# Viral hepatitis in sub-Saharan Africa 1

## Hepatitis B in sub-Saharan Africa: strategies to achieve the 2030 elimination targets

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This is the first in a **Series** of two papers on viral hepatitis in sub-Saharan Africa

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**The WHO global health sector strategy on viral hepatitis, created in May, 2016, aims to achieve a 90% reduction in new cases of chronic hepatitis B and C and a 65% reduction in mortality due to hepatitis B and C by 2030. Hepatitis B virus (HBV) is endemic in sub-Saharan Africa, and despite the introduction of universal hepatitis B vaccination and effective antiviral therapy, the estimated overall seroprevalence of hepatitis B surface antigen remains high at 6·1% (95% uncertainty interval 4·6–8·5). In this Series paper, we have reviewed the literature to examine the epidemiology, burden of liver disease, and elimination strategies of hepatitis B in sub-Saharan Africa. This paper reflects a supranational perspective of sub-Saharan Africa, and recommends several priority elimination strategies that address the need both to prevent new infections and to diagnose and treat chronic infections. The key to achieving these elimination goals in sub-Saharan Africa is the effective prevention of new infections via universal implementation of the HBV birth-dose vaccine, full vaccine coverage, access to affordable diagnostics to identify HBV-infected individuals, and to enable linkage to care and antiviral therapy.**

### Introduction

According to the most recent estimates of the Global Burden of Disease study and WHO, viral hepatitis is responsible for approximately 1·34 million deaths annually, which is similar to the annual number of deaths from HIV/AIDS (1·3 million), malaria (0·9 million), and tuberculosis (1·3 million).[1,2]

Mortality due to viral hepatitis has increased by 63% since 1990 and is now ranked the seventh leading cause of mortality worldwide; however, global recognition of the severity of the problem has not been achieved, and a global commitment to combat the disease is still needed.[2,3] Worldwide, most viral hepatitis morbidity and mortality is accounted for by hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, with 96% (95% uncertainty interval [UI] 94–97) of mortality and 91% (95% UI 88–93) of disability-adjusted life-years in 2013.[3] An estimated 95% of individuals with chronic HBV or HCV infection, or both, are unaware of their infection and so do not benefit from clinical care, treatment, and interventions that are designed to reduce onward transmission.

In May, 2016, 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: a 90% reduction in new cases of chronic hepatitis B and C, and a 65% reduction in mortality due to HBV and HCV infection, both of which rely on 80% of treatment-eligible individuals with chronic HBV and HCV infections being treated globally.[4]

Many countries in sub-Saharan Africa are now in the process of developing viral hepatitis management guidelines and strategic plans to achieve these goals for viral hepatitis elimination. Major challenges to the elimination of HBV in sub-Saharan Africa include curtailing mother-to-child transmission (MTCT) with implementation of the HBV birth-dose vaccine and full coverage of the HBV vaccination schedule; access to affordable diagnostic assays to identify individuals who are infected with HBV and enable efficient linkage to care and treatment with nucleoside analogue therapy for HBV-monoinfected individuals; and redressing of social stigmas associated with the diagnosis of HBV. This Series paper represents a collective perspective of clinicians and research hepatologists and gastroenterologists from sub-Saharan Africa.

### Epidemiology of hepatitis B

Hepatitis B is a global health problem, with an estimated 257 million people chronically hepatitis B surface antigen (HBsAg) positive.[2] The burden of chronic hepatitis B is increasing despite it being an entirely vaccine-preventable disease and effective vaccines being available since 1982. Globally, hepatitis B mortality is increasing, with 500 000 to 1·2 million deaths occurring annually, whereas mortality due to HIV/AIDS is decreasing with the advent of effective antiretroviral therapy (ART).[3]

According to the 2017 WHO Global Hepatitis Report, the number of HBsAg-positive individuals was highest in the WHO Western Pacific region (115 million, prevalence estimated as 6·2%; 95% UI 5·1–7·6) and African region (60 million, prevalence estimate 6·1%; 4·6–8·5), which together accounted for 68% of the global burden.[2] Seroprevalence differs depending on sex and ethnicity, and between rural and urban areas, with the highest prevalence of HBsAg infection found to be

in black men and boys born in rural areas, placing further economic burden on under-resourced rural health-care services.[5]

In the absence of effective prophylaxis, endemic and chronic HBV infection is established in early childhood, with HBsAg seroprevalence studies[6] showing no difference between children aged 5–9 years and adults. The risk of HBV infection being chronic is inversely related to the age of infection; for example, the proportion of individuals who become chronically infected is 90% after neonatal infection (ie, children born to mothers who are hepatitis B e antigen [HBeAg] positive or highly viraemic), 20–50% after childhood infection (aged <5 years), and less than 5% for adults infected after age 20 years. Hepatitis B is responsible for a substantial burden of clinical disease. Although the risk is variable, people with chronic HBV infection have a 15–40% risk of developing cirrhosis, liver failure, or hepatocellular carcinoma, and a 15–25% risk of dying from HBV-related liver diseases.[7]

