Reviews

Elimination of Vertical Transmission of Hepatitis B in Africa: A Review of Available Tools and New Opportunities

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ABSTRACT

Purpose: This review article focuses on preventing vertical transmission of hepatitis B virus (HBV) among pregnant women living in sub-Saharan Africa (SSA), where disease is endemic and the estimated maternal HBV seroprevalence is >8%. Available interventions that have been studied in low- and middle-income countries are compared in terms of efficacy and effectiveness in clinical practice. Global disease-elimination targets, barriers to HBV-prevention efforts, and critical research gaps are discussed.

Methods: A PubMed literature search in February 2018 identified relevant studies of interventions to reduce or prevent the transmission of HBV during pregnancy or in the peripartum period. Studies that focused on interventions that are currently available or could be made available in SSA were included. Trials conducted in SSA and other low-income countries were prioritized, although studies of interventions in middle- and high-income countries were included.

Findings: Among 127 studies and reports included in the review, 60 included data from SSA. The most cost-effective intervention to reduce HBV infection rates in SSA is timely birth-dose vaccination followed by completion of the 3-dose infant-vaccination series. The identification and treatment of pregnant women with elevated HBV viral load to further reduce the risk for vertical transmission in SSA show promise, but efficacy and tolerability trials in Africa are lacking.

Implications: Scale-up of currently available tools is required to reach HBV disease-elimination goals in SSA. Many countries in SSA are in the process of rolling out national birth-dose vaccination campaigns; this roll out provides an opportunity to evaluate and improve processes in order to expand coverage. Early antenatal care, promotion of facility deliveries, and increased awareness of HBV prevention are also key components of prevention success. Future studies in SSA should identity an HBV-prevention package that is effective, well tolerated, and feasible and can be administered in the antenatal clinic and tailored to vertical-transmission risk. (*Clin Ther*. 2018;40:1255–1267) © 2018 Elsevier Inc. All rights reserved.

Key words: hepatitis B antiviral therapy, hepatitis B in pregnancy, hepatitis B virus (HBV) infection, sub-Saharan Africa (SSA), vertical HBV transmission.

INTRODUCTION

There are 257 million people living with chronic hepatitis B virus (HBV) infection worldwide, 88% of whom reside in sub-Saharan Africa (SSA).[1–7] Viral hepatitis was the 7th leading cause of mortality worldwide in 2015, surpassing HIV, tuberculosis, and malaria infection.[7] If current trends continue, an estimated 63 million new cases of HBV will occur between 2015 and 2030. The World Health Organization (WHO) has set a goal of disease elimination by 2030; reaching this ambitious goal will require a significant scale-up of prevention and treatment efforts in SSA, with a focus on efforts to prevent the transmission of HBV during pregnancy and the

Accepted for publication May 21, 2018.
https://doi.org/10.1016/j.clinthera.2018.05.016
0149-2918/$ - see front matter

peripartum period.[8–12] Vertical transmission is a key factor driving endemic HBV-infection rates in SSA.[13]

Chronic, active HBV infection is usually asymptomatic, with only 9% of infected persons worldwide being aware of the infection.[14] Routine screening in the antenatal clinic consists of testing for the presence of HBV surface antigen (HBsAg), but screening is not consistently performed in pregnant women in SSA.[15] Similar to other viral infections in pregnancy, the risk for vertical transmission of HBV is directly correlated with the maternal viral load. Studies have documented that women with HBV DNA levels of >200,000 IU/mL (10^6 copies/mL) have a higher risk for vertical transmission.[16] Infectiousness is also predicted by positive maternal HBV e antigen (HBeAg) serostatus, which correlates with elevated HBV DNA levels (ranging from 2000 to >200,000 IU/mL).[5,17]

Vertical transmission of HBV is mucosal and caused by perinatal exposure to infected maternal blood and bodily fluids at the time of delivery. Transplacental transmission and transmission via breastfeeding are rare. Routine cesarean delivery for the sole purpose of reducing the risk for vertical transmission to HBV-exposed infants is not recommended, but data are limited.[18–20] A potential association between HBV infection and preterm delivery requires further validation.[21]

