Arresting vertical transmission of hepatitis B virus (AVERT-HBV) in pregnant women and their neonates in the Democratic Republic of the Congo: a feasibility study

Peyton Thompson, **Camille E Morgan**[*], **Patrick Ngimbi**[*], **Kashamuka Mwandagalirwa**, **Noro L R Ravelomanana**, **Martine Tabala**, **Malongo Fathy**, **Bienvenu Kawende**, **Jérémie Muwonga**, **Pacifique Misingi**, **Charles Mbendi**, **Christophe Luhata**, **Ravi Jhaveri**, **Gavin Cloherty**, **Didine Kaba**, **Marcel Yotebieng**, **Jonathan B Parr**

Division of Infectious Diseases, Department of Pediatrics (P Thompson MD) and Department of Medicine (J B Parr MD), Department of Epidemiology, Gillings School of Global Public Health (C E Morgan BSPH), University of North Carolina, Chapel Hill, NC, USA; Kinshasa School of Public Health (P Ngimbi MD, K Mwandagalirwa MSPH, N L R Ravelomanana MD, M Tabala MLT, M Fathy MD, B Kawende MD, Prof D Kaba PhD), National AIDS Control Program (J Muwonga PhD), National Blood Transfusion Program (P Misingi MD), Department of Gastroenterology, University Hospital (C Mbendi MD), and Expanded Programme on Immunisation (C Luhata MD), Kinshasa, Democratic Republic of the Congo; Department of Pediatrics, Division of Infectious Diseases, Northwestern University Feinberg School of Medicine, Chicago, IL, USA (R Jhaveri MD); Abbott Laboratories, Abbott Park, IL, USA (G Cloherty PhD); Division of General Internal Medicine, Department of Medicine, Albert Einstein College of Medicine, New York City, NY, USA (M Yotebieng PhD)

Summary

Background—Hepatitis B virus (HBV) remains endemic throughout sub-Saharan Africa despite the widespread availability of effective childhood vaccines. In the Democratic Republic of the Congo, HBV treatment and birth-dose vaccination programmes are not established. We, therefore, aimed to evaluate the feasibility and acceptability of adding HBV testing and treatment of pregnant women as well as the birth-dose vaccination of HBV-exposed infants to the HIV

Correspondence to: Dr Peyton Thompson, Division of Infectious Diseases, Department of Pediatrics, University of North Carolina, Chapel Hill, NC 27599, USA peyton_thompson@med.unc.edu.
[*]Joint second authors

For the French translation of the abstract see **Online** for appendix 1

For the Lingala translation of the abstract see **Online** for appendix 2

Data sharing

Datasets will not be made publicly available because they contain protected health information. However, the authors will share de-identified participant data, alongside the study protocol, statistical analysis plan, and analytic code, upon reasonable request and with approval by an independent review committee (ie, learned intermediary).

prevention of mother-to-child transmission programme infrastructure in the Democratic Republic of the Congo.

Methods—We did a feasibility study in two maternity centres in Kinshasa: Binza and Kingasani. Using the already established HIV prevention of mother-to-child transmission programme at these two maternity centres, we screened pregnant women for HBV infection at routine prenatal care registration. Those who tested positive and had a gestational age of 24 weeks or less were included in this study. Eligible pregnant women with a high viral load (200 000 IU/mL or HBeAg positivity, or both) were considered as having HBV of high risk of mother-to-child transmission and initiated on oral tenofovir disoproxil fumarate (300 mg/day) between 28 weeks and 32 weeks of gestation and continued through 12 weeks post partum. All HBV-exposed infants received a birth-dose of monovalent HBV vaccine (Euvax-B Pediatric: Sanofi Pasteur, Seoul, South Korea; 0·5 mL) within 24 h of life. All women were followed up for 24 weeks post partum, when they completed an exit questionnaire that assessed the acceptability of study procedures. The primary outcomes were the feasibility of screening pregnant women to identify those at high risk for HBV mother-to-child transmission and to provide them with antiviral prophylaxis, the feasibility of administrating the birth-dose vaccine to exposed infants, and the acceptability of this prevention programme. This study is registered with ClinicalTrials.gov, NCT03567382.

