surrogate indicator of the cumulative incidence of chronic HBV infection in the first 5 years of life, as most infections are acquired in this time frame. It is also monitored as an indicator of progress towards the SDGs. For HCV, data are more limited, and most incidence estimates derive from mathematical models that are based on prevalence data. Generating better data, especially for 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 more than 18 million new infections per year in the early 1990s to an estimated 4.7 million new infections in 2015, due to the introduction of the HBV vaccine.⁵ New HBV infections are predicted to remain close to 3 million a year by 2030 without further scale-up of prevention and treatment (figure 3).⁵ In 2015, WHO estimated that 1.3% of children aged 5 years or less 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 using surveys as a measure of the effect 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.⁶ As a result, the uncertainty interval (UI) around the 0.9% prevalence estimate for this region is relatively narrow (95% UI 0.6–1.3), whereas UIs are wider in regions such as Africa (3% [2.0–4.7]), where fewer surveys have been conducted.¹ Better data from sub-Saharan Africa are

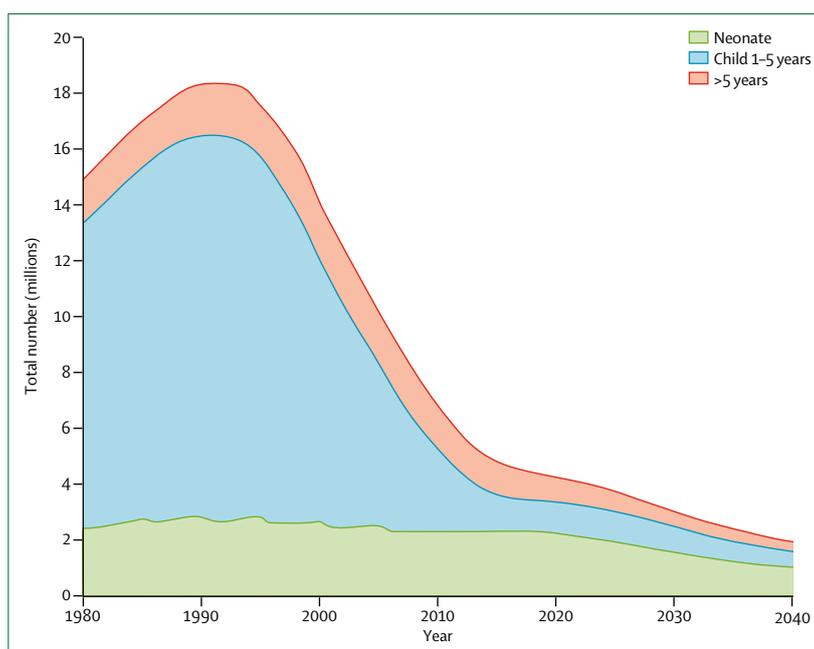


Figure 3: Estimated total number of new chronic carriers of HBV infection annually with current levels of intervention

Figure adapted from Nayagam et al.⁵

needed to estimate the effect 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 in 2015, there were 1.75 million new HCV infections worldwide (global incidence rate of 23.7 per 100 000).¹ The incidence of HCV infection can be estimated using several methods, including back-calculation from a curve of 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 generating estimates in regions where incidence is low or 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 might 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 for reported cases of acute HCV can provide information about time trends but are limited by substantial under-reporting 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.

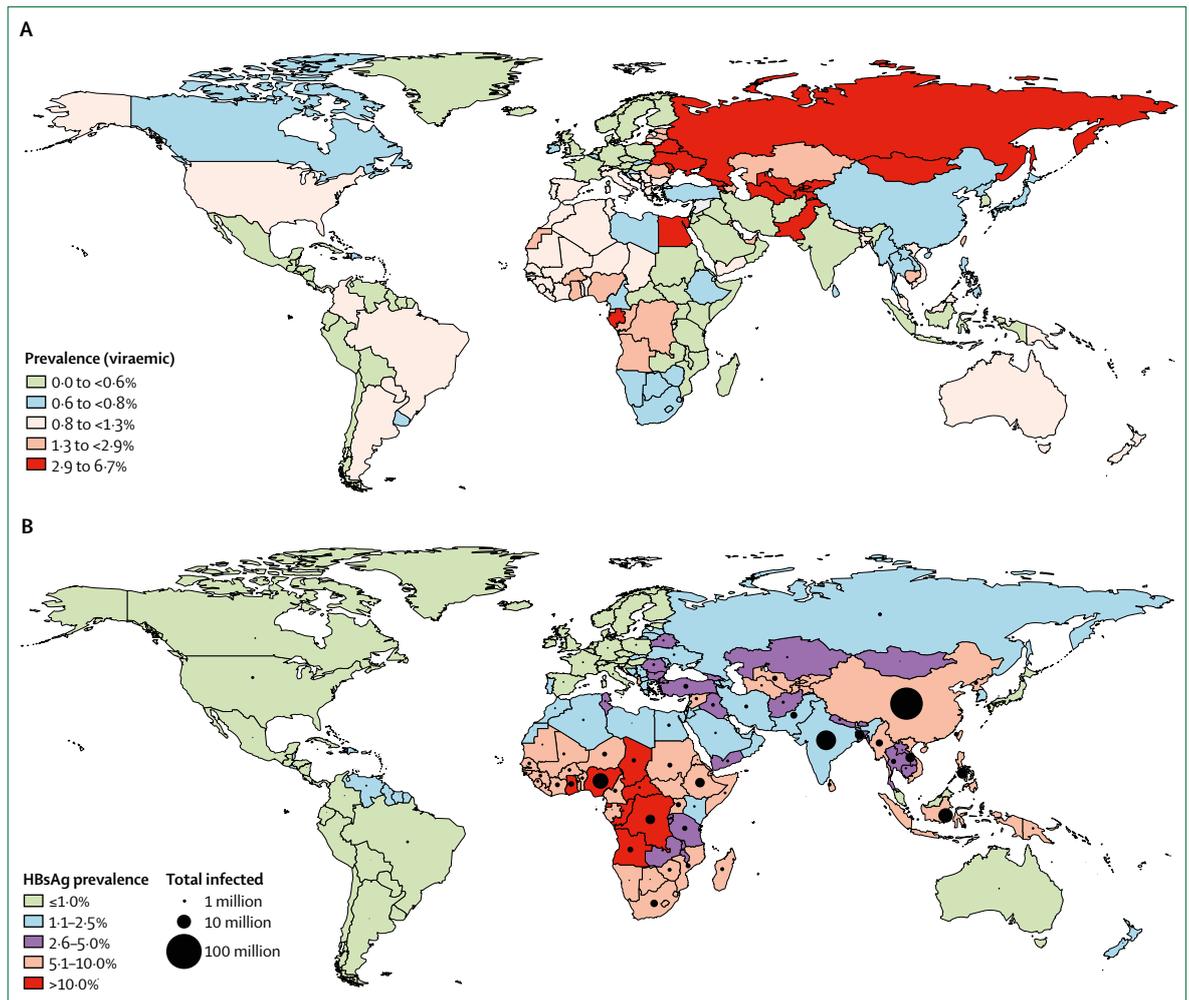


Figure 4: (A) Estimated numbers of viraemic HCV-infected individuals in 2015 and (B) estimated HBsAg prevalence in 2016^{7,8}

In 2015, WHO estimated that 257 million people (uncertainty interval 199–368), or 3.5% of the population, were living with HBV infection, and 71 million people (uncertainty interval 62–79), or 1% of the population, were living with HCV infection (figures 2, 4).¹ The change from reporting prevalence based on individuals with detectable anti-HCV antibodies to prevalence based only on those with active HCV infection (based on detection of HCV RNA) is important and reflects 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 HCV are the reference methods more commonly used to measure the prevalence of HBV and HCV infections, respectively. Countries that have a high burden of disease because of high prevalence, such as China,⁹ tend to conduct such surveys to guide their policies. In countries that have lower endemicity, however, 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.¹

WHO estimated that viral hepatitis was responsible for 1.34 million deaths in 2015.¹ 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.^{10,11} As such, estimates of mortality attributable to HCV and HBV vary depending on the data source.⁹ Improving and harmonising all estimates relevant to elimination is a priority for ongoing work that 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 coordination between key organisations should continue to improve the consistency and reliability of estimates; one important example of this is the announcement of greater collaboration between the Institute of Health Metrics and Evaluation (IHME) and WHO.¹²

Prevention of viral hepatitis

The shared routes of transmission for HBV, HCV, 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. Key priorities for prevention are summarised in panel 1.

The HBV and HCV epidemics vary substantially in different geographical settings, with different risk groups and risk factors for infection. As such, it is important that public health officials identify an appropriate mix of interventions that are adapted to the epidemiological 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.¹³ Similarly, in high-income countries, most HCV transmission occurs among PWID, whereas in many middle-income 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.¹⁴ 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

Worldwide, most HBV 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.¹⁵ The risk of mother-to-child transmission ranges from 5% for women without detectable circulating concentrations of hepatitis B e antigen (HBeAg; a marker for high viral load) to 90% for women with detectable HBeAg. 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.

Horizontal transmission of HBV infection can be prevented by administration of HBV vaccine in early life, with three doses of heptavalent vaccine shown to provide lifelong protection in more than 90% of individuals.¹⁶ WHO recommends that all children in endemic countries be vaccinated against HBV within 24 h 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 6 weeks of age.¹⁶ As of

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, with operational research into optimal delivery strategies
- 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 people who inject drugs

- Promote decriminalisation of drug use and engagement of services with people who inject drugs
- Increase coverage of harm reduction services through provision of opioid substitution therapy and needle exchange programmes
- Expand provision of HBV and HCV treatment services among people who inject drugs

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 HBV vaccination and risk reduction interventions among people 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

2015, universal childhood vaccination had been implemented in 185 countries, and 84% of children born in 2015 were vaccinated with three doses of heptavalent HBV vaccine (figure 2).¹⁷ The global scale-up of HBV vaccination has produced dramatic results, most notably in the Western Pacific region, where immunisation has averted an estimated 7 million deaths that would otherwise have occurred in the lifetime of children born between 1990 and 2014.¹⁸ Globally, existing prevention and treatment interventions are estimated to have reduced the incidence of new HBV infections by 83%, thus preventing 310 million chronic infections that would otherwise have occurred between 1990 and 2020.⁵ In Taiwan, for example, universal HBV vaccination, which was implemented in 1984 and has high

coverage rates, had reduced chronic liver disease and hepatocellular carcinoma-associated mortality by 90% in children and young adults who were vaccinated compared with those not vaccinated.¹⁹

Birth dose vaccination is a key component strategies recommended by WHO for prevention of mother-to-child transmission. However, progress in adopting the birth dose vaccine has been slower than 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 (figure 2).¹⁷ 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, and lack of coordination between vaccination and maternal health programmes. Financing is another barrier, as donor agencies such as Gavi, the Vaccine Alliance, 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, 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.²⁰ 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 amongst those available should be prioritised and what additional measures are needed to eliminate early-life HBV infection (appendix p 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. 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 and 2030; scaling up birth dose vaccination coverage to 80% would prevent approximately 18·7 million HBV infections in the same time period.⁵

Since the introduction of childhood HBV immunisation, progress has slowed; since 2010, global vaccine coverage has increased by only 1%.^{21,22} By 2015, only 126 of 194 countries had achieved the WHO target of 90% coverage of the third dose of HBV vaccine, and only 52 of these countries achieved more than 80% coverage in all districts.²²

Clearly, the main priority to reaching elimination goals is to identify strategies to increase the administration of birth dose vaccine while also improving coverage rates of childhood vaccination. WHO's Strategic Advisory Group

of Experts has made recommendations for strengthening national vaccine programmes, including advocating for stronger national leadership and commitment, securing investments, and enhancing surveillance and accountability mechanisms.²² 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.²³ The most direct way to improve birth dose coverage is to promote childbirth within health facilities and strengthen linkages between immunisation and maternal-child health programmes to ensure availability of vaccine and to promote awareness among health-care workers. For children born at home, HBV birth dose vaccine should be provided to birth attendants and community health workers. Structural interventions, such as simplified injection mechanisms and use of vaccine that does not require cold-chain storage could also help improve birth dose vaccine coverage.²³

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 conduct universal antenatal HIV testing, and serological testing for HBV could be incorporated at 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% (7·6–15·2) among women with HIV infection.²⁴ Nevertheless, as new HCV infections via other routes of transmission are reduced, mother-to-child transmission might account for a higher proportion of new infections. Direct-acting antivirals, which rapidly reduce HCV viral load and cure HCV infection in most 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 active HCV infection before they become pregnant is currently the best approach to reduce mother-to-child transmission and to improve the health status of these women.

