Progress towards elimination goals for viral hepatitis

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Abstract | The global burden of viral hepatitis is substantial; in terms of mortality, hepatitis B virus and hepatitis C virus infections are on a par with HIV, malaria and tuberculosis, among the top four global infectious diseases. In 2016, the 194 Member States of the World Health Organization committed to eliminating viral hepatitis as a public health threat by 2030, with a particular focus on hepatitis B virus and hepatitis C virus infection. With only 10 years to go until the 2030 deadline is reached, and although much progress has been made towards elimination, there are still some important gaps in terms of policy and progress. In this Viewpoint, we asked a selection of scientists and clinicians working in the viral hepatitis field for their opinions on whether elimination of viral hepatitis by 2030 is feasible, what the key areas of progress are and what the focus for the next 10 years and beyond should be for viral hepatitis elimination.

Is elimination of viral hepatitis by 2030 feasible?

Andrea L. Cox. Hepatitis B virus (HBV) and hepatitis C virus (HCV) combined are among the top four global infectious disease killers alongside tuberculosis, malaria and HIV[1]. Although the number of people in the world dying from HIV, tuberculosis and malaria have all declined since 2008, global deaths from chronic HBV and HCV infection continue to rise, with more than 1.4 million deaths each year[1]. Globally, HBV-related liver disease represents the seventh highest cause of mortality worldwide[2]. Given this burden, viral hepatitis elimination should be a priority. However, available evidence demonstrates that global viral hepatitis elimination by 2030 is highly unlikely. Rates of hepatitis B and C diagnosis are very low, averaging 8% and 18%, respectively, globally[1]. Although some regions are approaching prophylaxis and prevalence targets for HBV infection, studies suggest that all regions must substantially scale up rates of diagnosis and access to treatment to meet the global targets[3–5]. For HCV infection, 80% of high-income countries are not on track to meet HCV elimination targets by 2030, and 67% will not meet elimination targets even if given an additional 20 years to do so[6]. Elimination is even less likely in most low-income and middle-income countries (LMICs). In contrast to HBV, there is no prophylactic HCV vaccine. Thus, it is not surprising that the WHO (World Health Organization) incidence reduction targets are the most difficult to achieve for hepatitis C[6].

Manal H. El-Sayed. The WHO called on all countries/regions to "invest in eliminating hepatitis" through costing, budgeting and financing of elimination services within their universal health coverage plans. Achieving this goal requires, apart from an effective treatment, policies to address prevention of new infections, financial structure, political will, stakeholders' engagement and integration within the health-care system. Implementation of the Global Health Sector Strategy would prevent 7.1 million deaths between 2015 and 2030 (REF.[7]). Combining prevention and treatment to combat viral hepatitis makes elimination feasible, but entails substantial investments in health-care system strengthening and the full continuum of viral hepatitis services. The investment would provide direct, indirect and cross-sectoral economic benefits through saving lives and alleviating the cost burden of disease to the individual, their families and the state[8]. The WHO estimated that the cost of implementing the five key interventions in LMICs between 2016 and 2021 would be US$11.9 billion. The principal drivers of cost are testing and treatment for hepatitis B and C[7]. Economic analyses in Mongolia and Egypt (HCV), in Senegal and the Gambia (HBV), and China (HBV and HCV) indicate that population-based approaches to test and treat would be cost-effective[7]. An analysis published in 2019 found that a total of $58.7 billion is needed to eliminate viral hepatitis in 67 LMICs, which includes 230 million people with HBV infection and 52 million with HCV infection[9]. An investment of $6 billion per year would avert 4.5 million premature deaths by 2030 and more than 26 million deaths beyond that target date. The cost would increase to $118 billion if medicine remained inaccessible and patent protected in 13 of these LMICs[9]. Countries are currently investing hundreds of billions of US dollars to mitigate the effect of coronavirus disease 2019 (COVID-19), which will, in part, eventually support strengthening of surveillance and the health-care systems that can be used for enhancement of viral hepatitis services.

Jia-Horng Kao. Global elimination of HBV and HCV is feasible because of the characteristics of both viruses, reliable diagnostic assays and available cost-effective or cost-saving measures. These measures include: the implementation of universal hepatitis B immunization and antiviral treatment of highly viraemic mothers infected with HBV during the third trimester to prevent vertical transmission; blood donor screening for HBV and HCV; safe injection practices; stringent infection-control programmes to reduce the burden of HBV and HCV infections; and antiviral treatments for patients with HBV and HCV infection. However, global elimination of HBV and HCV by 2030 is an ambitious task and a huge amount of work is needed in the coming decade. For example, to meet the goal of the WHO to eliminate viral hepatitis, the diagnosis coverage worldwide should be increased from 9–20% in 2015 to 90% in 2030. In addition, treatment coverage should be improved from 7–8% in 2015 to 80% in

2030 (REF.[1]). In clinical practice, the treatment coverage is dependent on the diagnosis followed by linkage to care. Thus, countries have to scale up national plan efforts; however, important gaps still exist in current policies. In 2017, the WHO conducted a survey in all 194 Member States and 135 (70%) of them responded, as follows: 84 (62%) had developed a national plan, of which 49 (58%) had dedicated funding, and 62 (46%) had engaged with civil societies; those engaged with civil societies were more likely to have a funded plan than others[10]. Thus, WHO Member States need to finance these national strategies and ensure that those affected have access to hepatitis services as part of efforts to achieve universal health coverage[10]. A study of 45 high-income countries showed that even with the introduction of curative HCV regimens, 80% of these countries were not on track to meet HCV elimination targets by 2030, and 67% were off track by at least 20 years[6]. Immediate actions to improve HCV screening and treatment is, therefore, needed globally to make HCV elimination achievable. Hopefully, with sufficient capacity and endeavour, HBV and HCV elimination programmes can meet the goals of the WHO by 2030.

