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## Mother-to-child transmission of hepatitis B virus in Africa: is elimination feasible?

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### *The size of the problem*

Malaria, tuberculosis and HIV dominate our thinking when we are confronted with the question of the major infectious disease killers worldwide. In fact, whilst these infections are very important, there are a group of viruses which have been shown to be as significant in terms of their impact on global health. The global burden of diseases study published in 2012 in the *Lancet* showed HIV to be the cause of 1.47million deaths/year (yr) worldwide, tuberculosis caused 1.2 million deaths/yr, malaria 1.24 million deaths/yr and 1.3 million deaths/yr were the result of chronic viral hepatitis infection (1). Around 800,000 die from the complications of hepatitis B virus (HBV) infection, with the remainder attributed to hepatitis C virus infection.

Africa and Asia have the highest prevalence of HBV worldwide, with >8% seroprevalence of active hepatitis B infection (HBsAg positivity) (Figure 1). According to the WHO

approximately 12% - 240 million people of the two billion who have been infected (30% of the world's population) - have active hepatitis B infection. The long-term sequelae of HBV infection include liver cirrhosis and hepatocellular carcinoma (HCC or primary liver cancer). Of those who are infected approximately 40% of men and 15% of women with perinatally acquired infection will die of liver cirrhosis or HCC (2). In Africa HCC is the second most common cancer in men and is the third most common cause of death from cancer. It has previously been shown that most Southern Africans with HCC present very late in the course of the disease, when curative therapy is not possible and our recent data confirms this. Many will never have been diagnosed with HBV, nor had access to therapy. But possibly the most surprising fact about HBV is that we have had a safe and effective vaccine to prevent infection since 1981.