The likelihood of developing chronic HBV infection is inversely proportional to age at the time of HBV exposure.[7,16,20,22–28] Ninety percent of HBV-exposed neonates will develop chronic infection, compared to 5% to 10% of HBV-exposed adults. Interventions to prevent vertical HBV transmission are highly cost-effective since they reduce both short-term adverse outcomes and long-term morbidity and mortality.[29,30] The long-term outcomes of chronic HBV infection include cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC).[31] The risk for HCC after perinatal HBV infection is 5% per decade—100-fold higher than the risk for HCC following horizontal transmission later in life.[32] Medical and surgical management options for end-stage liver disease and HCC in SSA are limited; these limited options strengthen the rationale for allocating resources to disease-preventive efforts.[33,34] HIV/HBV coinfection is important as well, since an estimated 18 million women in SSA are living with HIV and most are of childbearing age.[35,36] Adults with HIV have an elevated risk for acquiring HBV, and HIV/HBV coinfected patients have a more rapid progression of liver disease to fibrosis and cirrhosis.[37] Most pregnancy outcomes in women treated for HIV/HBV coinfection are reassuring to date, and coinfection does not appear to increase the risk for vertical HIV transmission.[38,39]

Fewer than 1% of pregnant women worldwide, and very few women in SSA, are offered targeted antiviral therapy for HBV infection during pregnancy.[40,41] Several first-line antiretroviral therapy regimens used in SSA have dual activity against HIV and HBV (including tenofovir, lamivudine, and emtricitabine).[42] Although antiretroviral medications may be available free of charge through international and national HIV programs in SSA (eg, the US President's Emergency Plan for AIDS Relief), there is no equivalent program to cover the expense of antiviral therapy for HBV.

Fortunately, highly effective tools for preventing the vertical transmission of HBV, with records of long-term tolerability in pregnant women and neonates, are available. Low awareness about HBV prevalence and preventive interventions among providers and the general public in SSA limits uptake.[43,44] This review focuses on the HBV-preventive options that are available in SSA—namely, HBV vaccination and HBV-targeted antiviral therapy.[45–50] Gaps in knowledge and research priorities necessary for reaching the goal of eliminating vertical HBV transmission in SSA also are discussed.

MATERIALS AND METHODS

A PubMed search was conducted on February 19, 2018, to identify relevant studies of interventions to reduce or prevent the transmission of HBV during pregnancy or the peripartum period in humans. The terms or key words used in the search were *hepatitis B antiviral pregnancy, prevention of vertical transmission of hepatitis B, mother to child hepatitis B prevention, hepatitis B birth dose vaccination, hepatitis B infant vaccination, hepatitis B immunoglobulin* or *HBIG,* and *HBV therapy in pregnancy*. Studies conducted in Africa or other low-income countries were prioritized for inclusion, although studies of HBV-preventive interventions in middle- and high-income countries were included when relevant. Only articles written in English were reviewed. Studies of interventions to prevent horizontal transmission or to prevent HBV in adults were excluded. Articles were reviewed to address thematic areas of interest.

RESULTS

Overall, the search yielded a total of 4543 reports, of which 127 were relevant and reviewed for this publication. Sixty reports focused on or included data from countries in SSA. We address 10 thematic questions in the subsequent sections.

