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HEPATITIS B (JK LIM, SECTION EDITOR)

Hepatitis B Virus Elimination in the U.S.: Time to Dismantle Barriers and Implement Solutions

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Abstract

Purpose of Review The World Health Organization has set a target for the elimination of hepatitis B virus (HBV) infection as a public health threat by 2030, but the U.S. is not currently on track. In this review, we describe specific barriers to HBV elimination, provide examples of potential solutions, and offer recommendations for how the U.S. can reach HBV elimination goals.

Recent Findings In the U.S., there are many barriers to eliminating hepatitis B, worsened by the siloing of healthcare and public health services. In recent years, we have not seen progress toward improving HBV screening or adult vaccination, and acute cases are on the rise. Current policies, guidelines, and recommendations can hinder elimination progress.

Summary Simple policy and guideline changes will allow us to decentralize and scale-up hepatitis B screening, vaccination, and care. Dismantling current barriers will be critical to eliminating hepatitis B in the U.S.

Keywords Hepatitis B virus · Hepatitis B elimination · Hepatitis B vaccines · Hepatitis B screening · Hepatitis B treatment · Hepatitis B public health

Introduction

In 2016, the 196 countries of the World Health Organization (WHO) committed to viral hepatitis elimination as a public health threat by 2030 as part of the Global Health Sector Strategy [1]. Targets include universal blood and injection safety, harm reduction, childhood hepatitis B vaccination with adoption of universal birth dose, and a substantial increase in diagnosis and treatment of people living with viral hepatitis [1]. With available diagnostics, vaccinations, and/or treatments, the elimination of hepatitis B virus (HBV) and hepatitis C virus (HCV) is within reach and now requires a focus on implementation science and service delivery.

In the United States (U.S.), there have been national campaigns for HCV screening, now universally recommended for all adults by both the Centers for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force (USPSTF), to diagnose and connect people to curative therapies and halt the progression to cirrhosis and hepatocellular carcinoma (HCC) [2, 3]. However, not as much attention has been given to HBV even though it impacts between 700,000 and 2.2 million people in the U.S. [4–6]. Asian Americans, Pacific Islanders, and people from Africa are disproportionately impacted by HBV and comprise the majority of chronic HBV cases [7–10]. More recently, there has been an increase in acute HBV cases coinciding with the opioid crisis. CDC data show that acute HBV infection rates increased 20% nationally in 2015, with increases of up to 489% in Maine from 2015 to 2016 and 114% from 2009 to 2013 in Kentucky, West Virginia, and Tennessee [11, 12].

HBV screening is currently risk-based, and only 25 to 30% of those living with HBV in the U.S. are estimated to have been identified [13, 14]. The sectors that HBV intersects are diverse; deliberate coordination and integration rather than siloed disease state-specific efforts will be required for elimination. Impacted sectors include public health and disease

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surveillance, primary care, hepatology, maternal-infant care, pediatrics, cancer screening, vaccination, harm reduction, prison health, employee health, infectious disease, and immigrant and refugee health.

Addressing key populations and opportunities for integration are health equity components that will be critical for success—especially for a disease that disproportionately impacts non-mainstream, marginalized communities. In the WHO "Guidelines for the prevention, care and treatment of persons with chronic HBV infection" [15], one of the key principles is:

> Ensuring that human rights and ethical principles of fairness, equity and urgency guide the development of national treatment policies so that barriers in access to testing, prevention and treatment services, particularly among certain populations, are addressed.

Thus, we must approach HBV elimination with a holistic mindset by addressing health disparities, our fractured and complex health care system, challenges in accessing specialists, and the realities of following complex vaccination, screening, and treatment guidelines. Screening must be scaled up and effective interventions made widely accessible to those who most need it. Effective HBV vaccines make it possible to follow in the footsteps of other vaccine-preventable diseases like polio and smallpox. Beyond prevention, elimination also requires delivering life-saving care to those living with chronic infection to reduce the morbidity and mortality from hepatocellular cancer and cirrhosis.

In this review, we will describe specific barriers to HBV elimination, provide examples of potential solutions, and offer recommendations for how the U.S. can reach HBV elimination goals [1].

Elimination Strategy

While a recent analysis suggested that the U.S. would not eliminate HCV until after 2050 because of high incidence rates and inadequate diagnosis and treatment rates [16], no similar analysis has been performed as to whether the U.S. is on track to reach the WHO 2030 targets for HBV. However, it is highly unlikely that the U.S. will meet these targets.

