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Research Article
Viral Hepatitis

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A global investment framework for the elimination of hepatitis B

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Background & Aims: More than 292 million people are living with hepatitis B worldwide and are at risk of death from cirrhosis and liver cancer. The World Health Organization (WHO) has set global targets for the elimination of viral hepatitis as a public health threat by 2030. However, current levels of global investment in viral hepatitis elimination programmes are insufficient to achieve these goals.

Methods: To catalyse political commitment and to encourage domestic and international financing, we used published modelling data and key stakeholder interviews to develop an investment framework to demonstrate the return on investment for viral hepatitis elimination.

Results: The framework utilises a public health approach to identify evidence-based national activities that reduce viral hepatitis-related morbidity and mortality, as well as international activities and critical enablers that allow countries to achieve maximum impact on health outcomes from their investments – in the context of the WHO's 2030 viral elimination targets.

Conclusion: Focusing on hepatitis B, this health policy paper employs the investment framework to estimate the substantial economic benefits of investing in the elimination of hepatitis B and demonstrates how such investments could be cost saving by 2030.

Lay summary: Hepatitis B infection is a major cause of death from liver disease and liver cancer globally. To reduce deaths from hepatitis B infection, we need more people to be tested and treated for hepatitis B. In this paper, we outline a framework of activities to reduce hepatitis B-related deaths and discuss ways in which governments could pay for them.

Introduction

More than 292 million people (3.9% of the world's population) are estimated to be chronically infected with hepatitis B and a further 58 million people are estimated to have occult hepatitis B, resulting each year in more than 880,000 deaths worldwide from cirrhosis and liver cancer.[1,2] Hepatitis B disproportionately affects economically disadvantaged countries, with an estimated 248 million people living with hepatitis B residing in low- and middle-income countries (LMICs) in Asia, Africa, the Pacific and Latin America. These regions also bear the greatest hepatitis B-related mortality burden.[1–3]

Hepatitis B is transmitted most commonly at birth from mother to baby, in early childhood, or sexually through blood and body fluid contact.[4,5] Without treatment, the cumulative incidence of cirrhosis over 5 years is around 10–20% in people with chronic active hepatitis B infection, and 2–5% of those with cirrhosis develop liver cancer each year.[6] Those infected at birth are at greater risk of disease progression to cirrhosis and liver cancer.[7] The rising global prevalence of the metabolic syndrome and non-alcoholic fatty liver disease coupled with hazardous alcohol consumption will likely increase liver-related mortality rates in people living with hepatitis B through accelerated progression of hepatitis B-related liver disease and liver cancer.[8]

Hepatitis B also has an adverse impact on the quality of life, employment and personal finances of those living with the virus. In 2016, the estimated global impact of hepatitis B on human health and wellbeing was 5,160,000 age-adjusted

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disability-adjusted life years lost.[9,10] The broader societal and economic impact of hepatitis B is often overlooked in fiscal decision-making by governments and funders of health programmes due to the long duration of the disease that precedes the development of end-stage complications.[11,12]

In response to the substantial public health threat of hepatitis B, in 2016, the World Health Assembly adopted the WHO Global Health Sector Strategy (GHSS) on Viral Hepatitis 2016–2021.[13] This strategy broadly outlines the key activities to achieve viral hepatitis elimination and sets clear hepatitis B elimination targets to be achieved by 2030: a 90% reduction in new chronic infections and a 65% reduction in mortality compared to 2015 levels.[13] Though currently there is no cure for hepatitis B infection, elimination targets are made possible by the availability of a highly effective low-cost vaccine and safe, effective suppressive treatment that halts viral transmission and liver disease progression, reduces the risk of liver cancer and prolongs life of those affected by hepatitis B.[4] Despite the availability of vaccines and treatments to achieve elimination and a high global mortality burden from hepatitis B infection – comparable to other high-impact diseases such as tuberculosis, HIV and malaria – there has not been an equivalent political commitment to community mobilisation and investment in a strong hepatitis B response.[2,14] Lack of community awareness and activism demanding investment in hepatitis B, coupled with a disproportionate burden of disease in low-income countries, have contributed to poor political engagement and insufficient investment in hepatitis B elimination.

The WHO 2030 hepatitis B elimination targets are unlikely to be achieved at current levels of investment.[15] To date, 194 countries have endorsed the GHSS; however, few have developed national plans for viral hepatitis elimination or made the required investments to make viral hepatitis elimination a reality.[2] Rapid scale-up of hepatitis B vaccination has enabled global coverage of 3 doses of hepatitis B vaccination to reach 84% of infants worldwide, resulting in a reduction in HBsAg prevalence globally in children under 5 years from 4.7% in 2000 to 1.3% in 2015.[2] However, birth dose vaccination coverage worldwide remains unacceptably low at 39%.[2,15] Screening of donated blood for hepatitis B and C has improved over the last decade, yet at 97% it remains below the 2030 target of 100% screened and 5% of healthcare-related injections remain unsafe.[2] Despite off-patent generic hepatitis B treatment being available for as little as US$48 [12] for a 12-month course in many parts of the world, hepatitis B diagnosis and treatment rates remain well short of the WHO 2030 targets of 90% and 80%, respectively.[2] In 2016, modelling estimates suggest only 10% of the 257–292 million people living with hepatitis B worldwide were diagnosed and only between 5 to 17% of those eligible for treatment in accordance with international guidelines were receiving treatment,[1,2] despite nucleos(t)ide analogue therapy being proven to markedly reduce the risk of death from cirrhosis and liver cancer.

To achieve the elimination targets, major investments and resourcing are required at both national and global levels. In 2020, though there are encouraging signs of national-level investment and achievements, it is clear that investment globally is substantially below target to achieve hepatitis B elimination by 2030.[16] Domestic funding mobilisation through innovative financing sources will be critical to implement the GHSS, as the large-scale global investments by donors for HIV, tuberculosis and malaria are unlikely to occur for viral hepatitis in part due to a flattening of overseas development assistance for health.[17] As the global community battles the health, social and economic effects of the COVID-19 pandemic, competing priorities and opportunity costs of investment in other infectious and chronic disease management programmes are being weighed against immediate needs and careful justification of investment is essential.

We have therefore developed a strategic investment framework for viral hepatitis (B and C)[12] which provides a map of the required elimination activities and funding mechanisms to achieve WHO viral hepatitis targets by 2030. In this paper, we focus on hepatitis B elimination and describe how policymakers and others can use the investment framework and published cost modelling data to justify funding hepatitis B prevention, treatment, and care activities. We outline the key barriers to achievement of hepatitis B elimination, how to finance elimination activities, the financial return on investment and the key activities required to achieve hepatitis B elimination. Finally, we discuss ways in which investment in national COVID-19 responses can be leveraged to support hepatitis B elimination activities.

Box 1. Current programmatic challenges to hepatitis B elimination.