Jeffrey V. Lazarus. The world can eliminate hepatitis C as a major public health threat, as set out by the WHO in 2016, but that means meeting three principal targets: diagnosing 90% of people with viral hepatitis; treating 80% of eligible persons; and reducing incidence and mortality by 90% and 65%, respectively[11]. Although we might achieve this goal globally, some low-income countries, particularly those with weak health systems and in conflict zones, will struggle to reach it. Additionally, high-income countries increasingly face 'diagnostic burnout', in which the easy-to-reach cases are treated, but marginalized populations such as homeless people, prisoners and people who inject drugs as well as most cases among the general population remain undiagnosed. Such barriers have led to only 11 high-income countries currently being on track to eliminate viral hepatitis by 2030 (REF.[12]).

This lack of progress is a clear policy failing. In 2019, as part of the *Lancet Gastroenterology & Hepatology* Commission[13], we highlighted major policy deficiencies in 66 countries studied. These deficiencies included a lack of available national epidemiological data and publicly funded screening programmes for viral hepatitis. We found a wide spectrum of policy responses across countries. Some countries had all of the recommended policies in place and others ranked poorly, with only a single policy, for mandatory screening of blood products[14]. Furthermore, countries often did not have estimates of the potential economic impact of viral hepatitis or provide free HCV treatment for nationals[14]. In a parallel study, I worked with a group of colleagues to engage patient groups in assessing how well countries were implementing the recommendations and policies of the WHO. We found that from the perspective of these patient groups, there was substantial heterogeneity in the implementation of policies that were in place[15]. Countries were least likely to have policies addressing the most vulnerable populations, such as people who use drugs and migrants, and, when such policies did exist, they were poorly implemented[15].

Maud Lemoine. If we refer to the epidemiological definition of 'elimination', viral hepatitis elimination should mean a reduction to zero of viral hepatitis incidence in defined geographical areas as a result of deliberate efforts. However, elimination of viral hepatitis currently refers to the 2016 WHO elimination targets of viral HBV and HCV infections, which aim for control of viral hepatitis as defined by a reduction in their incidence, morbidity and mortality to a locally acceptable level, rather than elimination[11,16,17]. By dramatically increasing viral hepatitis service coverage, including prevention, screening and treatment, the WHO targets aim to reduce the incidence of HBV and HCV infections and their associated mortality substantially by 2030 (by 90% and 65%, respectively). Unfortunately, considering the number of people chronically infected with viral hepatitis (320 million individuals) and its catastrophic burden of disease worldwide (1.34 million annual deaths)[16] and considering the level of efforts currently deployed to tackle the disease, these targets are unlikely to be achieved over the next decade, especially in resource-limited settings. Indeed, to achieve these targets, the WHO called for multiple key interventions that are far from being implemented in most locations[16]. For example, it will be difficult to

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achieve a 90% HBV immunization coverage, including HBV birth-dose vaccine coverage, in regions such as Africa, where the current coverage of HBV birth-dose vaccine is estimated at 11%, and even lower in some resource-constrained locations[18]. Similarly, it will be extremely difficult to increase antiviral treatment provision to 80% by 2030 in most countries/regions, especially LMICs where only a minority (<5%) of people infected with HBV or HCV are currently tested and enrolled into care and treatment programmes[16]. In most LMICs, access to viral hepatitis testing and treatment at low cost is almost impossible, which represents a major barrier for scaling up screen-and-treat interventions for viral hepatitis[13]. In high-income countries, millions of people are still undiagnosed, and infected people with HBV or HCV are often vulnerable populations (undocumented migrants, injection drug users, homeless people) who are difficult to reach and enrol into care. In many locations, including LMICs, where the population is ageing and untested, we might even observe an increase in mortality due to viral hepatitis in 2030 compared with 2015. Finally, to track progress on the WHO elimination targets, it is critical that countries not only develop national hepatitis plans, but also surveillance systems to measure the incidence and burden of liver disease that are currently either non-existent or of poor quality in most LMICs[16].

Although we should acknowledge the remarkable efforts deployed by the WHO in collaboration with academic and non-academic actors to initiate viral hepatitis elimination, it has become urgent to develop and implement realistic strategies adapted to each environment and specific population to achieve the elimination goals. But this process requires a stronger mobilization of the civil society, health policy makers and funders, for whom current commitment in the fight against viral hepatitis remains largely insufficient. Compared with other infectious diseases, viral hepatitis is largely underfunded. In contrast to HIV infection, for example, there is no PEPFAR (President's Emergency Plan for AIDS Relief) for viral hepatitis and the support from the Global Fund in the fight against viral hepatitis has been limited. The Global Alliance for Vaccine and Immunization (GAVI) has still not confirmed its support for HBV birth-dose provision in LMICs. Moreover, funding opportunities for research specifically in viral hepatitis are scarce even from funders such as the Bill & Melinda Gates foundation, which have demonstrated great international support against other major public health threats worldwide.

Anna S. Lok. Elimination of viral hepatitis using the WHO definition of 90% reduction in infections and 65% reduction in deaths by 2030 was a stretch when those goals were declared in 2016 (REF.[11]). An intermediary goal was 30% reduction in infections and 10% reduction in deaths by 2020. Although the tools to achieve these goals were available in 2015 for hepatitis B — a safe and effective vaccine with >95% success in preventing infection, and safe antiviral drugs with proven efficacy in suppressing HBV replication and in decreasing the risk of cirrhosis, liver failure, liver cancer and liver-related deaths — the necessary systems and infrastructure to implement universal vaccination and to diagnose and link all infected persons to care were missing or inadequate in many countries/regions, including high-income countries. For hepatitis C, there is no vaccine to prevent infection but there is a cure — a short, 8–12-week course of orally administered direct-acting antiviral agents (DAAs) can cure >95% of HCV infection. The limiting factor is identifying those infected and providing them with the treatment. Given the safety of these drugs, treatment can be supervised by non-physician providers; thus, the major limitation is the cost of these drugs and the test to confirm HCV infection and cure.