HBV Testing Strategies in Pregnant Women and Infants in SSA

When women are screened for HBV infection during pregnancy in SSA, serologic testing for HBsAg is performed. However, since few pregnant women (0%−20%) are routinely tested for HBV in SSA, cross-sectional studies are used to document regional HBsAg prevalence.[51−53] Given the expense and expertise required for quantitative molecular diagnostic testing, HBeAg is the only available measure of infectiousness in most HBV-positive pregnant women in SSA. The feasibility of rapid antenatal HBV testing is under investigation.[54]

HBV Vaccine Products for Neonates and Infants

The first commercially available HBV vaccine was a plasma-derived product that was approved in 1981. Within 10 years, this formulation was replaced by a yeast-derived, recombinant DNA HBV vaccine product that remains in use today.[55,56] There are several HBV vaccine products currently available for pediatric populations in SSA; all contain 5 to 10 μg of HBsAg in a 0.5-mL standard-volume dose. Any licensed and approved vaccine for HBV can be used interchangeably in national vaccination programs. In SSA, the administration of a monovalent form of the HBV vaccine is recommended at birth in all infants (birth-dose vaccine), followed by HBV vaccination as part of a pentavalent combination vaccine (HBV/diphtheria-pertussis-tetanus/*Hemophilus influenzae* type b) at 6, 10, and 14 weeks of age. Three or four vaccines are required to complete the HBV series (4 if the birth dose is followed by the 3-dose pentavalent series). Although most HBV vaccines have a long shelf life (up to 4 years), current cold-chain requirements can be a challenge mandate transportation and storage of vaccine at 2°C to 8°C. Cold-chain requirements can be a challenge in areas of SSA with a lack of consistent electrical supply. Specific vaccine-storage details are available in the product package insert, and a WHO report focused on HBV prevention includes practical details for national HBV vaccination programs in low- and middle-income countries.[14]

HBV Vaccine Immunogenicity, Duration of Protection, and Tolerability

Fortunately, pediatric HBV vaccine is highly immunogenic, and vaccine series completion alone prevents 80% to 95% of vertical HBV transmission. Most healthy infants (>96%) have evidence of protective immunity on completion of the primary series.[57,58] Protection is more limited without vaccine series completion. The standard definition of *protective immunity* is a detectable antibody level of >10 mIU/mL at 9 months of age (1−2 months after the last dose). According to WHO recommendations, preterm, low-birthweight infants (<2000 g) should receive birth-dose vaccine followed by the 3-dose pentavalent series, and serologic response rates are excellent.[59] Although US recommendations for low-birthweight infants are similar to those in HBV-exposed infants (or if maternal status is unknown), the Centers for Disease Control and Prevention recommends HBV vaccination starting at 4 weeks of age among infants who are not HBV exposed.[60]

Infants with HIV infection appear to develop lower antibody levels in response to HBV vaccine, but vaccination recommendations are unchanged.[61] Studies show that the duration of the protective response after completion of the primary HBV vaccine series is long lasting (>20−30 years) in areas of both high and low endemnicity.[13,14,62−65] A booster dose of HBV vaccine is not recommended, but since 5% of infants do not respond to the vaccine, a search for underlying immunologic or genetic differences in this group is ongoing.[66] HBV vaccine is well tolerated in infants and children, with serious adverse events (anaphylaxis) occurring in <1.1 per million vaccinations.[67]

HBV Vaccination Timing

The ideal timing of HBV vaccination to prevent vertical transmission is at birth.[13,68] Receipt of the initial pentavalent vaccine at 6 weeks of age leaves an HBV-exposed neonate with inadequate protection for weeks, and many infants in SSA have delayed initiation of the series, which prolongs the risk period.[47] Although many studies have shown efficacy of the monovalent birth-dose HBV vaccine, only one controlled, non-randomized, vaccine-effectiveness trial compared infection rates among infants who did and did not receive birth-dose vaccination.[69] In Cote d'Ivoire, Ekra et al[70] compared HBV infection rates among 4600 infants vaccinated at 0, 6, and 14 weeks of age to rates in those

vaccinated at 6, 10, and 14 weeks of age. Infection rates at 9 months of age were 0.5% in both groups, but in a subgroup of 41 infants born to HBeAg-positive mothers, the infection rates were 38% in the birth-dose group and 59% in the group with series initiation at 6 weeks ($P = 0.18$). It is not clear why the infection rate was elevated in both groups despite vaccination, and study findings have not been replicated.