1. **Lack of awareness** among the general population and high-risk groups, politicians and policymakers leads to low demand for testing and treatment and subsequent low demand for investment
2. **Stigma and discrimination** reduce community demand for testing and treatment
3. **Weak surveillance systems and inadequate epidemiological data** result in limited data on the impact and cost burden of hepatitis B to drive investment
4. **Inadequate hepatitis B vaccination coverage, particularly birth dose** leading to risk of transmission across the lifespan
5. **Limited access to affordable diagnostics, monitoring tests and treatment**
6. **Inadequate health infrastructure and lack of integration of hepatitis B elimination programmes within existing health programmes** including antenatal, infectious disease and chronic non-communicable disease programmes
7. **Lack of hepatitis-specific funding pools and lack of global investment in hepatitis B research and development**

Key barriers to achievement of hepatitis B elimination

Hepatitis B poses unique challenges to elimination. It is a chronic disease whose mode of transmission, health impact and management change across the lifespan of the patient and therefore requires ongoing monitoring throughout its course.[6] Current international hepatitis B management guidelines are complex, as treatment is not currently recommended for all patients.[7,18] Moreover, unlike hepatitis C there is currently no cure, and even when the disease is well-controlled by treatment there remains a residual risk of liver cancer.[19] Key programmatic challenges to elimination are outlined in Box 1.[12]

A global investment framework for viral hepatitis elimination

Building on the work of the WHO GHSS on viral hepatitis (2016),[13] we developed a strategic investment framework (Fig. 1) for the global elimination of hepatitis B and hepatitis C by

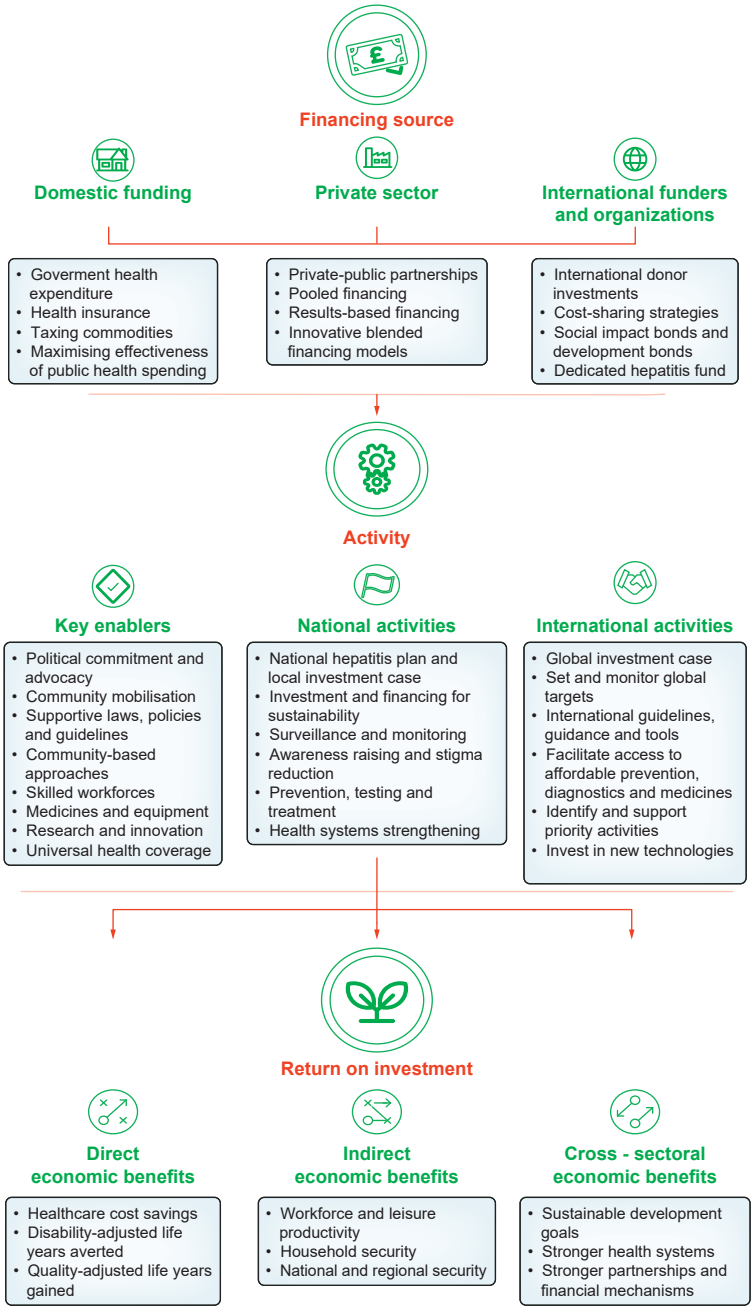

Fig. 1. Proposed Investment framework for hepatitis B and hepatitis C elimination. (Source: Pedrana A, Howell J, Scott N, *et al.* Global hepatitis C elimination: an investment case. Lancet Gastroenterology and Hepatology 2020[20]). (This figure appears in color on the web.)

2030.[20] The framework adopts a public health and health systems strengthening approach and identifies national activities for country-level implementation of viral hepatitis elimination strategies, highlighting national and international enablers that facilitate effective scale-up of hepatitis B programmes. The framework also outlines the hepatitis B elimination activities that are likely to achieve a return on investment.

Financing hepatitis B elimination activities

As of July 2018, the Global Fund had disbursed more than US $38 billion[21] for HIV/AIDS, tuberculosis, malaria and health systems since its founding in 2002. However, no such financing entity or a financing facility exists for viral hepatitis, despite viral hepatitis being included in the Sustainable Development Goal 3.3.[22] Hence, to mount an effective large-scale response to hepatitis B, countries must move forward with alternative financing solutions,[23] alongside continued advocacy work, to include viral hepatitis on the agendas of global donors.

Domestic funding is currently the mainstay of hepatitis elimination programmes in most countries.[14] Progress in investment has been slow: in 2017, a WHO member state survey (70% response globally) identified that only 37% of responding states had dedicated domestic funding for implementation of hepatitis B elimination activities, accounting for only 18% of

individuals living with hepatitis B worldwide.[24] 25% of low-income members states had dedicated funding, compared with 42% of low-middle and high-income countries.[24] Innovative- and blended-financing models should also be employed to augment domestic financing from regular budget sources and sustain the scale up of health programmes. An example of such a model is the use of private-public partnerships to fund roll-out of universal infant vaccination programmes in China with additional support from GAVI.[25,26] However, LMICs are constrained by limited health budgets, and have multiple competing health priorities.[25] As the major source of domestic funds will likely come through taxation, evidence justifying an increase in the proportion of taxation and other domestic funds assigned to hepatitis B elimination programmes at the expense of other health-related activities are needed to convince governments and the community alike that investment in hepatitis B elimination is worthwhile. Hence, strong epidemiologic data on the magnitude of the health burden of disease and the projected cross-sectoral gains from investments in health systems to eliminate hepatitis B are critical to inform fiscal decisions related to resource allocation. The 'Taskforce on Innovative International Financing for Health Systems'[27] (2008) identified innovative funding sources for health system strengthening in LMICs, and since then several innovative financing instruments have been developed to fund large-scale health programmes in these settings.[25]

