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Prescribing antiviral drugs to people with hepatitis B virus during pregnancy could lower mother-to-child transmission rates.

Halting mother-to-baby transmission

To eradicate hepatitis B, transmission of the virus from mothers to their children must be stopped. Research shows that giving antiviral drugs during pregnancy might further reduce infections. **By Liam Drew**

"I feel very blessed," says Alice Chan. Chan was born and raised in Hong Kong and emigrated to the United States in 1977. In 1983, in California, she became pregnant with her first child. Knowing how common chronic hepatitis B virus (HBV) infections were in Asian immigrants, Chan's obstetrician screened her for the virus.

When she tested positive, it sparked a familial reckoning. Chan discovered that her mother had kept her own HBV infection secret, and that it was probable that her mother had infected her. Processing this would take years, but it could wait. "At that time, I was not even thinking about my own health," says Chan. "I just worried about my newborn."

Fortunately, Chan's diagnosis offered her unborn son a chance to escape infection.

HBV passes between people through bodily fluids such as blood, semen and even tears. How often the virus passes from mothers to their offspring *in utero* is uncertain: it can, but this seems to lead only rarely to persistent infections. As an infant is born, however, they are inescapably exposed to their mothers' blood and other potential sources of infection, and the risk of transmission is high.

The consequences of infection at birth are grave: 90% of babies infected at birth develop chronic infections, which typically last a lifetime[1]. By contrast, infections in older children become chronic only around 30% of the time, and in adults only 5%.

Chronic HBV infection drastically increases the likelihood of developing liver fibrosis, cirrhosis and cancer. Normally, these conditions manifest in middle age, although they can occur in childhood. Across all individuals with chronic infections, the lifetime risk of developing liver cancer is 25–40% — but there is evidence that perinatal infections are associated with higher rates of liver disease than are chronic infections established later.

When Chan gave birth to her son, her obstetrician immediately disinfected his eyes, this being a potential viral entry route. Then, he injected the baby with immunoglobulin against HBV (HBIG) and vaccinated him.

In 1983, these latter two treatments were still under investigation, but at twelve months of age, and again around his second birthday, Chan's son tested negative for HBV. Three years later, her daughter received the same treatment and likewise avoided infection.

Today, as the World Health Organization (WHO) pushes to eradicate HBV by 2030,

the quest to halt perinatal mother-to-child transmission (MTCT) is becoming increasingly urgent. "Without elimination of mother-to-child transmission, it's impossible to eliminate hepatitis B," says Gonzague Jourdain, an epidemiologist at the French National Research Institute for Sustainable Development (IRD) in Marseille, France.

Around 300 million people worldwide currently have HBV infections, and the virus accounts for an estimated 820,000 deaths every year. But the advent of effective vaccines in the 1980s initiated a decades-long decline in new infections, and HBV elimination is now a tantalizingly achievable goal – although not necessarily by 2030.

The success of vaccination so far is, however, with regional variations, thanks largely to a global immunization programme in which infants are given an HBV vaccine along with inoculations against four other diseases. Crucially, such immunization commences at 6–8 weeks of age – too late to reverse an infection seeded at birth.

Consequently, the proportion of HBV infections caused by MTCT is rising. According to a 2016 modelling study[2], the fraction of new chronic HBV infections attributable to MTCT has grown steadily from 16% in 1990, and is set to reach 50% by 2030. "In high endemic settings all over the world, mother-to-child transmission is the residual route of transmission," says Shevanthi Nayagam, a hepatologist and epidemiologist at Imperial College London, who led the study.

The treatment Chan's children received – both HBIG and vaccination within 24 hours of birth – is an effective intervention, capable of reducing perinatal infections by more than 90% (ref. 3). And studies in the past decade have shown that MTCT rates could be lowered even further by adding a third layer of protection – giving antiviral drugs during pregnancy.

The key issue now, if the world is to respond effectively to the evolving epidemiology of HBV, is implementation. There are logistical and financial challenges to delivering MTCT prevention measures, and the unmet need is often most acute in countries with constrained resources. "Hepatitis B is endemic in low- and middle-income countries, more than it is in higher-income countries," says Chloe Thio, an immunologist at the Johns Hopkins University School of Medicine in Baltimore, Maryland. "Many of the women who are infected don't have good access to health care. A lot of them don't know they're infected."

Three layers

Widespread recognition of MTCT's contribution to endemic HBV emerged in 1975, when researchers showed that around 40% of babies born to HBV-infected mothers in Taiwan were infected by 6 months of age.

In the absence of vaccines, initial efforts to curb MTCT involved giving newborns HBIG, which is extracted from the blood of people with high counts of antibodies against HBV. HBIG evokes transient immunity by stimulating recipients' immune systems to fight the virus. In trials, HBIG has reduced MTCT by as much as 70% (ref. 4).

Vaccines offer sustained active immunity. But when the first HBV vaccine was approved in 1981, specialists feared that vaccinating newborns might increase the risk of chronic infections by inducing tolerance to HBV antigens. Ultimately, this concern was unfounded. But when Chan's son was treated in December 1983, the landmark trial[3] showing the efficacy of dual HBIG and vaccine administration was still four months from publication.