Preventing infection amongst high-risk adults

People who inject drugs

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

See Online for appendix

be essential to meet the global targets for elimination. Injection drug use has been reported in at least 179 of the world's countries and territories,²⁵ and according to the most recent estimates, there are currently 15.6 million (95% uncertainty interval 10.2–23.7) PWID aged 15–64 years globally.²⁶ However, these figures underestimate the true prevalence of injection drug use, due to under-reporting resulting from issues of legality and stigma.²⁷

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.²⁸ As a consequence, 52.3% (95% UI 42.4–62.1) of PWID are HCV-antibody positive, and 9.1% (5.1–13.2) are HBsAg positive.²⁶ Worldwide, the prevalence of HCV infection among PWID is 33 times higher, and of HBV is 2.5 times higher, than in the general population.^{29,30} 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.²

Implementation of a comprehensive package of harm reduction services for PWID is one of the priority actions outlined in the GHSS.² The package includes needle and syringe exchange programmes, opioid substitution therapy, HBV vaccination, information, education and communication on risk reduction, and diagnosis and treatment of chronic hepatitis infection.³¹ WHO also recommends the use of low-dead space syringes (a type of syringe with a design that seeks to limit dead space that exists between the syringe hub and needle) to reduce the transmission of virus when needles are shared, and the offer of peer interventions among PWID.³¹

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.³² However, vaccination rates have been poor in this population. Improving convenient access to vaccine (eg, in prisons, and via needle and syringe programmes, and drug treatment centres) and offering incentives have increased HBV vaccine coverage among PWID.³²

There is substantial evidence to support the effectiveness of both needle and syringe programmes and opioid substitution therapy in reducing injecting risk behaviour and hepatitis virus transmission among PWID, with the biggest individual risk reductions (70–80%) reported using a combination of needle and syringe programmes and opioid substitution therapy.^{33–36} However, despite multiple guidelines recommending these two approaches, and widespread endorsement from international agencies, the global response continues to be woefully inadequate.^{25,37} For example, there is still no provision of needle and syringe programmes and opioid substitution therapy in 52% and 48%, respectively, of the 179 countries where injection drug use has been reported.²⁵ A major barrier to 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 often harass and arrest PWID who are attending needle and syringe programmes and opioid substitution therapy distribution centres, limiting the availability and effectiveness of these programmes. 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.³⁸ Once appropriate policies are in place, harm-reduction programmes 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 is crucial to establish a more supportive environment.³⁹

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.⁴⁰ Accumulating evidence shows that PWID can achieve HCV cure rates similar to those reported for other populations, although re-infection rates are higher.^{41–44} The treatment of PWID also reduces the risk of transmission, which would contribute to reduced prevalence.^{45–47} Despite this, access to treatment is low in this population, in part because HCV drug eligibility policies exclude active injection drug users 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 in PWID. Economic evaluations suggest that, in many settings (where prevalence of chronic HCV infection is $\leq 40\%$), early treatment of PWID with direct-acting antiviral regimens is more cost-effective than treating other patient groups because of the potential additional benefit of averted transmissions.⁴⁸ Further, national models of HCV elimination (eg, in Georgia) suggest that targeting and prioritising PWID for HCV therapy is crucial 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 opioid substitution therapy. Thus, empirical evidence demonstrating that treatment can indeed prevent transmission of HCV in PWID remains key to strengthening international guidelines and driving change in clinical practice.^{49–51}

Prison populations

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.^{51–53} Globally, the prevalence of HBV and HCV infections is higher in prisons compared with the

general population, ranging from 1·4–23·5% for HBV and 1·8–20·6% for HCV.⁵⁴ Incidence of HCV among prisoners is also high, reported to be up to 30 cases per 100 prisoners per year.^{55,56}

In most countries, enforcement of strict drug laws results in over-representation of PWID in penitentiary systems.⁵³ Approximately half of the prison population in the European Union (EU) has ever used illicit drugs. The time immediately following release from prison is also a period marked by increased risk behaviours, such as sexual and drug use, which could lead to transmission of HBV, HCV, and HIV.⁵⁷

Most prisoners do not have access to recommended intervention services aimed to reduce the risk of infection; for example, only eight countries have implemented needle and syringe programmes in at least one prison.⁵⁸ 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 those 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 programmes that are 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 systems to address insufficiencies in medical staffing and education and to fund prevention and treatment services (including in the post-treatment phase).

In addition to enhancing prevention programmes in prisons, treatment needs to be more widely accessible. With the duration of treatment with direct-acting antiviral drugs for HCV now as short as 8 weeks, completion of treatment is feasible in prison settings. Because one of the obstacles for antiviral treatment in prisons is low awareness of infection status, the impact of screening for HBV and HCV upon entry and regular testing during the period of incarceration to identify those needing antiviral treatment needs to be evaluated.

Sexual transmission and men who have sex with men

Sexual transmission occurs for both HBV and HCV and is thought to be the main route of transmission of HBV among adults; approximately a quarter of sexual partners of people with acute HBV will become infected within 6 months.⁵⁹ Compared with the general population, sex workers, people with multiple sex partners, and men who have sex with men (MSM) have increased prevalence of HBV infection.⁶⁰ The HBV vaccine effectively protects against sexually acquired HBV infection, and existing guidelines recommend that people at increased risk of

sexually transmitted infection be vaccinated.¹⁶ Despite this, vaccine coverage remains low among these populations,^{61,62} and health-care providers often do not offer HBV vaccine to them.⁶³ 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 indirectly via 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. Incidence is very high among some HIV-infected MSM and associated with both high-risk sexual and recreational drug use practices. Incidence has increased in recent years, particularly in Europe.⁶⁴ According to one review, MSM with HIV were at 4·1 times higher risk of acquiring HCV infection (6·08 per 1000 person-years [95% CI 5·18–6·99]) than were MSM without HIV infection.⁶⁵ Barring vaccination, the strategies to reduce sexual transmission of HCV are the same as for HBV transmission. Although a unique concern is the high rate of HCV re-infection in this population,⁶⁶ early empiric data from the Netherlands suggest that unrestricted availability of direct-acting antiviral treatment has a major impact on new infections among MSM.⁶⁷

Health-care-associated transmission

Because 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.⁶⁸ 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.⁶⁹ Improved programme 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.⁷⁰ 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.⁷⁰ 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 injections must be based upon a three-prong approach⁷¹ that includes a 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 (including 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.⁷² Introduction of such devices will be key in countries where unsafe injections continue to fuel the HCV epidemic.⁷³ 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 any infection prevention and control programme is a reliable monitoring system that can assess the comprehensiveness, quality, and impact of infection prevention and control interventions. This can be challenging because of the wide range of recommended interventions and because some indicators require special surveys.⁷⁴

Hepatitis C vaccine

A vaccine that could effectively prevent HCV infection would be an important tool to help control the HCV pandemic, particularly for populations experiencing high rates of HCV infection and re-infection. Even with high coverage of direct-acting antivirals, a partially effective vaccine could reduce HCV prevalence among PWID.⁷⁵ Although there is proof of principle that protective immunity can be established from studies of PWID, the prospects for having such a vaccine remain distant.⁷⁶ 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.⁷⁷ Several candidate vaccines are in phase 1 or 2 trials, 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.

Screening, diagnosis, and cascade of care

Screening and diagnosis

Timely diagnostic testing is crucial 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,¹ 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 with 2% and 3% for India and Pakistan, respectively). It also 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 the quality of tests is variable and data are not routinely captured.

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 cost of testing receives less attention than does drug costs, and there is a strong correlation between gross national income (GNI) and proportion of individuals diagnosed with hepatitis C (appendix p 5). The main approaches to screening are a general population approach and a risk-based approach targeted to 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 key at-risk populations in certain regions might necessitate the inclusion of general population screening approaches.

Compared with HIV infection or non-communicable diseases, HBV is particularly appealing for mass screening of adults 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 remain so because of protective immunity elicited by 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^{78,79} 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 2018, as part of an effort to identify the still sizable population of

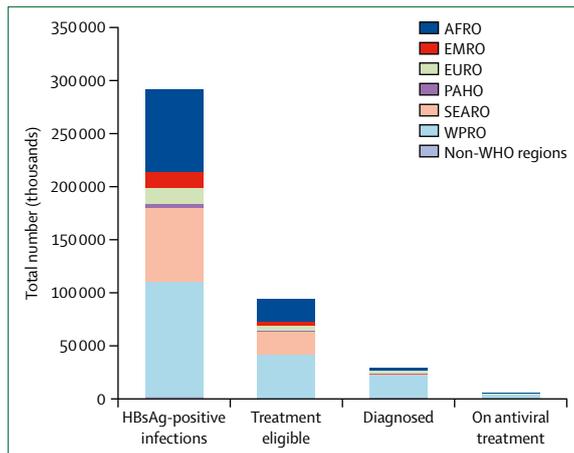


Figure 5: Global and regional cascade of care for HBV in 2016
 AFRO=Regional Office for Africa. EMRO=Eastern Mediterranean Regional Office. EURO=Regional Office for Europe. PAHO=Pan American Health Organization. SEARO=South-East Asia Regional Office. WPRO=Western Pacific Regional Office. Reproduced from reference 8.

undiagnosed individuals, Egypt announced ambitious plans for national screening. 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 years and prenatal women in France.⁸⁰ While these approaches have been shown to be cost-effective, implementation has been challenging; when used in isolation, these approaches might also miss a significant proportion of those infected.⁸⁰

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 several of these high-risk populations, frequent (eg, annual) testing is required to reduce transmission and achieve WHO elimination targets.⁸¹ However, there are relatively few data on the cost-effectiveness of different testing approaches, particularly in low-income countries⁸² 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.⁸³ However, while relatively simple to initiate, the economic considerations of such a strategy have been poorly assessed in low-income and middle-income countries. 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.⁴⁸ 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.

A staged, pragmatic, approach to screening may be necessary to achieve the high levels of diagnosis needed to achieve elimination. As a first step, countries might prioritise systematic screening in health facilities (eg, pregnant women and those attending liver services) and secure access to drugs and diagnostics. Screening can then be scaled up to at-risk groups and finally extended to the entire adult population where required.

Cascade of care and models of care

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 most infected individuals would be treated and, ideally, cured. However, many of the gaps in care occur long before treatment is considered (figure 5). 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. For example, access to care will be limited if confined to speciality-based models of care (eg, requiring hepatologists, infection specialists, or other skilled and expensive health-care 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 programmes for HIV, tuberculosis 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 re-infection 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 health-care system.

Cascade of care and improving care models for HCV

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 hepatocellular carcinoma. Initiation of treatment is often hampered by restrictions on eligibility of direct-acting antiviral prescribers, which is often limited to specialist settings. Such restrictions might particularly affect individuals in rural or remote areas with limited coverage by specialists.⁸⁴

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 before accessing HCV therapy.^{84,85} These requirements create barriers for entry into care, are a major challenge to elimination, and are not 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 (SVR) rates documented in individuals with ongoing active injection drug use.⁸⁶

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.^{87,88} There is also some evidence that integrating HCV care into drug, alcohol, and psychiatric services can increase treatment uptake.⁸⁹ 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. Data on screening and linkage to HCV care for PWID in low-income and middle-income countries are particularly scant, despite an increasing burden of disease among this population in many countries.

Until recently, the requirement for liver biopsy to assess the extent of liver fibrosis was a major barrier for retention in care. Transient elastography and other non-invasive measures of liver fibrosis have now largely replaced liver biopsy, and the immediacy of transient elastography results makes it particularly attractive. Use of transient elastography was shown to increase engagement in follow-up care among people with recent injection drug use, particularly for those with high fibrosis scores.⁹⁰ In most low-income and middle-income countries, where access to both transient elastography 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 has a 93% negative predictive value for cirrhosis⁹¹) and are universally available; these tests might also be useful in selecting patients who do not need follow-up for hepatocellular carcinoma screening after achieving SVR, as suggested by one US-based study.⁹²

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 direct-acting antiviral drugs for 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 direct-acting antiviral 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.⁹³ High quality evidence is emerging to support care outside of specialised services⁹⁴ 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 with treatment in a hepatology clinic.^{89,95} Task-sharing is particularly attractive to provide care in rural and remote communities as well as to serve hard-to-reach populations, such as PWID. Task-sharing has worked well in low-income and middle-income countries for management of patients with HIV and tuberculosis and could be adopted for viral hepatitis care in these settings. Currently, however, task-sharing 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.^{96,97} As such, approaches to minimise these gaps are a priority. Outreach into the community to test and immediately engage people into care (test and treat) has been advocated, particularly for marginalised populations. Offering patients treatment in familiar settings from trusted providers enhances treatment uptake and retention.^{88,98} This type of approach has been particularly important for reaching populations with significant social challenges, such as those with ongoing mental health and substance use issues or those in unstable housing. Delivery of HCV treatment in opioid substitution therapy clinics, community health centres, and drug and alcohol support programmes has demonstrated positive outcomes that extend beyond HCV cure rates,⁹⁸ including increased diagnosis rates. Modelling data suggest that a bring-a-friend strategy of care among members of drug-using networks will be more effective at reducing prevalence and preventing re-infection than strategies targeting treatment randomly.⁹⁹ 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.^{100,101} 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.⁹⁴ 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 transient elastography 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 account for culture-specific considerations that may affect how best to manage HCV in particular communities, such as PWID, Aboriginal communities, and Indigenous North 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 and efficacy of approved direct-acting antiviral 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 (eg, NCT03117569) and such approaches will ultimately need to be tailored to local settings and resources.

Cascade of care and improving care models for HBV

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. 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 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 no consensus about which infected individuals require treatment, and the need for treatment may change over time, necessitating multiple follow-up visits.¹⁰² 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.¹⁰³ 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 described and validated a scoring system (TREAT-B) based on serum HBeAg and ALT levels to identify patients who required therapy.⁹¹ 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 (eg, 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.¹⁰⁴

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 access to diagnostics

Monitoring recommendations 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 pangenotypic activity that can be used without eligibility criteria based on fibrosis, or monitoring of viral load to track treatment response, 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 treatment 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 HBV and HCV testing highlight the need for such a response.¹⁰⁵ Elimination of viral hepatitis cannot be achieved without comprehensive access to affordable, feasible, and high-quality diagnostics, to define the epidemic, focus programmatic resources, and facilitate the implementation of simplified pathways for diagnosis and care (panel 2).

Rapid-detection tests and point-of-care diagnostics

Advances in rapid diagnostic technologies have created new opportunities for enhancing access to testing and care, as well as monitoring treatment response, several of which were recently reviewed.¹⁰⁶ These include alternative sampling methods (dried blood spots, oral fluids, self-testing) and the 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 testing, and multi-disease polyvalent molecular platforms that make use of existing centralised laboratory-based or decentralised tuberculosis 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 (appendix pp 6–8), there is significant variability in their performance as alternatives to laboratory-based immunoassays. Recent systematic reviews of rapid detection tests for HBsAg and 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%).^{107,108}

Oral tests for detection of HCV-specific antibodies have slightly lower pooled sensitivity but comparable specificity versus blood-based tests, and might be especially useful in contexts in which venepuncture may be difficult, such as in subsets of PWID. Expression of small amounts of blood by finger stick is one option when standard venepuncture is not possible. The OraQuick HCV Rapid Antibody Test (OraSure Technologies, Bethlehem, Pennsylvania) is the best performing and the only one that is currently US Food and Drug Administration (FDA) approved. However, given the current pricing of the OraQuick test at roughly US\$7 per test,¹⁰⁹ it is unlikely to be widely adopted in resource-limited settings, and more affordable tests with comparable performance and accuracy in people with HCV infection and HIV-HCV coinfection are urgently needed.