Hepatitis B is estimated to account for 87 890 deaths annually in sub-Saharan Africa,[2] but longitudinal studies on the incidence of cirrhosis in individuals in sub-Saharan Africa has proven difficult because liver biopsy is not a routine procedure and non-invasive transient elastography is not readily accessible.[8] However, numerous reports[9–11] have shown the high incidence of hepatocellular carcinoma in sub-Saharan Africa, and 80% of cases are due to HBV infection. The age-standardised incidence of hepatocellular carcinoma in sub-Saharan Africa is as high as 41·2 per 100 000 people per year, with Mozambique having the highest recorded incidence (101 per 100 000 male individuals per year).[12] The published incidences of hepatocellular carcinoma probably underestimate the actual incidence because of the scarcity of cancer registries.[13] Cohort studies[12] have suggested that being male, a family history of hepatocellular carcinoma, cirrhosis, high HBsAg concentration, high HBV DNA concentration, HBV genotypes A and C, basal core-promoter mutations, and aflatoxin exposure are all important risk factors for hepatocellular carcinoma in sub-Saharan Africa. The prognosis for patients with hepatocellular carcinoma is poor, with 92% of individuals dying within 1 year of the onset of symptoms in under-resourced regions of sub-Saharan Africa because of the absence of surveillance programmes for small tumours.[12]

The prevention of neonatal and early childhood infection is crucial to prevent chronic infection and subsequent complications of chronic liver disease and hepatocellular carcinoma.

HIV co-infection adds considerably to the clinical burden, with 70% of the 36 million people worldwide who have HIV living in sub-Saharan Africa.[14,15] An estimated 2·6 million HIV–HBV-co-infected individuals are in sub-Saharan Africa. HIV–HBV co-infection increases the potential risk of perinatal HBV transmission and is associated with a more aggressive disease course of chronic hepatitis B.[14,16–18]

Similarly, HBV–hepatitis D virus (HDV) co-infection is associated with a more aggressive disease course and can present as a co-infection, superinfection, or chronic infection. HDV seroprevalence in Africa varies geographically, from low in countries south of the equator—eg, 0–0·6% in South Africa, 0% in Mozambique, and 0·6% in Kenya (south of Mount Kenya)—to high in countries north of the equator—eg, 31% in Kenya (north of Mount Kenya), 7–44% in Tunisia, 25–28% in Sudan, 17–56% in Somalia, 3% in Senegal, 6–12% in Nigeria, 15–33% in Mauritania, 9–67% in Gabon, 5–58% in Egypt, 2–22% in Djibouti, and 6–27% in Cameroon. Epidemic outbreaks have been reported in Gabon, Cameroon, Nigeria, and Mauritania.[19] Preventing HBV infection through vaccination prevents infection with HDV because the virus is dependent on HBV for propagation.

Achieving the goals of HBV elimination in sub-Saharan Africa will require intensification of both preventive and treatment strategies, addressing prevention of MTCT, universal vaccination, and identification of individuals infected with HBV, with the appropriate linkage to care.

## Effect of HIV

In contrast to high-income countries, HIV–HBV co-infection outnumbers HIV–HCV co-infection in sub-Saharan Africa and probably reflects the low prevalence of injecting drug use.[15] HBV is generally acquired in childhood before age 5 years, whereas HIV infection occurs later in life, predominantly via heterosexual intercourse. Chronic HIV–HBV co-infection is reported in up to 36% of individuals who are HIV positive, with the highest prevalence reported in west African and southern African cohorts.[15] HIV and HBV might share transmission routes in infants and children as a result of MTCT due to inadequate diagnosis of the mother, and hence absence of prophylaxis of blood-borne viruses in pregnancy and the peripartum period. Other potential shared routes of infection are blood and blood product transfusions, unsafe medical and injection practices, and traditional scarification practices. Blood-safety programmes funded by the US President's Emergency Plan for Aids Relief (PEPFAR), the Global Fund, and WHO programmes in 38 countries in sub-Saharan Africa have increased HBsAg screening of blood donations from 76% in 2000–04 to 94% in 2010–11, and have consequently reduced the risk of HBV transmission from donated blood (the median percentage of HBsAg-positive blood donations decreased from 7·1% to 4·4% during this period).[20] 40 WHO-supported African countries now report testing 100% of blood donations for all transfusion-transmitted infections; but problems still exist with inconsistent screening procedures, non-WHO prequalified test kits, and a scarcity of confirmatory nucleic acid testing.[21]

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HIV–HBV co-infection promotes an aggressive disease course of hepatitis B by the following mechanisms: increasing replication of the virus and rates of HBV reactivation; increasing risk of acute liver failure, chronicity of newly acquired HBV infections, and occult infection (characterised by absence of HBsAg and low viral replication; HBV DNA concentration <200 IU/mL); accelerating progression to fibrosis and cirrhosis, with hepatocellular carcinoma occurring at a younger age; and increasing the risk of ART hepatotoxicity.[14,15,17,18,22–29]

Liver-related mortality is twice as high for individuals who are co-infected with HIV–HBV as it is for those who are co-infected with HIV–HCV. Individuals with a CD4 cell count of less than 200 cells per mL have a risk of liver-related deaths that is 16·2 times higher than that of those with a CD4 count of more than 350 cells per mL.[30] Additionally, a potential association with adverse HIV outcomes in individuals who are HIV–HBV co-infected has been reported,[31–34] in which HIV-associated immune deficiency was aggravated in those with active HBV replication, resulting in increased progression to AIDS-related outcomes and all-cause mortality.