By 2017, roughly 70% of countries/regions worldwide had formulated a national plan to achieve the WHO goals of elimination of viral hepatitis, but fewer than 50% of the countries/regions had secured funding to support those plans and, even in those that did, the amount of funding would not cover the entire plan[16]. In 2020, the entire world was affected by the COVID-19 pandemic. The pandemic, which is still ongoing as of June 2020 and may well last until 2021 or 2022 unless safe and effective vaccines are available and accessible globally, is diverting the attention and resources of all governments, health departments and health-care professionals. The associated economic downturn affects every sector of the community, making it difficult for any commitment of new funding towards viral hepatitis elimination. It also jeopardizes funding and resources previously allocated for viral hepatitis elimination. With the attention of the WHO and the world being diverted, what was previously a laudable but hardly achievable goal is no longer feasible and the hepatitis community will need to reassemble when the COVID-19 pandemic is contained to assess the status of each country/region and to revise global and national goals and action plans. Although the pandemic has been devastating, much has been learned, including new systems of delivering care and collaborations between front-line providers and health-care departments, as well as collaborations among health-care departments worldwide.

Fabien Zoulim. The WHO has proposed a three-pronged approach for the future of viral hepatitis worldwide[19]: an aim for a world in which viral transmission of HBV no longer occurs and those living with viral hepatitis have access to safe, affordable and effective care; a goal to eliminate viral hepatitis as a major public health threat by 2030 (note, not the elimination of viral hepatitis); and an aim to substantially reduce the incidence of chronic viral hepatitis and the associated morbidity and mortality. The elimination of viral hepatitis as a major public health threat is going to be an extremely difficult task to achieve by 2030 despite the efforts made by the major stakeholders. The proportion of infected individuals diagnosed with chronic HBV infection remains low, as does the proportion of patients with hepatitis B who are receiving treatment (9% and 5%, respectively)[13]. Whilst the proportion of chronic HCV infection diagnosed is somewhat higher, the proportion of those who have been treated clearly remains insufficient (20% and 7.4%, respectively)[13].

There remain many challenges to the improvement of these statistics. These constraints are specific to each virus and are also dependent on the economic and health-care status of each region. For instance, for HCV, there is no vaccine. Despite the high curative rates of the new DAAs, because chronic infections are usually asymptomatic new infections can occur if prevention measures are not applied in high-risk groups (intravenous drug users, those that are incarcerated, migrant populations, and so on). Many studies have suggested that a test-and-screen strategy would be needed to eradicate those that are currently infected with HCV[13,20]. However, there are many issues related to this approach, mainly the difficulty of screening and identifying infected patients within these at-risk populations and also keeping the patients known to be infected with HCV in the health-care system to provide them with antiviral therapy. A large group of patients might still be undiagnosed and be at risk of transmitting the infection until a vaccine is available. However, the development of an HCV vaccine has proven

to be challenging and, therefore, might not be part of the global strategy to control HCV infection in the near future.

For HBV, the situation is very different as there is an efficient vaccine, but the currently available antivirals — nucleos(t)ide analogues (NUCs) — cannot eradicate the virus and only induce viral suppression[21]. As there are still more than 250 million chronic carriers of the virus, the elimination of HBV would require several lines of action: reinforcement of the global vaccine coverage, including the effective implementation of vaccination of all newborn babies in all regions of the world, especially those where HBV is highly endemic; improvement of the global access to long-term therapy with NUCs and improvement of disease management in all parts of the world (this step would be instrumental to decrease the health burden of chronic hepatitis B and decrease the risk of transmission); and broadening treatment indications to treat all viraemic patients, as the current international guideline recommendations do not fully support treatment of 'immune tolerant' patients with extremely high levels of virus nor those 'inactive carriers' with detectable viraemia who remain at risk of transmitting the infection and can contribute to the maintenance of the viral reservoir in the population, especially in highly endemic and resource-poor regions.

Hepatitis delta virus (HDV) infection has been neglected for too long. HDV usually requires a co-infection with HBV for transmission. Thus, HBV vaccine coverage is crucial to prevent co-infections or superinfections. The results of a prevalence study published in 2020 suggest that, worldwide, 0.16% of the general population, totalling 12.0 million people, were estimated to be anti-HDV positive. Among people positive for hepatitis B surface antigen (HBsAg), preliminary population attributable fraction estimates of HDV were 18% for those with cirrhosis and 20% for those with hepatocellular carcinoma (HCC)[22]. In an epidemiological study in Cameroon, evidence was found for substantial intra-household transmission of HDV as well as large differences in prevalence between regions, the reasons for which remain unclear[23]. The epidemiology of HDV infection has been overlooked for many years and data are now emerging from different parts of the world that will be instrumental to implement the best policies to control this infectious disease. Even in western countries, most patients are migrants who have difficulty accessing medical care. There is no curative treatment for HDV infection beside pegylated IFNα, which is not even formally approved for this indication and might also run out of supply. Novel drugs are in clinical trial evaluation[24], including myrcludex, lonafarnib and nucleic acid polymers, but most of them will be given in combination with pegylated IFNα or IFNλ to maximize cure rates. Thus, this issue remains an area in which further research is clearly needed.