The siloed approaches to HBV in the U.S. contribute to missed opportunities in all aspects of care. A recent example is the U.S. Preventive Services Task Force's draft recommendation statement: "Hepatitis B Virus Infection in Nonpregnant Adolescents and Adults: Screening" [17]. This organization provided compelling evidence for the importance of HBV care, stating:

> Up to 60% of HBV-infected persons are unaware of their infection, and many remain asymptomatic until onset of cirrhosis or end-stage liver disease. This contributes to delays in medical evaluation and treatment and ongoing transmission to sex partners and persons who share objects contaminated with blood or other bodily fluids that contain HBV. From 15% to 40% of persons with chronic infection develop cirrhosis, hepatocellular carcinoma, or liver failure, which lead to substantial morbidity and mortality [17]

Yet, they limited their screening recommendations to only those with identifiable risk factors. Complex, risk-based screening programs, focused on identifying those with current infection, siloed from programs to identify those who would benefit from HBV vaccination or those with increased risk due to prior exposure, will fail to reduce the burden of HBV infections in the U.S. There are discrete steps that can be taken to reduce barriers across the HBV care continuum and taken as a whole, bringing the U.S. closer to HBV elimination.

Goal 1 Improve the identification of people living with HBV and U.S. surveillance efforts.

Goal 1, Objective 1 Determine the number of people living with chronic HBV infection in the U.S.

To eliminate HBV, data on the number of cases are required to determine the magnitude of the problem, the resources needed for elimination activities, and to define metrics for the success of elimination activities. An easily implementable case definition is the first step in defining the magnitude of this disease.

Challenge The current case definition for chronic HBV infection, and the lack of surveillance for chronic HBV, leads to under-reporting of chronic HBV infection in the U.S. and under-estimation of the true burden.

The current case definition for chronic HBV used by state Departments of Public Health (DPH) and the CDC [18] includes:

1. Laboratory Criteria for Diagnosis: Either immunoglobulin M (IgM) antibodies to HBV core antigen (IgM anti-HBc) negative and a positive result on one of the following tests: HBV surface antigen (HBsAg), HBV e antigen (HBeAg), or nucleic acid test for HBV DNA (including qualitative, quantitative and genotype testing), or HBsAg positive or nucleic acid test for HBV DNA positive (including qualitative, quantitative and genotype testing) or HBeAg positive two times at least 6 months apart (any combination of these tests performed 6 months apart is acceptable)
2. Confirmed case—a person who meets either of the above laboratory criteria for diagnosis

3. Probable case—a person with a single HBsAg positive or HBV DNA positive (including qualitative, quantitative and genotype testing) or HBeAg positive lab result and does not meet the case definition for acute HBV

These definitions of chronic HBV infection are designed to identify cases of acute HBV infection. A consequence is that all other cases must "prove" that they represent chronic HBV infection to be officially counted [18]. Either IgM anti-HBc must be measured, which is only performed when an acute HBV infection is suspected, or two HBsAg results separated by at least 6 months are performed and successfully tracked by state DPHs, which pose logistical difficulties for many organizations. A single HBsAg positive result, which indicates current infection, is considered a "probable" case, and in some states, these results are not reported to the CDC. Since the case definition is biased toward identifying acute HBV infections, many chronic cases are not appropriately characterized and reported.

An example is the Massachusetts DPH report of confirmed and probable cases of chronic HBV infection (Fig. 1). In 2018, over 90% of cases were classified as "probable" (which are not reported as cases by the CDC) and over time, as additional data were obtained, increasing numbers of cases were reclassified as "confirmed" [19]. This case definition imposes a delay in the assessment and reporting of confirmed cases.

An additional challenge is the lack of a comprehensive national surveillance system to monitor chronic HBV infection in the U.S. Most health departments have few (or no) resources to conduct chronic HBV surveillance and follow-up of cases. Therefore, the true burden of infection is unknown, and chronic HBV as an important health issue is obscured. For example, in the 2017 CDC Viral Hepatitis Surveillance Report, California and Hawaii (states where chronic HBV is a reportable condition) reported zero (0) cases of chronic HBV [20]. This makes no sense. These are states that have sizable AAPI communities, and it is expected that there are people being diagnosed with chronic HBV every year. Community-based screening programs have found prevalence rates of 3–8% in these states [21–26]. The zero case reports do not reflect a lack of chronic HBV—they reflect a severe lack of capacity to identify and report cases. We need to accurately document the burden to appropriately address it.