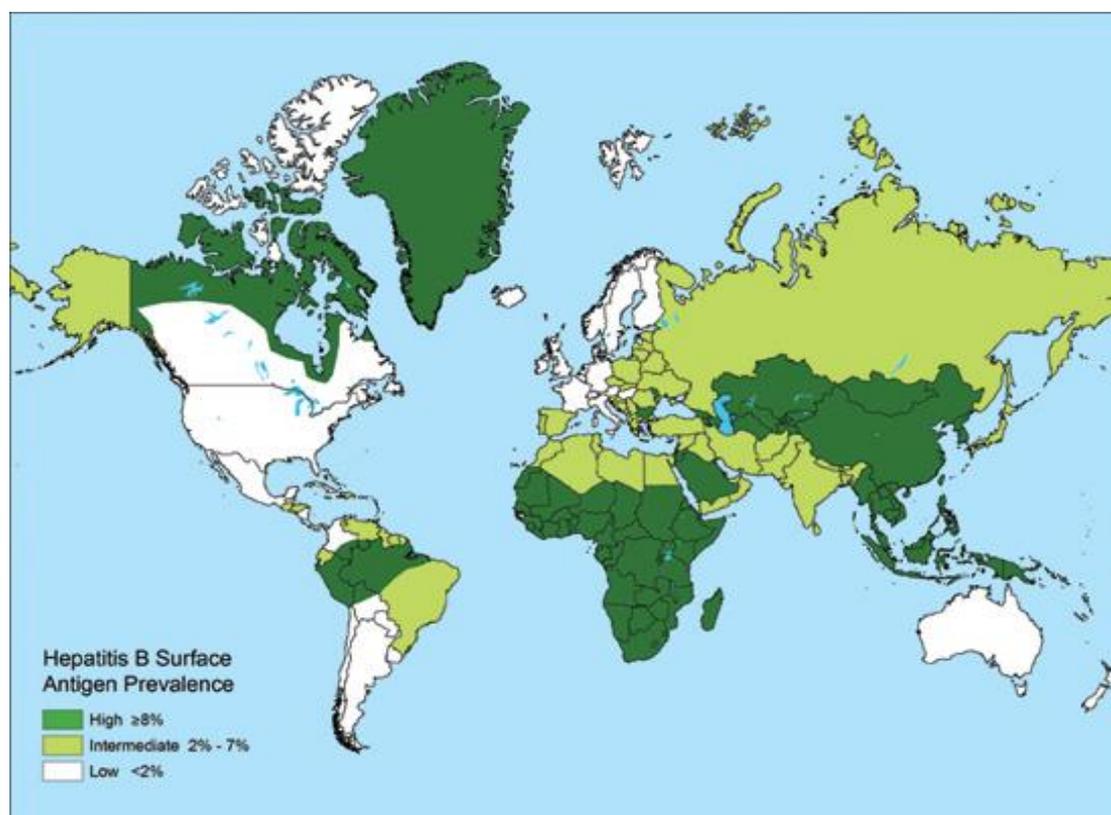


Figure 1. Hepatitis B surface antigen prevalence

### *Hepatitis B: the virus and its effects*

Hepatitis B virus is part of the Hepadnaviridae family. It has a small partially double stranded DNA genome, only 3.2kb. The virus produces many isolated surface proteins, rods and spheres, which act as a decoy for the virus and which mop up antibody. Ten different genotypes (A-J) have been identified across the world. Validated rapid HBsAg tests are available (3) and are a cost-effective and reliable way to screen for HBV in Southern Africa. For those at risk of complications antiviral therapy (ART) is used to control HBV replication and reduces the risk of developing cirrhosis and hepatocellular carcinoma. Whilst HBV is a DNA virus it undergoes a reverse transcriptase step during its replication cycle. Some of the drugs which act on HIV are also active against HBV e.g. lamivudine and tenofovir. HBV cannot yet be cured. Once infected with HBV, the virus forms its own 'chromosome' within the hepatocyte called

covalently closed circular DNA (cccDNA), which provides the template from which further HBV virions can be produced.

The natural history of hepatitis B is fascinating in its unpredictability. Infection may go through phases of immune tolerance, where liver damage is minimal; then switch unexpectedly to an active infection resulting in fibrosis and even cirrhosis. The damage being fuelled predominantly by the immune system rather than the virus itself. In other patients, infection may remain silent until presentation with enlargement of the liver secondary to the development of liver cancer. Chronicity is directly related to time of infection – 90% of infants and 30-50% of children aged 1-5 years will develop chronic disease, whilst 5% of adults will remain chronically infected (Figure 2).