Two antibody-based rapid detection tests for HBV and two for HCV have received WHO prequalification. Several CE-mark assays are commercially available but have not been prequalified. The WHO Prequalification Programme assesses the performance of in-vitro diagnostics and their suitability for use in resource-limited settings using samples from diverse geographic regions. More pre-qualified 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 prequalifications. Countries should ensure that they have a

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

Governments and implementing partners

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

Ministries of health

- Implement use of pangenotypic direct-acting antivirals 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 health-care 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

- Conduct 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 dried blood spots
- Validate dried blood spots for serology and virology and file for regulatory approval
- Initiate claims for virological tests addressing both diagnosis and monitoring of cure
- Invest (along with funders) in development of point-of-care tests adapted to resource-limited settings, including for serology, virology, blood safety, and staging

International organisations, governments, implementing partners, and other stakeholders

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

competent regulatory body that follows guidance of the International Medical Device Regulators Forum (formerly the Global Harmonization Task Force).¹¹⁰

WHO recently launched a model Essential Diagnostics List to satisfy the priority health-care needs of the population. This should help strengthen quality assurance, human resource training, and supply chain management.¹¹¹ 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. Most low-income and middle-income countries use serological assays for blood screening, because they are usually

simpler and more affordable than molecular testing.¹¹² However, these tests often suffer from high rates of false-positivity, resulting in unnecessary discarding of blood.¹¹³ As blood safety tests are subject to stricter regulatory requirements compared with 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, potentially leading to transfusion of infectious blood.^{112,113} The implementation of better quality control and assessment and more feasible product solutions are therefore urgently needed.

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; 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 pre-qualified HBV DNA tests, although several 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 or plasma: one commercially available but not yet SRA-approved (Mobio Diagnostics) and one in development (Cepheid).

SRA-approved assays for active HCV infection exist, including several laboratory-based and two near-patient options (suitable for use in or adjacent to clinical areas) from Cepheid (the CE-marked HCV Viral Load cartridge and instrument, Cepheid AB) and from Molbio Diagnostics (Truelab/Truenat HCV) that require serum or plasma.^{109,114} The Cepheid AB test is also the only WHO prequalified test available, and two studies have been conducted to date in resource-limited settings of India¹¹⁵ and Cambodia,¹¹⁶ demonstrating good performance. Additionally, Cepheid has developed a redesigned cartridge, recently CE-marked, to allow the use of whole blood from finger pricks with high accuracy,¹¹⁷ which will help overcome challenges associated with venepuncture in certain patient groups, simplify sample processing, and accelerate results. Another near-point-of-care assay that has been recently CE-marked is the Genedrive HCV ID Kit (Genedrive Diagnostics, UK);¹¹⁸ however, this system requires serum or plasma, therefore being most suitable for decentralised testing at the district and subdistrict health-care level.¹¹⁸

Detection of HCV core antigen could be an alternative strategy to HCV RNA testing^{119,120} for detecting active viral

replication, and given that an antigen test is usually cheaper, its use as 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 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 low-income and middle-income countries. 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. 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.^{121,122} 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.¹²¹

Financing diagnostics

There is limited information available on the extent of HBV and HCV country guidelines, policies, and 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 direct-acting antiviral pricing has been helpful in advocating for price reductions for diagnostics.¹²³ 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.¹⁰⁹ Even when manufacturers offer bundled pricing (ie, volume-based ceiling prices across a range of polyvalent tests rather than vertical pricing alone), some HCV tests can remain 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 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 commonly perceive the developing world market as small and fragmented, and they 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 (panel 2).¹⁰⁹

Access to medicines for viral hepatitis

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, but it is also a crucial time to explore ways to improve access to HBV treatment. Two key long-term HBV treatments are recommended in international guidelines, TDF and entecavir, which are sufficient for the management of most patients with chronic hepatitis B. As of 2018, both drugs are off-patent in most major markets, although access issues remain in some middle-income countries (eg, Russia and China). 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 USA for close to the same price as the branded drug in Europe (US\$6000 per year), despite the potential for it to be sold for under \$50 per year.¹²⁴

TDF is now widely available in low-income and middle-income countries following its licensing to the Medicines Patent Pool (MPP) in 2011 from Gilead and then the patent expiring in 2017–18 in most countries. The key role of TDF in HIV combination therapies has meant active competition among generics manufacturers, with TDF now widely available for under \$50 a year. There are also licences in place from the MPP that enable access to generic versions of the newer HBV treatment tenofovir alafenamide in 116 low-income and middle-income countries.¹²⁵ Despite great progress in HBV drug pricing, only an estimated 1.7 million of those infected are on treatment.¹ In many low-income and middle-income countries there remains a key paradox: funding is often only available for individuals with HBV-HIV co-infection, but not those with only HBV infection, and prices may be different for each indication.¹²⁶

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 2030.¹²⁷ 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 direct-acting antiviral-based therapies.^{1,128} The lack of access to affordable treatments is one of the key reasons why many patients chronically infected with HCV 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 direct-acting antivirals. Gilead, Bristol-Myers Squibb, Merck, and AbbVie have filed several types of patents on each direct-acting antiviral agent, with patent protection status varying by country.¹²⁹ The voluntary license agreements signed by some originator companies, either bilaterally or through the MPP, enable generic producers to manufacture and sell versions of sofosbuvir, ledipasvir, velpatasvir (Gilead),¹³⁰ daclatasvir and sofosbuvir/daclatasvir (Bristol-Myers Squibb-MPP),¹³¹ and glecaprevir/pibrentasvir (AbbVie-MPP)¹³² in the territories included in each agreement. Consequently, countries included in these agreements should be able to procure generic direct-acting antivirals from multiple licensees at generally affordable prices due to generic competition. The access price programme for countries in the Gilead licence territory allows procurement of drugs from the originator for approximately US\$250 per bottle (4 weeks of treatment) of sofosbuvir, and US\$300 per bottle of sofosbuvir/ledipasvir or sofosbuvir/velpatasvir.¹³³ Where multiple generic sources have registered and made their direct-acting antivirals available, prices can be much lower. The minimum cost of production of direct-acting antivirals, 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 US\$48–81 per person, including an estimated profit range of 10–50%.¹³⁴

Some countries have benefited from a significant reduction in the prices, with resulting improvements in access, while others have had less success. The most significant price decreases were seen in Pakistan and Egypt—countries included in voluntary licences that have dynamic generic industries—where 3 months of sofosbuvir/daclatasvir could be procured in local markets at US\$330 and US\$73 respectively in 2017.¹²⁸ 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 WHO prequalification, and US\$6 per bottle of generic daclatasvir.

Outside of the Gilead and Bristol-Myers Squibb-MPP licence territories, countries with a strong negotiating capacity and relatively high procurement volumes that allow savings based on economies of scale have achieved direct-acting antiviral price reductions with originator companies and have set up ambitious HCV elimination targets, as is the case for Australia.¹³⁵ More generally, in countries where direct-acting antiviral patents have been granted, competition between branded products has started to bring prices down. The 2017 US FDA and European Medicines Agency approval of AbbVie's pangenotypic 8-week glecaprevir/pibrentasvir treatment is beginning to influence the price of sofosbuvir-containing combinations.

Price reductions have been less marked to date in upper-middle income countries, which are excluded from voluntary licences. In Brazil, where the Ministry of Health has proposed to extend treatment to all patients with HCV, negotiation with originator companies has resulted in more modest price reductions (eg, 43% in Brazil compared with 93% in Egypt for sofosbuvir/daclatasvir between 2015 and 2017).¹³⁶ The modest nature of the price reduction has widespread implications given that Brazil is considered to be a benchmark for the establishment of direct-acting antiviral 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. A generic version of sofosbuvir was approved by the Brazilian Health Regulatory Agency in 2018.¹³⁷

In Malaysia, another upper-middle-income country, efforts by the Ministry of Health to negotiate a voluntary licence and an affordable price for sofosbuvir were unsuccessful. The government issued a compulsory government-use licence¹³⁸ to gain access to generic sofosbuvir at a 97% price reduction and initiate treatment scale-up.¹²⁸ This resulted in the addition of Malaysia and three other middle-income countries (Thailand, Belarus, and Ukraine) to Gilead's licence territory.

The continuous pressure created by over-priced medicines on public health budgets in high-income countries has led some of these countries to consider making use of the World Trade Organization Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement flexibilities. For example, the Italian Medicines Agency has refused to pay more than \$4000 per treatment and threatened to issue a compulsory licence to allow local production if they could not negotiate a better price with Gilead.¹³⁹ Chile has also taken the first step towards issuing a compulsory licence to allow importation of less expensive generic drugs.¹⁴⁰

AbbVie's pangenotypic HCV combination glecaprevir/pibrentasvir was approved in 2017 and, as an 8 week therapy, access to treatment will be important for efforts in scaling up treatment for elimination. It was announced in 2018 that it would be licensed through the MPP.¹³² Although the initial agreement does not cover the key

country of India, the arrangement should lead to improved access to glecaprevir/pibrentasvir in 99 designated low-income and middle-income countries. Perhaps more importantly, however, this combination could have a role in retreatment of patients where treatment with other direct-acting antiviral regimens has not achieved cure. Currently, the only licensed retreatment option for patients who do not achieve SVR with 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; as such, countries who can procure via Gilead's access programme pay \$400 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 DNDi programme of development, interim results of a phase 2/3 clinical trial of sofosbuvir plus the new NS5A inhibitor ravidasvir carried out in Malaysia and Thailand showed good efficacy (97% SVR12).¹⁴¹ 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.¹⁴² These countries should carefully analyse whether these patent applications deserve to be granted according to their own patent laws and the flexibilities of the World Trade Organization TRIPS agreement. Countries that have granted patents on direct-acting antivirals and remain confronted with expensive prices could issue a compulsory licence on sofosbuvir, following the lead of Malaysia, to access the more affordable sofosbuvir/ravidasvir regimen (panel 3).

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 required to register a product varies by country, taking as long as several years in some. The WHO prequalification programme evaluates the quality of generic medicines for HCV, HIV, tuberculosis, 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 direct-acting antivirals. As of October, 2018, three generic formulations of sofosbuvir have been pre-qualified by the WHO (Mylan, Hetero, and Cipla).¹⁴³ Two additional versions of sofosbuvir (Pharco and Strides) and three for daclatasvir (Cipla, Hetero, and Mylan) are quality assured via the Global Fund Expert Review Panel's risk-benefit analysis process;¹⁴⁴ additional dossiers for generic direct-acting antivirals have been submitted for WHO

prequalification quality assessment. Generic direct-acting antivirals are not assessed by the US FDA (as is done for generic antiretroviral drugs), as the President's Emergency Plan for AIDS Relief (PEPFAR) has yet to fund treatment for HCV or finance quality assessment for generics via the US FDA. With the exception of voxilaprevir, glecaprevir, and pibrentasvir, all approved direct-acting antivirals (including tenofovir and entecavir) are included in the 20th WHO Essential Medicines List.¹⁴⁵

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 in the squeezed middle 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 that also ensure equitable access across all middle-income settings (panel 3). Even in countries included in the voluntary licences, where intellectual property is not seen as a barrier, the major challenge of financing both HCV and HBV programmes lies ahead.

Innovative financing for viral hepatitis

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 research and development, 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.¹⁴⁶ By contrast, domestic sources currently account for most of the funding for development of country-level responses 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 most heavily burdened countries, most health spending is out-of-pocket (table 1).

At the country level, public financing for health (as for any sector) is determined by the fiscal space available to the government,¹⁴⁸ 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.^{149,150}

Panel 3: Key recommendations for access to medicines and financing

Access to medicines

- Ensure priority is given to access to both HBV and HCV treatment
- Consider compulsory licensing for hepatitis medicines for countries that cannot otherwise access generics to achieve affordable prices
- Ensure access policies (by originator companies) for low-income and low-middle income settings for drugs approved on WHO Essential Medicines List and WHO treatment guidelines
- Companies should continue to use the WHO prequalification programme for quality assurance and to access the collaborative registration process mechanism

Financing

- Consider launching a coalition of stakeholders to create innovative financing for viral hepatitis elimination, particularly focused on high burden, low-income countries
- Explore whether and how innovative financing tools developed for HIV, tuberculosis, malaria, and vaccination programmes can be adapted for viral hepatitis
- Emphasise development of investment cases for viral hepatitis, demonstrating the returns on investment by achieving elimination

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. However, while improvements in economic circumstances typically help countries to gradually increase domestic financing for health in line with real growth in gross domestic product (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.¹⁵¹ 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 for viral

	GDP per capita in 2016 (current US\$) *	Health spend per capita (2014; \$)	Health spend as % of GDP (2014) (%)	Government spending as % of total (2014)	Prepaid private % of total (2014)	Out-of-pocket spending as % total (2014)	Projected average real GDP growth 2018-22 (%)**
China	8123.2	697	5.1%	60.3%	5.0%	34.6%	6.2%
India	1709.6	253	4.5%	31.3%	2.4%	65.6%	7.9%
Pakistan	1443.6	132	2.7%	32.1%	6.1%	55.4%	5.8%
Indonesia	3570.3	265	2.5%	42.7%	2.7%	53.5%	5.5%
Egypt	3477.9	581	5.4%	39.9%	1.5%	58.3%	5.5%
Nigeria	2175.7	225	3.7%	22.1%	0.8%	70.1%	1.7%
USA	57 638.2	9237	16.6%	49.6%	38.8%	11.4%	1.9%
Russia	8748.4	1877	7.1%	51.8%	2.8%	45.5%	1.5%
Brazil	8649.9	1357	8.5%	45.9%	28.5%	25.5%	1.9%
Bangladesh	1358.8	92	2.9%	22.7%	0.0%	65.6%	7.0%
Mexico	8208.6	1088	6.3%	51.2%	4.2%	44.0%	2.5%
Japan	38 900.6	3816	10.2%	83.6%	2.4%	13.9%	1.9%
Vietnam	2214.4	398	7.0%	53.0%	6.9%	37.5%	6.2%
Myanmar	1195.5	121	2.5%	36.2%	0.0%	45.6%	7.5%
Ethiopia	706.8	85	5.5%	26.9%	0.0%	28.4%	7.9%
Thailand	5910.6	633	4.1%	78.7%	8.6%	12.1%	3.2%
South Korea	27538.8	2507	7.1%	56.0%	6.6%	37.4%	2.9%
Philippines	2951.1	330	4.7%	33.6%	10.2%	54.3%	6.8%
Democratic Republic of Congo	405.5	46	4.5%	21.3%	0.0%	37.4%	3.8%
Ukraine	2185.7	659	7.0%	51.3%	0.9%	46.8%	6.4%

Table 1: 20 countries GDP and health spend per capita, including out-of-pocket expenditure for 20 countries with greatest burden of viral hepatitis⁴⁷

hepatitis elimination efforts, 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 Millennium Development Goals at The International Conference on Financing for Development held in Monterrey, Mexico, in 2002.¹⁵² Many countries have successfully used domestic and international innovative financing to mobilise new and additional resources for health. For example, countries such as Egypt, the Philippines, and Thailand have used targeted taxes on tobacco to provide earmarked domestic funding for the health sector.¹⁵³ 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 mechanisms¹⁵⁴ and instruments¹⁵⁵—is instructive to explore how such mechanisms and instruments could be used for viral hepatitis.