The initiation of HBV vaccination at birth versus 6 weeks has been the subject of controversy in national programs in SSA. Although studies in Uganda (where birth-dose HBV vaccine is not available) have shown efficacy of vaccine series initiation at 6 weeks, large-scale HBV elimination in SSA depends on increasing access to birth-dose vaccine.[71–74] In one model, 50% of new chronic cases of HBV worldwide in 2030 will have been acquired by vertical transmission.[75] A population-based, cross-sectional study in children in the Amazon region documented the impact of a birth-dose vaccine program established in 2001.[76] The rate of chronic HBV infection decreased to 0.5%, and receipt of the birth dose decreased the risk for HBV infection by 95%. A similar rate of chronic HBV infection (0.4%) was noted in Israeli children following nationwide adoption of the birth-dose vaccine in 1992.[77] In Indonesia, low coverage of the birth-dose vaccine was cited as one explanation for persistent pediatric HBV-infection rates (seroprevalence as high as 6%) despite the adoption in 1997 of universal HBV vaccination starting at birth.[78] Randomized or other well-designed studies comparing HBV-transmission rates with vaccine initiation at birth versus 6 weeks are lacking.

HBV Vaccine Coverage, Availability, and Cost-effectiveness in SSA

Since 2009, the WHO has recommended universal HBV birth-dose vaccination for all infants (Figure).[13] HBV vaccination within 24 hours of birth is also recommended as a key performance indicator of national immunization programs.[14] HBV birth-dose vaccination has been supported by Gavi, the Vaccine Alliance, since 2000. Gavi recognizes HBV birth dose as a high-