For scale-up of hepatitis B prevention through vaccination, GAVI, a large global innovative financing mechanism,[23] is ideally placed. To date, GAVI has disbursed US$11.2 billion for vaccines across 76 LMICs, including hepatitis B vaccination since 2000. Importantly, GAVI has recently announced the addition of birth dose vaccine in its 2021–2025 Vaccine Investment Strategy to prevent mother to child transmission.[28] This will be critical to improve the implementation of birth dose vaccination in low-income countries where the need for timely birth dose vaccination of infants is greatest due to high population prevalence, sub-optimal childhood vaccination rates and lack of hepatitis B immunoglobulin availability for mothers living with hepatitis B infection.[2]

In 2018, the United Nations Secretary General launched the 'Financing the 2030 Agenda for Sustainable Development'[29] strategy. This strategy highlights key actions to enable countries to finance the Sustainable Development Goals (SDGs).[30] SDG funding pools, such as those for reducing maternal and childhood mortality, could be used to finance hepatitis B elimination activities where they facilitate SDG achievement.[30] Investment in viral hepatitis elimination activities should be integrated into universal health coverage (UHC, a target of SDG 3) to maximize service access and efficiencies in resource use in health systems, and reduce direct costs of care to individuals, thus minimising catastrophic health costs for the population.[31,32] A summary of the mechanisms used to improve affordability of hepatitis B elimination and examples of countries that have successfully used them to fund hepatitis B elimination activities are provided in Table 1.

Significant investment towards elimination targets for hepatitis C, HIV, tuberculosis, malaria and syphilis demonstrate that domestic funding and resources can be mobilised effectively and these resources can be harnessed towards hepatitis B elimination activities to reduce costs and improve efficiencies.[14,16,20] Moreover, channelling funding and resources available for chronic non-communicable diseases, such as diabetes and hypertension, may be appropriate in countries with moderate-high hepatitis B endemicity, as has been done effectively for hepatitis C in Egypt and Pakistan.[16] The Global Fund has also allowed remaining funds from other projects to be spent on hepatitis B and C-related activities for HIV-coinfected patients.

The return on investment of hepatitis B elimination

There are several components to consider when evaluating the return on investment for hepatitis B elimination: the epidemiological impact, the amount of investment required, the cross-sectoral benefits of investment and affordability. Several published global and country-specific cost-effectiveness models outline the clear impact of investment in hepatitis B elimination on morbidity and mortality.[11,15,36,42,43] Although hepatitis B intervention cost-effectiveness depends on the economic, health systems and epidemiologic contexts in each country, published models have universally demonstrated the cost-effectiveness of investment in hepatitis B elimination.[11,15,34,36,42,44,45] However, for many low-income countries, affordability, rather than cost-effectiveness, is a major barrier.[42] In these settings, highlighting the indirect returns on investment such as socioeconomic development, improved education, strengthening of health systems and economic returns support the argument for investment in hepatitis B elimination. Examples of cost-effectiveness models developed for hepatitis B are outlined in Table 2.

Epidemiologic impact of investment in hepatitis B

A global model was developed in 2016 by Nayagam and colleagues[15] to estimate the costs of global elimination of hepatitis B infection and the impact of scaling-up available public health interventions for its elimination. Under the continued status quo they projected that in 2020 there would be 4.3 million new chronic infections, 270 million people living with hepatitis B worldwide and 1 million deaths from hepatitis B. The continued status quo also projected that by 2050 the number of people living with hepatitis B would fall by 40% to 165 million, as a result of sustained levels of hepatitis B vaccination coverage. However, the annual number of deaths from hepatitis B would continue to increase to a peak of 1.14 million deaths in 2034, and then reduce to 1.06 million in 2050.

In this model, the scale-up of 3-dose hepatitis B vaccination coverage rates to 90% alone was estimated to avert 4.3 million new infections between 2015–2030; increasing birth dose coverage and perinatal antiviral coverage in the third trimester for hepatitis B-positive women to 80% would avert a further 19.3 million infections by 2030 and remained cost-effective. Also, additional investment to increase diagnosis and treatment coverage to 80% of those eligible would reduce annual hepatitis B-related deaths by 65% by 2030 and avert 7.3 million deaths between 2015 and 2030.

Tordrup and colleagues[44] have also developed models for the required investment to achieve WHO hepatitis B and C elimination targets by 2030 and likely outcomes, based on disease prevalence and costs across 67 LMICs with moderate-high prevalence of viral hepatitis. They modelled a progress scenario based on existing WHO screening guidelines, which would not achieve WHO 2030 elimination targets but would result in an

Table 1. Mechanisms to improve financing for hepatitis B elimination activities.

Mechanism	Approaches*	Examples
Reduction in treatment costs	Price negotiations with pharmaceutical manufacturers for hepatitis treatment and diagnostics	Australia, Brazil, Thailand[16,26]
	Local production of generic medicines	China, India[26]
	Inclusion of diagnostics and medications under UHC, list on Essential medicines and Essential diagnostics list	Rwanda, Pakistan, Brazil[26]
	Utilisation of TRIPs flexibilities to access affordable medicines and diagnostics	Thailand (hepatitis C medications)[26]
Maximise effectiveness of public health spending	Integration of viral hepatitis into existing health services for HIV, maternal child health programmes, and non-communicable diseases	Hepatitis B: South Africa,[33] Brazil[26]; Hepatitis C: Egypt, Pakistan[16,20]
	Adopting an investment case approach to guide investments	South Africa,[33] China,[26,34] Senegal,[35] The Gambia[36]
	Leverage WHO regional technical and resource support for viral hepatitis and other disease elimination activities to improve efficiency and effectiveness	Russian Federation (strategic planning), Ethiopia (surveillance reporting), Pacific Islands and Territories (vaccination)[16]
Share costs with other strategies	Immunization and blood safety	Rwanda, Brazil, China[26]
	Co-infection with HIV and service delivery	Rwanda, Brazil, South Africa[26]
	Prevention of mother-to-child transmission including investment to increase in-hospital births through MDG funding pools	China,[26] Fiji,[37] Malaysia[16]
	Hepatitis C programmes	Myanmar, Mongolia[16]
	Non-communicable disease programmes	Egypt (hepatitis C)
Increase innovation to increase efficiencies over time	Dried blood sampling	The Gambia[36]
	Non-specialist care and telemedicine	Australia[37,38]
	PoC multi-disease diagnostic platforms (e.g. GenXpert) to increase hepatitis B testing capacity	Rwanda[16]
	Cross-sectoral government ministry partnerships	South Africa- Ministry of Health and Ministry of Finance[16]
International donor investment	Hepatitis B vaccination	GAVI Alliance hepatitis B vaccination program (birth dose soon to be added to global program)[39]; utilization of MDG4 and 5 funds to increase vaccination coverage including birth dose- Fiji, Brazil, Rwanda[26]
	Prevention of mother-to-child transmission including investment to increase in-hospital births	Public- private partnerships-China[26] (Zeshan Foundation and Rotary International with Ministry of Health) China-GAVI-MoH partnership Global Fund
	Provision of effective treatment	Rwanda – CHAI; NGO and pharma funding partnership with MoH, Fiji, Kiribati, Samoa and Tonga (Gilead, HepB Free) Universal health coverage and essential medicines list-China, Brazil, Rwanda[16]
	Low-cost diagnostics	China, India Unitaid is partnering with the Foundation for Innovative Diagnostics (FIND) through a US $38 million grant to support the development point-of-care diagnostics[40] Development and validation of in-house HBV DNA assays with international support–The Gambia[41]
	Regional strategy support	Colombia, Brazil, Chile–leveraging the PAHO Strategic Fund to cover cost of diagnostics and treatment to increase affordability[16]
Innovative blended financing models	**Pooled financing:** Bringing together development and commercial actors to pool financing and increase scale up of blended finance models.	China-utilization of public-private partnerships to roll-out universal infant hepatitis B vaccination and catch-up programs, supported by the GAVI Alliance[26] Rwanda-Use of novel blend of private and public insurance and pooled community-based microfinancing to support treatment costs[16,26] Global Procurement Fund (GPRO)[31]-works with participating countries to pool medication orders from member countries and uses international competitive bidding to purchase products, working solely with manufacturers that operate either with a license from the originator-companies or those with a license from the Medicines Patent Pool. Civil society and regional public partnerships- Eastern Europe to fund STI prevention services[16]
	Results-based financing: Create market incentives to achieve critical social outcomes by only paying when results are achieved. Two main types: *Performance-based financing* targets the supply side, whereas *conditional cash transfers* target the demand side of a given market.	Health Systems Strengthening support (HSS) and the Immunisation Services Support (ISS) of the GAVI Alliance[2] The Global Fund has implemented a Results Based Financing model in Rwanda called the 'National Strategy Financing' to incentivize results and efficiency.