Solution Change the chronic HBV case definition and improve chronic HBV surveillance.

Recommendation Change the case definition for chronic HBV infection to "current HBV infection" and require one positive result for HBsAg, HBeAg, or nucleic acid test for HBV DNA (including qualitative, quantitative, and genotype testing) and remove the requirement for a negative IgM anti-HBc, which is often not tested in the clinical setting. Maintain the existing definition for acute HBV infection, where cases have both individual and public health implications. Implement HBV surveillance nationwide and provide guidance and resources to state and local health departments so they can accurately report and follow up all HBV cases.

Goal 1, Objective 2 Ensure people are receiving the appropriate laboratory testing to determine their HBV status.

Three tests are initially required to characterize a person's HBV status: HBsAg, anti-HBc (total or IgG), and anti-HBs. This combination of tests allows individuals to be categorized as having (1) current HBV infection (HBsAg-positive) who need for further management; (2) prior infection (HBsAg-negative and anti-HBc positive), at risk of HBV reactivation in the setting of immune suppression; (3) vaccine-induced immune

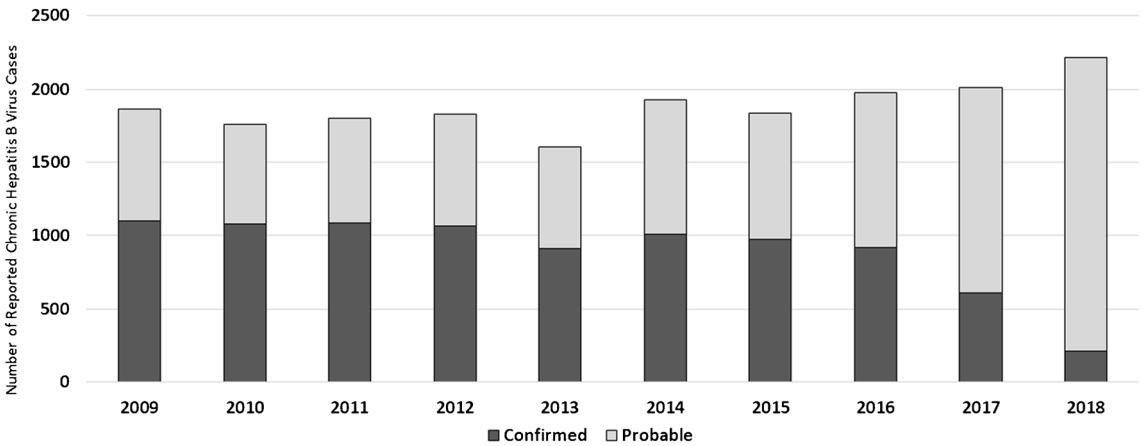

Fig. 1 Confirmed and probable chronic HBV virus cases reported in Massachusetts by year, 2009–2018. A total of 18,830 cases of confirmed or probable HBV infection reported to the Massachusetts Department of Public Health. Data were current as of March 5, 2019 and subject to change. Since the confirmed cases often required two tests taken at least 6 months apart, reported cases were classified as "probable" following the initial test result and reclassified as "confirmed" if additional test results were received. Note the increase in confirmed cases in 2017 and 2016 compared with 2018. Adapted from [19]

protection (only anti-HBs positive) which is life-long; and (4) susceptibility to HBV infection (no positive serologies) and thus should be considered for HBV vaccination.

Challenge Although the CDC and American College of Physicians (ACP) [27] recently recommended testing for HBsAg, anti-HBc, and anti-HBs in screening programs, the AASLD still recommends testing with HBsAg and anti-HBs alone [28]; thus, many patients do not receive all three tests. This is likely due to siloed initiatives, such as screening programs to identify people with current HBV infection, people who need vaccination, versus people at risk for HBV reactivation.

Solution Create an "HBV screening panel" laboratory order set.

Recommendation All hospital laboratories and commercial labs should offer a HBV screening panel that includes the recommended HBsAg, anti-HBc (total or IgG), and anti-HBs assays. This would simplify HBV testing and ensure that the appropriate tests are used to accurately assess HBV status.

Goal 2 Reduce new HBV infections.

There has been an effective HBV vaccine for over 30 years. The incidence of HBV infection in children under age 18 decreased 95% with the introduction of infant, adolescent catch up, and birth dose vaccination programs [29]. However, the U.S. still has about 1000 cases of perinatal transmission of HBV each year [30], and vaccination of adults is inadequate [31].