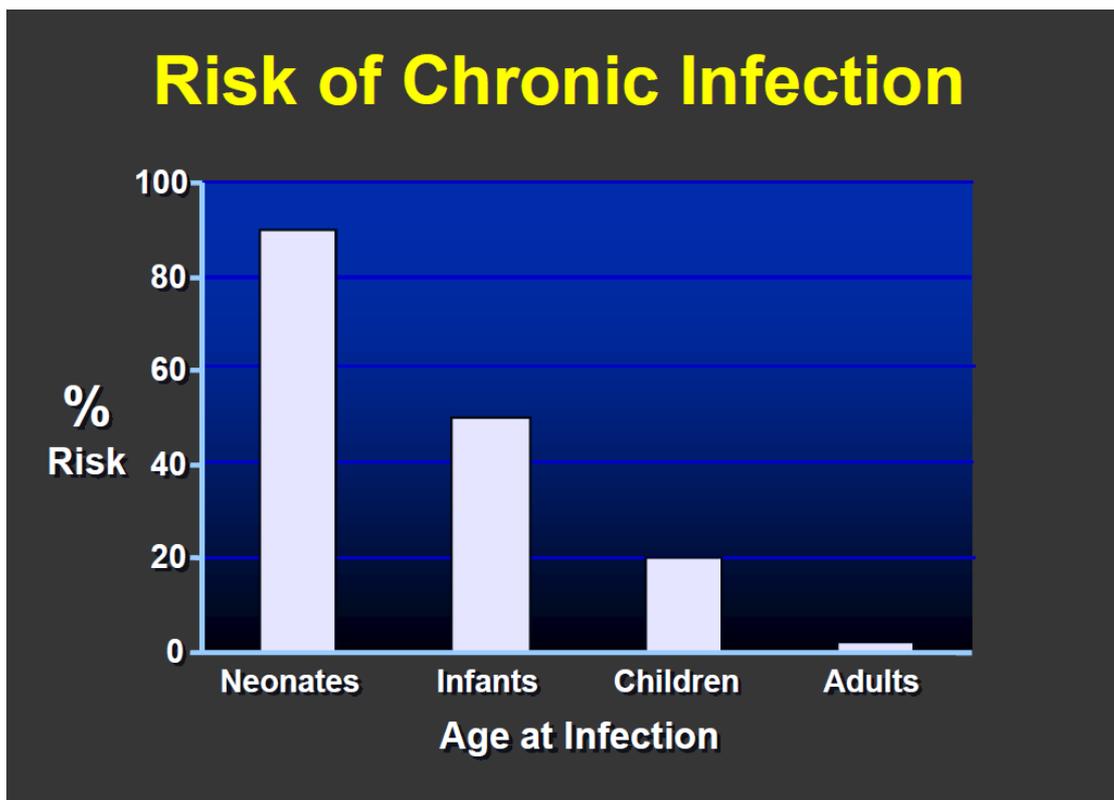


Figure 2. Risk of chronic infection

Mother-to-child transmission (MTCT) is the most common route of transmission in high prevalence areas. Those infants most at risk are those whose mothers have high HBV viral loads and produce the protein HBeAg (so-called HBeAg positive). Transmission can also

occur through sexual contact (most common in low prevalence areas), use of unclean needles and other injection equipment where sterilised medical equipment is not available or during unsafe drug use, blood products or through household contact.

## ***Addressing the problem***

The holy grail of infectious disease public health is eradication. This has been defined by the Ernst Strungmann Forum on Disease Eradication in the context of Global Health in the 21<sup>st</sup> Century as 'The absence of a disease agent in a defined geographical area as a result of deliberate control efforts'. There are certain criteria which need to exist before a disease can be considered for eradication: i) biological feasibility (Table 1 details the specific factors), (ii) an adequate public health infrastructure, (iii) sufficient funding, and (iv) sustained societal and political will. Experience has taught that 'eradication' is often an elusive goal. For hepatitis B this is the case, at least until the availability of curative therapy. But as the crux of perpetuating infection in a community is HBV MTCT, perhaps the way in which the greatest impact can be had is through the elimination of HBV MTCT. Is this a feasible goal?

### ***Box 1. Specific factors for biological feasibility***

Biological feasibility

- Effective intervention to interrupt transmission
- Practical sensitive and specific diagnostic tools
- Humans must be essential to the life cycle
- Not be a non-human reservoir/nor amplify in environment

### ***MTCT Transmission of HBV***

MTCT or vertical transmission is defined as hepatitis B surface antigen (HBsAg) positivity at 6 to 12 months of life in an infant born to an infected mother. Without prophylaxis the risk of infection in the infant is high. The transmission rate for the HBeAg positive is around 70-90% and for the HBeAg negative mother around 10-40%. Transmission can occur intrauterine, during delivery or post-delivery.

### ***Prevention of HBV MTCT***

There are three different prevention strategies available to prevent HBV MTCT.

#### **1. Vaccine**

The cornerstone of preventing HBV MTCT is active immunization at birth. HBV vaccine was the first available vaccine to prevent cancer and the first recombinant vaccine. The efficacy of HBV vaccine has been shown at an individual and population level. In a meta-analysis of the effectiveness of HBV vaccine compared with placebo/no intervention,

vaccine reduced hepatitis B transmission (Risk Ratio 0.28, 95%CI 0.20 to 0.40) (4). Another study showed 94% (95%CI 77-99%) vaccine efficacy in African adolescents vaccinated in infancy. In Taiwan the proportion of children who were carriers of HBsAg decreased from 10% in 1984 to 0.9% in 2009 (5). There was also a 70% reduction in the incidence of HCC in adolescents and children. The vaccine is safe and reports of an association with multiple sclerosis and autism have never been substantiated.

By 2012, 181 countries had implemented universal HBV vaccination with global coverage estimated to be greater than 79% (6). However, African countries have lower HBV infant vaccine coverage (only 72% coverage for the whole continent in 2012).

The WHO recommends commencing vaccination at birth, since vaccination later in life leaves the infant vulnerable to HBV MTCT. In much of Africa, however, the first dose is given at around 6 weeks of age, predicated upon findings that most African pregnant women with chronic hepatitis B were of low infectivity (HBeAg negative). More recent data shows that HBeAg prevalence may be higher than previously thought. In a South African study of HIV-infected women, the HBeAg prevalence was 43% and the rate of HBV MTCT transmission was 28% (7). A Malawian study in HIV-infected women and their HIV-exposed uninfected infants showed that 5% of women were positive for HBsAg and among those, 38% were at high risk of transmission (positive for HBeAg) (8). In that study, the rate of transmission of HBV was 10% and all infected infants were born to HBeAg positive women (8).