Q *Where have been the key areas of progress towards the 2030 elimination goals?*

M.H.E.-S. Between 2015 and 2019, the WHO provided tools to assist in the development of national strategies, test-and-treat guidelines for hepatitis B and C, cost-effectiveness calculators (for HBV and/or HCV infection), a global hepatitis reporting system and consolidated strategic information guidelines[25,26]. Progress in hepatitis elimination demonstrated a major breakthrough with the advent of a new generation of highly effective medicines. Lifelong treatment can suppress HBV replication; 12–24 weeks of treatment can cure chronic HCV infection and prevent onward transmission to others. Model test-and-treat programmes in LMICs (such as Egypt) have verified the feasibility of universal HCV screening and treatment, reaching 50 million adults and 9 million adolescents in 2019 in Egypt[27]. The affordability of these DAAs in many LMICs and the availability of generic forms offered opportunities for better access to treatment in both high-income countries and LMICs. The medicine patent pool negotiated public health-driven licenses for three HCV DAAs with patent holders and sublicensed drugs to generic companies[28]. Licensing terms encouraged the sale of affordable generic versions in resource-limited settings.

According to a study published in 2019, 62% of the Member States had national hepatitis plans, 27% of which were at the draft stage in 2017 (REF.[10]); 58% of plans included some domestic funding. Forty-five countries/regions have reported data in the new global reporting system for hepatitis. Notably, 62% of people with HCV infection live in locations that have access to generic DAAs for as low as $45 for 12 weeks of treatment and generic tenofovir available in resource-limited settings at $30 per year. On a global level, civil society bodies such as the World Hepatitis Alliance are continuing their engagement with donors and key multisectoral stakeholders, providing an evidence-based approach to the response.

A.L.C. Historically, the WHO Western Pacific Region (WPR) has had the world's highest prevalence of chronic HBV infection. Papua New Guinea, the Philippines, Vietnam, Lao People's Democratic Republic and China all have greater than 5% prevalence of chronic HBV and more than half a million people infected[29]. China has the largest burden of chronic HBV with ~86 million people infected[29]. In 1990, more than 8% of children at least 5 years of age in the WPR had chronic HBV infection[30]. In 2013, WPR countries/areas prioritized increasing hepatitis B vaccine birth-dose and third-dose coverage in an effort to reduce this figure below 1% by 2017, a WHO target[30]. This same target of <1% chronically infected globally was set for 2020, but the target was achieved both in the WPR and globally in 2017 with 5-year-old children having a prevalence of 0.93%[30]. In November 2018, GAVI expanded hepatitis B vaccine birth-dose coverage as part of its Vaccine Investment Strategy, making global reduction in infant HBV infection more likely.

The most substantial advance in HCV elimination has been the development of DAAs for HCV treatment. The DAAs have been truly revolutionary in the care of patients with HCV infection, with sustained virologic response reducing the risk of end-stage liver disease, HCC and extrahepatic manifestations of HCV infection[31]. The markedly enhanced tolerability profiles of later generation DAAs permits treatment of patients in the advanced stages of liver disease, providing the opportunity to reduce mortality more rapidly than prevention of infection does because of the approximate two decades from HCV infection to end-stage liver disease or HCC. In addition, improved tolerability and high cure rates justify expanded screening for HCV infection and recommendations in some guidelines for treatment of everyone infected with HCV without a short predicted life expectancy due to non-liver related comorbidities[32] (see Related Links).

J.V.L. We have seen progress in greater access to testing and treatment overall, and increased coverage of both, among marginalized populations, such as people who inject drugs and prisoners. For example, the negotiated purchasing of direct-acting antiviral treatment has substantially improved treatment coverage across high-income countries, while generic formulations are available in more than

100 countries, often at quite low prices, even for low-income countries. Additionally, there has been increased use of unique models of care for marginalized populations using point-of-care testing, as highlighted in a Comment published in 2019 in this journal[33]. Same-day receipt of testing results is available in some settings where this is urgently needed so as not lose the patient to follow-up, such as harm reduction centres and homeless shelters. In high prevalence settings such as needle and syringe services and safe injection rooms, RNA point-of-care tests that provide results in just an hour facilitate test-and-treat models. However, these models of care need to be replicated much more widely in most countries around the world.

F.Z. For HCV, major progress has been made in the past 10 years with the discovery of DAAs that can cure the infection. The cure rate is close to 100% for DAAs with treatment for 8–12 weeks[34]. The new generation of drugs are now pan-genotypic, and their cost has been reduced owing to generic manufacturing. This progress is facilitating the test-and-treat strategies in developing countries. In parallel, in developed countries, both the incidence and prevalence of chronic HCV infection has decreased as well as its complications and the need for liver transplantation[35–37].

For HBV, the last generation of NUCs were developed >10 years ago but their long-term safety and efficacy, in terms of prevention of liver complications of chronic hepatitis B, including cirrhosis and HCC, have been confirmed[38]. The availability of generic medication has reduced the cost of treatment and opened access to treatment in many countries. The development of polyvalent vaccine formulations that include HBV vaccine for infants and children is also an important step to the improvement of vaccine coverage worldwide.

M.L. Regarding HBV infection, major progress has been made in terms of immunization coverage; by the end of 2018, hepatitis B infant vaccine was introduced in 189 countries/regions and the global coverage with three doses of vaccine was estimated at 84%[18]. However, the estimates remain insufficient (76%) in Africa, and HBV birth-dose vaccine coverage globally is still very low (38%), especially in Africa, where only 11% of newborn babies receive the HBV birth dose within 24 h of birth as recommended[18]. Progress has been made in terms of public and political awareness. Many countries/regions have observed the emergence of viral hepatitis patient associations, non-governmental groups (for example, Coalition for Global Hepatitis Elimination, International Coalition to Eliminate HBV) and national hepatitis programmes. However, in 2017, only a half of all WHO Member States were estimated to have a national elimination plan for viral hepatitis with dedicated funding[10].