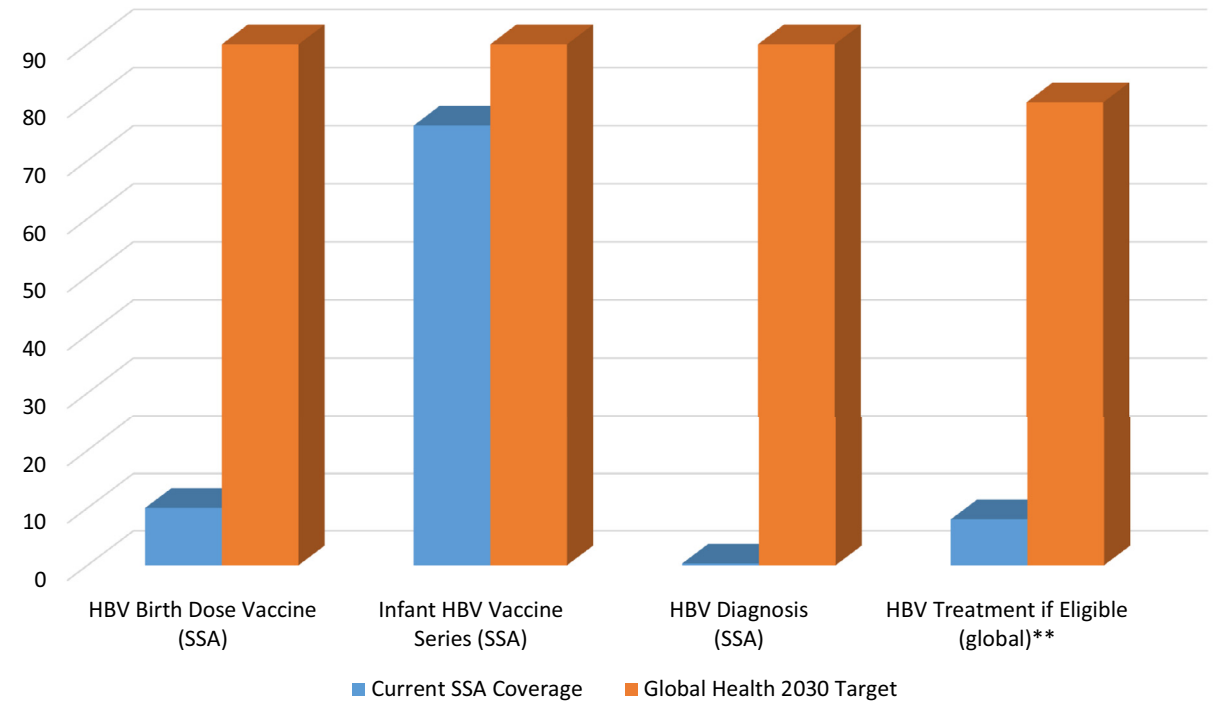

Figure. Current rates and 2030 targets for hepatitis B virus (HBV) elimination in sub-Saharan Africa (SSA).*

*According to the Global Health Sector Strategy, which was later adopted by the World Health Organization.[9] **Routine antiviral therapy is recommended for eligible adults, but no recommendation was made about routine treatment in pregnancy.

impact vaccination that should be included in SSA vaccination platforms. Despite these longstanding recommendations, coverage of the HBV birth-dose vaccine in 2015 was only 38% worldwide and 10% in SSA.[50] Fewer than 100 countries (97), and only 11 of 54 countries in SSA, have adopted a policy of birth-dose vaccination, although many are working toward adoption.[15,79] Rates of completion for the 3-dose pentavalent HBV-containing vaccine series are 87% worldwide and 76% in SSA.[15,47] HBV-vaccination rates in infants in SSA are correlated with higher maternal age and education, urban residence, and access to health care.[47,80]

The monovalent vaccine is quite affordable at US $0.20 per dose, although country procurement costs and patient charges may be significantly higher. Gavi does not currently provide financial support for the birth-dose vaccine as it does for the pentavalent vaccine. The cost-effectiveness of HBV prevention with vaccination is favorable, whether analyses include short-term outcomes of infection prevention in children or long-term outcomes of HBV-associated morbidity and mortality.[29,81,82] At an estimated cost of $15.5 million, scale-up of HBV birth-dose vaccination in South Africa was shown to be more cost-effective compared to several other intervention efforts modeled to reduce national viral hepatitis rates.[83]

Methods To Improve HBV Vaccine Coverage in SSA

There are 4 critical barriers to wider implementation of the birth-dose vaccine in SSA: (1) limited awareness of HBV prevalence and preventive interventions; (2) lack of vaccine availability; (3) out-of-facility deliveries; and (4) cold-chain storage requirements.[84,85]

Training and supervision of health care workers to increase awareness about the importance of HBV birth dose, ensuring consistent vaccine supply, and developing standing orders for birth-dose vaccination in facilities significantly improved vaccine coverage in the western Pacific.[86] Similarly, in China, birth-dose coverage improved when facilities' delivery rates increased from 58% to 93% and access to vaccine was ensured.[87] In the Philippines, timely birth-dose coverage was 40% in 2011, but private facilities had lower coverage rates compared to those of government facilities.[88] Since many health officials and antenatal providers in SSA have worked to promote facility deliveries in order to improve a variety of maternal and infant health outcomes, facilities' delivery rates in most countries now approach 80%.[89,90] However, in regions where out-of-facility delivery rates remain high, innovative strategies to offer HBV birth-dose vaccination have been developed.[91] One effective project in rural Asia provided regional and local health care workers with mobile phones to track home deliveries; birth-dose coverage in intervention districts was 57% compared to 20% in control districts.[92]

HBV monovalent vaccine is relatively heat stable according to in vivo and in vitro studies.[14,93–95] These studies provide some indication that HBV vaccine may retain its potency in the absence of continuous cold-chain transport and storage. There are no thermostable HBV vaccine products available at present, but ongoing studies are promising given the relevance of this challenge in SSA.[96–99]

Data from national birth-dose HBV vaccination campaigns from outside of SSA provide useful information for national programs that are in the process of adopting or rolling out their own birth-dose vaccination programs (including Benin, Cameroon, Cote d'Ivoire, Ethiopia, Ghana, Republic of the Congo, and Sierra Leone).[10,47] Published findings highlight the need to ensure consistent access to vaccines, engage relevant clinical and public health partners in training opportunities, and conduct public-awareness campaigns about the importance of HBV-prevention efforts.