## MTCT of HBV

The prevalence of HBV infection largely reflects the failure of maternal and child health programmes to prevent MTCT and early childhood transmission.

In sub-Saharan Africa, horizontal transmission in children between the ages of 6 months and 5 years is common because of close interaction with infected household contacts and playmates. However, vertical transmission also occurs, and HIV–HBV co-infection increases this risk. Pregnant women who are HIV–HBV co-infected are twice as likely to test positive for HBeAg, three times more likely to have detectable HBV DNA, and have higher HBV DNA serum concentrations than those who are HBV monoinfected, thereby greatly increasing the risk of MTCT.[14,17] In one west African study,[16] maternal HIV–HBV co-infection increased the probability of MTCT of HBV by 2·5.

Universal HBV vaccination will reduce the risk of childhood infection. However, prevention of MTCT of HBV requires identification of pregnant women who are infected with HBV with high viraemia, assessment of the need for prophylactic antiviral therapy in the third trimester of pregnancy, incorporation of the HBV birth-dose vaccine into the universal HBV vaccination schedule, and implementation of full HBV vaccine coverage.

### HBsAg screening

Antenatal HBsAg screening is essential to identify women who are infected with HBV and is recommended by WHO in countries where HBsAg prevalence is 2% or higher.[2] No formal documentation has been published detailing which sub-Saharan countries have a formal policy for HBsAg screening during pregnancy. Pregnant women are almost always screened for HIV; however, many countries in sub-Saharan Africa do not routinely screen pregnant women for HBsAg and screening is usually only encouraged by doctors. A systematic review and meta-analysis[35] examined the pooled risk of MTCT and found that annually an estimated 1% of newborn babies in sub-Saharan Africa are infected with HBV.

HBsAg screening should be done during the first trimester of pregnancy and pregnant women who are not immunised against HBV should receive HBV vaccination, since vaccination is entirely safe during pregnancy. Women who are positive for HBsAg should be referred for additional testing, counselling, and medical management. Identification of women who are HBsAg positive provides further opportunities to screen, vaccinate, and identify potentially infected partners, siblings, and children, thereby identifying clusters of HBV infection and breaking cycles of HBV infection within families.

Women of childbearing age in the immune tolerant (HBeAg positive with HBV DNA concentration >200 000 IU/mL) or immune control phase (HBeAg negative with HBV DNA concentration <2000 IU/mL) are not candidates for HBV treatment. However, MTCT risk needs to be considered in pregnant women with high HBV viral loads (HBV DNA concentration >200 000 IU/mL) irrespective of HBeAg status.[36,37] Combined treatment of newborn babies with hepatitis B hyperimmune globulin and HBV birth-dose vaccine within 24 h of delivery prevents MTCT of HBV in 80–95% of cases.[38,39] However, hepatitis B hyperimmune globulin is expensive, not readily available at most primary health-care clinics in sub-Saharan Africa, and thus initiation of prophylactic nucleoside analogue antiviral therapy in the third trimester of pregnancy should be considered to reduce the risk of MTCT.

### Universal HBV vaccination and the birth-dose vaccine

In 1991, WHO recommended the incorporation of an HBV vaccine into the Expanded Programme of Immunization (EPI)[40] since it is the most effective way to reduce the global burden of HBV. So far, 196 countries worldwide and 47 in the WHO region of Africa have incorporated HBV vaccination into their EPIs. Ott and colleagues conducted a systemic review[41] using worldwide HBsAg seroprevalence data collected over a 27-year period (1980–2007) to estimate HBsAg prevalence for 1990 and 2005 using an empirical Bayesian hierarchical model. They confirmed that HBsAg seroprevalence has decreased in many regions of the world as a result of universal HBV vaccination, and the vaccine is estimated to have prevented more than 1·3 million deaths. Although universal vaccination has globally decreased HBsAg prevalence in children younger than 5 years from 4·7% in the prevaccination era (1980s to early 2000s) to 1·3% in 2015,[2] HBsAg prevalence in the WHO region of Africa remains at 3%.[2]

Most countries in sub-Saharan Africa administer the HBV vaccine to babies at 6, 10, and 14 weeks to prevent childhood infection between 6 months and 5 years. In 2009, WHO recommended use of the HBV birth-dose vaccine in all countries.[42] A monovalent HBV vaccine should be administered within 24 h of delivery. However, only nine (19%) of the 47 countries in the WHO Africa region had introduced universal HBV birth-dose vaccination by July, 2017 (table).[2,43] Barriers to providing HBV birth-dose vaccine in sub-Saharan Africa include the cost, because funding from Gavi was not available for the monovalent HBV birth-dose vaccine; transporting and administering the vaccine in the setting of home-births; and concerns about appropriate vaccine storage—eg, refrigeration, security, and storage outside the cold chain.

