Towards the elimination of hepatitis B and hepatocellular carcinoma

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Hepatitis B (HBV) remains a global health problem despite the availability of effective vaccines since 1982 and effective antiviral therapy. The global burden of disease is substantial, with HBV resulting in 887 220 deaths in 2015: acute hepatitis (87 076), cirrhosis (462 690) and hepatocellular carcinoma (337 454). The World Health Organization has a vision to eliminate viral hepatitis as a public health threat by 2030. Although HBV and its associated complications of cirrhosis, liver failure and hepatocellular carcinoma are entirely vaccine preventable, there is no cure for chronic hepatitis B as yet. HBV elimination strategies will need to focus on effective and implementable preventive and therapeutic strategies such as upscaling HBV birth-dose vaccination, full HBV vaccine coverage, vaccination of high-risk groups, prevention of mother-to-child transmission, and identification of HBV-infected individuals and linkage to care with sustainable access to antiviral therapy.

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Hepatitis B (HBV) remains a global health problem despite the availability of effective vaccines since 1982 and effective antiviral therapy. Two billion people have serologic evidence of past or ongoing HBV infection and an estimated 257 million people or 3.5% of the world's population, are chronically infected with HBV.[1] The lifetime risk of cirrhosis, liver failure and hepatocellular carcinoma (HCC) is 15 - 40%. Globally, hepatitis B mortality is increasing, while HIV/AIDS mortality is decreasing with the advent of antiretroviral therapy (ART).[2] Globally in 2015, HBV caused 887 220 deaths: acute hepatitis (*n*=87 076), cirrhosis (*n*=462 690) and HCC (*n*=337 454); in Africa, HBV was responsible for 87 890 deaths.[1]

In May 2016, the World Health Organization (WHO) adopted a global hepatitis strategy with the goal of eliminating viral hepatitis as a public health threat by 2030. The targets to be achieved by 2030 are ambitious: 90% reduction in new cases of chronic hepatitis B and C; 65% reduction in mortality due to hepatitis B and C; and 80% of treatment-eligible persons with chronic hepatitis B and C infections being treated.[3]

Hepatitis B epidemiology

HBsAg seroprevalence varies geographically. According to the recent 2017 WHO Global Hepatitis Report, the number of HBsAg-positive individuals was highest in the Western Pacific (115 million, prevalence estimate 6.2%; 95% uncertainty interval 5.1 - 7.6%) and Africa (60 million, prevalence estimate 6.1%; 95% uncertainty interval 4.6 - 8.5%) regions, which together accounted for 68% of the global burden.[1] The annual incidence of hepatocellular carcinoma correlates with the hepatitis B surface antigen (HBsAg) seroprevalence; the highest incidence is found in sub-Saharan Africa (SSA) and South East Asia.

In the absence of effective mother-to-child-transmission (MTCT) prophylaxis, HBV endemicity and chronicity is established in early childhood, with HBsAg seroprevalence studies showing no difference between children aged 5 - 9 years and adults.[4] The risk of chronicity of HBV is determined by the age of acquisition of infection: 90% after neonatal infection (in children born to HBeAg-positive or highly viraemic mothers), 20 - 50% with childhood infection (<5 years of age) and <5% for adults >20 years.

HIV/HBV co-infection has a further impact as HIV promotes a more aggressive natural history of hepatitis B. HIV co-infection promotes increased HBV replication and rates of HBV reactivation; increased hepatitis B e-antigen (HBeAg) seroconversion; increased rates of occult HBV; chronicity of newly acquired HBV infections with a five times faster progression to fibrosis and cirrhosis; HCC also occurs at a younger age and is more aggressive.[5-16]

Achieving elimination of hepatitis B

In order to achieve the WHO's ambitious 2030 targets of elimination, it will be essential to recognise the burden of disease within one's own country, i.e. know the seroprevalence and potential high-risk groups; implement HBV vaccine programmes for high-risk groups; address the risk of MTCT; identify HBV-infected individuals and ensure linkage to care; recognise and address potential stigma associated with hepatitis B; and have implementable preventive, surveillance and treatment strategies. It is imperative to recognise and address potential challenges associated with achieving the elimination of HBV while recognising that hepatitis B and its associated complications are entirely vaccine preventable.