That study – by researchers at the University of Hong Kong – found that if the children of mothers with high HBV loads were given a placebo, nearly 75% were found to be infected at six months of age. In infants vaccinated within 24 hours of birth (with follow-up doses at 1, 2 and 6 months of age), this number fell to 21% – a similar efficacy to those given HBIG alone. But if a dose of the vaccine was given at birth alongside one dose of HBIG, the infection rate fell to roughly 7%.

Maternal viral load is important. HBV infections can be either dormant, with low circulating virus levels, or active, generating abundant blood-borne virus particles. It is now established that perinatal MTCT occurs predominately in mothers with active infections and viral loads of greater than 200,000 international units per millilitre (ref. 5). Now, vaccination at birth is recommended for all newborns by the WHO. Meanwhile, in health-care settings where it is available, HBIG is indicated specifically for infants born to mothers with high viral loads.

Troublingly, however, vaccination at birth plus HBIG performs less well in real-world settings than in clinical trials. In the worst cases, mothers with high viral loads still transmit HBV 30% of the time (ref. 6). Many factors contribute to this, says Jourdain, including the challenge of administering treatment quickly after birth, and the need to store and handle the temperature-sensitive materials appropriately.

Over the past decade, researchers have sought to further thwart MTCT by also prescribing antiviral medicines during pregnancy. Trials have now shown that administering such drugs from the third trimester onwards reduces viral loads to such an extent that perinatal infections are rarer than with the HBIG and vaccine treatment alone.

The antiviral drug of choice is tenofovir, which was developed initially as part of HIV therapy. Trials show that tenofovir reduces residual MTCT by at least 70% – and that might be understating the benefit. In 2018, Jourdain published a Thailand-based study which used the triple combination of maternal tenofovir prophylaxis, then HBIG and vaccination in the infants[7]. None of the 147 babies became infected.

Interpreting this work was complicated by the fact that only 3 of the 147 infants in the control group (who were given HBIG and the vaccine at birth, but whose mothers were given a placebo in place of tenofovir), were infected. Jourdain says he underestimated how effective the HBIG and vaccine treatment would be when done in a tightly controlled trial setting. Still, he maintains that the data are "very consistent with the idea that antivirals are useful – because at time of delivery, the viral load is so low, the risk of transmission is very low".

Tenofovir's effectiveness is supported by a review and a meta-analysis of available HBV antiviral trials, led by Yusuke Shimakawa, an epidemiologist at the Pasteur Institute in Paris, that was commissioned by the WHO[8]. "We found a sufficient number of papers for tenofovir therapy," Shimakawa says, "and all of these showed that this treatment is effective in preventing mother-to-child transmission". The analysis also found no adverse events associated with the drug. This work underpinned the WHO's decision to recommend tenofovir prophylaxis in July 2020.

Workable solutions

Although it exists globally, HBV is most prevalent in many low- and middle-income countries, especially in Africa and Asia. Across these nations MTCT elimination programmes vary hugely, partly because of epidemiological considerations, availability of health-care resources and political prioritization.

Among the most successful are those in Taiwan and the Chinese mainland, where HBV has been prioritized since the 1980s and each preventive measure has been quickly and widely implemented. In Taiwan, for example, HBV prevalence fell from 9.8% in 1984, when universal vaccination was initiated, to 0.5% in 2014 (ref. 9). Rates of MTCT, which stood at 40% in 1975, have also plummeted[10]. Introducing screening during pregnancy, coupled with administering HBIG and the vaccine at birth, reduced rates to around 10% (ref. 9). Then, in 2015, a multi-centre study[11] in Taiwan showed that adding tenofovir prophylaxis could decrease the rate of MTCT to just 1.5%. Antivirals were recommended for use during pregnancy in a 2019 national HBV policy statement.

But in many countries, HBV reduction is lower on the political agenda and health-care resources are more scarce, so much remains to be done.

Thio, for example, works in the Thailand–Myanmar border region, attempting to improve the outlook for the large, underserved refugee population there. But it is in Africa, where efforts to prevent MTCT remain limited, that much attention is now focused.

Historically, MTCT has been a low priority in sub-Saharan Africa because – for reasons that are incompletely understood – HBV viral loads during pregnancy tend to be much lower in this region than in Asia[12]. Therefore, the baseline risk of MTCT in Africa is lower than in Asia.

With community transmission in children being the much greater source of chronic infections, it made sense for African countries to focus on implementing the WHO's Expanded Programme on Immunization, which protects children from HBV from 6 to 8 weeks, but does not affect MTCT. Pertinently, vaccination programmes across Africa rely heavily on Gavi, The Vaccine Alliance – a well-backed private–public global health partnership based in Geneva, Switzerland – which, since 2000, has supported this programme but not birth-dose HBV vaccines.