The importance of the HBV birth-dose vaccine is now being recognised. The report from the WHO regional consultation on viral hepatitis control in the WHO African region, held in Brazzaville, Congo, in 2016, stated that Benin, Cameroon, Congo (Brazzaville), Côte d'Ivoire, Ethiopia, Ghana, and Sierra Leone were planning to implement the HBV birth-dose vaccine in 2017 or 2018, whereas South Africa and Guinea remained undecided.[44] São Tomé and Príncipe and Mauritius only offer the HBV birth-dose vaccine to infants with HBsAg-positive mothers.[43] An average of four WHO African countries per year will need to introduce the HBV birth-dose vaccine to meet the regional target by 2020. Of concern, in 2014, less than 38% of babies born worldwide received the HBV birth-dose vaccine within 24 h of birth.[2] Monovalent HBV vaccines can be administered at the same time as the BCG and oral polio vaccines, hence no additional infrastructures are required; however, innovative approaches need to be developed to enable administration of the HBV birth-dose vaccine to babies who are delivered at home. A WHO review[45] of published and manufacturer data suggests that some monovalent HBV vaccines are heat stable beyond the standard cold chain range of 2–8°C, and so previous concerns about the cold chain in rural areas should no longer be a barrier to the administration of the HBV birth-dose vaccine.[46]

The birth-dose vaccine should be followed by two or three doses to complete the primary series. One of the following two options is considered appropriate by WHO:[47] a three-dose schedule, with the monovalent HBV birth-dose vaccine followed by the second and third doses given as part of the multivalent vaccine, with each vaccine dose given 4 weeks apart; or four doses of vaccine, in which the monovalent HBV birth-dose vaccine is followed by three multivalent vaccine doses given according to the routine EPI schedule. Multivalent vaccine products that include an HBV vaccine are widely used in EPI schedules, but only monovalent HBV vaccines can be used at birth, and access to the monovalent vaccine is becoming increasingly difficult.[47]

| | Date of implementation |
|---|---|
| Algeria | 2004 |
| Angola | 2015 |
| Benin | Planned for 2017–18 |
| Botswana | Pre-2000 |
| Cape Verde | 2002 |
| Cameroon | Planned for 2017–18 |
| Congo (Brazzaville) | Planned for 2017–18 |
| Côte d'Ivoire | Planned for 2017–18 |
| Ethiopia | Planned for 2018 |
| The Gambia | 1990 |
| Ghana | Planned for 2017–18 |
| Mauritania | 2013 |
| Namibia | 2014 |
| Nigeria | 2004 |
| Senegal | 2016 |
| Sierra Leone | Planned for 2017–18 |

Data from WHO–UNICEF estimates of national HBV immunisation coverage, July, 2017.[43]

***Table:*** **Countries in the WHO region of Africa that have implemented or are planning to implement the HBV birth-dose vaccine**

A four-dose vaccine schedule is easier to implement and does not immunologically compromise infants who might not have access to the HBV birth-dose vaccine. The risk of chronic HBV infection, despite HBV birth-dose vaccination, is 3·74 times higher if the interval between the first and second vaccine doses is more than 10 weeks, making adherence to appropriate vaccine schedules essential.[48]

A Taiwanese study[49] has shown that full HBV vaccine coverage is essential, with incomplete vaccination being the most important risk predictor for hepatocellular carcinoma (hazard ratio [HR] 2·52, 95% CI 1·25–5·05; p=0·0094), fulminant hepatic failure (4·97, 3·05–8·11; p<0·0001), and chronic liver disease (6·27, 3·62–10·84, p<0·0001; HRs calculated after adjustment for maternal HBsAg status) in those who become infected with HBV. Unfortunately, full vaccine coverage with three HBV vaccine doses is poor: WHO–UNICEF estimated that in 2015, only 77% of infants in Africa received full vaccine coverage.[2,43]

The success of the HBV birth-dose vaccine and full vaccine coverage in preventing childhood HBV acquisition has been shown in China. A partnership between Gavi and the Chinese Government supporting free HBV birth-dose vaccination, in combination with the upscaling of the full HBV vaccine schedule and use of village-based health-care workers to administer the HBV birth-dose vaccine, reduced HBsAg seroprevalence in 2009 to 0·96% in children younger than 5 years compared with 9·67% in 1992.[50]

## Third-trimester antiviral prophylaxis

Combined immune prophylaxis with hepatitis B hyperimmune globulin and HBV birth-dose vaccine fails

in 10–30% of infants born to mothers with HBV DNA concentrations greater than 6 $\log_{10}$ copies per mL.[38,51,52]