Universal HBV vaccination

Vaccination remains the cornerstone of any elimination strategy. The WHO recommended incorporation of HBV vaccination into the Expanded Program of Immunization (EPI) in 1991 as the most effective way to reduce the global burden of HBV. WHO's 2030 target is 90% full HBV vaccine coverage and in 2015, the global HBV 3 dose vaccine coverage was 84%, but only 77% in the WHO Africa region. In contrast, the Western Pacific region has achieved 90% coverage.[1,17]

Universal vaccination has globally decreased HBsAg prevalence in children under 5 years of age from 4.7% in pre-vaccination era to 1.3% in 2015, but the prevalence in the WHO Africa region remains high at 3%.[1] The Western Pacific region has reduced their HBsAg prevalence in under-5-year-olds to 0.9%. By 2013, universal HBV vaccination had prevented 14.2 million cases of chronic HBV

infection among children aged 0 - 5 years worldwide and more than 1.3 million deaths.[18]

Mother-to-child transmission of hepatitis B

HBV MTCT prevention strategies include antenatal HBsAg screening, hepatitis B birth-dose (HepB-BD) vaccination, administration of hepatitis B immunoglobulin to the newborn, and third-trimester antiviral therapy for women with high infectivity risk (HBeAg-positive and/or HBV DNA >200 000 IU/mL) and full HBV vaccine coverage.[19-21] Modelling studies have suggested that an 80% global scale-up of HepB-BD vaccination plus infant vaccination, compared with scaling-up of infant vaccination alone, could avert 18.7 million new chronic infections over the next 15 years, confirming its importance as a PMTCT tool.[22]

In 2009, WHO recommended HepB-BD vaccination, with a monovalent HBV vaccine administered within 24 hours of delivery for all countries.[23] However, globally in 2014, only 96 of 194 countries (49%) reported offering HepB-BD as part of their national immunisation programmes and <38% of babies born worldwide received HepB-BD within 24 hours after birth.[1,17] Of concern, only 11 of 47 WHO Africa region countries (23%) had introduced HepB-BD vaccine by July 2017, and this is far below the WHO 2030 vaccination target of 90% birth-dose vaccination coverage.[24] HepB-BD vaccine given within 24 hours after birth and followed by at least two subsequent doses, is ~90% effective at preventing perinatal HBV infection. Innovative approaches to ensure timeous administration of Hep B-BD vaccine that have been successfully employed in Vietnam, Indonesia and China, i.e pregnancy tracking and administration of the Hep B-BD by village lay workers as well as the use of compact pre-filled auto-disposable devices (Uniject; Becton, Dickinson and Company, USA) are translatable to SSA.[25-27]

While the risk of MTCT of HIV is well recognised and policies are in place to screen all pregnant women for HIV and initiate ART, many countries in SSA do not have similar policies in place for HBV despite WHO recommending antenatal HBsAg screening in countries where HBsAg prevalence is ≥2%.[1,28,29] This is concerning as the annual number of infants perinatally infected with HBV is twice the number of incident paediatric HIV infections in SSA.[30] Standard-of-care procedures need to be in place to communicate the HBsAg status to the delivery unit to assess the need for third-trimester tenofovir prophylaxis for HBeAg-positive or highly viraemic (HBV DNA >200 000 IU/ml) pregnant women and to emphasise the importance of timely HBV birth-dose vaccination within 24 hours of delivery.[28] Timeous administration is important as there is an increased risk of HBV transmission if HB-BD is given 7 days after delivery compared to 1 - 3 days post delivery (OR 8.6).[28] Immunisation programmes also need to ensure a timely second dose of HBV vaccination to infants born to mothers with chronic HBV infection as the risk of becoming chronically infected was 3.74 times (95% confidence interval (CI) 0.97 - 14.39) higher if the interval between the first and the second doses exceeded 10 weeks.[31] Identification of HBsAg-positive pregnant women also provides the opportunity to identify potentially HBV-infected partners, siblings and children and thereby link them to care and break ongoing cycles of infection.