Regarding HCV infection, some locations such as Egypt[39] and Georgia[40] are on track to control hepatitis C. Both governments have deployed massive efforts in the fight against hepatitis C over the past years. These programmes have been successful because they have engaged civil society, political actors, industry and funders, as well as used existing platforms of care (for example, for tuberculosis or HIV) involving health-care workers in decentralized areas. In addition, these locations have been able to negotiate tests and antiviral drugs at very low costs.

A.S.L. The reinstitution of support for birth-dose HBV vaccine by GAVI has been one major area of progress. Because the risk of chronic HBV infection is highest when infection is acquired at birth, support for birth-dose HBV vaccine has been projected to avert 0.3–1.2 million perinatal infection-related deaths and 1.2–1.5 million cases from 2021–2025 (REF.[41]). In the past 5 years, there has also been a lot of momentum as well as industry investment in developing new therapeutics for hepatitis B[42]. Although none of these new therapeutics has yet made its way to phase III trials, and each new drug on its own likely will not be sufficient to 'cure' hepatitis B, development of new drugs targeting different steps in the HBV life cycle as well as innate and adaptive immune responses pave the way for combination therapies that could result in a 'cure' in a higher proportion of patients than can be achieved with current therapies. Developing a sterilizing cure for hepatitis B has been challenging because HBV DNA can be integrated into host DNA and the integrated HBV DNA can continue to make HBV protein even when the virus DNA is no longer replicating[42]. Also, HBV DNA exists in the nucleus of infected hepatocytes as covalently closed circular DNA (cccDNA), which has a long half-life and is minimally inhibited if at all by currently available treatments. The cccDNA serves as a template for replication of HBV DNA and production of HBV proteins, and its removal is believed to be largely dependent on turnover of infected hepatocytes. Furthermore, patients with chronic HBV infection have an impaired immune response to HBV. Thus, instead of aiming for a sterilizing cure, experts are aiming for a functional cure whereby HBV replication remains suppressed after a finite course of therapy but cccDNA that is no longer transcriptionally active and integrated HBV DNA would still be present. For HCV, the major progress has been the availability of pan-genotypic DAAs and real-world data showing that similarly high cure rates as compared with clinical trials can be achieved in community practice with minimal monitoring, making it feasible for these treatments to be implemented outside of major medical centres in high-income countries.

J.-H.K. Using Taiwan as an example, the key areas of progress towards the 2030 elimination goals include: the prevention of vertical HBV transmission by hepatitis B immunization and antiviral treatment for highly viraemic mothers infected with HBV; potent, safe and affordable treatments for HBV and HCV infections countrywide; and changing reimbursement policies of HBV and HCV therapy. Although Taiwan has a high prevalence of both HBV and HCV infections, it is not a Member State of the WHO. Nevertheless, when the World Health Assembly adopted the Global Health Sector Strategy on viral hepatitis in 2016, it immediately caught the attention of the Taiwanese government and civil societies, and efforts towards the elimination of HCV were seriously considered. After 2 years of planning and efforts, government leaders have culminated in a consensus of reaching the WHO goals by 2025 — that is, 5 years earlier than the 2030 deadline set by the WHO. Accordingly, the Taiwan Hepatitis C Policy Guideline 2018–2025 was approved and published at the beginning of 2019 (REF.[43]). The government will provide $1.7 billion within 8 years for the control of HCV infection, and actions include: lowering the barriers of access to care; screening strategies; continuum of care; preventive measures for high-risk populations; improving liver health literacy on the prevention of new infections and reinfections; liver disease management; and outcome evaluation of policy and interventions[43]. Following the launch of this policy guideline, the number of patients with HCV infection treated annually has remarkably increased, rising from 9,500 patients in 2017 to 46,000 in 2019. More than 58,000 patients are projected to be treated in 2020. After including 80,000 patients already successfully treated with pegylated interferon and ribavirin therapy before the direct-acting antivirals era,

treatment coverage is expected to reach 50% by the end of 2020. Thus, Taiwan is on track to eliminate HCV by 2025 (REFS[44,45]).

Regarding the elimination of HBV, Taiwan was the first country to implement universal hepatitis B vaccination since 1986 and the overall HBsAg carriage rate in the vaccinated cohort was down to 0.5% in 2016 (REF.[46]). In addition, anti-HBV treatment has been reimbursed since 2003 and the treatment indications have been expanded over time, including the use of anti-HBV agents for HBV-infected mothers with high HBV DNA levels to prevent vertical transmission[47,48]. Furthermore, Taiwan made tremendous efforts to identify patients infected with HBV or HCV in need of treatment. The government reimburses HBsAg and anti-HCV testing once in a lifetime during the health check-up for adults >45 years of age. In addition, several civil societies conducted community screening programmes for HBV and HCV infection with linkage to medical care[49].

What should be the focus for the next 10 years? Where should efforts and money be invested to achieve the elimination goals?

F.Z. There is a chronic lack of funding for hepatitis programmes worldwide. We need to increase general public awareness of the substantial disease burden of viral hepatitis to better leverage funding amongst key stakeholders. This step will aid in the implementation of public health programmes with the aim of eliminating viral hepatitis. There is important synergy within the screening, prevention and treatment programmes for HIV, sexually transmitted diseases and viral hepatitis. We should use this synergy to our advantage to increase funding for viral hepatitis. Specific actions should be undertaken to develop and provide affordable, easy-to-use and rapid point-of-care tests to implement test-and-treat strategies for all hepatitis viruses and HIV.