HBIG Efficacy and Availability in SSA

Hepatitis B immune globulin (HBIG) contains high levels of purified HBsAg-specific antibodies from plasma donors. HBIG provides short-term protection to HBV-exposed neonates for 3 to 6 months after delivery, when provided along with birth-dose vaccination. From an ethics perspective, HBIG should be available to HBV-exposed neonates in every country, but unfortunately, it is not widely available in SSA. Even if a local supply is identified, HBIG is rarely affordable, at a cost up to several hundred dollars per dose. Tolerability concerns further limit the feasibility of HBIG administration in SSA.[14] Current evidence shows that HBIG provides HBV-exposed infants with protection that is additive to that afforded by the birth-dose vaccine, particularly among women with an elevated HBV viral load.[68,69,100] However, studies also show minimal benefit of HBIG in HBV-exposed infants who are born to HBeAg-negative women; additional study defining the precise role for HBIG in

low and middle-income countries will be helpful.[101–103] According to the WHO,[13] the option of HBIG immunoprophylaxis in SSA will be of limited utility until cost, further efficacy, and tolerability concerns are addressed.

Antiviral HBV Treatment in Pregnancy To Reduce Vertical Transmission

The main causes of failure of prophylaxis for vertical transmission are high maternal viral load or HBeAg positivity, in utero infection, escape mutants, and poor maternal immune status.[104] Of these, high maternal serum viral load (HBV DNA level >200,000 IU/mL) appears to be the major cause of prophylaxis failure, with up to 9% of perinatal transmissions despite both active and passive immunization.[105]

Antiviral drugs administered in the third trimester are well tolerated and effective in preventing intrauterine transmission of HBV and are generally recommended for HBV-infected pregnant women with a high viral load, followed by neonatal HBV vaccination.[106,107] Guidelines from some major international liver societies recommend antiviral therapy in women at higher risk for vertical transmission of HBV, with initiation during the third trimester (28–32 weeks' gestational age) and cessation during the postpartum period in women who do not meet the criteria for continuation of therapy.[43] Antiviral therapies that have been used to decrease HBV DNA levels during late pregnancy include nucleotide/nucleoside analogue polymerase inhibitors: lamivudine, telbivudine, tenofovir, and entecavir. Although lamivudine and tenofovir may be available at no cost to treat patients with HIV or HIV/HBV coinfection in SSA, no program covers the expense of these medications in adults with HBV monoinfection. Since antiviral therapy is necessary to reach elimination targets, increased global funding is needed to expand access to these medications.[10,83]

Lamivudine was the first antiviral drug used in HBV-infected mothers to lower vertical transmission rates. A nucleoside analogue and reverse-transcriptase inhibitor, it can significantly reduce the HBV viral load. In 2014, 45 women in Ireland met criteria for lamivudine treatment, and no cases of perinatal transmission were reported in infants born to mothers who received treatment.[108] The investigators concluded that lamivudine therapy in highly viremic, HBV-infected pregnant women could help to reduce the rate of vertical transmission. In 2011, a meta-analysis of data from randomized controlled trials including 1693 HBV-infected mothers showed that lamivudine initiated at 28 weeks was associated with substantially reduced vertical HBV transmission compared to that with immunoprophylaxis with HBIG alone.[109]

Telbivudine has anti-HBV activity with no known fetal toxic effects. Wu et al[110] performed a prospective study in 450 HBeAg-positive pregnant women, with 279 women receiving telbivudine and 171 women participating as controls. None of the infants whose mothers were given telbivudine tested positive for HBsAg at 6 months of age, compared to 14.7% of infants in the control group. The investigators concluded that telbivudine was well tolerated and significantly reduced vertical transmission of HBV.