This immunization programme has achieved 72% coverage in the WHO African region – still well below the global target level of 90%, but sufficient to cut community transmission and to shift attention to MTCT. "As we shrink childhood transmission, mother-to-child transmission becomes more prominent," says Olufunmilayo Lesi, a hepatologist at the University of Lagos, Nigeria, and viral hepatitis lead of the WHO's global HIV, hepatitis and sexually transmitted infections programmes. "That's where we are now. We're in transition."

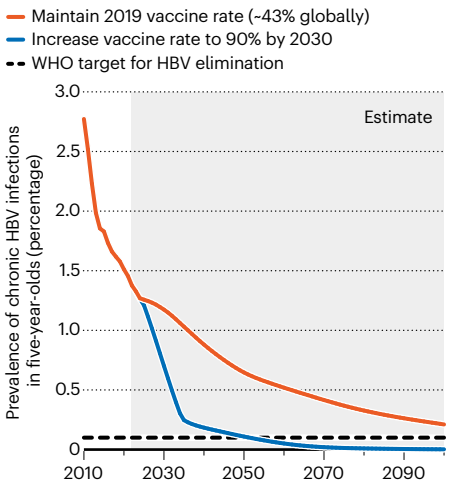
Any plan for tackling MTCT in Africa, Lesi explains, must acknowledge available resources. Most pointedly, widespread use of HBIG is not an option. This human blood product is expensive, difficult to prepare and needs intensive contamination screening and a refrigerated supply chain. "Immunoglobulin is a great thing," says Lesi, "but it is a high-income country strategy."

The current priority is therefore to boost vaccination at birth. And here the statistics are troubling: across the African region, only 6% of infants are vaccinated against HBV within 24 hours. Lesi points to examples of successful expansions of birth-dose vaccine delivery in Botswana, Gambia and Senegal. But it is national policy in only 15 of 47 countries in the region.

A 2021 modelling study[13], co-authored by Nayagam, indicated that globally scaling up birth dose coverage to the 90% target level could prevent HBV claiming the lives of more than 700,000 people born before 2030, with Africa benefiting the most (see 'Vaccination towards elimination'). She is planning a study with health-care workers in Gambia to characterize barriers to implementing vaccination at birth, then to hopefully measure the effects of increasing vaccination rates. Among the local challenges is the fact that roughly half of all births in Africa take place at home, where no medical professional is present to administer the vaccine. Also, many births are in rural areas, where neonatal care services are difficult to access – and vaccine supply chains are notoriously unreliable.

VACCINATION TOWARDS ELIMINATION

Steadily increasing birth-dose vaccination rates to 90% globally by 2030 would bring chronic HBV in 5-year-olds to target levels by 2052.



One cause for optimism is Gavi, shifting its position to support infrastructure for administering the vaccine at birth. However, delays in delivering this policy have been further extended by COVID-19, adding to numerous disruptions to HBV services caused by the pandemic.

Then there are the possibilities offered by antiviral drugs. The attractions of tenofovir prophylaxis are multiple. First, says Lesi, "this is a ridiculously cheap drug because it is an HIV drug" – which also means it is already widely used in African health-care systems. It does not require cold storage. And, unlike vaccines that must be given by a trained professional within a day of birth, this is a pill that can be prescribed to those who are pregnant throughout their third trimester.

Notably, although many women in Africa do not give birth in health-care settings, around 74% receive some prenatal care – which should allow tenofovir to be provided to those who need it. Such a scheme does, however, require another level of infrastructure: birth dose vaccines are recommended for all infants, but tenofovir is recommended only for mothers with high viral loads, necessitating screening for active infection.

The screening gold standard is measuring maternal viral load directly, but this uses sophisticated instrumentation to quantify DNA levels – technology that is unavailable in many health-care settings. The good news is that a second option was validated in 2021.

People with active HBV infection produce the HBV 'e antigen' (in contrast to the 's antigen' present in all chronic HBV infections). In addition to reviewing the effectiveness of tenofovir prophylaxis, Shimakawa and his colleagues also conducted a WHO-backed meta-analysis of whether the e antigen can be used as a marker to detect mothers at high risk of MTCT[5]. They found that it can – a conclusion with significant implications given that cheap, easy-to-use, point-of-care tests for the e antigen are becoming increasingly available.

Thio thinks that administering such tests routinely could be aided by utilizing infrastructure already in place for addressing maternal HIV in low- and middle-income countries. "It's really just adding a test when a pregnant mum comes in to be checked for HIV," she says. "If we could bring hepatitis B diagnosis up to that same level, I think we'll make good progress."

Back in California, after Chan became a mother, she began working with refugee groups to spread awareness of HBV; teaching people about screening, vaccination and maternal-health options; and advocating for better services. She continues this work today.

Chan's young children often accompanied her to community centres. She says that among her happiest and proudest achievements is when her son and daughter went to university, they enlisted in campaigns to inform their fellow students about HBV risk and prevention. Advocacy and action had passed down the generations, not the virus.

SOURCE: REF. 13

Liam Drew is a freelance writer in Kent, UK.

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