For HCV, the high-risks groups are those who are more difficult to reach. Programmes to develop harm-reduction services and facilitate access to treatment for intravenous drug users should be prioritized, as well as programmes for other high-risk populations such as those that are incarcerated or migrants, for instance[20]. For HBV, programmes to provide timely doses of HBV vaccine at birth in Africa and other highly endemic regions are urgently needed[50]. As most of the HBV-infected patients live in resource-poor locations, there is an urgent need to expand access to diagnosis, treatment and cure. As HBV is the main cause of HCC, HCC screening programmes should be implemented in those infected with HBV[51].

J.-H.K. In the next 10 years, the focus and efforts should be on increasing public awareness for HBV and HCV infections by undertaking mass screening programmes with simple and rapid methods as well as linking patients to point-of-care. Health education, including increasing knowledge of the risk factors of HBV and HCV infections and the consequences of chronic liver disease, is also important. Through health education, people are willing to be screened and it can also ease the stigmatization of hepatitis virus infections. Notably, health education should be customized for some special populations. For example, people at high risk of hepatitis virus infections (such as men who have sex with men, prisoners or sex workers) should be educated to increase their knowledge on the risk of virus infections, preventive measures, benefits of screening and effective treatment regimens. It is also helpful for them to modify risky behaviours and make them aware of the existing public health policies that could support them if they get infected. Governments or civil societies should deliver these messages to correctional institutions or infectious disease clinics to treat HIV or other sexually transmitted diseases. Countries with limited resources should receive international investments on viral hepatitis programmes with prevention and treatment strategies. In addition, blood safety and harm reduction programmes in the group of people who inject drugs need to be improved to reduce transmission of HBV and HCV. The treatment coverage of HBV and HCV infections can be raised by reducing the cost of drugs, including the introduction of generic agents. Last but not least, development of curative regimens for HBV and effective vaccines for HCV will definitely facilitate the achievement of elimination goals[52].

J.V.L. Resources should go towards expanding testing and providing treatment, which will likely require epidemiological studies to maximize the investment[53]. Furthermore, we must focus on enhancing monitoring and evaluation in line with the WHO recommendations. At a minimum, this should involve reporting the key steps from the consensus cascade of care: estimating prevalence, diagnosis, treatment initiation and sustained virologic response[54]. Health systems should also focus more on microelimination[55], which targets key subpopulations such as people with haemophilia or those infected with HIV, transplant recipients and donors, those on dialysis or opioid substitution therapy, or those in prison as well as in a particular setting like an island or a region, to make the elimination targets less daunting and more achievable. As such, we must employ unique models of care[56] that are person centred as well as setting specific and patient specific. Models of care should ideally address all stages of the cascade of care and increase the number of people on treatment. We must also increase screening among key populations, in particular people who inject drugs. This approach will require decentralized services including, in some settings, mobile and community-based services in addition to simplified diagnostic procedures[57]. Some countries/regions and many clinics already have eliminated co-infection of HCV in specific patient populations such as people with haemophilia, people living with HIV, people receiving dialysis, and people who have received or donated organs. Lastly, we should also focus on increasing engagement with a range of stakeholders including policy makers and diverse types of health professionals to expand the types of prescribers and services provided, as well as with affected communities to better address their distinct needs.

M.H.E.-S. In-country and global advocacy must be maintained to keep viral hepatitis high on the political agenda. The major hurdle to eliminate hepatitis by 2030 is a lack of financial resources. Although most countries/territories are on track to meet the 2030 target of the WHO of <0.1% HBsAg prevalence among those under 5 years of age, without further investment this target is currently unachievable for 20 countries/territories[58]. Investment in prevention remains the mainstay for elimination. Expansion in implementation of the hepatitis B birth-dose vaccine is a critical intervention for elimination of HBV and HDV, and coverage is still low in LMICs, particularly in Africa. It is anticipated that the GAVI support for low-income countries in 2021 could avert 0.3–1.2 million perinatal infection-related deaths and 1.2–1.5 million cases between 2021 and 2035 (REF.[41]). GAVI estimate a support for 284 million doses between 2021 and 2035 at a cost of $0.20 per dose, complementing the broader package of health-care system strengthening[41].

The incentive of affordable treatments and models of care should encourage more LMICs to develop national plans for integrated upscaled programmes for viral hepatitis testing and mass drug administration, to reach millions of people per year, without encountering unrealistic health disbursements. Microelimination for both HBV and HCV infection should be adopted to capture marginalized populations, including children, adolescents, pregnant women, women of childbearing age and migrants and/or refugees to ensure complete elimination and equity in access to services, leaving no one behind. The global estimate for HCV viraemic prevalence in the paediatric population (0–18 years) corresponds to 3.26 million children in 2018 (REF.[59]).

The control of viral hepatitis relies on investments and critical advances in affordable point-of-care testing. This step would in turn increase the number of people tested, facilitate task-shifting and outreach programmes and engage more actively with civil society to support national programmes. Implementation of viral hepatitis strategies should also include awareness-raising activities to create demand for viral hepatitis services concurrently with supportive legislations, policies and guidelines to reduce stigma. With fast-growing newer technologies and communication systems, innovations can be tailored for delivery of services to improve access to care and treatment.

M.L. Compared with hepatitis C, hepatitis B has been largely left behind mainly because of the absence of curative therapy and the complexity of its clinical management. It is, therefore, extremely important to reinforce the public–private partnership between industry and academia to accelerate HBV cure. HBV elimination will not be achieved without finding and treating the millions of HBV-infected people at risk of hepatic complications (such as cirrhosis and liver cancer)[50]. In LMICs that are most affected by the HBV epidemic, millions of people are unaware of their infection and <5% of those in need of treatment are receiving antiviral therapy[16]. One of the reasons for this is the complexity and cost of the current guidelines for the diagnosis and management of viral hepatitis, especially hepatitis B. Thus, major efforts are needed to develop simplified diagnostic and treatment algorithms based on inexpensive tests that can be implemented easily in rural areas to find the 'missing millions' and improve the viral hepatitis cascade of care, including treatment coverage[13].