Goal 2, Objective 1 Eliminate mother to child (perinatal) transmission in the U.S.

Challenge One of the biggest challenges is implementation of the HBV vaccine birth dose. According to the CDC's 2018 National Viral Hepatitis Progress Report, we have not yet met the universal birth dose target to "increase the percentage of infants who receive HBV vaccine within three days of birth" to 85% by 2020 and 90% by 2026 [32, 33]. As of 2016, we met this goal for only 60.6% of U.S.-born infants [32]. Another gap across the perinatal HBV continuum includes caring for mothers who have chronic HBV, both during and after pregnancy. Women living with HBV should not only receive HBV care during pregnancy—to evaluate those with high HBV DNA levels who are at greater risk of transmitting HBV to their newborns and could benefit from antiviral treatment [28]—but should continue after pregnancy for their own health. The Hep B Moms program implemented at Charles B. Wang Medical Center in New York City (NYC) published a study showing that > 20% of pregnant women had elevated HBV DNA (> 200,000 IU/mL) and were at high risk for transmitting the virus perinatally [34]. Additionally, identification of pregnant women with HBV infection should prompt testing in the household to identify family members with HBV or those who need immunization, an important public health step not routinely prioritized.

Solutions Provide additional support for the National Perinatal HBV Prevention Program; scale-up and replicate effective programs that improve outcomes for mothers and babies; ensure birth dose is universally implemented.

Recommendation This is perhaps the most achievable HBV elimination objective. Test all pregnant women, implement universal HBV vaccine birth dose, complete the infant HBV vaccine series, and provide comprehensive pre- and post-exposure prophylaxis for at-risk mother-child pairs. We have all the necessary tools: vaccine, infrastructure, and capacity. We have a strong Perinatal HBV Prevention Program run through the CDC, and most pregnant women are tested for HBV in the U.S.

Yet, there have not been a rigorous documentation of challenges to implementing birth dose in the U.S., which would be useful to design future interventions. There have been strategies that have effectively increased hospital compliance, including eligibility to participate in TotTrax (which provides hospitals and birthing facilities with HBV vaccine at no cost) and addition of HBV birth dose as a National Quality Forum (NQF) measure [35]. Immunization Action Coalition developed a national HBV Birth Dose Honor Roll, publicly recognizing hospitals with high birth dose coverage rates and assisting hospitals who want to improve their birth dose outcomes [36]. The NYC DPH also publishes birth dose rates by hospital, so that community members can see which hospitals have high completion rates. The Hep B Moms Program at Charles B. Wang Community Health Center is an excellent example of care coordination between a mother's obstetrician, primary care provider, and pediatrician—it provides education and counseling to pregnant women, HBV evaluation and treatment during pregnancy, tests household contacts, and links mothers to postpartum care to ensure they receive continued monitoring for HBV [37]. With additional funding and support, this type of program can be replicated around the U.S.

Goal 2, Objective 2 Identify all infected individuals and protect all adults at risk for HBV.

Challenge It is estimated that only 25–30% of individuals with HBV infection in the U.S. are aware of their infection (diagnosed), and only 25% of adults have been vaccinated against HBV [5, 6, 38]. Current U.S. guidelines for both testing and vaccination are complex and difficult to implement, and programs to screen patients for chronic HBV infection are often

siloed from HBV vaccination programs. CDC's adult risk-based vaccine recommendations for HBV were published in 2006 [39], and 14 years later, most adults are still not protected. Additionally, since the publication of the CDC testing recommendations in 2008 [40] and the USPSTF testing recommendations in 2014 [41], there has been no evidence of an increase in testing in the U.S. Thus, current recommendations have failed.

The complexities of the current testing and vaccination recommendations serve as a challenge to integrating HBV testing and vaccination into electronic health record (EHR) systems, as many of the risk factors are not easily identified in EMR so building accurate reminder/pop-up prompts is difficult. This forces providers to accurately remember who to test and vaccinate—and HBV knowledge remains low [42–44]. Some risk factors may be stigmatizing, such as a history of drug use, immigration status or multiple sexual partners, and some may be unknown such as the HBV status of all sexual partners or household contacts (such as unrelated roommates). When both current risk factors (such as current sexual activity) and future potential risk factors (such as pregnancy or the risk of developing chronic liver disease or diabetes) are taken into account, the majority of individuals in the U.S. either currently or will meet criteria for testing.