Several studies have suggested that antiviral therapy with lamivudine,[53] telbivudine,[54] or tenofovir[55] during the third trimester of pregnancy could be clinically cost-effective in reducing vertical HBV transmission compared with no treatment or placebo. The efficacy in the prevention of MTCT and the safety of tenofovir prophylaxis in the third trimester have been reported from China.[55] In a multicentre, randomised controlled study, 200 pregnant women who were HBeAg positive with HBV DNA concentrations of more than 200 000 IU/mL were randomly assigned to receive no antiviral therapy or tenofovir 300 mg daily from gestational week 30–32 to 4 weeks post partum. All infants received prophylaxis with hepatitis B hyperimmune globulin and HBV birth-dose vaccine. At post-partum week 28, the proportion of MTCT was significantly lower in infants born to tenofovir-treated mothers than in those born to untreated mothers, both by per-protocol analysis (0% *vs* 7%, p=0·01) and intention-to-treat analysis (5% *vs* 18%, p=0·007).[55]

The American Association for the Study of Liver Diseases suggests the initiation of tenofovir 300 mg daily at 28–32 weeks of pregnancy if HBV DNA concentrations are higher than 200 000 IU/mL to further reduce the risk of perinatal transmission. The European Association for the Study of the Liver recommends that all pregnant women with HBV DNA concentrations higher than 200 000 IU/mL should start tenofovir 300 mg daily at 24–28 weeks of pregnancy and continue for up to 12 weeks after delivery.[56,57]

The 2015 WHO guidelines on prevention, care, and treatment of people with chronic hepatitis B[58] made no formal recommendation regarding the routine use of nucleoside analogue therapy, but this policy is under review.

Tenofovir is a category B teratogenic antiviral drug, and is the recommended nucleoside analogue for prophylaxis in pregnancy. Data from both HBV-infected and HIV-infected pregnant women suggest that the use of tenofovir is safe in pregnancy, with a similar prevalence of birth defects compared with the general population—ie, 2%.[58] Tenofovir can be stopped 3 months after birth, if it was prescribed only to prevent MTCT.

Identification of pregnant women who are highly viraemic is a prerequisite for appropriate antiviral prophylaxis. This identification requires testing for HBeAg, or, ideally, HBV DNA quantification, which is expensive and not readily available in many countries. A recent Taiwanese study[59] suggested that HBsAg quantification was able to predict perinatal transmission. A strong positive quantitative correlation was found between maternal HBsAg and maternal HBV DNA concentrations, especially in pregnant women who were HBeAg positive. The optimal cutoff of maternal HBsAg concentration to predict perinatal HBV transmission was 4·1 $\log_{10}$ IU/mL or 12 500 IU/mL, with a sensitivity of 100% and specificity of 71%.[59] However, quantitative HBsAg testing in sub-Saharan Africa is not routinely available.

If assessment of HBV DNA concentrations in pregnant women who are HBsAg positive is not possible, the option of starting tenofovir in the third trimester to prevent MTCT could be advantageous, and these mothers could then be referred for assessment regarding the need for ongoing antiviral therapy after birth.

## The efficacy of universal HBV vaccination

The universal HBV vaccine has proven to be exemplary in Taiwan. Introduced in 1984, together with a catch-up vaccination programme and improved maternal screening, universal vaccination resulted in a decrease in the prevalence of HBsAg positivity in children younger than 15 years from 9·8% in 1984 to 0·3% in 2009.[60,61] HBV infection as measured by hepatitis B core antibody seropositivity decreased from 38% in 1984 to 4·6% in 2009.[62] Furthermore, the average annual hepatocellular carcinoma incidence in children aged 6–14 years decreased from 0·7 per 100 000 children in 1981–86 to 0·36 per 100 000 children in 1990–94.[63] A similar decline in HBsAg seroprevalence and hepatocellular carcinoma incidence has been seen in other HBV-endemic countries that have implemented universal HBV vaccination.[64–66]

In rural China, neonatal vaccination reduced the mortality of infant fulminant hepatitis and severe end-stage liver disease with efficacies of 69% (95% CI 34–85) and 70% (15–89), respectively. Vaccination also reduced hepatocellular carcinoma incidence with an 84% efficacy (95% CI 23–97).[67]

Continuing to assess the ongoing efficacy of hepatitis B vaccination programmes is important, and countries in sub-Saharan Africa will need to incorporate monitoring of these vaccination programmes into their action plans. In South Africa, following the introduction of universal HBV vaccination into the EPI in April, 1995, overall HBsAg seroprevalence declined from 12·8% in 1995 to 3% in 2009 in children younger than 5 years.[68] South Africa has no HBV birth-dose vaccine and no catch-up programme, and studies[69–73] have shown that HBsAg prevalence in adults ranges from 3% to 25%, with the highest prevalence in adults who are infected with HIV.

