Mother to child transmission of hepatitis B: What more needs to be done to eliminate it around the world?

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Abstract

Mother-to-child transmission (MTCT) of hepatitis B virus (HBV) is a key component of the hepatitis B burden worldwide. Despite its efficacy to prevent HBV transmission, infant vaccination is not enough to control HBV MTCT. Additional efforts are urgently needed to evaluate and scale-up preventive strategies especially in endemic countries, which are most affected with the epidemic.

This review highlights the efficacy and barriers of the currently validated measures for the prevention of HBV MTCT and proposes alternatives adapted to resource-limited settings to eventually achieve HBV elimination worldwide.

Background

Viral hepatitis is responsible for nearly 1.4 million deaths annually and estimated 257 million persons are chronically infected with hepatitis B virus (HBV) globally. This burden of HBV infection is concentrated in the Western Pacific and African Regions, which account for 115 million and 60 million of cases, respectively.[1] The epidemic is maintained despite the availability of safe and highly effective prevention and treatment tools, which are not scaled-up to optimal levels, particularly in most endemic low-middle income countries. (LMICs).

In 2016 the World Health Assembly adopted the first global health targets for elimination of viral hepatitis as a public health threat and viral hepatitis was incorporated in the sustainable development goals.[2] The WHO's Global Health Sector Strategy HBV impact targets, included a 90% reduction in new infections and a 65% reduction in mortality by 2030, with an aim to reduce the prevalence of hepatitis B surface antigen (HBsAg) in children to 1% by 2020 and <0.1% by 2030. Although the growing political momentum for viral hepatitis was strongly welcomed by the hepatitis community and public health organisations, these targets were recognised as ambitious in scale. To reach these incidence reduction targets, a substantial scale-up of interventions to prevent mother-to-child transmission (MTCT) is needed. An estimated coverage of timely administration of hepatitis B vaccine at birth, a key intervention to control MTCT, at baseline in 2015 was 38%; this needs to be increased to 90% by 2030.[3] In addition to the global targets, some WHO regions have also adopted their own region-specific targets. For example, in 2017, the WHO's Western Pacific Region (including East Asia and the Pacific islands) endorsed a regional framework for the triple elimination of MTCT of HIV, HBV and syphilis.[4]

Since 1981 safe, inexpensive and effective vaccines against HBV have been available. In 1992 the WHO recommended that childhood hepatitis B vaccines should be included in all immunization programs and it has been integrated successfully into the Expanded Programme on Immunizations (EPI) of most countries. However, in many countries the vaccines were scheduled at 6, 10 and 14 weeks as a combined vaccine (pentavalent or hexavalent), with diphtheria, tetanus, pertussis, Haemophilus influenza type B (HiB) with or without polio vaccines. This infant vaccination schedule interrupts horizontal (child-to-child) transmission of HBV and the scale-up of infant vaccination has already had significant impact on the reduction of HBV prevalence and hepatocellular carcinoma (HCC) incidence worldwide.[5,6] But infant vaccination alone does not effectively control HBV MTCT.

In the pre-vaccination era, it was estimated that 40% of HBV transmission was occurring from mother-to-child in Asia, compared to 10% in Africa.[7] Several theories have been proposed to explain the differences in perinatal transmission risk by region, including HBV genotype differences[8,9], varying levels of HBV DNA and differences in obstetric complications.[10] In East and Southeast Asia, genotypes B and C predominate, the latter is associated with a higher risk of MTCT and increased severity of liver disease, whereas in Africa, where horizontal transmission is responsible for a greater proportion of transmission, genotypes A, D and E are more common.[8,11] However, established patterns of transmission are likely to play a key role in why a certain mode of transmission predominates in a given region.