Efficacy of universal hepatitis B vaccination: Impact on liver disease

This has proved exemplary in Taiwan, where universal vaccination, introduced in 1984, together with a catch-up vaccination programme and improved maternal screening, resulted in a decrease in the prevalence of HBsAg positivity in children aged <15 years from 9.8% in 1984 to 0.3% in 2009 and continues to decrease 30 years after initiation of universal vaccination.[32-34] Furthermore, HCC incidence per 10^5 person-years has decreased from 0.92 in unvaccinated to 0.23 in vaccinated cohorts.[35]

In Alaska, universal newborn HBV vaccination, vaccine catch-up programmess and mass screening since 1981 have eliminated acute symptomatic HBV infection and early-onset HCC as a public health threat among Alaskan Native (AN) children. The incidence of acute symptomatic HBV infection in AN persons <20 years of age decreased from 19/100 000 in 1981 - 1982 to no reported cases since 1992. The incidence of HCC in AN persons <20 years decreased from 3/100 000 in 1984 – 1988, with no reported cases since 1998. The number of identified HBsAg-positive AN persons <20 years declined from 657 in 1987 to 2 cases identified since 1999; the last HBsAg-positive AN person <20 years of age was identified in 2010.[36]

A similar decline in HBsAg seroprevalence rate and in HCC incidence has been seen in other hepatitis B endemic countries which have implemented universal HBV vaccination.[37-39]

Full HBV vaccine coverage is important, as incomplete immunisation has been shown to be an important risk predictor for HCC (HR 2.52; 95% confidence interval (CI) 1.25 - 5.05; p=0.0094) and chronic liver disease (HR 6.27; 95% CI 3.62 - 10.84; p<0.0001) after correction for maternal HBsAg status.[40]

Public-private partnerships play an important role in achieving the elimination of hepatitis B. The success of HepB-BD vaccine and full vaccine coverage in preventing childhood HBV acquisition has been demonstrated in China. A partnership between Gavi, the Vaccine Alliance and the Chinese government supporting free HepB-BD vaccination in combination with up-scaling of the full HBV vaccine schedule and utilising village lay healthcare workers to administer the HepB-BD vaccine, has reduced HBsAg seroprevalence in 2009 to 0.96% in children <5 years of age compared with 9.67% in 1992.[41]

Durability of universal HBV vaccination

In a 30-year follow-up study, 243 individuals of a cohort of 1 578 AN adults and children who had responded to the original primary series but received no subsequent booster doses were screened for immunity; 125 (51%) individuals had an anti-HBs level ≥10 mIU/mL at 30 years. Among participants with anti-HBs levels <10 mIU/mL who were available for follow-up, 88% (n=75/85) responded to a booster dose with an anti-HBs level ≥10 mIU/mL at 30 days, indicating immunological memory. Thus, ~90% (range 74 -100%) had evidence of protection 30 years after vaccination.[42]

A meta-analysis of 22 studies assessed 11 090 persons 5 - 20 years post vaccination and showed no evidence of chronic infection and 0.7% evidence of past exposure (anti-HBc-positive).[43] Boosters were not needed in immunologically competent individuals following a full primary course of HBV vaccination.[43,44]

Identification of HBV-infected individuals and linkage to care

In 2015, it was estimated that globally only 9% of HBV-infected individuals (22 million) were aware of their diagnosis and only 8% of diagnosed HBV-infected individuals (1.7 million) had been treated.[1] In order to prevent the life-threatening complications of cirrhosis, liver failure and HCC, it is essential to identify HBV-infected individuals to assess the need for treatment and appropriate frequency of follow-up. Accurate WHO pre-qualified HBV point-of-care (POC) testing that can be easily administered at primary levels of healthcare is essential to upscale diagnosis and treatment.