## Prevention of adult acquisition and transmission

Since adult infection is invariably symptomatic and infrequently leads to chronic infection (<5%), adult catch-up vaccination programmes are not cost-effective. However, with an elimination strategy, high-risk individuals must be identified and vaccinated, including health-care workers, individuals with underlying chronic liver disease, immunocompromised individuals, men who have sex with men, and seronegative partners of those with chronic HBV infection. This strategy

requires the ability to screen for HBsAg and hepatitis B surface antibodies and administer HBV vaccines at all levels of care.

## Diagnosis and access to care for individuals who are infected with HBV

Although vaccination is effective in reducing incident chronic disease in high prevalence countries, the effect on the incidence of advanced liver disease will not be seen for several decades. A large reservoir of chronic hepatitis B remains in sub-Saharan Africa. To prevent the life-threatening complications of cirrhosis, liver failure, and hepatocellular carcinoma, identification of individuals who are infected with HBV is essential to assess the need for treatment and appropriate frequency of follow-up. This identification is difficult because chronic hepatitis B is an asymptomatic disease, only presenting when complications arise. Diagnostic testing is expensive and accurate WHO-prequalified HBV point-of-care testing that can be easily administered at primary levels of health care will be important.

The Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) project assessed the diagnostic accuracy of three point-of-care tests (Alere Determine HBsAg [Alere, Waltham, MA, USA], VIKIA HBsAg [BioMérieux, Craponne, France], and Espline HBsAg [Fujirebio Inc, Tokyo, Japan]) in field and laboratory settings in the Gambia. Sensitivity and specificity of the Determine test was 88·5% and 100% in the field and 95·3% and 93·3% in the laboratory setting, respectively. The Vikia test had 90·0% sensitivity and 99·8% specificity in the field, and Espline had 93·9% sensitivity and 94·7% specificity in the laboratory. All three point-of-care tests had acceptable ranges of diagnostic accuracy and were rapid, inexpensive HBsAg screening alternatives to laboratory-based testing.[74] The PROLIFICA project also showed that large-scale test-and-treat programmes are feasible and cost-effective in sub-Saharan Africa if a high coverage of community-based screening and good linkage into care are present, since only a small proportion of individuals who are HBsAg positive will need treatment.[75,76]

Once HBV is diagnosed, these infected individuals must be given appropriate treatment, especially since clinicians frequently do not recognise the need to treat an individual in the absence of symptoms. The history of HBV infection is complex and involves a spectrum of signs and symptoms, from relatively inactive disease to life-threatening complications. Treatment indications are based on patterns of viral replication and the degree of necroinflammation and fibrosis.

WHO has developed guidelines for the management of HBV infection that are applicable to resource-limited countries and regions, but each country should develop their own guidelines that are adapted to the needs of the individual country.[58] Appropriate clinical assessment for treatment requires a detailed clinical history, physical examination, full blood count, prothrombin time, creatinine, liver profile, alpha-fetoprotein, and ultrasound imaging. Non-invasive methods of assessing for advanced fibrosis to identify and prioritise patients with advanced liver disease will be required and can be linked to existing HIV test-and-treat infrastructures.

The aspartate aminotransferase (AST) to platelet ratio index (APRI) score and transient elastography (Fibroscan, [Echosens, Paris, France]) have been validated as non-invasive markers of fibrosis, with the APRI score being WHO's preferred method, but assessment using these methods in sub-Saharan Africa has been minimal. Fibroscan is not widely used because of the high cost of the equipment, need for trained operators, and the costs of maintenance. Tests that use the APRI score are readily available at most hospitals, cost less than a few US dollars each, and can potentially increase identification of individuals with cirrhosis who should be treated. HBV DNA testing, which is essential to identify individuals with high viraemia, remains costly (US$100–400 per test), and therefore inaccessible in resource-limited countries and regions.

WHO guidelines suggest that treatment should be targeted at individuals at highest risk of disease progression, and are primarily based on the detection of persistently raised alanine aminotransferase (ALT) concentrations and HBV DNA concentrations higher than 20 000 IU/mL in individuals older than 30 years. All individuals with cirrhosis should be treated regardless of their ALT concentrations, HBeAg status, or HBV DNA concentrations. Less than 20% of individuals who are infected with HBV require treatment. Most HBV-infected individuals have low HBV replication, minimal necroinflammatory disease without advanced fibrosis, and are at low risk of progression, and hence do not require treatment. However, ongoing minimal monitoring is required, imposing an additional health-care burden in resource-limited regions. Assessment of the risk of progression requires clinical assessment, including assessing the family history of hepatocellular carcinoma and monitoring of ALT, HBV DNA, alpha-fetoprotein, and ultrasound every 6–12 months, with an annual non-invasive assessment of fibrosis. Point-of-care testing of HBV DNA concentrations is urgently needed, as well as non-invasive portable imaging to better estimate progression risk and appropriate follow-up.