Solutions One lesson from the failure of risk-based testing to identify many people living with HIV or hepatitis C infection is that complicated and sometimes stigmatizing risk factors are inadequately assessed in practice. We now test all persons ages 13 to 64 for HIV and all persons ages 18 to 79 for hepatitis C [3]. It is time for universal testing and vaccination recommendations for HBV.

Recommendations Test all adults for HBV infection and vaccinate all adults who lack evidence of prior HBV infection or vaccination a nd are susceptible to infection. The new Division of Viral Hepatitis 2025 Strategic Plan includes updating the HBV vaccine and screening recommendations [33]. We strongly urge CDC to adopt universal, coordinated recommendations for both.

Goal 3 Reduce mortality associated with HBV infection.

Objective All persons living with chronic HBV infection will receive ongoing evaluation, appropriate treatment, and liver cancer surveillance.

Challenge HBV is an important contributor to health disparities in the U.S. Over half of individuals living with chronic HBV infection in the U.S. identify as Asian, and immigrants from Asia, the Pacific Islands, and Africa comprise a high proportion of people living with chronic HBV infection [7, 9, 45]. Limited English proficiency, immigration status, socio-cultural barriers, and lack of health insurance are potential barriers for care [46–48]. Although the majority of people living with HBV infection do not see liver specialists (many of whom are not yet diagnosed), most primary care providers (PCPs) feel uncomfortable with or lack appropriate knowledge to manage chronic HBV due to lack of training and complex HBV guidelines, which are often written by liver specialists for specialists [49–50, 51••].

A large real-world study of the care received by people living with HBV infection demonstrated the substantial gaps along the HBV care continuum [52]. Of patients with diagnosed chronic HBV, 78% had at least one ALT performed per year, but only 37% had at least one HBV DNA measurement performed, and 18% had no recorded HBV DNA tests. Thirty-two percent (32%) of patients were prescribed antiviral therapy, and in the subgroup that had cirrhosis, only 56% were on antiviral therapy. Also, for patients with HBV and cirrhosis, 53% had at least one liver imaging study, but only 27% had at least annual liver imaging [52]. Nationally, fewer than 25% of people who are eligible for antiviral treatment for chronic HBV infection are actually receiving appropriate treatment [10, 13, 53, 54]. Current HBV treatment guidelines are too complex for broad adoption by non-liver specialists and are a barrier to treatment access.

Solution We need to decentralize HBV care and empower primary care providers with straightforward guidance on managing uncomplicated chronic HBV in the primary care setting. The experience with HCV treatment has demonstrated that there are an insufficient number of hepatologists to treat everyone with viral hepatitis. Models of HCV care within primary care have shown excellent outcomes around the world including Australia [55], and the U.S. [56], and HCV guidance co-managed by AASLD and the Infectious Disease Society of America has a section called "Simplified HCV Treatment for Treatment-Naive Patients" that is dedicated to providing simple HCV evaluation and treatment guidance for non-specialists [57].

The authors of this review participated in a multidisciplinary working group of primary care physicians, pharmacists, public health experts, hepatologists, and infectious disease physicians that developed *HBV Management: Guidance for the Primary Care Provider* to simplify recommendations and increase the pool of providers who can deliver high-quality HBV care [58••]. The HBV Primary Care Workgroup hypothesized that current HBV management guidelines from professional organizations such as AASLD were too complex for effective implementation by non-hepatologists and created an 8-page document with simplified algorithms for HBV testing and interpretation as well as counseling, evaluation, management, and treatment of the HBsAg-positive patient in the primary care setting. While certain complications do require specialist input,

there are a number of vital roles that all primary care providers can have (Table 1).

Community health centers have developed innovative strategies for delivering primary care–based HBV care to marginalized populations. Charles B. Wang Community Health Center (NYC) and North East Medical Services (San Francisco Bay Area) have implemented universal HBV screening of adults [59] and HBV patient registries to support primary care–based chronic HBV management and liver cancer surveillance in their primarily Asian immigrant populations. North East Medical Services' in-house radiology department has adopted the Ultrasound Liver Imaging Reporting and Data System (US LI-RADS) [60] for HCC surveillance of chronic HBV patients with EHR prompts for ordering ultrasounds and serum AFP for men over age 40 and women over age 50. Charles B. Wang Community Health Center participates in NYC's Check Hep B Program that utilizes patient navigators to ensure that all patients screened positive for HBV by community-based organizations or health centers are linked to care with an HBV provider and coordinates specialty care when needed [61].

Recommendation Primary care providers should manage the majority of patients living with chronic HBV infection, and specialists should be reserved for more complicated HBV cases such as cirrhosis, HDV co-infection, or suspected HCC.