The PROLIFICA project has validated 3 point-of-care rapid diagnostic tests (Determine, Vikia and Espline), both in the field and laboratory settings in the Gambia. All 3 tests had acceptable ranges of diagnostic accuracy and are inexpensive alternatives to laboratory-based testing.[45] Once diagnosed, HBV-infected individuals need to be linked to care and this will require the establishment of clear pathways of referral. Less than 20% HBV-infected individuals require treatment and the need for treatment and frequency of follow-up is determined by age, ALT, presence of fibrosis, HBeAg status, HBV DNA levels and family history of cirrhosis or HCC.[46]

The PROLIFICA project also demonstrated that large scale test-and-treat programmes are feasible and cost-effective in endemic countries such as SSA.[47,48]

Appropriate HBV antiviral therapy has been shown to have an impact on the development of cirrhosis and risk of HCC, improving liver-related and all-cause mortality.[49-52] Lamivudine, entecavir and tenofovir have all been shown to decrease mortality. Tenofovir, which has a high barrier against resistance, is the WHO preferred antiviral.[46] Unfortunately, although tenofovir and lamivudine/emtricitabine are widely available as part of ART, these nucleotide analogues are not always accessible to patients with HBV mono-infection in many SSA countries.

Addressing important co-factors in HCC development in chronic HBV infection

There are a number of important co-factors that increase the risk of hepatitis B-related HCC that also need to be addressed.[53,54] The mycotoxin aflatoxin B1 (AFB1) is potent hepatocarcinogen that contaminates crops, especially maize, groundnuts and sorghum in tropical and subtropical climates such as South-East Asia and sub-Saharan Africa, especially in West Africa. AFB1 contamination occurs during the growth of crops and during improper storage, and individuals are exposed as early as *in utero* as AFB1 crosses the placenta. Subsistence farming, poor crop storage and suboptimal processing increase the risk of AFB1 exposure.[55] HBV and AFB1 are synergistically hepatocarcinogenic and a systematic review and meta-analysis revealed an overall population attributable risk of AFB1-related HCC of 17% (14 - 19%), with 21% in HBsAg-positive and 8.8% in HBsAg-negative individuals. The relative risk of HCC was 54.1 (95% CI 21.3 - 137.7) with dual exposure.[56]

Other important HCC co-factors that need to be addressed are alcohol, iron overload and increasingly obesity and associated non-alcoholic fatty liver disease.[57,58]

Cumulative HCC risk scores for HBV-related HCC have mainly been validated in Asian patients and are weighted for the presence of cirrhosis and increasing age.[59] These HCC risk-predictor models have not been validated in SSA, where 40% of HCC occurs in young non-cirrhotic patients.

Conclusion

Hepatitis B and its associated complications of cirrhosis, liver failure and HCC are entirely vaccine preventable. In order to achieve the WHO 2030 vision of eliminating HBV, it is imperative that countries implement the WHO recommendations of HBV birth-dose vaccine, full vaccine coverage, and upscale diagnosis and linkage to care of HBV-infected individuals.

The WHO Global Health Sector Strategy on Viral Hepatitis is to reduce new cases of chronic HBV infection by 30% by 2020, which is equivalent to 1% HBsAg prevalence amongst children aged 5 years, aiming for 0.1% HBsAg prevalence in 5-year-olds by 2030.

The full clinical impact of HBV birth-dose vaccination will take 2 - 3 decades and it is essential that HBV-infected individuals are linked to care with appropriate therapy and follow-up, and high-risk non-immune individuals are vaccinated. Although antiviral therapy has reduced both liver-related and all-cause mortality, the risk of HCC in HBV-infected individuals, albeit reduced, is not eliminated and lifelong antiviral therapy and follow-up are usually necessary. Future therapeutic endeavours are aimed at not only a functional cure but also a virological cure with eradication of the intrahepatic HBV reservoir, the covalently closed circular HBV DNA.[60]

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