Prevention of HBV MTCT is important for the following reasons. Firstly, the chance of becoming a chronic carrier of HBV if infected perinatally is as high as 90%.[7] Secondly,

modelling studies have offered an insight into the changing epidemiology of transmission. They have suggested that, given the success of infant vaccination, in the future the relative contribution of HBV MTCT among new infections will be higher in all regions, not just in Asia which was originally thought to be the region where HBV MTCT predominates.[3] Furthermore, a systematic review suggested that over 350,000 newborns are infected with HBV each year at birth in sub-Saharan Africa, which is twice the number of incident paediatric HIV infections in the region.[10] Thirdly, it has been suggested that the mode of HBV transmission may be one of the determinants of the natural history of chronic HBV infection. Several studies have shown that, compared to people who established chronic HBV infection through horizontal transmission, those who have acquired infection through perinatal MTCT have lower chance of spontaneous HBeAg and HBsAg loss, and higher risk of persistent viral replication, high alanine transaminase (ALT) levels, severe fibrosis requiring treatment and hepatocellular carcinoma (HCC), than those acquired horizontally.[11-14] In The Gambia, West Africa, a long-term (28 years) follow-up of children with chronic HBV infection found that the risk of having significant fibrosis was 5.0 times higher in those with HBV-infected mothers than in those with HBsAg-negative mothers, suggesting that the role of MTCT was two-fold: not only increases the risk of chronic HBV infection, but also the risk of liver complications.[11]

HBV PMTCT Interventions

There are additional tools that can be added to infant HBV vaccination that are effective to prevent HBV MTCT: timely birth dose vaccination (TBDV), as defined as, the administration of the first dose of HBV vaccine to babies within 24 hours after birth, hyperimmune hepatitis B immunoglobulin (HBIG) and, more recently, antiviral therapy for HBV-infected pregnant

mothers with high risk of infants' immunoprophylaxis failure despite receiving TBDV and HBIG. [15,16] However, the coverage of these interventions is globally highly heterogenous, with data from a recent study by the Polaris group suggesting that in 2016 only 46% of infants received TBD vaccine, 13% of infants born to HBsAg-positive mothers received HBIG and completed a series of hepatitis B vaccines including birth dose and <1% of mothers with high viral load received antiviral treatment.[17]

China is an example of a high HBV burden country, which has made substantial progress in its efforts toward elimination of HBV MTCT. Sequential national sero-surveys have shown the dramatic reduction in under 5-year-old HBsAg prevalence from 9.67% in 1992 to 0.32% in 2014.[18] This has been spearheaded through strong political commitment with early introduction of universal infant and HBV vaccination at birth, a partnership between the Government and GAVI, the Vaccine Alliance, to provide free BDV and the increasing of number of deliveries that occur in hospitals through a rural reform policy. Modelling studies suggest that with continued coverage at such high levels could lead to China reaching a target HBsAg prevalence of <0.1% even ahead of the global targets (*unpublished*).

1. Timely Birth Dose Vaccination (TBDV)

In the absence of preventive measures the risk of HBV MTCT from HBsAg-positive/HBeAg-positive mothers is estimated at 70-100% in Asia and 40% in Africa; this risk is lower from HBsAg-positive/HBeAg-negative mothers estimated at 5-30% in Asia and 5% in Africa.[10,19-21]

HBV TBDV has been shown to significantly reduce the risk of HBV MTCT to 10-30% in babies born to HBeAg-positive mothers and less than 0.5% in babies born to HBeAg-negative mothers[10,22,23] The efficacy and cost-effectiveness of TBDV in preventing MTCT, compared to placebo or no immunisation intervention, has been well established in Asia but not in Africa. [24-27]

Although the benefits of HBV TBDV have been poorly documented in Africa and despite many challenges related to its implementation, since 2009 the WHO has recommended universal HBV TBDV regardless of the HBV status of the mothers and irrespective of the HBV endemicity of the country of birth. However, some countries have chosen different approaches including adoption of a targeted HBV BD intervention for only babies born to HBsAg-positive women.[28]

In a non-randomized study conducted in Côte d'Ivoire Ekra et al. compared two vaccination schedules: 0-6-14 weeks (interventional group with HBV BDV) and 6-10-14 weeks (control group without BDV). The study did not show any statistical difference between both groups on the risk of HBV MTCT (HBsAg positivity in infants aged 9 months: 0.5% (9/1896) in the HBV BDV group and 0.5% (10/1900) in the group with BDV.[29] These results should be interpreted with caution, as it is a non-randomized study, in which two health centers were allocated to the intervention and two others to the control. In addition, the condition of the vaccine storage might have been suboptimal. An ongoing study in Burkina Faso (NéoVac study) is assessing the effectiveness of HBV BDV compared to the conventional hepatitis B vaccination schedule starting at 8 weeks (clinical trials.com).