Findings—Between Sept 24, 2018, and Feb 22, 2019, 4016 women were approached and screened. Of these pregnant women, 109 (2·7%) were positive for HBsAg. Of the 109 women, 91 (83%) met the eligibility criteria for participation. However, only data from 90 women—excluding one woman who had a false pregnancy—were included in the study analysis. The median overall age of the enrolled women was 31 years (IQR 25–34) and the median overall gestational age was 19 weeks (15–22). Ten (11%) of 91 women evaluated had high-risk HBV infection. Nine (90%) of the ten pregnant women with high-risk HBV infection received tenofovir disoproxil fumarate and one (10%) refused therapy and withdrew from the study; five (56%) of the nine women achieved viral suppression (ie, <200 000 IU/mL) on tenofovir disoproxil fumarate therapy by the time of delivery and the remaining four (44%) had decreased viral loads from enrolment to delivery. A total of 88 infants were born to the 90 enrolled women. Of the 88 infants, 60 (68%) received a birth-dose vaccine; of these, 46 (77%) received a timely birth-dose vaccine. No cases of HBV mother-to-child transmission were observed. No serious adverse events associated with tenofovir disoproxil fumarate nor with the birth-dose vaccine were reported. Only one (11%) of nine women reported dizziness during the course of tenofovir disoproxil fumarate therapy. The study procedures were considered highly acceptable (>80%) among mothers.

Interpretation—Adding HBV screening and treatment of pregnant women and infant birth-dose vaccination to existing HIV prevention of mother-to-child transmission platforms is feasible in countries such as the Democratic Republic of the Congo. Birth-dose vaccination against HBV infection integrated within the current Expanded Programme on Immunisation and HIV prevention of mother-to-child transmission programme could accelerate progress toward HBV elimination in Africa.

Introduction

Viral hepatitis is a leading infectious killer globally, with hepatitis B virus (HBV) alone accounting for nearly one million deaths annually.[1] Despite the existence of an effective

childhood vaccine, the prevalence of HBV infection in sub-Saharan Africa remains unacceptably high. Mother-to-child transmission silently drives HBV endemicity. In the absence of any intervention, 70–90% of mothers with high-risk HBV infection (ie, a viral load 200 000 IU/mL or HBeAg positivity, or both) will transmit the virus to their infants, compared with 10–40% of mothers who are HBeAg-negative.[2] WHO recommends that all infants receive a birth dose of HBV vaccine, preferably within 24 h of delivery, followed by at least two additional vaccine doses.[3] The three-dose series provides a protection level of 95% or more against HBV infection, but breakthrough transmission despite vaccination can occur in infants born to women with high-risk HBV infection.[4,5] In WHO's 2020 guidelines on HBV prevention of mother-to-child transmission, WHO recommends that women with high-risk HBV infection should receive antiviral prophylaxis from the 28th week of pregnancy to delivery or beyond in order to prevent breakthrough mother-to-child transmission.[3,6,7] Most women in lowincome and middle-income countries who are co-infected with HIV and HBV receive tenofovir disoproxil fumarate as part of their antiretroviral regimen. However, the feasibility of providing antiviral prophylaxis for HBV mono-infected pregnant women in low-resource settings in sub-Saharan Africa is not well established. Only one study[8] was done in Burkina Faso, which attempted to address this issue; this study found large gaps in HBV prevention of mother-to-child transmission and did not attempt to leverage the existing HIV prevention of motherto-child transmission programme.

The prevalence of HBV infection in the Democratic Republic of the Congo is 3·3%, with a high prevalence of 2·2% among children younger than 5 years, which correlates to at least 300 000 Congolese children living with chronic HBV infection and at risk for liver disease and premature death.[9,10] Although HBV vaccination has been part of the Democratic Republic of the Congo's Expanded Programme on Immunisation since 2007, the first dose is not administered until 6 weeks of life, which is too late for the prevention of peripartum mother-to-child transmission. Similarly, no screening programmes to identify and treat pregnant women with high-risk HBV infections exist, despite established infrastructure for the prevention of mother-to-child transmission of HIV. The Expanded Programme on Immunisation delivers other birth-dose vaccines (eg, BCG and polio) and so can be leveraged alongside the HIV prevention of mother-to-child transmission infrastructure both to deliver the birth-dose vaccine and to screen and treat women with high-risk HBV infection.[11,12] In this study, we therefore aimed to assess the feasibility of building upon the existing Expanded Programme on Immunisation and the HIV preven tion of mother-to-child transmission infrastructure in Kinshasa, the Democratic Republic of the Congo, as well as the acceptability of this prevention programme in delivery of HBV birth-dose vaccines, and to identify and treat HBV-infected pregnant women at high risk of mother-to-child transmission according to WHO guidelines.