Major efforts should be also deployed in the prevention of HBV mother-to-child transmission (MTCT) in LMICs. This field has been long neglected, especially in Africa where only 12 countries/regions have integrated the HBV birth-dose vaccine in their immunization programmes, but most of the newborn babies do not receive the first dose of the vaccine at birth; moreover, in LMICs, pregnant women are not systematically screened for HBV and interventions to prevent MTCT are often non-existent[18]. However, efforts should be deployed urgently as HBV MTCT is associated with an increased risk of liver complications[60]. As previously underlined, securing sustainable funding for viral hepatitis elimination is urgently needed[61].

A.L.C. Continued commitment to and enhanced coordination among programmes that offer different hepatitis B prevention interventions as well as an increase in diagnosis and treatment of those eligible are needed to achieve hepatitis B elimination. Because a high proportion of HBV infections occur by MTCT, all pregnant women should be tested for hepatitis B and, if infected, their babies should promptly be given hepatitis B immunoglobulin to prevent infection. Because hepatitis B immunoglobulin administration has been challenging in LMICs where MTCT is common, HBV diagnosis and treatment of eligible women of child-bearing age could also be used as a strategy to reduce MTCT[62]. Diagnosis and treatment of more HBV-infected individuals in general is required for HBV elimination[3–5]. An important goal for the next decade will be the discovery of agents that functionally cure rather than simply suppress HBV infection. Goals for HCV therapeutics include long-acting DAAs. Although long-acting agents to cure HCV in a single dose might be of benefit, the single biggest deficit in the tool chest for HCV elimination is the lack of a prophylactic HCV vaccine. By analogy, a single dose of penicillin treats syphilis, but syphilis has not been eliminated in even high-income countries despite the availability of this simple and inexpensive treatment for more than half a century. Because HCV is often clinically silent until advanced liver disease is present, the DAAs do not prevent reinfection in those at ongoing risk, such as health-care workers and people who inject drugs, and the risk of liver failure and HCC are reduced but not eliminated by sustained virologic response, so maximal reduction in mortality from HCV will likely require preventing HCV infections in the first place[63]. The first efficacy trial of a vaccine to prevent chronic HCV infection did not meet the efficacy end point, but demonstrated an effect of vaccination on HCV viraemia and the feasibility of testing HCV vaccines in people who inject drugs, the population at the highest risk of HCV infection[64]. Ideally, analyses of these vaccine-induced immune responses following HCV exposure will be explored to enhance next-generation vaccine design. Although a vaccine to prevent chronic HCV infection might be difficult, it will be impossible without dedication of substantial efforts and research dollars to HCV vaccine development. We certainly will not develop a prophylactic HCV vaccine if we do not even try.

A.S.L. Prevention is always better than cure. Thus, the focus for the next 10 years should be universal birth-dose vaccination for all newborn babies globally. Another focus would be to diagnose those who are infected and link them to care[65]. Each country and each community has to develop its own strategy that is practicable and sustainable. For these strategies to be successful, there must be parallel efforts to remove the stigma associated with hepatitis B. Because of the public's misunderstanding of how HBV is transmitted, patients with chronic HBV infection are often considered to have acquired the infection through 'bad behaviours' or are discriminated for fear that they might spread the virus through casual contacts[66]. For hepatitis C, the focus should be diagnosis and cure. Each country must determine the most feasible and high-yield strategy to identify as many patients with hepatitis C as possible, before they progress to cirrhosis, and to offer curative treatment. This step requires global efforts to make direct-acting antivirals and HCV PCR testing readily available and affordable.

Q *What should be the future directions for 2030 and beyond?*

M.H.E.-S. The ongoing COVID-19 pandemic should provide governments with insights to prioritize investments in the health-care system and fast-track universal health coverage. Global donors and investments need to be redirected to strengthening infectious disease surveillance, reinforcing preventive strategies and providing well-funded research platforms for data information systems, diagnostics, vaccine and drug development.

Global strategies require modification to be inclusive of other types of hepatitis viruses. Hepatitis A, E and D have often been overlooked, but they contribute to

substantial liver disease morbidity and mortality in children and adults. Their prevention needs to be clearly addressed, particularly in resource-limited settings. HCV will not be eradicated unless an effective vaccine is readily available to prevent the incident new infections and outbreaks in vulnerable populations with high-risk behaviours including injection drug users. The development of an effective vaccine has been stymied by the discovery of a cure for hepatitis C and repurposing investments towards DAAs. Encouraging innovations in hepatitis vaccine development and delivery methods are critical to eradicate hepatitis beyond 2030. The current innovations in drug development technology should also accelerate the progress in discovery of a sterilizing cure for hepatitis B.

New policies are required to ensure advancement in preclinical and clinical development of innovative medicines and vaccines, including virtual research and development, in addition to consolidating the role of partnerships in improving global access to medicines and vaccines, procurement and immunization coverage. The efficiency of research and development, supply chain tools and trends in packaging technologies improving delivery, prequalification and registration is required to ensure optimal investments, alignment and stability of supply of medicines and vaccines in resource-limited settings. In addition, novel hepatitis data registry and surveillance tracking systems, interactive tele-education and tele-medicine are needed to improve service delivery.