In its recommendation the WHO recommends the TBDV "preferably within the 24 hours". However, the efficacy of HBV birth dose vaccine when its administration is delayed beyond 24 hours remains unclear, and whether such a delay should be accepted is still a matter of debate. Theoretically the efficacy should be reduced progressively with increasing delay in the first dose administration.[30] Indeed, observational studies found that receiving the first dose beyond 7 days after birth, compared to the BDV, was associated with higher rate of positive HBsAg in infants born to HBV-infected mothers[31] and also in infants born to mothers with any HBV status[32-34]. However, these studies failed to show that delaying the first dose beyond 24 hours but within 7 days is associated with higher risk of infant HBsAg positivity than BDV administration. But the HBV TBDV poses many challenges and its global coverage is estimated to be only 40%[1,17] and is highly heterogenous between regions. The Western Pacific region managed to increase the coverage of BDV from 2% in 2000 to 83% in 2015 which was credited to a regional commitment and goal for control of HBV infection.[35] In sharp contrast, in the African region, only 12 countries have implemented BDV into national policy with reported regional coverage level of only 10%. More worryingly, studies have revealed even lower coverage rates within 24 hours of birth than nationally reported data. For example, a study in The Gambia found that, between 2004 and 2014, despite BDV being part of the national policy, only 1.1% of newborns received their first dose of HBV vaccine within 24 hours of birth, 5.4% by day 7 and 58.4% by day 28.[36] This finding of low coverage in The Gambia, was replicated by another study which found that only 9% of infants received HBV BDV and the median time to "birth dose" vaccination was 11 days (IQR 6-16 days).[37] Heterogeneity in interpretation by health care workers of the definition of a timely birth dose vaccination may also contribute to this disparity.

2. HBIG

The addition of passive immunisation with HBIG increases the chance of controlling HBV MTCT, from around 70% with TBDV alone to 90% when used in combination.

HBIG, in addition to TBDV has been found to be cost-effective in some high or upper middle-income settings, including China were it has been successfully implemented to high levels.[38-40] However, the use of HBIG is very variable. In some settings, like China, UK and USA, it is given to all children born to all HBsAg positive mothers. Whereas in some other settings, like Taiwan, free HBIG is offered only to hepatitis B e antigen (HBeAg) positive mothers who have higher risk of MTCT with TBDV alone.[41] On a global scale, however, coverage is low and HBIG is not a universal WHO recommendation given its high costs, need for cold chain and supply and safety (blood product) issues. Given the associated costs and logistical requirements, it is likely to remain a supplementary intervention to reduce the risk of perinatal transmission, in selected settings. Furthermore, emerging data suggests that HBIG does not provide additional protection, compared to birth dose alone, in infants born to mothers who are HBeAg negative with low viral loads.[10,23]

3. Peripartum antiviral therapy

The risk of HBV MTCT is closely related to high HBV DNA levels usually over 200,000 IU/ml. Data mainly from Asia have confirmed the efficacy and safety of peripartum antiviral therapy using tenofovir disoproxil (TDF) in addition to TBDV and HBIG to control HBV MTCT in mothers with the highest risk of HBV MTCT.[42-44] The 2016 study by Pan and colleagues from China

provides strong evidence to support the efficacy of this strategy.[45] This open labelled randomised trial of 200 HBeAg-positive mothers with HBV viral loads over 200,000 IU/ml, showed a significant reduction in rates of MTCT among those who were treated with TDF (in addition to TBD and HBIG) during the last trimester of pregnancy versus those who received standard passive (HBIG) and active (TBDV) immunisation alone (rate of HBV MTCT in intention to treat analysis: 5% versus 18% (p = 0.007) and in per protocol analysis: 0% vs 7% (p=0.01)). However, current coverage of HBV peripartum antiviral therapy on a global level is still low and limited to experienced hepatology centres in high-income countries. Peripartum antiviral treatment now forms part of international guidelines including EASL and AASLD [46,47] but is not yet part of the WHO recommendations, although this is being reviewed.