Methods

Study design and procedures

We did a feasibility study implemented over 6 months in the two largest maternity centres in Kinshasa: Binza and Kingasani (both private and not-for-profit clinics; appendix 3 p

8). The two facilities were chosen because of their size and long-standing collaborations with our HIV prevention of mother-to-child transmission team. In collaboration with the Expanded Programme on Immunisation, the required monovalent vaccine doses were acquired and stored within the existing cold-chain system. We leveraged the infrastructure of a pragmatic randomised trial (NCT03048669) of continuous quality interventions on long-term antiretroviral therapy outcomes among pregnant or post-partum women across Kinshasa province, through which we were already screening HIV-infected pregnant women for HBV and hepatitis C virus infections.[13,14]

All pregnant women registering for prenatal services at either of the two clinics were provided with group counselling on HBV and prevention of mother-tochild transmission thereof, and they were invited to be screened for HBV infection. Those who verbally agreed were screened using point-of-care ALERE DETERMINE HBsAg testing (Abbott Diagnostics, Abbott Park, IL). Pregnant women who tested positive were referred for evaluation and inclusion in this feasibility study. To be eligible for prospective follow-up, pregnant women who screened positive for HBsAg needed to meet the following additional criteria: have a gestational age of 24 weeks or less (allowing time for viral load and HBeAg testing and return of results before initiation of tenofovir disoproxil fumarate treatment between 28 weeks and 32 weeks of gestation), have the intention to continue care at one of the two maternity centres throughout the pregnancy and post-partum period, and not be unwell enough to be admitted to the hospital. We obtained written informed consent for the prospective follow-up in the participant's preferred language (ie, French or Lingala). At the time of the study, pregnant adolescents (aged 15–18 years) were considered emancipated minors in the Democratic Republic of the Congo and they were allowed to provide consent. At the time of consent, we used a structured questionnaire to collect information about demographics and clinical characteristics. All women were followed up for 24 weeks post partum, when they completed an exit questionnaire that assessed the acceptability of study procedures.

All participants underwent venous blood collection at baseline to determine their risk status for HBV infection, including HBeAg (Abbott ARCHITECT HBeAg assay, Abbott Park, IL) done at the National Blood Transfusion Center in Kinshasa and HBV DNA (Abbott RealTi*m*e HBV viral load assay, Abbott Park, IL), done at the National AIDS Control Program laboratories in Kinshasa. Baseline kidney function (blood urea nitrogen and creatinine concentrations) and liver function (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) was evaluated in all enrolled women. Women with a viral load of 200 000 IU/mL or more or HBeAg positivity, or both, were considered at high-risk for HBV motherto-child transmission and were further assessed for eligibility for prophylactic treatment with tenofovir disoproxil fumarate.[3,15,16] Women with high-risk HBV infection, without signs of reduced kidney function (glomerular filtration rate <50 mL/min) or abnormal liver function (as determined by the study physician), were initiated on 300 mg/day of oral tenofovir disoproxil fumarate (Gilead Sciences, South San Francisco, CA) treatment between 28 weeks and 32 weeks of gestation and continued through 12 weeks post partum. We ensured that any women with a co-infection of HIV and HBV were on a tenofovir disoproxil fumarate-containing regimen. Details of follow-up procedures for women with high-risk HBV infection are in appendix 3 (p 5). To assess tenofovir

disoproxil fumarate adherence, tenofovir diphosphate concentrations in dried blood spots were measured at the University of North Carolina's Eshelman School of Pharmacy using dried blood spot samples collected from women with high-risk HBV infection at delivery. Tenofovir diphosphate concen trations represent an average of expected adherence over a several month period, as the medication has a long half-life in red blood cells.