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Table 1. (*continued*)

Mechanism	Approaches*	Examples
	Social and Development Impact Bonds: Draw on elements of impact investing or blended finance as well as public-private partnerships and allow outcome funders to pay directly for the achievement of outputs or outcomes rather than for inputs or compliant behaviour. Investors provide upfront risk capital (opportunity for return), play a critical role in improving service delivery by bringing private sector discipline into practice.	**The International Finance Facility for Immunization** uses donor pledges to issue vaccine bonds to raise money for Gavi Alliance.
	Dedicated hepatitis fund: Create a global viral hepatitis fund to leverage resources and cultivate synergies through innovative public-private partnerships, and catalyse action on viral hepatitis; primarily support the most-affected countries and communities where national health systems cannot address hepatitis epidemics. Specific high-impact activities would be supported through the structures of the UN World Health Assembly and Regional Committees.	The Hepatitis Fund (World Hepatitis Alliance)

*All activities and examples are for hepatitis B unless otherwise stated.

increase in hepatitis B testing to 2,400 million people compared with the status quo of 93 million people tested by 2030, and treatment for 24.1 million people compared with 1.4 million people (status quo). This scenario would avert an estimated 2.4 million deaths by 2030 and a total estimated 7.3 million deaths beyond 2030. They also modelled an ambitious scenario that would achieve WHO 2030 elimination targets by increasing hepatitis B testing to 5,592 million people and treatment to 32.2 million people between 2016 and 2030. This scenario for elimination of hepatitis B and C provided estimated health investment returns of 4.5 million (4.6%) premature deaths averted and an increase of 51.5 million healthy life-years (9.6%) between 2016 and 2030. Specifically, the ambitious scenario was estimated to avert 3.3 million cases of decompensated cirrhosis and 4.5 million hepatitis B-related liver cancer cases.[44]

Investment needed to achieve WHO elimination targets for hepatitis B

Nayagam and colleagues[15] projected that US$88.7 billion in global funding would be needed to meet the WHO targets by 2030, peaking at US$7.5 billion in 2025 and averaging at US$5.5 billion per year between 2015–2030. LMICs would require 45% of this total investment, with their overall costs peaking at US$3.4 billion annually. Screening (39%) and drug costs (59%) were the main components of the estimated costs.[15] From 2030 there would be a rapid decline in annual costs due to screening of unvaccinated people being almost complete across populations and fewer people requiring treatment. If a cure became available, elimination targets would be achieved more rapidly. In this model, the avoided costs of cirrhosis and liver cancer were not included to offset investment in diagnosis and treatment, therefore presented costs are likely to underestimate the cost-effectiveness of investment in hepatitis B elimination in countries where health care is available for people with cirrhosis and liver cancer and is at least partially government subsidised.

The progress investment scenario modelled by Tordrup and colleagues[44] estimated that implementation of current WHO screening guidelines for hepatitis B across 67 moderate and high prevalence LMICs would require a total US$19.9 billion investment for hepatitis B diagnostics, monitoring and treatment between 2016–2030 and a further US$9.1 billion for programme costs (to support both hepatitis B and C programmes). This compares to the status quo projected hepatitis B costs of US$5.5 billion.[44] Similarly to Nayagam,[15] annual estimated costs for screening, assessment and monitoring combined were greater than treatment.[44] Achieving the WHO 2030 elimination targets was estimated to require a total US$30.3 billion for hepatitis B between 2016–2030, as well as US$20.0 billion for programme costs (to support both hepatitis B and C elimination),[44] an amount almost 10× the current level of spending on hepatitis B elimination activities across these 67 LMICs. This represents a US$58.7 billion increase in resource requirements to achieve the WHO's ambitious SDG, if hepatitis B and C are included[44]; to place this investment in context, a relative increase in resource requirements is also needed to achieve WHO SDGs for other infectious diseases, including HIV (US$102 billion), tuberculosis (US$7 billion) and malaria (US$51 billion).[44]

Modelling by the Centre for Disease Analysis has estimated the timeframe to break even with national investment in hepatitis B elimination, beyond which investment becomes cost saving.[50] For example, investment in hepatitis B elimination is estimated to provide cost savings in the Philippines by 2024 and in Vietnam by 2027. By 2035, for every dollar spent on hepatitis B elimination activities there would be an estimated return of US$2.23 in the Philippines and US$1.70 in Vietnam.[50]

Cross-sectoral economic benefits of hepatitis B elimination

Achieving the SDG 3 target of UHC by 2030 requires global investment in health systems.[31] Integrating hepatitis services within existing health systems reduces costs compared to a 'siloed' approach because a large proportion of the required costs are for human resources.[12] Community-based diagnosis, monitoring and treatment for hepatitis B is feasible, particularly with simplified management guidelines,[51,52] making integration into existing healthcare services highly achievable. Adequate human resources to scale-up hepatitis B diagnosis and management may already be available through existing programmes such as antenatal care, HIV, tuberculosis and other non-communicable chronic disease programmes, allowing rapid up-scaling of testing and treatment with less financial, infrastructure and training support than would otherwise be needed for new stand-alone hepatitis treatment programmes, substantially offsetting up-front investment. This programme model has been shown to be highly effective in Egypt for hepatitis C screening when

Table 2. Examples of impact and cost-effectiveness models developed for hepatitis B elimination.