In low-income endemic countries systematic treatment of all HBsAg-positive pregnant women irrespective of HBV viral loads has been raised in order to simplify treatment evaluation without the need for viral load testing.[48] However, this strategy is highly questionable in countries where the number of infected pregnant women is high, proportion of pregnant women with high viral load is low and the related cost-effectiveness of such a strategy remains uncertain.[49]

What remains to be done?

1. Strategies to increase TBDV

The reasons for the low coverage of TBDV are multifactorial. The scale-up and delivery of TBDV to ambitious global target levels poses financial and logistical challenges, particularly in sub-Saharan Africa, due to the high fertility rate and number of out of hospital births.

Furthermore, the perceived need for cold chain, lack of awareness and education and lack of integration of the TBDV within maternal child health programmes have all been identified as barriers.[50] Despite the many challenges to the delivery of TBDV, there has been progress and innovations in some settings, which provide opportunities and lessons to be learnt and for possible translation into other regions.

A recent study showed HBV TBDV coverage was positively correlated with institutional delivery rates and skilled birth attendance rates, both worldwide and in the African, South-East Asian and Western Pacific Regions.[51] A recent multi-centre study assessed barriers to TBDV across 78 health facilities in 5 African countries at various stages of introduction of TBDV policy. Among the main barriers the authors identified the lack of outreach programmes to cover out of hospital births, TBDV given at discharge from health facility, absence of weekend vaccination services and low staff awareness about safety of BDV.[37]

Overcoming the challenge of high out-of-hospital births and unassisted births is likely to be difficult in the African region. However, such an approach is likely to have an overall positive impact on maternal and newborn health which will extend beyond facilitating the administration of TBDV. In China, increasing the number of health facility based births was done through establishment of insurance programmes to allow all pregnant women to have access to birthing facilities and this was demonstrated in China to have contributed to improved TBDV coverage rates.[32]

Outreach services for vaccine delivery for out-of-hospital births:

Innovative vaccine tools:

Compact prefilled auto-disposable device (CPAD):

An innovative solution in some settings including Indonesia is the use of a compact prefilled auto-disposable device (CPAD) called Uniject to deliver HBV TBDV, which has been found to be safe and effective, increase coverage rates and is cost saving compared to standard multi-dose vials.[52] However, apart from in Indonesia the device has not been used on a national scale, outside pilot studies in Asia and the Western Pacific region. The high cost of the device and sole manufacturer are possible reasons for this. However, the use of such a device for delivery of HBV BDV has never been assessed in the African region. Studies have also looked at the use of the Uniject system for the administration of other interventions like oxytocin and pentavalent vaccines, by minimally trained community workers, with encouraging results.[53,54]

Microneedle patches:

Recently, coated metal microneedle patches (cMNPs) and dissolvable microneedle patches (dMNPs) that deliver adjuvant-free hepatitis B vaccine to the skin in a simple-to-administer manner have been developed and positively assessed in mice. This technology is still under development and has never been assessed in humans.[55]

Cold Chain Requirements:

Vaccine cold chain requirements have often been reported as a barrier to TBDV, particularly in rural health facilities and in settings where there is a high number of out-of-hospital births. However, data is accumulating on the heat-stability of hepatitis B vaccines raising the possibility of a controlled temperature chain (CTC) strategy, which is one that allows vaccines to be kept outside of the cold chain for a limited time period. A review by the WHO has shown

that most HBV vaccines are thermo-stable up to 45 °C for one week, and up to 40 °C for several weeks.[56] A survey of 25 countries in the Western Pacific and African regions, found that 72% of responding countries thought that a CTC licenced HBV vaccine would help with the provision of BDV, through helping facilities with cold chain restraints as well as to reach out-of-hospital births.[57] However, cost of the CTC licenced vaccines would determine their decision with 60% only willing to accept a price of less than $0.50 per dose. A recent modelling study estimated that a CTC strategy would impact on hepatitis B related burden of disease through increasing coverage of timely birth dose vaccination and be cost-effective, or even cost-saving, in most world regions.[58]