To date three innovative financing mechanisms¹⁵⁴ have reached global scale, namely the Global Fund (established in 2002), Gavi (established in 2000), and Unitaid (established in 2006). These innovative financing mechanisms link different elements of the financing value chain to mobilise funding from multiple sources (eg, governments, private foundations, and the private sector), pool finances, and 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 billion¹⁵⁶ for HIV/AIDS, tuberculosis, malaria, and health systems; Gavi had disbursed US\$11.2 billion¹⁵⁷ for vaccines; and Unitaid had invested more than US\$2 billion¹⁵⁸ 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 their implementation and performance to achieve better health outcomes at a large scale.¹⁵⁴ 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, diagnostics, and health products to substantially lower prices and to improve access.

In addition to innovative financing mechanisms, several innovative financing instruments have been developed,¹⁵⁵ 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 were used for programmes for new and underused vaccines, HIV/AIDS, malaria, tuberculosis, and maternal and child health. These instruments—which include global health bonds, debt

conversion instruments,^{159,160} market commitment instruments,^{161–163} social and development impact bonds,^{164,165} and global solidarity taxes and levies (appendix pp 9, 10)—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 solidarity taxes and levies

Innovative financing holds much promise to provide catalytic funding to augment financing from domestic sources to rapidly scale up access to diagnostics and medicines for viral hepatitis. There is enough evidence of the success of innovative financing instruments in mobilising funds and innovative financing mechanisms in channelling them to countries to provide a rapid access to novel diagnostics and treatments. There is an opportunity to use a combination of innovative financing instruments, by replicating those with a record of success, to mobilise funds, and frontload funding (by providing larger proportions of the available funds up front to rapidly scale up prevention and treatment interventions) to augment those from domestic sources. Frontloading of funds to rapidly expand access to treatment not only benefits the infected individual but also contributes to prevention via interrupting transmission. However, several steps are needed to make this a reality.

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 in-country and global responses.

The second step should involve the development of an investment case for viral hepatitis, to demonstrate the feasibility of elimination and quantify the health, social, and economic benefits of potential investments. For example, a recent analysis on HCV in Egypt estimated that, as of 2015, the HCV epidemic reduced GDP by 0·3% (US\$1 billion) each year, and led to a drop in living standards equal to 1·5% of GDP (US\$5 billion) each year.¹⁶⁶ The study estimated that the spending on demand-driven treatment would be refinanced by cost savings within 6 years, and would result in a financial rate of return of 24%, even before taking into account the value of any health gains. The study showed that elimination was cost effective, that treatment and screening policies would achieve considerable health gains largely free of cost, and that reduced mortality would result in a gain in living standards equivalent to 0·6–0·8% of GDP.¹⁶⁶

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.¹⁵⁴ Further, in addition to inherent risk of failure, establishing a new funding mechanism in an already crowded global architecture would not be timely nor likely to be welcomed by the donor community. Unitaid, which already funds HCV programmes and has collaborated with Gavi 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 donors, philanthropic agencies, the private sector, and innovative financing instruments (eg, solidarity levies). In addition, Unitaid established and hosts the MPP.

As a fourth step, several innovative financing instruments with successful track records could be replicated to mobilise new and additional funding 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 organisations, could produce impactful results to eliminate viral hepatitis. Depending on the setting and the need, each of these instruments could be used. 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

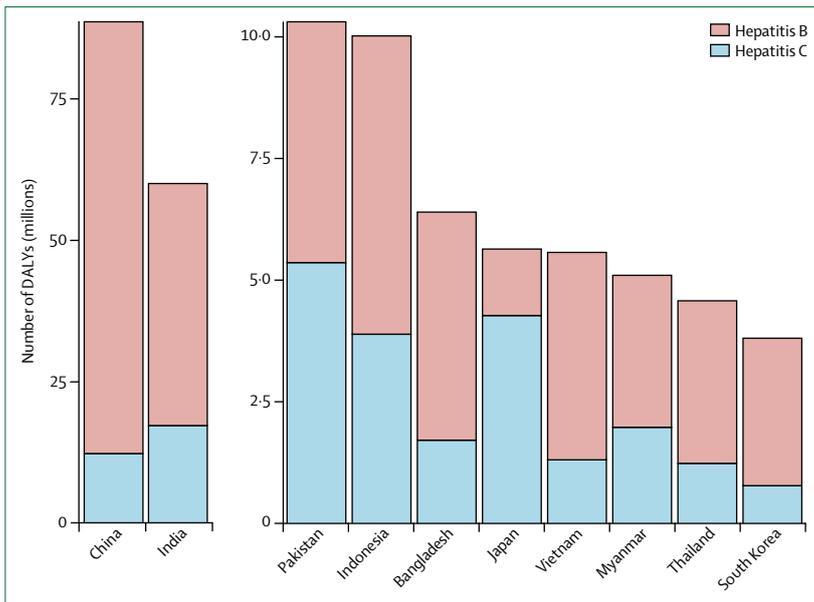


Figure 6: The ten countries with the greatest burden from viral hepatitis in Asia (data from Global Burden of Disease, 2016)

conversion instruments would be useful in countries where domestic financing is low and where programmes do not exist to stimulate investment and 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 viral hepatitis screening and treatment. Innovative financing, with its untapped potential, holds the promise of being the catalyst for elimination of viral hepatitis (panel 3).

Viral hepatitis in Asia

Asia experiences a greater challenge from HBV and HCV infections than any other region of the world,⁹ with half of the 20 most heavily burdened countries being from this region. The region accounts for 74% of deaths from liver cancer globally, mainly attributable to HBV and HCV.¹⁶⁷ The region is home to approximately 180 million HBsAg positive individuals and 31 million viraemic with hepatitis C.^{7,8} Countries in Asia with a high burden of viral hepatitis span the economic spectrum from high income (Japan, South Korea), 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.¹⁶⁸

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).¹⁶⁹

Deaths from HBV-associated liver cancer increased from 1990 to 2013 in many countries and territories, most dramatically so in Myanmar, Taiwan, Vietnam, and Thailand, whereas deaths due to HBV-related cirrhosis declined in Bangladesh, mainland China, 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 6), with more than around 80 million people estimated to be chronically infected.⁸

Success stories and ongoing challenges

Major success stories in the region include the implementation of highly successful programmes of HBV vaccination, inclusion of HBV treatments in social health insurance programmes, and the widespread availability of effective generic direct-acting antivirals for treatment of HCV infection. However significant challenges remain, including ongoing mother-to-child transmission of HBV, unsafe injection practices, and still-limited access to direct-acting antivirals despite availability of generics.

Several high-income countries and territories in Asia—including Japan, South Korea, and Hong Kong—have demonstrated what can be achieved by scaling up HBV vaccination. All three have long-standing vaccination programmes that have differed in their success to date. Vaccination was introduced in Hong Kong in 1983, with universal implementation in 1988.¹⁷⁰ As a result, a marked decrease in the prevalence of HBV in Hong Kong was reported in pregnant women born after 1984 compared with those born before 1984, with the former up to 68% less likely to be infected by HBV.¹⁷¹ Vaccination of health-care workers in Hong Kong was also prioritised in 1983 and is now a key method of maintaining immunity in medical workplaces.¹⁷⁰ Japan similarly prioritises vaccination of health-care workers, but only recommends vaccination of newborn babies of HBV-infected mothers.¹⁷² Neonates born to HBV-infected mothers in Japan are also treated with hepatitis B immunoglobulin (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 eighth to 16th in terms of hepatitis-related mortality. Among lower-income countries, Bangladesh was one of the first to introduce HBV vaccination in 2003 and as a result, HBV prevalence in Bangladesh declined from 8% in 1984 to 5.4% in 2007.¹⁷³

China has met and exceeded the WHO Western Pacific region target for HBV vaccination and reduction of HBsAg prevalence among those less than 5 years of age. In mainland China, universal HBV vaccination in newborn babies started in 1992, and the vaccine has been

provided free of charge since 2002; vaccination services for newborn babies has also been free since 2005.¹⁷⁴ 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, and from 9·7% in 1992 to an estimated 0·32% in 2014 in those aged less than 5 years.¹⁷⁵ The enormous effort and great success in prevention and control of HBV by universal vaccination in China has been highly praised by WHO and awarded by WHO Western Pacific region.

Timely birth dose of HBV vaccine is key to preventing mother-to-child transmission of HBV in China,¹⁷⁶ 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 2014.¹⁷⁷ 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, and has provided 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.²⁰ 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 the birth dose vaccine and HBIG for newborn babies of mothers who are HBsAg positive, and antiviral therapy during the third trimester for mothers with high viral load. By March 2017, 106 project hospitals had been recruited into the project, more than 2000 doctors have been trained and 4502 pregnant women infected with HBV had been treated under the scheme.^{178,179}

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 zidovudine—have been included in the national reimbursement list for the insured since 2010.¹⁷⁴ Due to the advocacy of all stakeholders, the price of TDF for treating HBV has been dramatically reduced in mainland China 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 TDF¹⁸⁰ has steadily increased, 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 programme has been offered to more than 9000 local doctors who work at hospitals in 60 small or medium-size cities which are home to a majority of people who are chronically infected with HBV in mainland China (Jia J, 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 2006.¹⁷⁴

Unsafe medical injection remains a major challenge in the region. In 2015, WHO launched new injection safety guidelines,⁷² 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 community-based intervention in rural Pakistan designed to improve knowledge and practice of safe medical injections was shown to 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).¹⁸¹ 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.

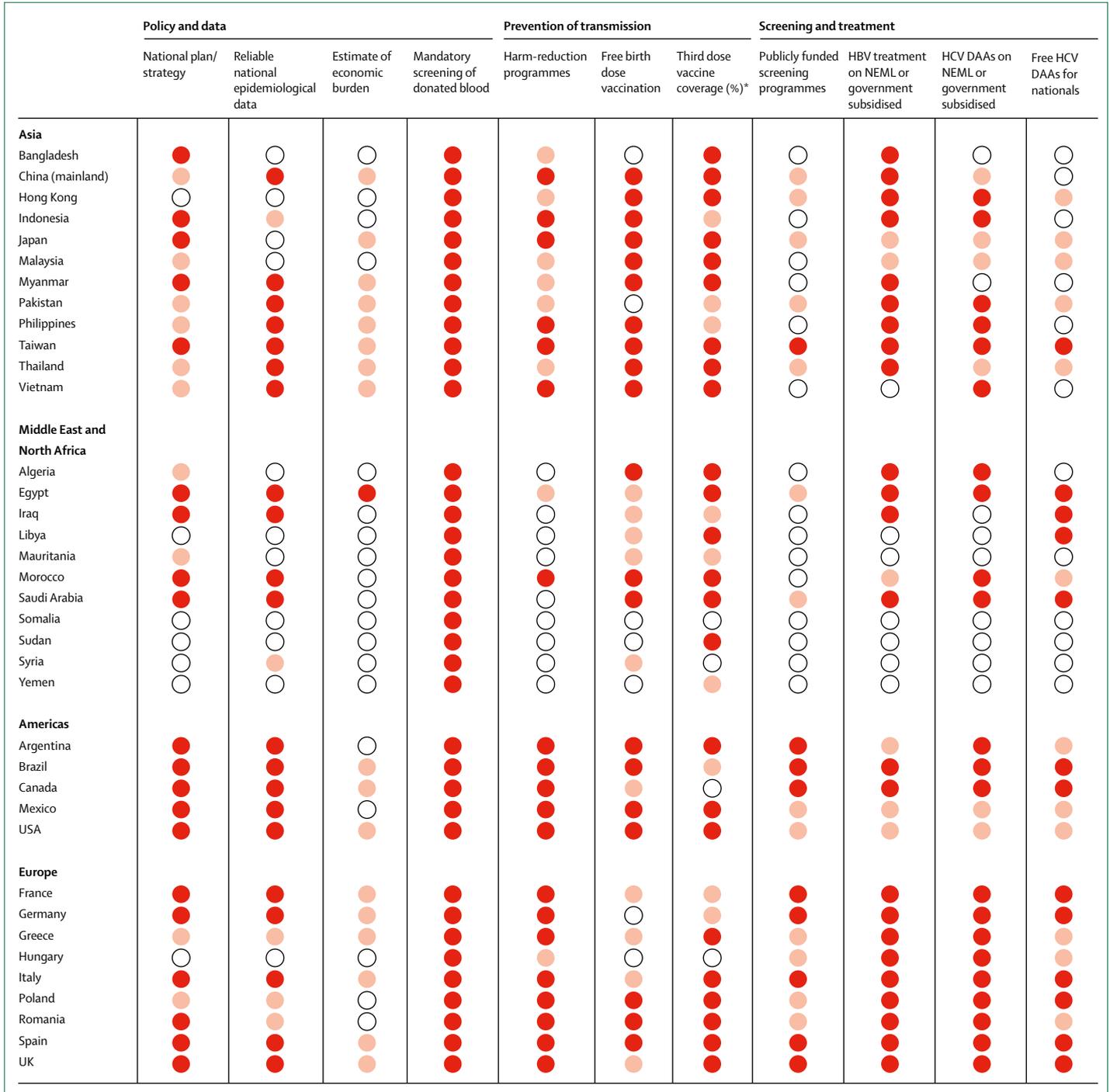
Although access to treatment with direct-acting antivirals is still limited within the region (figure 7), India and Bangladesh have become global powerhouses for the manufacturing of generic antiviral therapy for HCV. Voluntary licences for sofosbuvir, daclatasvir, velpatasvir, and voxilaprevir have the potential to bring direct-acting antiviral costs into an affordable range, and 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 licence, is a positive move toward addressing the problem of accessibility and affordability. However, in mainland China, only a few direct-acting antivirals have been recently approved and are available, and their high cost has precluded them from wide coverage in the basic social health insurance programme. So far only a few provinces have included direct-acting antivirals in their list of medications for reimbursement.

Where available, provision of direct-acting antiviral 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 3000 physicians have been trained.

Non-governmental organisations (NGOs) have an important role to play in advocacy for patients with hepatitis throughout the region. Notable achievements

include those of the China Foundation for Hepatitis Prevention and Control, 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



(Figure 7 continues on next page)

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 using social media. Their advocacy efforts toward reducing drug prices and including TDF and direct-acting antivirals in medication reimbursement lists have been successful at the national (TDF) and regional (direct-acting antivirals) levels. NGOs and civil society will need to play a bigger role with respect to elimination efforts in the future.