One major drawback that complicates lamivudine and telbivudine use is HBV antiviral resistance. In contrast, tenofovir disoproxil fumarate, a nucleotide reverse-transcriptase inhibitor, is a potent medication with minimal resistance and a favorable pregnancy safety profile. Tenofovir is the antiviral therapy of choice for HBV in pregnancy, according to the American Association for the Study of Liver Diseases.[111] Data about the efficacy of tenofovir in reducing vertical HBV transmission are mixed. A retrospective review of data from 48 women treated with tenofovir throughout pregnancy reported a vertical transmission rate of 0%, with a first-trimester spontaneous abortion rate of 6%.[112] Two large-scale, randomized, controlled trials have studied the impact of tenofovir on rates of vertical transmission of HBV. In the first trial, from China, involved $HBeAg^+$ women with an HBV DNA level of >200,000 IU/mL during the third trimester. The rate of vertical transmission was 5% among those who received tenofovir therapy compared to 18% among those who received usual care without antiviral therapy.[113] In contrast, in a second, multicenter, double-blind clinical trial performed in Thailand, tenofovir therapy in 331 HBeAg-positive pregnant women did not result in a significantly lower rate of HBV transmission compared to that in women who did not receive antiviral therapy (0% vs 2%; $P = 0.12$) when provided in conjunction with HBIG immunoprophylaxis and HBV vaccination.[114] Findings from that study may not be generalizable to SSA, where immunoprophylaxis is not consistently available. There is significant interest in the potential role of tenofovir alafenamide fumarate (a prodrug of tenofovir disoproxil fumarate with improved bone and renal safety profiles

in adults) administered during pregnancy, but studies have not yet been reported.

Entecavir, another nucleoside analogue that inhibits reverse transcription and DNA replication, has an excellent resistance profile and efficacy and tolerability comparable to those of tenofovir in the treatment of HBV. However, data about its efficacy in reducing vertical transmission in pregnancy are limited.[115]

Combination Interventions To Reduce HBV Prevalence in SSA

Several models to identify high-impact interventions have been created, using current tools (single or in combination) to reach global HBV-elimination goals. In a recent model by Nayagam et al,[75] worldwide scale-up of birth-dose vaccination would prevent an estimated 18.7 million new cases of HBV by 2030, while scale-up of pentavalent-vaccine coverage without birth-dose vaccine would prevent 4.3 million new infections. In another model, a package of interventions (population-wide test and treat, peripartum antiviral treatment in HBeAg-positive women, universal birth-dose vaccination and series completion), new chronic HBV infections worldwide would be reduced by 90%, and mortality, by 65%. A response of this scale would be required to reach the elimination goals set by Global Health Sector Strategy (**Figure**).[10] The study also enumerates the high cost of this intervention package ($5.5 billion/y) and some of the challenges of scale-up in SSA, where disease prevalence is high and public health resources are limited.

Studies have also compared the cost-effectiveness of various antenatal HBV-preventive strategies: universal birth-dose vaccination, universal infant vaccination starting at 6 weeks, or maternal HBsAg screening with targeted birth-dose vaccination for exposed infants. In Cameroon, universal HBV vaccination with birth dose may be the most effective strategy in terms of reducing pediatric HBV infection by age 10 years at a willingness-to-pay threshold of $150.[46] Similarly, universal HBV vaccination with birth dose was the least costly HBV-preventive option in a population in Thailand with a maternal seroprevalence of 7%.[116] The provision of HBIG to infants born to HBV-infected women in Thailand was cost-effective at a willingness-to-pay threshold of $1200.

A package optimal for preventing vertical HBV transmission in SSA would include the identification of pregnant women who are highly infectious, since these women may transmit HBV vertically despite birth-dose vaccination and HBIG. This risk averages 8.5% but can be as high as 30% among women with elevated HBV viral load.[16,24,117,118] The identification of these women during early antenatal care would allow time for providers to discuss the risks and benefits of antiviral therapy administered during pregnancy.