Cost:

The cost of monovalent HBV vaccine, although inexpensive (US$0.20 per dose) still remains a barrier to wide-scale implementation as the cost implications to the country is much higher than just the cost of the vaccine itself and include infrastructure and systems for delivery of the vaccine. Although in most countries TBDV has not been supported by funding agencies, The Global Vaccine Alliance (GAVI), has recently expressed conditional support of the HBV TBDV in their 2021-2025 strategy subject to replenishment of funding.[59] This is likely to have an impact on the number of countries who introduce it into national policy over the coming years.

Monovalent BD vaccination:

Monovalent TBDV is available in single dose or multidose (up to 10 doses per vial). Many countries in Africa have adopted a multi-dose vial vaccination policy.[37] However, vaccinator reluctance to open multi-dose vials if there are only a few births, due to perception about wastage of doses, has been found to be a barrier to TBDV coverage.[57] Whether this could be

overcome by education of staff administering vaccinations or whether single dose monovalent vaccines should be purchased for all births or for use in facilities with low birthing rates remains to be explored.

Education:

Integral to all these efforts is improved health promotion aimed at both health providers and parents in order to increase awareness about the importance of administering hepatitis B vaccine within 24 hours of birth. Empowerment of women and equipping them with the knowledge and tools for seeking TBDV could increase uptake of interventions. A study of 147 health facilities in The Philippines, a country which introduced a national TBDV policy in 2007, found that the coverage of HBV TBDV was lower amongst neonates born in private hospitals compared to those born in government clinics or government hospitals (50%, 90%, 87%, p = 0.02).[60] The reasons surrounding this low coverage included failure to provide TBDV in the health facility, poor knowledge or training and patients being charged for TBDV, despite it being available for free through the national EPI programme. This highlights that in countries where there is a substantial private sector, policy and education need to be co-ordinated across public and private sectors.

Further research is needed about the optimal method of increasing coverage of HBV TBDV in a method that is acceptable, feasible and cost-effective, particularly amongst rural or out-of-hospital births.

2. Systematic antenatal screening for HBsAg among all pregnant mothers.

Systematic antenatal screening for HBsAg is recently recommended by WHO in all countries with a prevalence over 2%.[61] Unfortunately this does not form part of national policy in many countries, particularly in the African region and many women remain undiagnosed through pregnancy, missing an opportunity for intervention. Systematic screening would provide an ideal opportunity to identify mothers at high risk of MTCT, allowing women to be offered the appropriate education and tailor interventions to reduce HBV MTCT. Antenatal screening for HIV has reached high coverage rates in many countries and therefore the addition of HBsAg testing should not add a major incremental burden on health systems. The availability of low-cost rapid point-of-care tests for HBsAg, which have been shown to have high specificity and sensitivity in the field settings[62], should be used for HBV screening at all levels of health facility, especially in low-income countries.

3. Simplification of diagnosis and risk stratification of HBV infected mothers

Although there are now intervention options for virtually eliminating HBV MTCT with the triple combination of TBDV, HBIG and peripartum antiviral therapy, such a strategy requires risk stratification of mothers at high risk of HBV MTCT. The current standard method to risk stratify includes testing for HBeAg and/or HBV viral load quantification; high-income countries base their intervention on HBV DNA levels. However, HBV DNA measurement is currently costly and requires high quality laboratory facilities and trained staff. The new HBV DNA GenXpert cartridges developed by Cepheid at low cost represent a good alternative to the standard HBV DNA systems but need to be validated in Africa.