Barriers to elimination

Despite the overall high burden of disease, there are great disparities in governmental responses to the viral

hepatitis epidemic in Asia. 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. The CEVHAP¹⁶⁹ 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

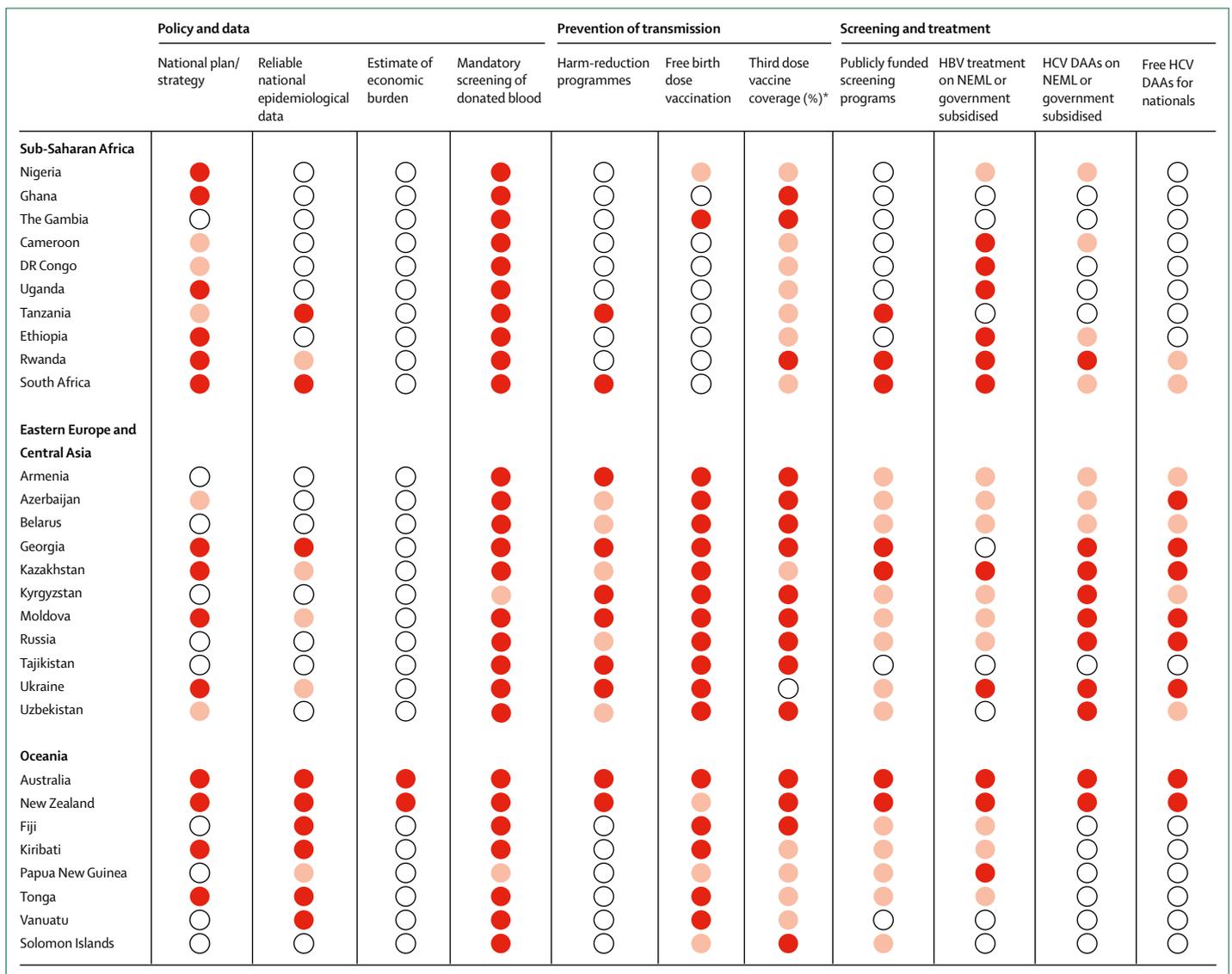


Figure 7: Progress towards elimination targets in the most heavily burdened countries within each region reviewed (as assessed mid-2018)

Red circles denote the existence of a policy; pink circles denote that a policy is in development, is not well applied, or is in place for specific subpopulations; white denotes the absence of a policy.

*Shows coverage of infant immunisation programmes including at least three doses of HBV vaccine, where: red symbolises ≥90% coverage (2020 target), pink symbolises 60–90% coverage, and white symbolises <60% coverage or no policy. NEML=national essential medicines list. DAA=direct-acting antiviral.

Panel 4: Key priority areas for action for Asia

- Increase political engagement in the elimination effort, particularly in 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 emphasis on maximising birth dose vaccination and preventing mother-to-child transmission
- Control the spread of viral hepatitis through nosocomial means, particularly unsafe injection practices
- Capitalise on the availability of cheap generic medications in the region for treatment of both HBV and HCV and develop strategies to increase access significantly

strategic plans to eliminate viral hepatitis in line with WHO targets (figure 7). However, budget allocation towards implementation of these plans is still to be confirmed in most 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. Only Japan, Hong Kong, and 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.¹⁶⁹ Discrimination against people with chronic HBV infection still exists, particularly among less well-educated individuals.¹⁸² To protect rights to education and employment, tests for HBV infection at recruitment of students and employees have been banned in mainland China since 2010.

There are fewer success stories among PWID, which comprise a population of at least 2·8 million in Asia.^{183,184} For example, Malaysia and China are among the few countries in Asia to implement a methadone substitution programme for PWID.¹⁸⁵

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.^{186,187} Pakistan is estimated to have the highest use of therapeutic injections in the world at 13–14 injections per person per year (compared with the WHO standard of one or two injections per person per year¹⁸⁸). The high rate of medical injections, alongside other risk factors such as blood transfusions, dental treatments, and individual risk behaviours like tattooing,¹⁸⁶ has contributed to an

estimated 150 000–200 000 new HCV infections each year in Pakistan¹⁸⁶ These challenges are shared in many other countries in the region.¹⁸⁹

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.^{190–192} Moreover, in many countries there is a disparity between urban and rural populations in terms of access to diagnostics and treatment.¹⁹²

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 engage in elimination efforts, much work is needed to achieve political engagement, particularly in high-burden, low-income countries (panel 4). 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 serosurveillance 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 a 15-year horizon.¹⁹³ 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; for example, only 32·5% of men received all three recommended doses of the vaccine in 2006–08, primarily because of a lack of public awareness about the necessity of vaccination.¹⁹⁴ 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.¹⁹⁵ 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.¹⁸⁶

With regard to access to direct-acting antivirals, 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 pangenotypic direct-acting antiviral regimens would be beneficial alongside greater efforts to ensure drugs are registered rapidly once available.

Asia has a higher 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 vaccination campaigns against HBV in some countries and availability of oral generic medications to treat both hepatitis B and C, challenges remain particularly in areas of high nosocomial transmission despite wide access to medications. 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).

Viral hepatitis in the Middle East and North Africa

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.^{7,8} Prevalence of HBV and HCV varies across the 22 countries in the region; HBV prevalence ranges from 16% to 19% in Mauritania and Somalia to 0·5% in Bahrain (appendix pp 11, 12). 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.^{196–198} Egypt also dominates the region with respect to DALYs attributable to viral hepatitis (figure 8). Of the estimated 6·6 million HCV-viraemic individuals below 15 years of age globally,¹⁹⁹ 820 000 (12·5%) live in the MENA region (appendix pp 11, 12).¹⁹⁹ 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.

Programmes 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 health-care 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 a substantial progression path to elimination of viral hepatitis (figure 7).

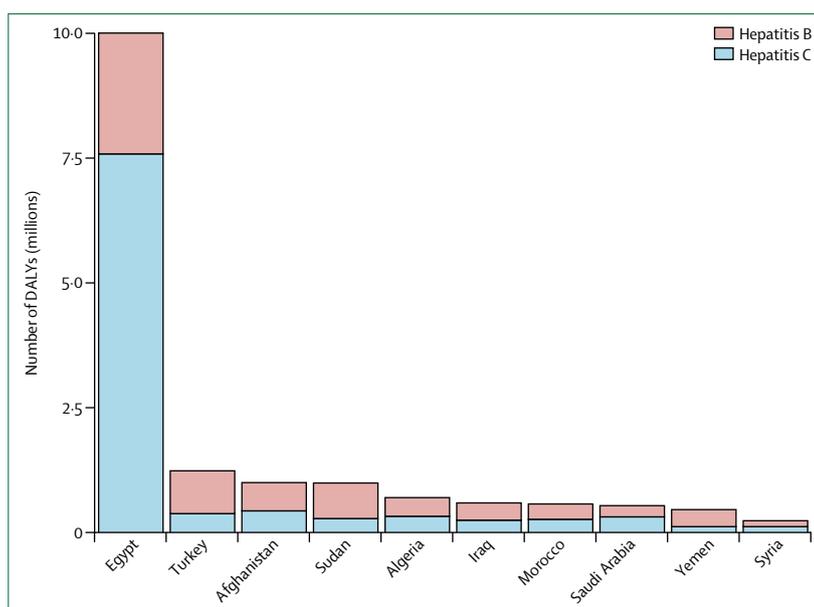


Figure 8: The ten countries with the greatest burden from viral hepatitis in the Middle East and North Africa (data from Global Burden of Disease, 2016)

Success stories and ongoing challenges

The huge burden of HCV in Egypt and HBV in Saudi Arabia, and the efforts undertaken to control the epidemic and eliminate viral hepatitis in these countries, are exemplary and illustrate how a well planned and executed national programme 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.^{200,201} This represents the largest ever iatrogenic spread of blood-borne infection, with millions of people exposed to HCV, resulting in the high prevalence of HCV infection that remains today.^{202,203} 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.^{204,205} The NCCVH set a national strategy and established specialised treatment centres managed by qualified hepatologists. Through the programme, treatment is paid for by the state, including full reimbursement for laboratory tests and treatment. In 2014, an action plan was developed that aimed to reduce the national prevalence of HCV to less than 2% by 2025 and less than 1% by 2030, potentially preventing more than 250 000 deaths between 2015 and 2030 (appendix p 13).²⁰⁶ As part of this plan, the NCCVH negotiated the price of direct-acting antivirals down to 1% of the US price,²⁰⁷ without precluding local production of generics. The introduction of locally produced generics in late 2015 reduced the cost of 12 weeks' treatment with sofosbuvir/daclatasvir to about US\$80, resulting in a massive treatment uptake of about 1 million patients in 2016 and 2017.^{204,208} As a result, Egypt is on the path to meet

elimination targets for HCV by 2030 or even earlier. By May, 2018, close to 2 million patients with chronic hepatitis C had been treated with direct-acting antivirals; the treatment rate has now exceeded 25% of the infected population.

The programme in Egypt had to overcome several unanticipated challenges during the first phases of its initiation, which serve as lessons for other countries in the region and elsewhere.⁸³ The initial challenge was management of the number of patients to be treated upon initiation of the programme, 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 programme to less than 10 000 patients per month in 2017. To address this, the Ministry of Health started a national screening programme in October, 2018, with the aim of testing all individuals over the age of 18 years in Egypt for HCV antibodies (using rapid diagnostic tests at an estimated cost of less than US\$0.6 per test) as part of a novel national programme to test and treat HCV, hypertension, diabetes, and obesity. 57 million individuals will be screened within the first year, and within the first month, 6.4 million individuals have been evaluated, with 5% testing antibody positive and who are now being assessed for HCV treatment.²⁰⁹ This effort will put Egypt even further on the road to elimination of HCV.

Several factors contributed to the initial success of Egypt's national HCV treatment programme, 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 direct-acting antivirals with excellent safety and tolerability profiles, the decreasing costs of brand medications at the outset of the programme, and the approval and use of effective cheap local generic medications facilitated the escalation of the programme. Although Egypt remains the country with the highest prevalence of HCV in children (1.08%), a dedicated paediatric programme for treatment of HCV sets it apart from other countries in the region. To date, more than 1000 children aged 3 to 18 years have been treated with pegylated interferon through an NGO-sponsored programme. Direct-acting antivirals approved for children are currently being used in some centres but are yet to be introduced into the national treatment programme. The NCCVH action plan also included guidelines for ensuring

blood safety, injection safety, and strict infection control,²¹⁰ which were applied to a few model dialysis centres and were instrumental in reducing incidence and prevalence of HCV,²¹¹ 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 a quarter of adult men, more than 10% of women, and 7% of children.²¹² As part of the national plan, a vaccine programme was launched in 1989,²¹³ with a catch-up programme to vaccinate all children at school entry, and vaccination of all health-care workers and patients receiving haemodialysis. As of October, 2007, all people aged 24 years or younger (about 60% of the population) had been vaccinated,²¹⁴ and vaccination coverage is now close to 100%. The vaccination programmes were coupled with strict national blood safety and health-care infection control policies, including mandatory testing for HBV, HCV, and HIV as part of a compulsory premarital screening programme, as well as recommended screening for HBsAg among pregnant women,²¹⁵ resulting in almost complete blood safety. As a result, the prevalence of HBV in Saudi Arabia has dropped substantially over the past two decades, with the virtual elimination of HBsAg among vaccinated children aged 1–12 years.^{216,217} 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 acknowledgment 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 direct-acting antivirals or patients with HBV 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 programmes or affordable generics. The cost of HCV diagnostic tests is also increasing (the cost of diagnostic tests in Egypt's national programme 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 core antigen 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 occurs in health-care settings, and strict infection control standards must be enforced throughout government and private health-care settings. The growing size of the youth population in the MENA region (160 million people aged 14 years or younger; appendix p 14) represents another potential barrier to HCV elimination, and prevention, diagnosis, and management of HCV at an early age is essential (panel 5).