Appropriate HBV antiviral therapy has been shown to have an effect on the development of cirrhosis and risk of hepatocellular carcinoma, improving liver-related and all-cause mortality.[77–79] The efficacy of large-scale interferon-based therapy is uncertain, since the effectiveness of pegylated interferon is restricted, the side-effects of therapy are substantial, and monitoring of patients is impractical in sub-Saharan Africa. Most individuals who are infected with HBV in sub-Saharan Africa do not fit the clinical profile for interferon-based therapy and will usually require lifelong nucleoside analogue treatment to suppress HBV DNA replication.

Tenofovir, which has a high barrier to resistance, is the WHO-preferred nucleoside analogue, and although lamivudine and tenofovir are widely available as part of ART, these nucleoside analogues are not always accessible to monoinfected patients with HBV in many countries in sub-Saharan Africa. For those patients, access to tenofovir treatment at all levels of care will be essential to prevent the development of complications of chronic hepatitis B and to further prevent HBV transmission. Tenofovir alafenamide, an oral phosphonoamidate prodrug of tenofovir, has now been approved for the treatment of chronic hepatitis B in adults with compensated liver disease. This prodrug has similar efficacy to tenofovir both in individuals who are HBeAg positive and in those who are HBeAg negative, but has fewer detrimental effects on bone mineral density and creatinine clearance.[80,81]

Despite the precipitous decline in drug costs (generic tenofovir costs less than US$50 per annum in sub-Saharan Africa), cost linked to gross national product is still high in regions where most patients pay for their own treatment and nucleoside analogue treatment is usually lifelong. Crucially, HBV diagnostics and antivirals need to be available at more affordable prices in sub-Saharan Africa.

## Overcoming challenges

### Prevention of HBV MTCT

Integration of HBV birth-dose vaccination into newborn-care policies and practices is essential, as well as assigning responsibility for administering the birth dose. The capacity for vaccine storage, handling, administration, reporting, and recording needs to be increased. Antenatal visits are a key opportunity for education because 74% of pregnant women in the WHO region of African have at least one antenatal care contact, providing the opportunity to educate pregnant women and other caregivers during the antenatal period regarding the importance and timing of HBV birth-dose vaccination.[47] Innovative approaches to ensure the timely administration of the HBV birth-dose vaccine that have been successful in Vietnam,[82] Indonesia,[83] and China[50]—ie, pregnancy tracking, administration of the vaccine by village-based care workers, and the use of compact, prefilled autodisposable devices (HB-Uniject [BD Pharmaceutical Systems, Franklin Lakes, NJ, USA])—should be easily translatable to sub-Saharan Africa. These strategies have enabled districts to achieve between 84% and 97% vaccination coverage in rural home-based birth settings.[82,83] The WHO 2030 goal of 90% HBV birth-dose vaccine coverage should prevent 84% of HBV-related deaths, compared with prevention of just 68% of deaths without the birth-dose vaccine. Integration of HBV birth-dose vaccination into an early postnatal care package (home visits within 1 day of a home-birth), as recommended by WHO–UNICEF in 2009, has the dual benefit of improving newborn survival and reducing long-term HBV mortality.

### Diagnosis and linkage to care

Importantly, scaling up the use of antiviral therapy for HBV infection in a manner that is feasible in resource-limited regions must be emphasised. Affordable diagnostics must be available at all levels of care to identify individuals who require treatment and appropriate follow-up. WHO-prequalified point-of-care diagnostics would increase diagnostic capacity, as would the use of the same diagnostic platforms for HBV DNA concentration quantification that are available for HIV DNA concentration quantification—eg, Gene Xpert Tests (Cepheid Inc, Sunnydale, CA, USA). The PROLIFICA project has validated an in-house quantitative real-time PCR method—an assay based on SYBR Green—against two commercial assays: COBAS TaqMan (Roche Molecular Diagnostics, Pleasanton, CA, USA) and Abbot Real Time HBV assay (Abbott Laboratories, Lake Bluff, IL, USA). The in-house quantitative real-time PCR assay had good intra-assay and inter-assay reproducibility over a range of $45–4{\cdot}5\times10^8$ copies per mL, detected loads as low as 5 IU/mL, was rapid (4 h 15 min per assay), and two-to-three times cheaper.[84]

Supranational purchasing and volume discounts could allow transient elastography technology to be installed in regional centres and enable portable machines to be put in outreach clinics, thus facilitating recognition of substantial fibrosis. Programmes such as the Extension for Community Healthcare Outcomes (ECHO) Project that enable delivery of best-practice care for individuals with chronic viral hepatitis in disadvantaged communities play a crucial role in "democratising" knowledge and practice by increasing the local capacity to identify and treat disease.[85]

The high number of annual deaths and the economic burden of HBV, even despite the development of effective vaccinations, are preventable, and this needs to be accepted by governments. State-sponsored treatments should be provided if necessary to make change possible.

Clear referral pathways of care need to be established with sustainable access to antivirals for individuals who are HBV monoinfected, as well as community education programmes around transmission routes to break down the stigmas associated with HBV diagnosis within families, the community, and the workplace.