J.-H.K. Although HBV and HCV can be suppressed or cured by effective antiviral therapy, patients with advanced hepatic fibrosis or even cirrhosis are still at risk of developing liver cancer. Thus, monitoring these patients with novel biomarkers for risk stratification is clinically important. Future development of chemopreventive agents to reduce or halt hepatocarcinogenesis after viral control or cure is another direction of research. Beyond 2030, and once the burden of viral hepatitis has been reduced, there should fewer instances of advanced liver diseases attributable to HBV or HCV infection; however, other aetiologies of liver disease such as metabolic liver disease (non-alcoholic fatty liver disease or non-alcoholic steatohepatitis), alcoholic liver disease or drug-induced liver injury could prevail and become of great clinical concern[67]. Health education regarding the risk factors for these liver diseases and how to maintain a good lifestyle and promote liver health is of paramount importance in the coming decades.

M.L. Whilst the next decade should focus on the key research areas previously listed, the direction for 2030 and beyond will certainly be implementation research. To accelerate the development and delivery of approaches identified for viral hepatitis elimination it will be extremely important to link research, clinical practice and health policy with the support of national hepatitis programmes and ministries of health. This step is essential to scale up interventions at a national and regional level. As a result, substantial funding should be allocated to research on viral hepatitis. In the face of the COVID-19 pandemic and its economic and sociopolitical consequences, both short term and long term, viral hepatitis is at risk of being more neglected than before. Bigger efforts in the fight against viral hepatitis have never been so urgent.

F.Z. For HCV, the development of a vaccine would be a major asset to complement the test-and-treat strategies for the elimination of this disease. Despite the fact that HCV vaccine development is facing major scientific challenges[68], hope remains for a vaccine development by 2030. For HBV, drug discovery efforts should be continued to find a functional cure for the infection, which would enable the treatment of all infected patients[24]. This step is a crucial factor which, in addition to vaccination programmes, would enable HBV eradication globally.

A.S.L. Hopefully, by 2030 universal birth-dose vaccination will be in place globally and at least one-third of those chronically infected will have been diagnosed and linked to care. The focus beyond 2030 should be development of curative therapy. The possibility of eliminating HBV is much higher if HBV can be 'cured' (even if it is only a functional cure with loss of hepatitis B surface antigen, but not eradication of HBV) with a finite course of oral medications that is safe and affordable, more so than current treatments that often require years of if not lifelong medication. For hepatitis C, it is hoped that, by 2030, the vast majority of patients with hepatitis C in high-income and middle-income countries will have been cured and an increasing proportion in low-income countries will have access to a cure. Going into the future, all patients with hepatitis C should be cured. Government policies, implementation plans, funding and willpower are all needed to make hepatitis elimination possible, but this feat will not be achieved by 2030.

A.L.C. Hepatitis elimination will require substantial financial and political commitment and global prioritization. Without concerted global efforts to control chronic viral hepatitis, HBV and HCV are predicted to kill more people by 2040 than HIV, malaria and tuberculosis combined[1]. Ideally, the next 10 years will yield effective and well-tolerated HBV functional cures and at least a moderately effective prophylactic HCV vaccine. Unfortunately, shortages of medical equipment and closure of needle and syringe and opiate use disorder clinics owing to COVID-19 will likely increase the risk of iatrogenic and other exposures to viral hepatitis. Resources required for the development of treatments for and a vaccine against COVID-19 will limit capital for the development of a vaccine against HCV and an HBV functional cure. However, introduction of HBV cures to infected populations and the initial roll out of a prophylactic HCV vaccine to higher risk populations followed by universal HCV vaccination once vaccine safety has been demonstrated will deal the final death blow to chronic hepatitis B and C.

J.V.L. We need strong monitoring and evaluation to maintain gains and to identify where specific actions need to be initiated or intensified. Most of the world is not adequately addressing viral hepatitis elimination, and it remains far down the policy agenda for most governments. Across sub-Saharan Africa, for example, many countries/regions are treating just a handful of people and are testing equally as few. Particularly concerning is the lack of technical assistance from the WHO to countries and, due to its limited human resources, a challenge that will be exacerbated during and likely after the COVID-19 pandemic. Moreover, many country-level barriers exist from procurement to deployment to absurd restrictions on who can prescribe or be prescribed.

Even if 2030 is our target for eliminating viral hepatitis as a major public health threat, there will likely be considerable work to do in the years beyond. Although I believe that the world can and will eliminate viral hepatitis, it is probable that not all countries will have eliminated viral hepatitis by then. Furthermore, reaching the targets does not mean that all people living with viral hepatitis will have been diagnosed and treated in successful countries/regions by

2030, as the aforementioned WHO targets imply. Therefore, we must ensure that viral hepatitis is removed from the list of major public health threats by 2030 whilst keeping sustained attention on the issue.

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Competing interests

M.H.E.-S. has received an educational grant from Gilead. J.-H.K. declares that he has acted as a consultant for Arbutus, Gilead Sciences and Roche, and appeared on speaker's bureau for Bristol-Myers Squibb, Gilead Sciences, Fujirebio, Merck Sharp & Dohme and Roche. J.V.L. reports grants and personal fees from AbbVie, Gilead Sciences and MSD, and personal fees from CEPHEID, GlaxoSmithKline, Intercept and Janssen, outside of the submitted work. M.L. has received funding and fees from Gilead and Viiv Health care. A.S.L. acknowledges research grants (to the University) from Assembly, Bristol-Myers Squibb, Gilead, and TARGET, and has served on advisory boards or as a consultant for Gilead, GlaxoSmithKline, Huahui, Spring Bank and TARGET. F.Z. has research contracts through INSERM with Evotec and Roche. He has also acted as an advisor or consultant for Assembly, Aligos, Evotec, Galapagos, Gilead, GlaxoSmithKline, Myr Pharma, Roche Molecular Systems, Transgene and Vir Bio. A.L.C. declares no competing interests.

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