Viral hepatitis in the Americas

The Americas account for just under 10% of both deaths and DALYs attributed to viral hepatitis globally. By contrast with Asia, HCV is the greatest challenge to public health in the region, accounting for 70–80% of hepatitis-related deaths (figure 9). The USA, Brazil, and Mexico account for approximately half of the regional disease burden (figure 9), and are home to approximately 4.2 million HBsAg positive individuals and 7 million individuals with HCV viraemia.^{7,8} An estimated 2.7–3.5 million people live with chronic HCV in the USA alone.²¹⁸ 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,^{10,219,220} which remains the leading cause of cirrhosis and hepatocellular carcinoma in the country.²²¹ The USA and Brazil, which have similar burdens of disease but very different economic resources (per capita income of USA is approximately six 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,²²² representing over 90% of births within the region, although this is not yet widely implemented in Canada (figure 7). The USA and Brazil have achieved high full series coverage of HBV vaccination; coverage of the three-dose vaccine 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 with 72% in USA). Several countries including Argentina, Brazil, Peru and the USA, have extended vaccination to older groups and have implemented catch up vaccination campaigns.²²²

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 per 100 000 individuals, and among underserved communities. For example, HBV was endemic in the 1970s among the Alaska Native People (HBsAg prevalence of 3–8%),²²³ but a comprehensive screening and vaccination programme in the 1980s reduced transmission from over 200 symptomatic cases per

Panel 5: Key priorities for action in the Middle East and North Africa

- 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 programmes that have been disrupted due to conflict
- Implement maternal screening for HBV in all countries
- Implement vaccination programmes 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

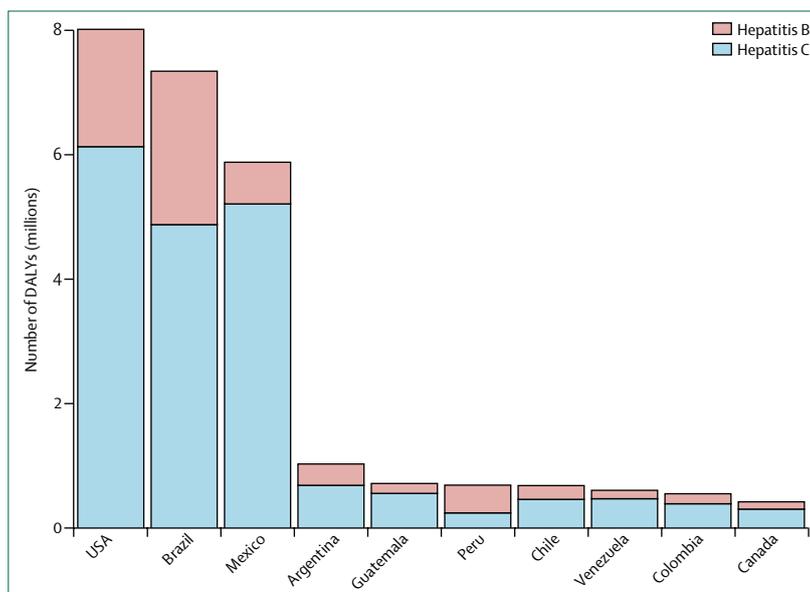


Figure 9: The ten countries with the greatest burden from viral hepatitis in the Americas (data from Global Burden of Disease, 2016)

100 000 to none. Annual incidence in this population is now less than one per 100 000 individuals, and no child under 20 years of age is known to have chronic HBV.²²⁴ Substantial declines in childhood HBsAg prevalence have also been documented in Peru,²²⁵ Colombia,²²⁶ and Canada.²²⁷ Vaccination efforts in Brazil have resulted in a change in the country's HBV endemicity status from intermediate to low.²²⁸ However, there remain marked regional differences²²⁸ with particularly high HBsAg prevalence (up to 6.2%) in areas of the Amazon.²²⁹ In the USA, 84–88% of pregnant women are tested for HBsAg.

Despite this, an estimated 800–1000 infants are infected at birth.²³⁰ 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.²³¹

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 programme (Sistema Unico de Saude), and periodically publishes guidelines for viral hepatitis management in the country.²³² In 2015, direct-acting antiviral therapy was made available, although as of early 2018, direct-acting antiviral therapy was limited to those with significant fibrosis or high risk of complications.²³² In 2011, the government implemented rapid HCV testing, with around 3 million tests done annually in the last few years,²³³ as compared with estimates of 20 000 HCV infected patients diagnosed annually and as few as 10 000 treated each year in 2013.^{220,234} Falling drug prices are expected to make treatment more widely available, with more than 60 000 patients already receiving direct-acting antiviral treatment between 2015 and 2017.

In the USA, one-time HCV testing is recommended for people born between 1945 and 1965, as an estimated 75% of all HCV-infected individuals 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.^{235,236} Advocacy for this approach is emerging elsewhere in the region, including Canada and Brazil.²³⁷ 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 2015.²³⁸ Reductions of HCV incidence have been documented among PWID,²³⁹ and this population is an ongoing focus of prevention efforts. The US prison population is another major barrier to elimination efforts. Over a million people are incarcerated in the USA at any given time with limited access to health care, including hepatitis testing and treatment.²⁴⁰ Testing and treatment for HCV in correction facilities represents an enormous opportunity to achieve elimination goals.^{241,242}

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 programme.²⁴³ 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 programmes, and designating pharmacies as sources of safe injection equipment.

In Brazil, major geographical, social, and economic disparities exist among the different regions of the country, creating inequities in access to care, especially for sub-populations 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 direct-acting antiviral 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 HCV antibody-positive patients in the region were lost to follow-up (lapse of more than a year since the last clinical appointment).²⁴⁴ And despite increased HCV testing in Brazil, the proportion of those diagnosed remains low.^{220,234}

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.²⁴⁵ 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.²⁴⁶ This gap is reflected by the low (about 50–60%) awareness of HCV infection in USA.²⁴⁷ Furthermore, many primary-care clinicians in the USA remain unprepared to provide direct-acting antiviral 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 people with chronic HBV migrating to the USA in 2004–08,²⁴⁸ 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 higher than 2% HBsAg prevalence.

Incomplete epidemiological and surveillance data are another major impediment to achieving elimination goals in the USA (panel 6). At present there are insufficient resources to provide the case surveillance data needed to monitor the number of HBV-infected people, and 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 and Prevention (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 serological surveys of high risk populations, an endeavour that could be facilitated by leveraging existing HIV-HCV and cancer registries and electronic clinical care data.²⁴⁹ 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 most countries lacked access to direct-acting antivirals.²⁵⁰ The Pan American Health Organisation's strategic fund has incorporated direct-acting antivirals as of 2017, which allows pooled procurement of essential medicines and strategic health supplies. The fund can supply interest free credit lines to countries, Colombia being among those who have used them.²⁵⁰

Viral hepatitis in the European Union

The burden of viral hepatitis in the 28 member states of the EU varies significantly from country to country, but is greatest in Italy and Germany (figure 10). A relatively high prevalence of viral hepatitis in new member states have added to the overall regional disease burden (figure 10).

In 2016, the prevalence of chronic hepatitis B in the EU was estimated at 0.89% (4.5 million individuals), with country level HBsAg prevalence ranging from 0.1% to 5.5%.⁸ 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 in the EU aged 5 years was 0.11% in 2016;⁸ 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 (appendix p 15).¹

In 2015, the prevalence of HCV in the EU was estimated at 0.64% (95% UI 0.41–0.74) corresponding to 3 238 000 (95% UI 2 106 000–3 795 000) RNA positive infections.²⁵¹ The highest burden of the disease in the EU is found in Italy, Germany, France, UK, Spain, Romania, and Poland (figure 10). 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 PWID²⁵² and there is a higher prevalence amongst prisoners, migrants, and the homeless compared

Panel 6: Key priorities for action in the Americas region

- Ensure adequate resources for surveillance and data collection systems to monitor and evaluate progress towards elimination goals
- Account for new infections due to migration in achieving elimination targets for HBV
- Ensure a greater focus on access to care and treatment for incarcerated populations, particularly in the USA
- Support the development of decentralised services and prescribing by non-specialists to reach underserved populations far from large urban centres
- Ensure countries throughout the region can use existing mechanisms to ensure procurement of affordable medicines (eg, using the Pan American Health Organization)

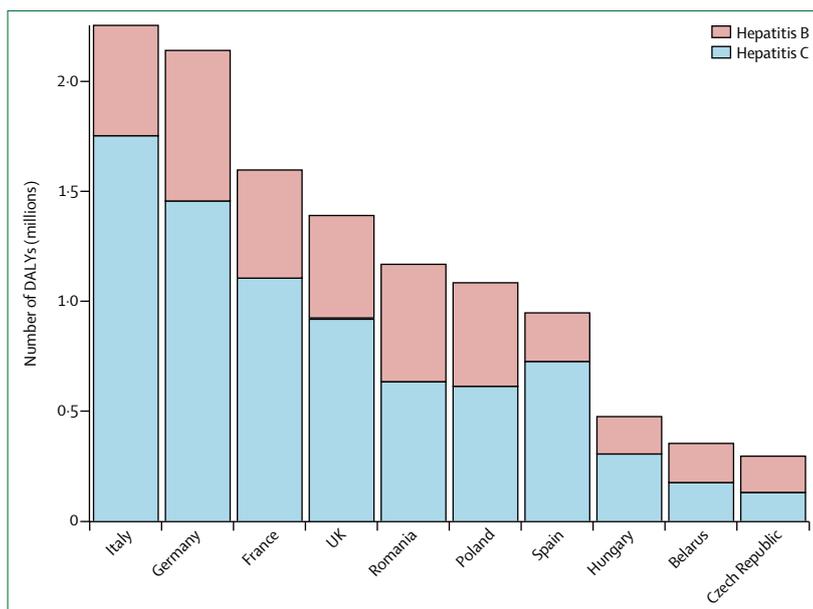


Figure 10: The ten countries with the greatest burden from viral hepatitis in the EU (data from Global Burden of Disease, 2016)

with the general population.²⁵³ A high proportion of PWID in the region are under 25 years of age (29.8%), recently homeless or with unstable housing (21.9%) and have a history of arrest (66.6%) or incarceration (36%), highlighting the challenges of prevention and treatment in this population.²⁶ 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 aged 45 to 60 years, suggesting a possible birth-cohort group for targeted screening programmes.

In the WHO Euro region, an estimated 14% of all HBV infections are diagnosed,¹ 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 with 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.²⁵⁴

Europe has well characterised cohorts with HCV-HIV co-infection.²⁵⁵ Data from the EuroSIDA HIV-infected observational cohorts show that the prevalence of people positive for HCV antibodies varies: in eastern and southern Europe (where HIV is frequently acquired via injection drug use), 58% and 29% of patients are HCV-antibody positive, respectively, and modelling suggests that eliminating HCV from HIV-positive populations will be possible.²⁵⁶ In northern and western Europe (where sexual transmission among MSM is the major route of HIV transmission), 17% and 20% HIV-positive individuals are anti-HCV antibody positive respectively.²⁵⁷ 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.^{67,258} 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.²⁵⁹

Success stories and ongoing challenges

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;¹²⁷ in Spain and Portugal, more than five times more people reached SVR than there were new infections in 2016.¹²⁷ 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, programmes 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 in Portugal. 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; by comparison, less than 1% of infected individuals 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 to examine those achieving SVR between 1997 and 2016, one report found that the apparently higher incidence of hepatocellular carcinoma after direct-acting antiviral therapy might be explained in part by differences in clinical characteristics of groups receiving different treatments.²⁶⁰ The UK clinical and public health systems are providing some of the strongest evidence of the success of direct-acting antivirals on the clinical burden challenge of HCV.^{261–263}

Barriers to elimination

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.²⁶⁴ Limited data indicate that prevalence of HBV and HCV is higher in migrants to the EU and the EEA countries compared with the population as a whole, reflecting prevalence rates in their countries of birth.²⁶⁴ The number of new HCV infections in the EU is estimated at 57 900 (95% UI 43 900–67 300) per year, with another 30 400 (95% UI 26 600–42 500) new infections diagnosed amongst migrant populations.⁷ An estimated 1–2 million migrants to Europe have chronic hepatitis B.²⁶⁵ Migrants therefore are a key group for case finding and treatment and constitute an important relative contribution to the 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 1800 new cases through immigration in the same year.²⁶⁴

Most newly acquired chronic HBV infections are perinatal,²⁶⁶ and the prevalence of HBV among women of child-bearing age is highest among immigrant populations.²⁶⁵ 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.²⁶⁷ In 2016, the European Monitoring Centre for Drugs and Drug Addiction 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.²⁶⁸ Only ten 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.²⁶⁸ In seven countries, less than 30% of the target population was estimated to be receiving opioid substitution therapy.²⁶⁸ As in other parts of the world, opioid substitution therapy and (particularly) needle

and syringe programmes 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.²⁶⁹

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.²⁷⁰ 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).

Viral hepatitis in sub-Saharan Africa

HBV is endemic in sub-Saharan Africa. WHO estimates prevalence of HBsAg at 6.1–8.8%³⁰ with approximately 80 million chronically infected and 1.96 million co-infected with HIV.⁸ The burden of HCV is also significant, with approximately 10 million infected.⁷ In west and central Africa, 5.7% are co-infected with HCV and HIV.^{271,272} HBV and HCV infection in the ten most heavily burdened countries in sub-Saharan Africa (figure 11) account for approximately 200 000 deaths annually, equating to just under a fifth of the global mortality.⁹ HBV alone is implicated in more than half of liver cirrhosis and three-quarters of hepatocellular carcinoma cases.²⁷³

New highly effective treatments, innovative diagnostics, and the new global political landscape focused on hepatitis make elimination of viral hepatitis in sub-Saharan Africa feasible. Many countries are developing national viral hepatitis plans, and some countries already have such plans (figure 7). Nonetheless, WHO targets are formidable in a region comprising 47 countries with a mean per capita GNI of less than \$1657 and a total health expenditure of only 5.5% of GDP.²⁷⁴ Many countries in sub-Saharan Africa share health-care challenges related to large rural populations, poor health infrastructure, shortages of health-care 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 sub-Saharan Africa) and 33 000 were estimated to be treated, which equates to less than 1% of those

Panel 7: Key priorities for action in the EU

- Develop a cohesive regional European strategy for coordination of data, context-based screening, and drug procurement
- Develop costed elimination delivery plans and ensure that appropriate resources are in place to provide access
- Develop and implement, or strengthen, HCV screening, treatment, and harm reduction programmes among high-risk groups
- Ensure access to national health and insurance services among migrant populations, with efforts to remove stigma
- Promote widespread adoption of decentralised care and implement point-of-care testing in high-prevalence environments (prisons, addiction centres, and high-prevalence regions)

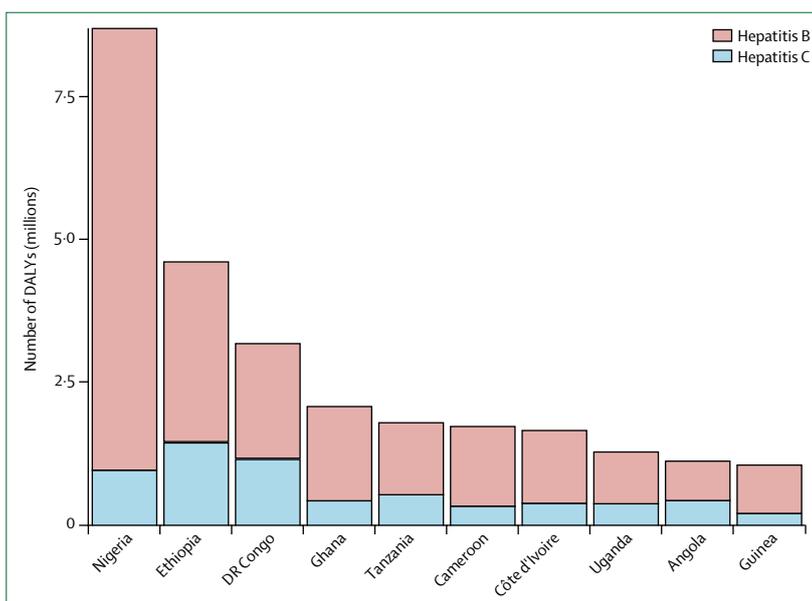


Figure 11: The ten countries with the greatest burden from viral hepatitis in sub-Saharan Africa (data from Global Burden of Disease, 2016)

eligible.⁸ 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 sub-Saharan Africa had developed a costed hepatitis plan (Ghana, Nigeria, Ethiopia, Côte d'Ivoire, Senegal, South Africa, and Mauritania) whereas 15 other countries (including Cameroon, Tanzania, and Democratic Republic of Congo) had drafts in various phases of development). In many parts of sub-Saharan Africa, the lack of detailed and reliable HBV and HCV seroepidemiological data hampers planning, despite existing data suggesting considerable burden. This must not be used as an excuse to retard implementation.