Country context	Analysis type	Outcome	Factors with greatest impact on impact and costs	Authors
Global Model	Simulation dynamic deterministic state transition model and costing model to estimate total costs of interventions	Impact on new infections and mortality, comparing status quo versus achieving 2015 SDGs for HIV, tuberculosis and malaria applied to hepatitis B	1. Scale-up infant vaccination coverage 2. Scale-up birth dose vaccination coverage 3. Effectiveness of vaccination 4. Use of peripartum tenofovir 5. Population-wide testing and treatment 6. Adherence to treatment	Nayagam S *et al.* (2016)[15]
Global Model focused on 67 low- and middle-incomecountries	WHO SDG investment model extended to include costs for hepatitis B	Health impact (deaths averted, health lives gained) and cost of scale-up of existing HBV testing and treatment programs to achieve WHO 2030 elimination targets	1. Diagnostics 2. Staff costs	Tordrup *et al.* (2019)[44]
Global	Cost-effectiveness analysis using a Markov state transition model	1. Cost-effectiveness of use of HBV vaccine outside of cold chain (controlled temperature chain) 2. HBV-related DALYs averted	1. HBV prevalence 2. Proportion timely birth dose delivered	Scott N *et al.* (2018)[46]
Australia	Cost-effectiveness analysis using a Markov state transition model (healthcare system perspective)	1. Cost-effectiveness of upscaling current programs to achieve WHO elimination targets by 2030 2. Total cost of implementation programs to achieve WHO targets and remain under the cost-effectiveness threshold	1. Drug costs 2. Disease progression rates (e.g. impact of treatment, timing of treatment)	Xiao Y *et al.* (2019)[45]
Cambodia	Cost-effectiveness analysis using decision tree modelling based on existing Regional Framework for Triple Elimination of Mother to Child Transmission of HIV, HBV and syphilis in Asia and the Pacific 2018–2030	Impact on mother-to-child transmission and cost-effectiveness of integration of HBV prevention (antenatal testing, birth dose vaccination, HBIg, +/− tenofovir)	1. Drug cost 2. HBIg cost and procurement	Zhang L *et al.* (2019)[47]
China	Cost and health impact analysis using a dynamic Markov state transition model	1. Health impact of upscaled comprehensive hepatitis B elimination package 2. Cost of package to achieve elimination targets 3. Return on investment of comprehensive elimination package 4. Co-financing strategies simulation	1. Diagnostics 2. Drug costs 3. Financing model (eg public-private partnerships from societal perspective)	Nayagam S *et al.* (2016)[34]
South Korea	Cost-effectiveness analysis using Markov state transition model	Cost-effectiveness of standard birth dose vaccine and HBIg compared with additional antiviral therapy in third trimester for perinatal prevention of mother-to-child transmission	1. Drug costs 2. Prevalence maternal high viral load	Lee D *et al.* (2018)[48]
The Gambia	Cost-effectiveness analysis using a Markov state transition model	Community-based screening and treatment	1. Drug cost 2. Diagnostics cost 3. Targeted facility-based screening 4. Integration into existing services to reduce staff costs	Nayagam S *et al.* (2016)[36]
Senegal	Cost and health impact analysis using a Markov state transition model adapted from The Gambia	1. Health impact towards achieving WHO 2030 targets of gradual and rapid (twice gradual) up-scale testing and treatment scenario 2. Costs of programs- including breakdown of costs of individual elimination activities in Senegal	1. Diagnostics cost 2. Drug cost	Ministry of Health and Sport (2019)[35]

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Table 2. (*continued*)

Country context	Analysis type	Outcome	Factors with greatest impact on impact and costs	Authors
		3. Financing gap compared with current National Strategic Plan and modelled strategies to reduce costs		
South Africa	Cost model and dynamic deterministic state transition model	Health Impact and cost-effectiveness of birth dose vaccination, prevention mother-to-child transmission and HBV treatment	Using prevention of mother-to-child transmission programs to source cases for HBV treatment	Hecht R *et al.* (2018)[11]
Netherlands	Cost-effectiveness analysis using a Markov state transition model	Cost-effectiveness of migrant hepatitis B and C screening program for all migrants from high prevalence areas in a low prevalence country	1. Drug costs (in high income country) 2. Prevalence in migrant target population 3. Cost-effective when HBV and HCV combined screening	Suijkerbuijk AWM *et al.* (2018)[49]

combined with community-based diabetes and hypertension screening.[26] Modelling work by Tordrup *et al.*[44] estimated that to achieve 2030 elimination targets, additional staff time of 432.3 million days for doctors and 247.8 million days for nurses would be required for screening, monitoring and treatment, excluding prevention activities.[31,44] Their costings were based on utilisation of existing antenatal screening infrastructure for HIV and syphilis. When combined with hepatitis C elimination costs that would draw on the same estimated programme-related costs, this would increase the WHO SDG investment health-care strengthening scenario costs by 1.5%, which is in line with the proportion of SDG budget currently ascribed to other diseases (HIV 2.5%, tuberculosis 1.4%, malaria 1.3%, and non-communicable diseases 10.7%).[44]

Overall health system strengthening would also help reduce transmission through improvements in blood screening and safety, injection safety and infection control to reduce blood-borne virus transmission.[44] Cost models have also established the cost-effectiveness of hepatitis B maternal-to-child prevention strategies when integrated with existing HIV and sexually transmitted infection screening programmes,[47] fast-tracking achievement of SDG goals through resource sharing and resulting in cross-sectoral benefits in neonatal and maternal morbidity/mortality alongside hepatitis B elimination.[47]

Affordability of investment in hepatitis B elimination

Affordability is a major challenge to hepatitis B elimination, particularly in LMICs. Middle-income countries have the potential to generate additional funds through economic growth over time that can feed into UHC. Countries currently paying for medical costs of cirrhosis and liver cancer may leverage investment off the cost-savings generated against existing expenditure on hepatitis B-related disease. However, low income countries have limited scope to increase revenue from sources such as taxation, so alternative solutions need to be found.[53] External catalytic funding to kick-start screening and treatment programmes may be required, coupled with strategies to reduce costs and increase efficiencies (Table 1, Table S1), including embedding hepatitis B management within existing health infrastructure, leveraging health system strengthening delivered by UHC, and legislative and market strategies to drive down prices of diagnostics and therapeutics.