Most women tested positive for HBeAg have high HBV viral load and are considered at risk of HBV MTCT. HBeAg rapid point-of-care testing should contribute to improving prevention of HBV MTCT. However, to data, the few commercialised rapid diagnostic tests for the detection

of HBeAg (Standard Diagnostics Inc., Gyeonggi-do, Republic of Korea); Insight (Tulip Diagnostics Ltd., Goa, India); and OneStep (AMS UK Ltd., Antrim, UK)) have low analytical sensitivity compared to the laboratory-based chemiluminescent immunoassay [63].

Simplification of risk stratification would allow for targeted HBV PMTCT interventions to be rolled out on a population level in low-income countries or rural settings where there is limited access to laboratory facilities. Whether HBeAg is a good marker of HBV viral load in African HBV-infected patients is still uncertain. However, if confirmed to be an accurate marker of high viral load, it could be used instead of HBV DNA measurement to select pregnant women for antiviral therapy. Hepatitis B core-related antigen (HBcrAg) levels, strongly correlated with HBV viral loads[64] has been also found to be an accurate tool to discriminate clinically relevant HBV DNA levels in African patients; in patients with chronic HBV infection the sensitivity and specificity to diagnose high HBV DNA levels (> 200,000 IU/ml) was 91.4% and 93.2%, respectively.[65] Therefore, HBcrAg levels, which can be measured by a serological test at a relatively low cost (<15 USD), deserves to be validated in pregnant women, to select women for peripartum antiviral treatment.

4. Filling data gaps particularly in Africa

Prevention of HBV MTCT is an underestimated public health issue in Africa and remains a neglected field of research for many years. As underlined in the WHO guidelines for the management of chronic hepatitis B[66] and recent international review commission,[67] there is an urgent need for more research into HBV MTCT, particularly in the African region. Currently, strategies for the prevention of HBV MTCT are mainly built on data from Asian and Western studies.[43,45,68,69] In the African region, the prevalence of HBsAg among pregnant women has

been widely documented, although in the absence of a national antenatal screening programme for HBV, these data are often not nationally representative. There is also limited and conflicting data on the proportion of women at high risk of HBV MTCT (HBeAg positive/High HBV DNA levels) and efficacy of HBV PMTCT interventions. Furthermore, longitudinal data on the rate of HBV MTCT stratified by both HBeAg and HBV viral load is lacking. This lack of high-quality data, in the African region is proving an impediment to public health action and makes accurate policy planning challenging. For example, many governments in Africa are unsure whether a scale-up of TBDV is needed to achieve HBV elimination, what impact it would have and the associated cost- effectiveness of such an intervention.

5. Opportunities for synergy with other health programmes

The international consensus seems to be a move away from purely vertical programmes, where possible, back towards more horizontal programmes of integrated health care delivery.[70] Along with the lack of a global funding mechanism for viral hepatitis, the development of another vertical programme, solely to address HBV epidemic is unlikely to be appropriate. Rather, extending existing efforts to address this high-burden condition, whilst incorporating other programmes seems a more plausible solution. In this regard HBV is fortunate as it straddles many components of existing health systems; with strong synergies with HIV treatment, blood safety and maternal and child health – which should be capitalised on. Integration into these existing health systems is likely to help both financially and overall to population health. It would facilitate delivery of HBV PMTCT interventions and leverage

existing infrastructure that has already been developed for HIV, particularly in sub-Saharan Africa. However, the acceptability, capacity and funding of such shared platforms for both the population and members of the health community need to be explored. Particularly, issues around potential stigma should be minimised.

The effectiveness of package of simplified interventions integrated in existing health care services need to be assessed for the prevention of HBV MTCT in LMIC.

Conclusions

How individual countries move towards elimination of HBV MTCT will vary depending on local epidemiology, financial implications and existing healthcare infrastructures, and importantly political will. The main challenges are envisaged in low-income, high burden settings, particularly in the African region. The development of a carefully constructed strong national hepatitis action plans which incorporate HBV PMTCT into national strategy is needed and ensuring that all populations, whether in rural or urban settings get equal access to HBV PMTCT interventions is critical. This is likely to require a coordinated approach between immunization services and maternal health services, expanding vaccine management systems, innovative outreach approaches to provide vaccine for home and non-medicalised births and a strong political commitment to eliminating HBV MTCT.

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