Panel 8: Key priorities for action in sub-Saharan Africa

- Ensure full vaccine coverage and universal implementation of HBV birth dose vaccine within 24 h of delivery
- Prioritise universal antenatal screening for HBsAg
- Ensure availability of affordable, high-quality nucleic acid tests for both HBV and HCV
- Ensure sustainable access to treatment for HBV mono-infected individuals, in addition to those with HBV-HIV co-infection
- Develop education programmes around HBV and HCV to decrease public stigma around viral hepatitis
- Mobilise community-based activist or support groups to support viral hepatitis programmes
- Decriminalise high risk groups (eg, men who have sex with men and people who inject drugs)

Success stories and ongoing challenges

Rwanda was one of the first countries in sub-Saharan Africa 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 direct-acting antiviral regimen approach.²⁷⁵ Rwanda's hepatitis C programme has continued to grow rapidly. By mid-2018 300 000 individuals had been tested for HCV and free HBV and HCV was available to all citizens,²⁷⁶ 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 there is governmental commitment to strengthening health infrastructure and provision of adequate financing for compulsory health insurance.

The testing of blood products for transmissible infection has improved significantly in sub-Saharan Africa. 40 WHO Africa countries in the region now report testing 100% of all blood donations for transfusion-transmitted infections,²⁷⁷ although overall coverage is still lower than other regions.

Barriers to elimination

Horizontal transmission in childhood is the predominant route of HBV transmission in sub-Saharan Africa, responsible for about 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 in this region.^{278,279}

By 2017, only nine countries in sub-Saharan Africa 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 (eg, 40–50% of deliveries in Uganda and Nigeria). Additional barriers to providing the birth dose vaccine in sub-Saharan Africa include cost; 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 or her to a health-care facility for vaccination.²⁸⁰

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 health-care workers to administer the vaccine have been successfully used in Vietnam, Indonesia, and China^{281–283} and require evaluation in sub-Saharan Africa (panel 8). Integration of the birth dose vaccine into an early postnatal care package that includes home visits within a day of home birth, as recommended by WHO and UNICEF, would have the dual benefit of improving neonatal survival and reducing long-term HBV mortality.²⁸⁴ Introduction of monovalent HBV birth dose vaccine within 24 h 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.

Injection drug use is a barrier to elimination efforts in sub-Saharan Africa, as elsewhere. 8% of PWID globally are estimated to live in sub-Saharan Africa.¹⁸⁴ However, few countries have government supported needle and syringe programmes or opioid substitution programmes,²⁸⁵ 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 countries in the region.

Another major barrier to elimination in sub-Saharan Africa is the lack of awareness about viral hepatitis among both patients and health-care workers. Data from west Africa reported that fewer than 1% of participants knew of their hepatitis B status,⁷⁸ and health-care workers often lack adequate knowledge of viral hepatitis, in stark contrast with their HIV knowledge.²⁸⁶ 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, health-care 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 health-care 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,²⁸⁷ as compared with less than 20% in southern African countries such as South Africa, Namibia, Mozambique,

and Botswana, where government health-care financing is greater.²⁸⁸ Even with falling prices for viral hepatitis therapy, treatment and diagnostics remains unaffordable for many people in the region.

Only 3% of the global health-care workforce resides in sub-Saharan Africa and this shortage hinders the equitable delivery of health care, including for viral hepatitis. International migration, attrition, training shortfalls relative to population growth, and poor remuneration and working conditions contribute to these shortages.²⁸⁹ WHO estimates that 4·3 million health-care workers are needed to fill this gap in 57 countries in Africa and Asia.²⁹⁰ Expedited training of middle-level health-care medical, nursing, and laboratory personnel is required for health care in general. With the development of new rapid diagnostics and mobile health technologies, community health-care 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 health-care workers is a high priority in sub-Saharan Africa.^{291,292}

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 people 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, the Global Fund, and other global donors. With the decline in donor funding, the establishment of viral hepatitis programmes within the context of universal health care is currently being advocated by WHO, is supported by many countries within sub-Saharan Africa and is essential to achieve the viral hepatitis elimination targets.²⁹³

Viral hepatitis in eastern Europe and central Asia

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 9·9 million individuals with HCV viraemia⁷ in the region and a particularly high prevalence of viral hepatitis–HIV co-infection among PWID.²⁵⁵ In addition, approximately 8 million individuals in the region have chronic HBV infection.⁸

As in sub-Saharan Africa, there is a lack of reliable epidemiological data on viral hepatitis in most EECA countries due to an absence of national registers and large-scale testing campaigns or studies (figure 7).²⁹⁴ The greatest burden of disease in the region is found in Russia (figure 12). HCV prevalence estimates among the general population range from 1·2% (Kazakhstan) to 8–12% (Ukraine).²⁹⁴ HBV prevalence estimates range from 0·04% (Tajikistan) to 8% (Uzbekistan),²⁹⁴ although the low reported prevalence in Tajikistan likely reflects low

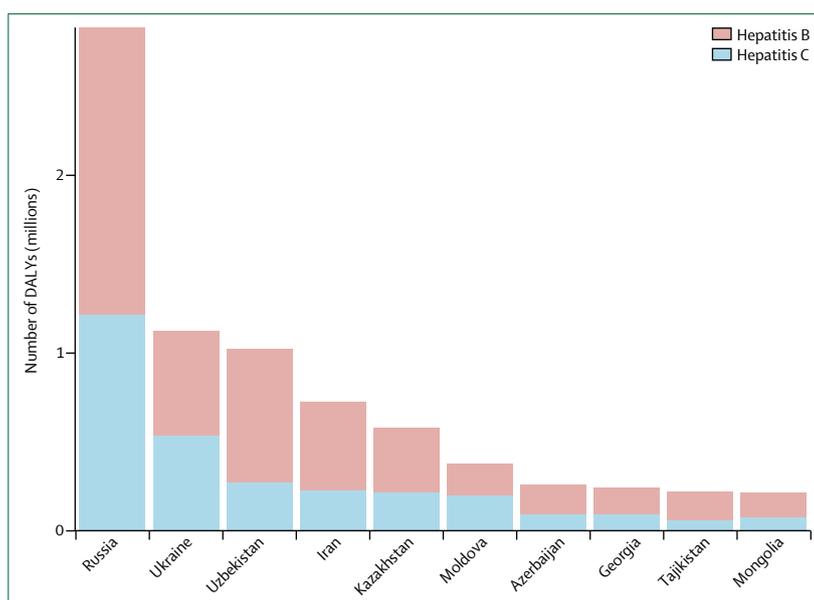


Figure 12: The ten countries with the greatest burden from viral hepatitis in eastern Europe and central Asia (data from Global Burden of Disease, 2016)

quality surveillance data. HBV vaccination is supported by governments, international organisations (eg, Gavi, UNICEF), or both, in most surveyed countries. Average coverage of HBV vaccination is 89%, but coverage ranges widely, with some regions having very low coverage (eg, 28·8% in Ukraine). Available data on 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.²

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 these individuals. 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 Russia). HBV prevalence among PWID ranges from 0·1% (Belarus) to 56% (Kyrgyzstan).²⁹⁴ For HCV, PWID are specified as a key population in national plans and guidelines in all countries. MSM, health-care workers, and patients undergoing invasive or hospital-level procedures are specified in national plans of ten countries. The EECA region has low coverage of antiretroviral therapy, estimated at 21%, meaning those living with HIV are particularly vulnerable to accelerated liver disease progression.

Success stories and ongoing challenges

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 health-care workers (5%).²⁹⁵ Treatment for HCV is freely available within the National HCV Elimination Programme. Civil 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 programmes are available in Georgia, Azerbaijan, and Moldova. Treatment for HBV and HCV is offered as part of state programmes 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 viraemic HCV infection was 11% and that of HBsAg was 11.8%.²⁹⁶ According to national statistics, liver cancer is the most prevalent cancer of all cancers in Mongolia.²⁹⁶ 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 hepatocellular carcinoma. The government allocated 232 billion Mongolian tögrög (US\$96 million) for the programme 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, health insurance will provide US\$75 for branded Harvoni and US\$65 for generic Harvoni. As of 2018, approximately 20 000 people have been treated with direct-acting antivirals, with a cure rate of 98–99% (Baatarkhuu O, personal communication).

In 2015, Alliance for Public Health with support from the Global Fund and Gilead, launched treatment programme in Ukraine specially targeted at PWID providing direct-acting antiviral-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 (Médicins Sans Frontières), Kazakhstan (AbbVie), and Kyrgyzstan (the Global Fund).

Barriers to elimination

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 PWID 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 a third of prisoners in the region, although they could account for 50–80% of the prison population in some countries.⁶¹

In countries where possession of micro-doses of drugs (eg, >0.005 g opium extract in Ukraine) classifies as a drug violation, harm reduction programmes face different serious barriers, up to detainment and prosecution of outreach workers in possession of used (exchanged) syringes. As a result, drug users often refuse to participate in needle and syringe programmes, which are available in all surveyed countries but to widely varying degrees (eg, >1600 needle and syringe programmes sites in Ukraine, but only four in Russia). Needle and syringe programmes in prisons and other parts of the penal system are provided only in Armenia, Kyrgyzstan, Moldova, Ukraine, and Tajikistan. Access to opioid substitution therapy is also limited, with no programme in Uzbekistan and prohibition of these programmes in Russia. Almost 900 patients from non-government-controlled areas of Donetsk and Luhansk oblasts were deprived of opioid substitution therapy at the beginning of the armed conflict between Russia and Ukraine in 2014, and the opioid substitution therapy programme in Crimea was discontinued. In Georgia, prisoners can receive opioid substitution therapy only for detoxification in some pre-trial detention facilities. HCV treatment for individuals undergoing opioid substitution therapy also occurs in prisons in Moldova.

In April, 2016, during the United Nations General Assembly Special Session, Ukraine, Moldova, and Georgia signed a statement²⁹⁷ 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 decreases in 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 most cases.

Despite some progress in the region, recent estimations indicate only 1% of people with HCV have access to treatment.²⁹⁴ Three countries (Azerbaijan, Georgia, Uzbekistan) can access generic daclatasvir (from Bristol-Myers Squibb) thanks to the agreement between Bristol-Myers Squibb and the MPP. Most others can potentially procure daclatasvir from the MPP licences if there is no patent infringement. The bilateral Gilead voluntary licensing agreement for sofosbuvir covers Belarus, Kyrgyzstan, Tajikistan, Ukraine, and Uzbekistan.

In 2015–16, 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 the NGO Humanitarian Action, which resulted in exclusion of pro-drug formula from the patent. Starting from January, 2017, the drug manufacturer Nativia is conducting clinical trials of generic sofosbuvir 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 direct-acting antivirals through buyers' clubs²⁹⁸ is documented in four countries: Belarus, Kazakhstan, Russia, and Ukraine. In Belarus, a buyers' club is reportedly the main procurement source for treatment. Key priorities for action in eastern Europe and central Asia are shown in panel 9.