Impact of COVID-19 on hepatitis B elimination

With the world in the midst of a pandemic with unpredictable and far-reaching health, social, geopolitical and economic impacts, how we sustain chronic disease programmes, revitalise economies and replenish devastated health infrastructure is a critical concern. In all countries, to varying extents, the focus for health services and governments has shifted to pandemic responses. Countries with moderate to high hepatitis B endemicity are also disproportionately represented among the most vulnerable national health systems and economies, which will bear the greatest impact from COVID-19. Beyond the impact on domestic resources and funding, external funding is likely to be massively curtailed due to diversion of the funds to the pandemic and also depletion through contracting economies. Despite these seismic impacts, there are opportunities to harness national and global COVID-19 investment for hepatitis B elimination activities. Significant investments in surveillance and reporting systems to track COVID-19 may also be used to collect

data on hepatitis B epidemiology and to monitor progress toward elimination. Many elements of the health system response such as rapid training and mobilisation of skilled health workers, decentralisation of services, novel community-based remote models of care such as telemedicine, resource and task-sharing and integration of multiple health systems to deliver the COVID-19 public health response can be utilised for hepatitis B elimination activities without requiring significant additional investment. Improved universal precautions will reduce spread of hepatitis B in healthcare settings, expanded laboratory capacity and point-of-care (PoC) multi-disease platforms can be utilised to deliver hepatitis B diagnostics and strengthened supply chains for medications will also facilitate hepatitis B treatment access in the post-pandemic phase. Negotiation of existing and new trade and intellectual property agreements may also facilitate increased access and affordability of diagnostics and medications. Moreover, investment in hepatitis B programmes also strengthens health systems enabling integration of COVID-19 activities at reduced cost and improved efficiency. Sustained investment in vaccination programs to avoid precipitous drops in hepatitis B vaccine coverage will be essential to deliver high coverage of a future SARS-CoV-2 vaccine.[54] At this stage, data to support the success of these approaches are lacking and the future remains uncertain. It is vital that all opportunities are taken to minimise the substantial additional economic and health system burden from hepatitis B for countries with high endemicity. Strong advocacy will be essential to ensure CHB is a public health priority post-pandemic.

Key elimination activities for hepatitis B

The framework identifies key national and international elimination activities and enabling factors for scaling up hepatitis B testing and treatment to achieve WHO 2030 elimination targets (outlined in Table S1 and Box 2). The framework also highlights enabling contextual factors that facilitate viral hepatitis elimination and how these may be financed. Fig. 2 highlights what may be achieved with different levels of investment in hepatitis B elimination activities.

National activities

National activities form the cornerstone of hepatitis B elimination efforts through context-specific scale-up of hepatitis B diagnosis, linkage to care and treatment pathways tailored to local epidemiology, budgets and health system constraints.

Develop a national hepatitis B strategy and local investment case

Creating a local investment case, using available tools and a national hepatitis strategy supported by regional and international expertise are essential first steps to place hepatitis B on national health and cross-sectoral government agendas, mobilise funds and plan realistic and sustainable elimination responses.[14] Table 2 outlines examples of national cost-effectiveness models that have been developed in partnership with ministries of health that have successfully informed development of National hepatitis strategies and investment prioritisation.

Investment and financing for sustainability

Development of a national strategy for hepatitis B elimination must incorporate national sustainable financing solutions. Most global donors, including The Global Fund[55] and the Bill & Melinda Gates Foundation,[56] currently do not fund hepatitis B activities other than on a small scale for individuals co-infected with HIV, and this policy is unlikely to change in the near future. Incorporating elimination programmes into UHC and ensuring hepatitis B diagnostics and medications are on national essential medicines lists helps offset costs. Investment in maternal-child health programmes by global donors may also represent avenues to deliver improved birth dose vaccine delivery through increased antenatal care coverage and skilled health-worker birth attendance.[53]

Box 2. Essential activities requiring investment to achieve hepatitis B elimination.

1. **Raise awareness** among populations at risk, policymakers and politicians through population-level education campaigns, targeted outreach, advocacy and civil society activities
2. **Reduce stigma and discrimination** through population education, advocacy and changes in current policy and legislation frameworks to protect the rights of people living with hepatitis B
3. **Increase coverage of hepatitis B infant vaccination including birth dose** and catch up programmes for unvaccinated at-risk groups
4. **Increase coverage and access to affordable diagnosis, linkage to care and treatment** including expansion of hepatitis B diagnosis and monitoring programmes under Universal Health Coverage and inclusion of hepatitis B treatment in the Essential Medicines List
5. **Improve surveillance systems and epidemiologic data collection** to inform context of local epidemics and driving factors for transmission and provide feedback on progress towards achieving elimination goals
6. **Invest to improve quality, access, affordability and coverage of health services and infrastructure** to deliver hepatitis B elimination programs nested within existing public health programmes to allow rapid scale-up, facilitate cost-effective resource utilisation and limit up-front expenditure
7. **Support research and development of novel diagnostics and new therapeutics** to increase coverage of hepatitis B diagnosis and monitoring and achieve hepatitis B cure

Improve surveillance and monitoring to provide data-driven decision-making

A lack of reliable surveillance data and cause-specific mortality data for liver cancer and liver failure[57,58] leads to a substantial underestimate of the cost and societal impact of hepatitis B. The WHO Viral Hepatitis Continuum of Care Monitoring and Evaluation Framework provides guidance for surveillance systems investment[59] for LMIC and high-income country contexts. These data are essential to describe national disease burden and guide the scope and scale of investment in elimination activities. In 2018, the WHO established the Global Reporting system for viral hepatitis,[60] a major milestone for viral hepatitis reporting against elimination targets. In 2017, 62% of WHO members states had functional data collection, surveillance and reporting systems in place: however, many of these systems have not been harnessed for hepatitis B reporting.[16] Electronic medical record and data collection systems such as Open MRS (OpenMRS Inc.) supported by the WHO can support local data collection activities to monitor hepatitis B elimination programmes.

Advocacy, stigma reduction and awareness raising

Lack of awareness of hepatitis B and low health literacy both in the general population and among at-risk communities, coupled