Goal 4 Eliminate stigma and discrimination associated with HBV infection.

Objective Create a movement centralized around community and patient engagement that will empower people living with HBV to share their stories and normalize discussions around HBV.

Challenge HBV is a highly stigmatized disease [62••]. People living with HBV face stigma and discrimination, which serve as sizeable barriers to testing, care, and treatment [62••]. Stigma keeps impacted communities hidden in the shadows and promotes under-prioritization of HBV nationally.

Solution In the U.S., the burden of HBV falls heavily on Asian Americans, Pacific Islanders, Africans, Caribbean, and other foreign-born populations and their children. Because HBV disproportionately affects certain communities, these key populations must be targeted and engaged. As seen with HIV and cancer, active and vocal participation of community groups and patients can increase public awareness of the disease, increase uptake of care, combat stigma, and elevate prioritization in funding and research. For viral hepatitis, countries that have engaged civil society are further ahead in their elimination planning including having dedicated funding and laws or policies against discrimination [63••, 64]. Community coalitions such as Hep B United, a CDC-funded national coalition of community organizations dedicated to improving access to HBV screening and care and reducing the health disparities related to HBV, will be critical to these efforts. Campaigns such as the #JustB storytelling campaign are important for putting a face on the disease and creating empathy, and these

Table 1 Roles of primary care and specialists in HBV elimination and reducing HBV morbidity and mortality

What can be managed in primary care?	What should be referred to a liver specialist?
• HBV screening and interpretation for all patients	• Liver lesion on imaging suspicious for HCC (e.g. US LI-RADS3, CT-MRI LI-RADS 5)
• HBV and HAV vaccination for all patients	• Compensated and decompensated cirrhosis
• Initial evaluation and counseling of the HBsAg(+) patients (Refer to HBV management: guidance for the primary care provider) [58••]	• Hepatitis D co-infection (requires interferon treatment)
• Substance use screening/harm reduction counseling	• Persistent elevation of liver enzymes that do not correlate with HBV DNA levels or metabolic syndrome risk factors (may need liver biopsy)
• Smoking cessation	
• Alcohol moderation/abstinence counseling	
• Management of metabolic syndrome risk factors such as obesity, diabetes, hyperlipidemia, and hypertension	
• HBV lab monitoring every 6 months for both patients on and not on treatment.	
• Liver cancer surveillance ultrasound every 6 months for men > 40, women > 50, persons with cirrhosis or family history of liver cancer	
Dependent on comfort level of the primary care provider, may be managed in primary care or in consultation with a specialist:	
• Initiation of and monitoring on HBV antiviral treatment	
• Perinatal HBV management	

individual level stories can help to prioritize HBV among practitioners, policymakers, and funders.

Recommendation Stigma and its effects must be addressed as part of national elimination planning efforts, and patients and communities should be empowered to be partners in all strategies and programs that will affect them. Funding should be dedicated to expanding efforts that engage impacted communities and elevate HBV as an urgent public health priority.

Conclusions

HBV is the most common bloodborne infection in the world, yet has been underrepresented in research, funding, and overall public health prioritization. With urgency and equity as guiding key principles in the approach to hepatitis elimination as set forth by the WHO guidelines, we must reevaluate our current approach and pivot. We need a significant scale up of HBV testing, care, and treatment. Decentralizing and integrating HBV-related services into primary care will allow for a broader reach beyond what can be delivered by specialists. Simplification of guidelines and ECHO type models of training can empower and equip frontline staff. By viewing HBV services as preventative services, tasks such as HBV screening, vaccination, and liver cancer screening can be implemented by primary care. However, as we have described, there are significant barriers, many the result of the siloing of healthcare and services. Dismantling these barriers is critical to successful elimination.

There are at least two dozen drugs in the research pipeline that could serve as a "functional cure" for HBV within the next decade [65]. The solutions we are recommending will take time to implement, so we need to start now to ensure that everyone living with HBV infection will be able to benefit from these therapeutic advances [66].

Though we discuss programmatic efforts on international, national, state, and community levels, we are reminded that ultimately, it is individual patients we are trying to reach. Breaking down the silos and integrating efforts will allow us to deliver better person-based care and expand our ability to find the missing millions and give the next generation a hepatitis-free future.

Compliance with Ethical Standards

Conflict of Interest Su Wang, Chari Cohen, Amy S Tang, and Camilla S. Graham declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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