Although HBV vaccination in South Africa has been administered at 6 weeks, there has been an impact on HBsAg prevalence in children in South Africa. The HB vaccine was introduced into South Africa almost two decades ago, when the HBsAg prevalence in children was approximately 10%. One South African study from the north of South Africa, found that in children between the ages of 5 and 24 months the overall prevalence of HBsAg was 0.9% (9). Another cross-sectional study from South Africa comparing a pre-vaccination cohort to a post-vaccination cohort based on their age showed that the overall prevalence of HBsAg decreased from 4.2% in the pre-vaccination cohort to 1.4% in the post-vaccination one (10).

## 2. Hepatitis B Immunoglobulin

Hepatitis B immunoglobulin (HBIG) reduces the risk of HBV transmission and is used in resource rich settings where pregnant women have high viral loads. A meta-analysis of the benefit of adding immunoglobulin to the vaccine for the prevention of HBV MTCT has shown that compared with placebo/no intervention, HBV vaccine plus HBIG significantly reduced hepatitis B occurrence (Risk Ratio 0.08, 95% CI 0.03 to 0.17). However, HBIG is expensive, scarce and has stringent storage conditions. These logistical problems reduce its usefulness in resource poor settings and as a result HBIG is not available to the majority of African women.

## 3. Antiviral therapy during pregnancy

Even where women have access to birth dose vaccine and HBIG there remains a 5-10% failure rate. This occurs in women with high HBV viral loads. For these women, ART during pregnancy has been shown to significantly reduce the risk of MTCT. Where mothers do not need ART for their own health, therapy can be used during pregnancy with the primary aim of reducing the risk of MTCT of HBV. Tenofovir, lamivudine and telbivudine are nucleos(t)ide inhibitors which act as chain termination in DNA elongation and can be administered from 28 weeks gestation. Many of the early studies were performed using lamivudine and whilst the benefit of using this drug to reduce transmission was evident, it has been associated with the emergence of resistance because of its low genetic barrier. Tenofovir has a high barrier to resistance and has been used extensively in the setting of HIV. In studies of tenofovir in pregnancy, significant reductions in HBV viral load and risk of transmissions in treated mothers were reported (11,12). No obstetric or adverse events were noted in these studies. So whilst ongoing caution is advised; the lack of adverse event data in women and their infants exposed to ART during pregnancy to date are reassuring (13).

The use of ART in pregnancy has dramatically altered the risk of HBV MTCT. This is a prevention modality which could feasibly be rolled out across Southern Africa as part of a strategic plan to eliminate HBV MTCT. Tenofovir is part of many first line HIV regimens across Southern Africa and is

therefore available in many primary care, community clinics. Unfortunately in many areas this drug may not be available to those who are HBV monoinfected. Work is needed to ensure that tenofovir is made available to those who have chronic HBV.

## *Infrastructure*

The existence of adequate health care infrastructure is a prerequisite for eliminating an infectious disease. Health related development assistance has increased over the past decade as funding for HIV scale-up has had knock on effects on funding for other health related programmes e.g. malaria. Major donors have recognized the importance of investing in health systems and with it has come investment into training and capacity building. The infrastructure which supports HIV management includes rapid testing for HIV, identification of patients who need therapy, follow-up of patients including supporting adherence and monitoring for adverse events, whilst also providing screening for complications of disease. These are the same steps needed for the management of HBV. So whilst there is undoubtedly a need for further investment to support the management of HBV, the backbone of this infrastructure already exists. Studies are needed to model the economic impact of managing HBV and different strategies to reduce HBV prevalence in Africa.

In conclusion, addressing the problem of HBV deserves attention. The tools to dramatically reduce HBV MTCT are available. Birth dose HBV vaccine, increasing coverage of HBV vaccine, screening women for HBV and starting ART in those who need it is technologically feasible. What is clear is that strategic investment now could see the eradication of HBV MTCT in Africa and ultimately potentially the elimination of this major public health problem.

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