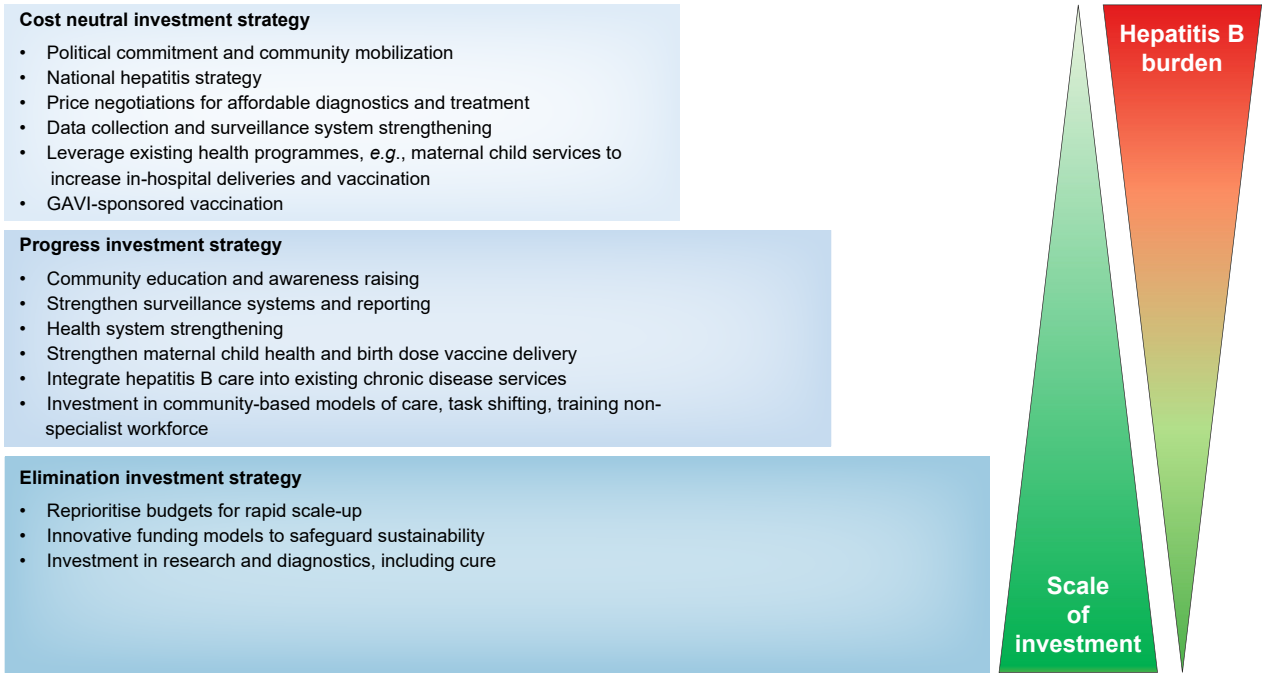

Fig. 2. Hepatitis B elimination activities and disease impact by different levels of investment. Countries can make important gains towards achieving hepatitis B elimination with various levels of investment, however the greatest impact on burden of disease and therefore the greatest returns on investment are achieved with investment in an elimination strategy.

with stigma and discrimination against people living with hepatitis B, contribute to low demand for diagnosis and treatment globally.[2,61,62] Taking a public health approach to hepatitis B awareness programmes, non-discriminatory policy (such as ensuring equitable access to education and employment regardless of hepatitis B status), plus investment in community advocacy organisations and involving the affected community in key hepatitis B policy decisions are critical to increase public demand and leverage funding (Table S1).[62–64] Community advocacy has successfully pressured governments to invest in hepatitis B and C elimination activities in countries such as Australia, Brazil, Georgia and Rwanda.[26] There is also a clear association between level of engagement between WHO member states and civil society organisations and the development of national hepatitis B strategies and dedicated investment in hepatitis B activities.[24] Eighty-four percent of WHO member states who had formal engagement with civil society had national action plans and 52% had dedicated hepatitis B funding compared to 44% with national strategies and 23% dedicated investment among WHO members states with no civil society engagement.[24]

Hepatitis B prevention

Strategies to overcome financial and logistical barriers to birth dose delivery include utilisation of skilled birth attendants outside of health facilities, use of vaccine outside of cold chain and use of auto-disposable syringes.[65,66] Modelling work by Scott and colleagues[46] demonstrated that adopting a controlled temperature chain strategy for birth dose vaccination was cost-effective in most world regions with high hepatitis B prevalence; this is now supported by Strategic Advisory Group of Experts on Immunisation (WHO).[67] Integrating hepatitis B birth dose vaccination with Millennium Development Goal 4 (reducing infant and child mortality) and 5 (reducing maternal mortality) activities promotes mutual health system strengthening and efficiency gains.[43,47,68] GAVI has committed to support birth dose vaccination from 2021.[39] Among adults, integration of targeted catch-up immunisation programmes with other vaccines such as pertussis reduces costs.[26,37] Regional pooled procurement could improve hepatitis B immunoglobulin access in LMICs[2] and tenofovir disoproxil fumarate (TDF) for pregnant women with high viral loads should be incorporated into the essential medicines list. Provision of TDF in the third trimester for pregnant women with hepatitis B who are HBeAg positive with a high viral load reduces transmission risk to <1%[69] and is supported by the WHO as a cost-effective strategy for achieving the WHO elimination target of <0.1% prevalence among children by 2030.[15,43,70,71] This strategy may reduce transmission risk in settings where timely birth dose delivery is difficult to achieve.[14] New 2-dose hepatitis B vaccines are now available that have high efficacy and may improve full schedule completion rates due to easier adherence; they warrant inclusion in future modelling work.

Increase coverage and access to affordable diagnosis, linkage to care and treatment

Access to affordable diagnostics is a key barrier for many countries, with diagnostics often costing more than treatment.[14,72] Pooled procurement, national production and supportive legislation are options to drive down the price of current diagnostics. High-quality, low-cost viral hepatitis PoC diagnostics that are simple to use with minimal training and meet WHO prequalification criteria are required to improve accessibility and affordability of testing and to promote decentralisation of hepatitis B management.[73] Whilst hepatitis B HBsAg PoC rapid diagnostic

tests that have WHO prequalified approval are available and have been shown in multiple settings to be cost-effective alternatives to improve diagnosis access,[36,51] PoC RDTs required to determine treatment eligibility and evaluate liver disease severity are urgently needed to increase treatment rates. Novel diagnostics that provide more affordable alternatives to PCR-based HBV DNA quantification such as hepatitis B core-related antigen[74] and LAMP-based HBV DNA quantification,[75] and novel PoC alanine aminotransferase tests[76] are in development. A PoC core antibody test would also be beneficial to determine previous exposure prior to vaccination and may be cost-saving, and also to determine the risk of occult hepatitis B infection and potential for reactivation with immunosuppression. However, modelling of the impact of these tests on elimination targets and their cost-effectiveness compared with the status quo is required.

Dried blood spot (DBS) testing circumvents cold chain barriers due to its stability at high temperatures for 14 days and avoids the need for a trained phlebotomist to draw blood.[41] DBS sampling in combination with centralised laboratory testing is accurate for HBsAg and HBV DNA measurement and should be supported by diagnostic test registration for DBS.[77] Financial and technical support for development and implementation could be provided from industry partners and the Foundation for Innovative Diagnostics (FIND), while the WHO Essential Diagnostics List supports national investment in hepatitis B diagnostic testing.[14]

Also, despite entecavir and TDF compound patents having expired in 2010 and 2017 respectively, there are major discrepancies in prices across LMICs.[78,79] Since 2011, TDF patents were licensed to the Medicines Patent Pool including for the indication of hepatitis B. Consequently, quality assured low-price TDF has been available well before the patent expired. Today, a year's course of TDF can be purchased for as little as US$32 and entecavir for US$427.[80] However, few countries have taken advantage of these prices; even in countries where TDF is licensed, procurement still occurs through private mechanisms at unaffordable prices. Inclusion of TDF and entecavir in the national essential medicines list supported by the WHO 20th essential medicines list recommendation allows countries with high prevalence to leverage generic pharmaceutical companies to supply drug at affordable prices, or generate local production markets to boost revenue and drive down costs (Table S1).[26]

There is increasing interest in novel approaches to treatment that simplify current guidelines, as was the case with hepatitis C,[81] and obviate the need for complex and expensive testing to determine treatment eligibility, such as a "test and treat-all" approach.[82] Whilst such an approach has not yet been explored in a clinical trial, a novel pilot study evaluating the cost-effectiveness and affordability of such an approach is currently underway in Uzbekistan.[82]