## Assessing the impact of national viral hepatitis action plans

To monitor progress in sub-Saharan Africa, an interim assessment of progress towards the 2030 objectives will be needed in 2020. Individual countries should audit the effectiveness of their plans against the recommended WHO 2020 targets. Notable focus areas should include HBV birth-dose vaccine administration, full HBV-vaccine coverage, accredited testing of 95% of blood donations, safe injection practices (50% coverage with safe devices), needle and syringe exchange programmes, and upscaled diagnosis of chronic infection, with at least 30% diagnosed.[86]

### Search strategy and selection criteria

We identified references for this Review using PubMed with the search terms "hepatitis B", "elimination strategies", "WHO Africa region", "sub-Saharan Africa", "burden of liver disease", and "hepatitis B birth dose vaccine" from June 1, 2000, until April 30, 2017. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

## Conclusions

HBV is endemic in sub-Saharan Africa and, despite the introduction of universal HBV vaccination, the estimated overall HBsAg seroprevalence remains high at 6·1%. Most individuals with chronic hepatitis B are unaware of their infection and thus do not benefit from clinical care, treatment, and interventions designed to reduce onward transmission and disease progression.

To achieve the WHO goals of eliminating HBV by 2030, sub-Saharan Africa will need to actively prioritise implementation of several elimination strategies (panel). Antenatal HBsAg screening, prevention of MTCT with administration of tenofovir to pregnant women who are HBV monoinfected with HBV DNA concentrations higher than 200 000 IU/mL, together with HBV birth-dose vaccination, and ensuring subsequent full HBV-vaccine coverage should form the cornerstone of any HBV elimination strategy. Similar strategies involving pregnancy tracking and involvement of community health-care workers that have proved successful in China,[50] Indonesia,[83] and Vietnam[82] in ensuring timely administration of the HBV birth-dose vaccine could be adopted in rural settings in sub-Saharan Africa where home-births are common.

Although maternal HIV and HBV transmission has been reduced by ART, MTCT prevention programmes, and early infant HBV vaccination, a concerning Zambian study[15] revealed that ART upscaling was associated with a decline in routine vaccination coverage because health-care systems could not effectively cope with both tasks. Furthermore, although increasing the scale-up of global ART should limit HBV-related liver disease through dual antiviral activity in HIV–HBV co-infected individuals, individuals who are HBV monoinfected are still at a disadvantage since they frequently remain undiagnosed with restricted access to therapy.

Development of locally applicable management guidelines and affordable HBV point-of-care testing that enables increased diagnosis and linkage to care, with sustainable access to antivirals, will be important to prevent the development of complications associated with chronic hepatitis B and further transmission. Implementation of these elimination strategies will require the active support of national departments of health, with the appropriate allocation of funds and development and strengthening of appropriate infrastructures.

### *Panel:* Recommended priority actions for the elimination of hepatitis B in sub-Saharan Africa

- Prevention of mother-to-child transmission (MTCT)
  - Mandatory antenatal hepatitis B surface antigen (HBsAg) screening: screening tests using available laboratory infrastructures—eg, ELISA-based serology or point-of-care tests
  - Initiation of tenofovir 300 mg daily at 28–32 weeks of pregnancy if hepatitis B virus (HBV) DNA concentration is higher than 200 000 IU/mL to further reduce risk of perinatal transmission
  - Real time quantitative PCR or in-house quantitative PCR to establish MTCT risk
  - Hepatitis B e antigen (HBeAg) testing if quantitative HBV PCR not available
  - If HBeAg and quantitative HBV PCR not available, treat pregnant women based on HBsAg positivity and refer for further assessment of whether antiviral therapy is needed after delivery
  - Baby treated with HBV birth-dose vaccine within 24 h of birth
  - Ensure full coverage of universal hepatitis B vaccination
- Identify high-risk groups, especially family members, household contacts, and sexual contacts for HBsAg screening, HBV vaccination, or linkage to care
  - Use of affordable WHO prequalified point-of-care testing for HBV serology and HBV DNA concentration quantification to upscale identification of individuals infected with HBV
- Ensure that health-care workers are screened and vaccinated against HBV
- Establish pathways of linkage to care for individuals who are HBV monoinfected
- Ensure sustainable access to tenofovir for individuals who are HBV monoinfected

The ultimate elimination of viral hepatitis will require an effective partnership between affected communities, professional and community organisations, governments and national departments of health, researchers and health professionals, and pharmaceutical companies. Chronic viral hepatitis must finally be recognised as a health priority by governments in countries where the disease is prevalent to reduce the clinical burden of HBV that continues despite vaccination programmes. Non-equitable systems for HIV-related versus HBV-related services must be eliminated to solidify coordinated efforts and interventions.

#### Contributors

CWS drafted the manuscript. All authors contributed equally to reviewing the available literature, providing country specific perspectives, formulating consensus recommendations, and reviewing the manuscript. MWS and GD provided additional technical expertise.

#### Declaration of interests

GD reports personal fees from Gilead Sciences and Bristol-Myers Squibb outside the submitted work. All other authors declare no competing interests.

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