Research Gaps in the Prevention of Vertical HBV Transmission In SSA

Research innovation on several fronts simultaneously is needed for launching new efforts to reach targets for eliminating vertical HBV transmission in SSA: diagnosis, vaccination, and treatment.[119] For diagnosis, universal screening for HBsAg in all pregnant women would increase the awareness of infection status in this key population. The development of rapid and affordable point-of-care diagnostic testing with excellent performance characteristics would also advance the field. Point-of-care HBeAg testing could be a useful strategy in SSA to determine treatment eligibility in the antenatal clinic. Another pragmatic goal would involve the incorporation of HBV testing into a single testing platform to facilitate the diagnosis of multiple infections (HIV/HBV/syphilis) at the time of the initial antenatal visit in SSA.

For vaccination, innovative implementation studies in SSA are needed to optimize facilities' delivery rates and maximize access to monovalent birth dose in any birth setting compared to initiation at 4 to 6 weeks. Additional studies to develop an effective and well-tolerated heat-stable HBV vaccine product are crucial. National campaigns working on birth-dose vaccination should reduce patients' cost constraints as much as possible.

In terms of HBV therapy, there are many new, exciting pharmacologic developments in the pipeline, including combination therapies and new life-cycle targets. Each new antiviral therapy or strategy will require well-designed, prospective studies to determine drug tolerability and efficacy in pregnant women and infants exposed to antiviral medication in utero.[41,120] In the meantime, studies in SSA documenting the efficacy and tolerability of tenofovir use in HBV-infected pregnant women are needed. Relevant questions for the use of tenofovir therapy during pregnancy include: participant selection (in the absence of routine virologic testing), duration of therapy, timing of cessation of therapy (to reduce disease flares postpartum), mode of delivery, and breastfeeding tolerability.[121–123] Treatment outcomes with the newest formulation of tenofovir

(tenofovir alafenamide fumarate) should also be investigated, since, in nonpregnant adults, tenofovir alafenamide fumarate has been associated with lower rates of bone and nephrotoxicity compared to tenofovir disoproxil fumarate.[43] Additional studies of cost-effectiveness are needed to help prioritize preventive options. Since effective antiviral therapy is already available in much of SSA (but limited to those with HIV), pregnant women with HBV will need better access to affordable therapy if HBV "treatment as prevention" becomes the standard of care.[124–126] Examples of successful HBV treatment programs in SSA already exist, but expansion will be necessary if certain pregnant women become eligible for routine antiviral therapy in the future.[127]

CONCLUSIONS

HBV infection is endemic in SSA and a major cause of morbidity and mortality. New and ambitious elimination targets provide an ideal opportunity to focus resources on optimizing the prevention of vertical HBV transmission. Current prevention efforts in SSA require universal access to timely HBV vaccination at birth. Public health officials and providers in SSA must continue to work to develop effective national HBV-elimination strategies that are well resourced, sustainable, supported by the community, and linked to other antenatal infection–prevention efforts (eg, HIV prevention). Models with SSA-specific data should be used to prioritize cost-effective intervention combinations and to advocate for appropriate allocation of resources. The optimal antenatal HBV-prevention package in SSA is yet to be defined, but future research will define the efficacy, tolerability, and feasibility of a package that may include universal antenatal testing, targeted antiviral therapy during pregnancy, and provision of HBV vaccine starting with the birth dose in all infants.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

ACKNOWLEDGMENTS

This work was supported by NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development grant K23 HD090993 (J.D.O.).

JDO conducted the literature search, and wrote the first draft of the manuscript. BN helped with the literature search, wrote the section on HBV Antiviral Treatment in Pregnancy and provided critical revisions to the manuscript. AT provided oversight of the study design, literature search results, data interpretation and provided critical revisions to the manuscript.

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