Invest to improve quality, access, affordability and coverage of health services and infrastructure

Over-reliance on centralised specialist services to deliver hepatitis services, shortage of specialist health workforce and lack of simplified guidelines facilitating community-based care are obstacles to hepatitis B elimination in LMICs.[80] Linkage to care and retention in care are vital for successful hepatitis B management.[14] Integration of hepatitis B into current community-based models of care and other chronic disease management programmes will improve access, reduce late presentation and costs, improve efficiencies and increase retention in care. Civil society and community organisations can also support linkage and retention in care. Task-shifting and redistribution of existing health staff by integration of hepatitis B programmes within existing programmes can substantially offset the up-front costs and proved viable in HIV programmes in sub-Saharan Africa.[36,83,84] Policymakers can leverage the roll-out of UHC and existing SDG-related activities for investment in hepatitis programmes that facilitate other disease programmes such as tuberculosis or diabetes.[13,85] The WHO has developed global recommendations and guidelines on task-shifting;[86] other resources include the GHSS on Viral Hepatitis 2016–2020,[13] the Essential Medicine List[87] and injection safety and blood safety policies.[66]

International activities

International agencies, multilateral organisations, NGOs and donors can support advocacy to address funding gaps to strengthen the community sector and civil society,[79,88] leverage funding from donors, provide technical expertise including guidelines and training modules, support investment case development, and support regional approaches to drug and diagnostics procurement, particularly price negotiations.[37] Tools are available to support national activities including the WHO viral hepatitis continuum of care and the monitoring and evaluation framework.[13,85] Investment in local production and new technologies for diagnostics and therapeutics can be facilitated by public-private partnerships through access to markets and the scale-up of prevention and treatment programmes.[77,89,90] Accelerating regulatory approval for WHO (or equivalent) prequalified products[73,87] and pool capacity of regulatory authorities for pre-market assessment and registration of new medicines and diagnostics is also important. International agencies and donors can also fund health system improvements such as enhanced data connectivity to support quality assurance and supply chain management.[72] Greater advocacy by civil society including community-based organisations is paramount to encourage international funding bodies to invest in hepatitis B elimination as has been the case with other infectious diseases such as HIV.

Investment in hepatitis B cure

The final hurdle to achievement of hepatitis B elimination is the lack of a safe, well tolerated, easy-to-administer hepatitis B cure. To achieve hepatitis B cure, international private and public partnerships, agencies and donors need to come together to support research and drug development.[77] Such efforts need to ensure up front that the resulting products are affordable to the communities that need access to them. The International Coalition to Eliminate Hepatitis B (ICE-HBV)[91] seeks to increase global awareness, facilitate collaboration for research discovery and support research in hepatitis B cure and mirrors the effective multisector campaign for HIV drug development. Modelling has demonstrated that availability of hepatitis B cure would accelerate achievement of global hepatitis B elimination.[15] However, LMICs with the greatest hepatitis B burden may endure delays in accessing cure due to prohibitive costs, as has been seen with HIV and hepatitis C therapies. If hepatitis B cure becomes a reality, it will be important that low-cost and/or generic drug procurement is rapidly implemented. There should be some optimism this is possible given the price reduction and broad availability of generic drugs observed with hepatitis C therapies.

Box 3. Key recommendations to achieve hepatitis B elimination.

1. Raise the profile of viral hepatitis elimination and build political commitment through global, regional, national and local forums that engage affected communities, healthcare professionals and the broader community.
2. Invest in activities to reduce stigma and discrimination against people living with hepatitis B infection, including education campaigns, law and policy change to ensure equitable healthcare access and mandate protection of the rights of people living with viral hepatitis
3. Build the local investment case for elimination that delivers achievable country-specific targets through prioritising strategic action and optimal resource allocation; embed these within universal health coverage.
4. Scale-up hepatitis B vaccination coverage, including birth dose delivery embedded within existing SDG-related programmes
5. Increase access to low-cost hepatitis B diagnostics and generic treatment through international advocacy, private-public partnerships and patent licensing agreements.
6. Strengthen health systems and integrate activities into existing health programmes such as antenatal screening, HIV and tuberculosis programmes to strengthen infrastructure, improve coordination and optimize resource allocation.
7. Catalyse international investment in research and drug development to deliver hepatitis B cure.

By investing in hepatitis B elimination programmes now, the scene will be set for rapid introduction and scale-up of hepatitis B cure when such treatment becomes available.[92]

Conclusion

Hepatitis B elimination is achievable but requires greater commitment from governments, international institutions, civil society and donors. Modelling shows that the required financial investment is likely to peak by 2025 but then rapidly fall in 2030 and beyond, with investment in hepatitis B activities likely to be cost-effective and cost-saving in many countries in the medium- to long-term. However, for countries currently not funding hepatitis B elimination activities, affordability of investment at the expense of competing priorities must be addressed. The investment framework presented in this study identifies key activities to achieve hepatitis B elimination targets and solutions to funding shortfalls to achieve maximal impact. Financial support by international agencies and donors for elimination activities are vital for many LMICs to successfully achieve elimination targets (Box 3).

Abbreviations

DBS, dried blood spot; GHSS, Global Health Sector Strategy; HCC, hepatocellular carcinoma; LMIC, low- and middle-income country; PoC test, point of care test; RDT, rapid diagnostic test; SDGs, sustainable development goals; TDF, tenofovir disoproxil fumarate; UHC, universal health coverage; WHO, World Health Organisation.

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Conflict of interest

JH has received investigator-initiated funding and speaker fees from Gilead Sciences. AHS reports grants to her institution from ViiV Healthcare. ETH is the former director of the Medicines Patent Pool. NS has received investigator-initiated research funding from Gilead Sciences. AP has received investigator-initiated research funding from Gilead Sciences, MSD and AbbVie, and honoraria from Gilead Sciences. JVL reports grants and personal fees from AbbVie, Gilead Sciences and MSD, personal fees from CEPHEID and Janssen, all outside the submitted work. MS is principal investigator in an investigator-initiated trial sponsored by Gilead Sciences (received no PI fees, trial closed April 17th 2019) and reports an educational grant to travel to EASL 2019 (Gilead Sciences). SJH received honoraria from Gilead, unrelated to submitted work. AJT is advisory board member for Gilead Sciences, Arbutus Biopharma, AbbVie, BMS, Bayer, Roche, Ipsen, Eisai, Immunocore Ltd, Clear B Therapeutics, ViR therapeutics and has received speaker fees and investigator-initiated funding from Gilead Sciences, AbbVie and BMS. MH's Institute receives investigator initiated research funding from Gilead Sciences, Abbvie and BMS. JH received the Gilead Sciences Australia fellowship (2017). DW, CK, RA, RBL, MB, LA, AG, SH, RH, WL, RBM, SO, RP, MS, CWS, MT, ESS have nothing to declare.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contribution

JH and MH conceived the manuscript. JH and AP wrote the manuscript. All other authors provided interviews to inform the Framework content, intellectual input, draft revision and editing and approved the final manuscript.

Data availability

The manuscript does not contain data.

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