Viral hepatitis in Oceania

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.²⁹⁹ In 2016, the combined DALYs due to hepatitis B and C in Australia, New Zealand, Papua New Guinea, Solomon Islands, Fiji, Vanuatu, Guam, Tonga, Kiribati, and Samoa was approximately 1.5 million (figure 13). The region is home to an estimated 1 million individuals with chronic hepatitis B⁸ and 400 000 individuals with hepatitis C viraemia.⁷ The region provides an illustration of the contrast between high-resource 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 health care, heavily subsidised medications, and surveillance systems for notifiable infectious diseases, including viral hepatitis. The estimated prevalence of HBsAg in 2015 was 1.0% in Australia and 4.1% in New Zealand,^{30,300} 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%),^{29,301,302} with most new infections occurring in PWID.²⁹ HBV and HCV cause significant morbidity and mortality in Australia and New Zealand, accounting for 1.4% and 1% of deaths, respectively, in 2013,²⁹⁹ and the burden of viral hepatitis-related liver cirrhosis and hepatocellular carcinoma is rising. HCV accounts for 41% of annual cases of hepatocellular carcinoma, whereas HBV accounts for 22% of cases.^{303,304} 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,

Panel 9: Key priorities for action in eastern Europe and central Asia

- Develop reliable national surveillance system both for hepatitis B and C
- Develop and implement antidiscrimination policies in national strategies, including decriminalisation of personal drug use without intention to sell
- Ensure state funding to scale up harm reduction services including opioid substitution therapy and needle and syringe programmes
- 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 direct-acting antivirals and application of different strategies including the use of TRIPS (Trade Related Aspects of Intellectual Property Rights) flexibilities for scaling up access to generics
- Strengthen cooperation between civil society organisations and government and ensure community involvement at all levels of response to the epidemics

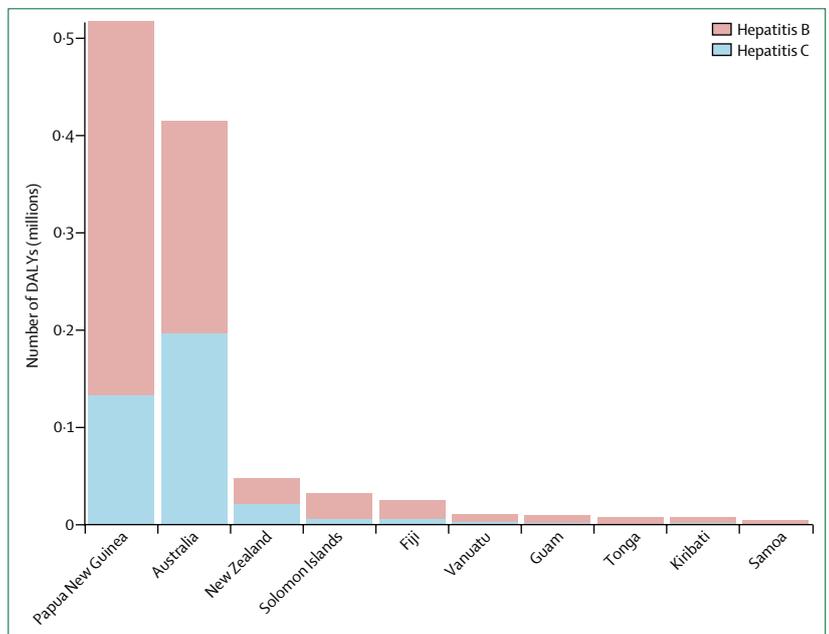


Figure 13: The ten countries with the greatest burden from viral hepatitis in Oceania (data from Global Burden of Disease, 2016)

respectively.³⁰⁵ Indigenous populations (eg, Aboriginal and Torres Strait Islanders in Australia, Māori in New Zealand) experience worse health outcomes and have higher prevalence of disease compared with the population as a whole.³⁰² Indigenous populations have lower HBV vaccination rates, higher rates of injection

Panel 10: Key priorities for action in countries and territories in Oceania

- Improve education among health-care workers and communities to increase awareness and demand for testing
- Initiate national government and advocacy group-led public health campaigns to reduce stigma associated with viral hepatitis
- Invest in improved HBV vaccine birth dose delivery
- Improve surveillance and data collection systems to outline, monitor and evaluate progress towards elimination goals
- Invest in health workforce and health system infrastructure
- Ensure access to government-subsidised, quality-controlled diagnostic testing for HBV and HCV
- Ensure universal access to HBV and HCV treatment through initiatives such as pooled procurement and use of generics

drug use, and a higher prevalence of cofactors for liver fibrosis and carcinogenesis, including alcohol misuse and the metabolic syndrome.^{306,307} Australia and New Zealand also have high levels of immigration, resulting in an increased prevalence of HBV and viral hepatitis as a whole.³⁰⁸

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.³⁰⁹ The prevalence of HBV in the Pacific Island countries and territories ranges from 3% to 23%^{30,310} (appendix pp 16, 17), 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.³¹¹ 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.³¹⁰ Data on HCV in this region are scarce (appendix p 18), but prevalence estimates are generally low (<0.5%).^{9,29,312} The prevalence of liver cirrhosis and liver cancer in this region is poorly characterised,³¹⁰ but 2016 GBD estimates show that mortality from viral hepatitis (predominantly HBV) exceeds that from malaria, HIV, and tuberculosis combined for all of the Pacific Island countries and territories except Vanuatu and Solomon Islands.²⁹⁹ 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.³¹³

Success stories and ongoing challenges

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 (approximately 80%) among those infected.^{301,314} Australia has also led the way in making HCV treatment universally accessible through an initial 5-year investment of over AUD\$1 billion (approximately US\$720 million) in a risk-sharing arrangement with pharmaceutical companies. This arrangement enabled provision of direct-acting antiviral treatment for all chronically infected patients,^{315,316} and boosted treatment uptake substantially, with over 30 000 people receiving direct-acting antivirals in 2016.³¹⁷ Modelling studies suggests this approach is cost-effective and will be vital for achieving the 2030 targets.^{318–320} Australia's HCV programme includes health promotion and education; general practitioner-initiated treatment and nurse-led care; treatment in prisons; needle and syringe programmes and opioid substitution therapy for PWID; and prevention programmes for sexual partners of infected individuals.^{99,321}

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 strategies³²² and screen-and-treat outreach programmes (Gane E, personal communication).³²³

Universal infant HBV vaccination and catch-up programmes have been in place in New Zealand and Australia for nearly two decades,^{305,324,325} with resulting declines in HBV notifications, as documented in many other regions.^{302,326} In New Zealand, universal vaccination has eliminated HBsAg prevalence in Māori children living in the eastern Bay of Plenty as of 1992.³²⁷ New Zealand also has a successful community-based programme 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 programme has identified around 30 000 HBsAg carriers among adult Māori, Pacific and Asian New Zealanders (Gane E, 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.^{302,328,329}

The HBV vaccination programme 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 programme,^{311,330} 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^{331,332}), despite being ineligible for Gavi-supported vaccination programmes and without

100% government funding.³³³ 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 2012.³³¹ Novel strategies to improve hepatitis B vaccine birth dose delivery include use of vaccines outside of cold chain in geographically remote areas of Kiribati.³³⁴

Barriers to elimination

Key priorities for action in Australasia and the Pacific Islands countries and territories are outlined in panel 10. Despite subsidised HBV screening in Australia and New Zealand and specialist management and treatment for infected individuals, there are major barriers 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.³³⁵ Barriers to treatment include lack of awareness of the risks of HBV infection among patient populations, general practitioners, and health-care workers;^{336–338} 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.³³⁹

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 programmes for adults are inadequate,³¹¹ and birth dose vaccination delivery varies significantly across the region.^{340–343} 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.^{310,344} Neither HBIG nor antiviral therapy in the third trimester are routinely provided in most Pacific Island countries and territories due to prohibitive cost and limited supply.³¹¹ 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.³¹⁰

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.³⁴⁵

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 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 programmes, 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 Island countries 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 are in development (Gane E, personal communication) and are a positive step.

Sustaining progress towards hepatitis elimination

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 past 3 years have seen substantial progress towards elimination, including the universal adoption by countries of the WHO GHSS in 2016 and adoption of more detailed regional action plans; the specific inclusion of viral hepatitis in the SDGs; the emergence of next-generation pangenotypic direct-acting antiviral drugs for HCV; the singular success in the Western Pacific region of reducing mother-to-child transmission; 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 for the ambitious WHO elimination goals to be achieved.

In this Commission we have emphasised 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 to identify those approaches which will best suit individual countries. Of the 20 highest burden countries (figure 1), some (eg, India, Nigeria, Russia, and Bangladesh) have yet to make significant progress towards elimination, particularly for HCV. 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.

	National priority actions	International priority actions
Prioritise investments to support countries with greatest burden of viral hepatitis	All heavily burdened countries to have fully funded elimination plans by 2020	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, non-governmental organisations); provide international support for financing measures (Unitaid, Global Fund, 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 (eg, 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 (non-governmental organisations, WHO, civil society); ensure appropriate funding for HBV vaccine, including birth dose (Gavi, WHO); support research and development into HCV vaccine development (research funders and pharmaceutical companies)
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 requirements for specialised prescribing	Support operational research into simplified pathways (research funders, Unitaid)
Diagnostics	Ensure testing is integrated into the wider health-care system, rather than centralised facilities	Ensure access to quality diagnostics through essential diagnostic list and prequalification (WHO, funders); support implementation science for models of care and research and development into novel diagnostics suitable for decentralised settings (research funders, Foundation for Innovative New Diagnostics [FIND], industry)
Access to treatment	Ensure all essential medicines for viral hepatitis are included in national programmes, with an emphasis on pangenotypic regimens; apply comprehensive policy approach to promoting access, including compulsory licensing	Ensure all essential medicines are prequalified and either available through voluntary licensing or Medicines Patent Pool (WHO, non-governmental organisations, civil society, funders); support shared procurement mechanisms for treatment (Pan-American Health Organization)
Monitor progress	National plans need clearly defined, measurable objectives; develop new indices of national progress	Progress of individual countries needs to be closely monitored towards elimination goals (Polaris, WHO, creation of elimination index); develop greater capacity for advocacy in high burden regions (all)

Table 2: Priority areas for action

Key recommendations are outlined in table 2. 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 tuberculosis and HIV. Some organisations have been leaders in this regard, notably the WHO, Unitaid, and Clinton Health Access Initiative, but more can be done. There are several areas these and other organisations can prioritise to support hepatitis elimination efforts. 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. 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 emphasised data from the GBD programme, which combines data on mortality with years of healthy lives lost (DALYs) to estimate the burden of viral hepatitis. This provides additional information compared with most estimates (including those from WHO), which focus on numbers of people affected and annual deaths. The

distinction is important as it places hepatitis within the context of other disease when prioritising finite health resources. It is hoped that the recent announcement of a partnership between IHME and WHO will allow these data to be presented together more regularly.

There has been real progress in improving access to generic medications. While drug access remains a global priority, particularly in relation to access to pangenotypic regimens (notably glecaprevir/pibrentasvir), 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 prequalification to ensure provision of high quality diagnostics and provision of 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 programmes as part of universal health-care coverage is vital, and potential approaches have been outlined within this Commission. 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 also cost-saving. As such, greater emphasis will need to be placed on returns on investment in hepatitis programmes.¹⁹³ 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 on the 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 programmes.¹⁹³

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.

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 became 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 a 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 (eg, Iceland and Georgia) will be able to achieve the WHO elimination goals well ahead of schedule. For larger, more heavily burdened countries, aiming to eliminate HBV or HCV infection in key subpopulations (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 years of age in Alaska. This will become especially important as countries make progress towards nationwide elimination and to provide success stories to maintain political will if progress toward elimination (and thus reduced prevalence and mortality) lessens the immediate imperative for action.

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 to its member states, makes it harder for WHO alone to assess measures of progress and identify those countries that are lagging behind.

The development of the first health-related index measuring progress towards the SDGs³⁴⁶ is a helpful example but has its limitations. The SDGs monitor the prevalence of HBsAg in those under 5 years of age as a good indication of progress in vaccination and preventing mother-to-child transmission, but this does not 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.

Through this Commission we have identified key areas of progress needed at national and global level (table 2). Furthermore, we have identified key examples of progress towards elimination in diverse geographic and economic settings. Despite the barriers that remain, some countries are beginning to make marked progress towards elimination and serve as examples to others. With sustained and coordinated efforts, the 2030 elimination targets are within our reach.

Contributors

SZW led the section on prevention. ML, JJF, and TRR led the section on diagnostics and models of care. BS and TLA contributed to sections on diagnostics. BS also collated data captured on national progress to elimination. IA-M and JRB led the section on access. RA led the section on finance. MGG analysed Global Burden of Disease data for figures in the Commission. BET and CG contributed to all sections on issues relating to patient advocacy. SH led the Asia section with JLH (APASL representative) and JJ. IW led the Middle East and North Africa section. DLT and BJM (AASLD representatives) led the Americas section with JJF, HC (ALEH representative), and JWW. MWS, OAL, and CWS led the sub-Saharan Africa section. GD led the Europe section with JVL (EASL representative). JVL also contributed significantly to the executive summary. LM led the eastern Europe and central Asia section with NK. MEH and JH led the Oceania section. HR contributed to the executive summary and the discussion. GSC oversaw the coordination and writing of the Commission and contributed to each section. Other contributors to the various sections can be found in the appendix.

Declaration of interests

GSC reports grants from Gilead Sciences and personal fees from Gilead Sciences, and Merck Sharp & Dohme, outside the submitted work. TLA reports grants and travel reimbursements from Abbott Diagnostics, and non-financial support from Cepheid. GD reports grants from Gilead Sciences, and Merck; and personal fees from Gilead Sciences, Abbvie, Bristol-Myers Squibb, and Janssen, outside the submitted work. JFF reports grants from Abbvie, Gilead Sciences, Merck, and Janssen, and personal fees from Abbvie, Gilead Sciences, Merck, Contravir, and Medimmune. CG reports grants from AbbVie, Merck, Gilead Sciences, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Sanofi, Inovax, Alere, Abbott, Roche, Alnylam, Laboratories Beker, Pharco, Cepheid, and OraSure Technologies, outside the submitted work. MEH reports grants from Gilead Sciences, Abbvie, and Bristol-Myers Squibb, outside the submitted work. JLH reports grants and personal fees from Bristol-Myers Squibb GlaxoSmithKline, Novartis, and Gilead Sciences, outside the submitted work. JH reports grants from Gilead Australia Fellowship, outside the submitted work. JJ reports grants from Bristol-Myers Squibb, and personal fees from Bristol-Myers Squibb, Abbvie, Gilead Sciences, GlaxoSmithKline, and Merck Sharp & Dohme, outside the submitted work. NK reports grants from Global Fund on AIDS, TB and malaria, Gilead Sciences, Open Society Foundation, USAID, Levi Strauss Foundation, and Centers for Disease Control and Prevention, during the conduct of the study. JVL reports grants from AbbVie, Gilead Sciences, and Merck Sharp & Dohme; and personal fees from AbbVie, Gilead Sciences, Merck Sharp & Dohme, Janssen, and Cepheid, outside the submitted work. HR reports grants from John C Martin Foundation, ZeShan Foundation, Gilead Sciences, AbbVie, and Intercept Pharma, outside the submitted work. CWS has received grants from Gilead to fund a Project ECHO programme on viral hepatitis in sub-Saharan Africa, outside the submitted work. BET reports grants from AbbVie, Merck, Gilead Sciences, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Sanofi, Inovax, Alere, Abbott, Roche, Alnylam, Laboratoires Beker, and Pharco, outside the submitted work. IW reports grants and personal fees from Abbvie, Gilead Sciences, Janssen, Marcyrl, Merck Sharp & Dohme, Onxio, and Pharco, outside the submitted work; and non-financial support from Abbvie, Gilead Sciences, and Pharco. IA-M, RA, JRB, HC, MGG, SH, ML, OAL, LM, BJM, TRR, BS, MWS, DLT, JWW, and SZW declare no conflicts.

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