All exposed infants were given a birth-dose of monovalent HBV vaccine (Euvax-B Pediatric: Sanofi Pasteur, Seoul, South Korea; 0·5 mL), ideally within 24 h of life. The timing of birth and of vaccination were recorded. Infants were monitored for at least 24 h after receipt of the vaccine, and adverse reactions were recorded. Infants underwent point-of-care HBsAg testing at 24 weeks.

We obtained Institutional Review Board approval from the University of North Carolina at Chapel Hill (number 17–2090) and the Kinshasa School of Public Health (CE/ESP/001/2018) before initiation of this study.

Outcomes

The primary outcomes were the feasibility of screening pregnant women to identify those at high risk for HBV mother-to-child transmission and to provide them with antiviral prophylaxis, the feasibility of administrating the birth-dose vaccine to exposed infants, and the acceptability of the study procedures (ie, maternal blood draw, infant blood draw, infant vaccination, and—for those with high-risk HBV—taking tenofovir disoproxil fumarate). The secondary outcomes were the safety of tenofovir disoproxil fumarate prophylaxis, which was evaluated by screening for adverse events and for the percentage of women who developed an elevated serum concentration of ALT during or after antiviral treatment, and safety of the birth-dose vaccination, which was evaluated by screening for any adverse events among infants who received the monovalent vaccine at birth.

Statistical analysis

To assess the feasibility of viral prophylaxis for women at high risk of HBV mother-to-child transmission, we calculated the following proportions: women who accepted to be screened, women who tested positive by HBsAg screening, HBsAg-positive women who consented for enrolment, eligible women with high-risk HBV infection who accepted tenofovir disoproxil fumarate prophylaxis, and women on tenofovir disoproxil fumarate who adhered to treatment as measured by pill count, viral suppression at delivery (defined as an HBV viral load <200 000 IU/mL), and tenofovir diphosphate concentration in the blood of mothers. Acceptability of the study procedures was further assessed by calculating frequencies of aggregate responses on the exit questionnaire. A predetermined cutoff of 80% reporting the programme to be very acceptable or somewhat acceptable on survey responses was deemed acceptable.

Secondarily, we evaluated the safety of tenofovir disoproxil fumarate prophylaxis by screening for adverse events and the percentage of women who developed an elevated serum ALT concentration during or after antiviral treatment. We also evaluated the safety of birth-dose vaccination by screening vaccinated infants for adverse events. Timeliness of birth-dose vaccination was calculated as the proportion of infants who received birth-dose vaccine

within 24 h of life. The incidence of HBV mother-to-child transmission (the proportion of infants who tested positive for HBsAg at 24 weeks) was calculated. Finally, we calculated the proportion of women who were lost to follow-up by delivery and by 24 weeks post partum.

Demographics of enrolled women were analysed from the enrolment questionnaire; missing data were described where observed. 95% CIs for prevalence were calculated using the formula:

$$\hat{p} \pm Z\sqrt{\frac{\hat{p}(1-\hat{p})}{N}}$$

where p is the prevalence, Z is the Z score, and N is the total sample size of women screened for HBsAg.

We used the Wilcoxon rank-sum test to compare continuous data and the Fisher's exact test to compare categorical data. A principal component analysis was used to combine household attributes into a wealth index (appendix 3 p 1).[17] Wealth quartiles were calculated from a principal component analysis including the following variables: people per household room, number of beds in household, number of radios in household, number of televisions in household, number of phones in household, number of refrigerators in household, ownership of a car, presence or absence of electricity in household, cooking with electricity, cooking with wood, and private water source.

We did all statistical computations and analyses using R (version 4.0.3). This study is registered with ClinicalTrials.gov, NCT03567382.

Results

Between Sept 24, 2018, and Feb 22, 2019, we approached 4016 pregnant women, all of whom accepted HBV screening (figure 1). Of these pregnant women, 109 were HBsAg positive, indicating an overall HBsAg prevalence of 2·7% (95% CI 2·2–3·2). Of the 109 women, 91 (83%) met the eligibility criteria. In total, 37 (41%) of 91 women did not complete the study. 11 (12%) women voluntarily withdrew by 24 weeks post partum, three (3%) did not have living children (two miscarriages and one stillbirth), one (1%) infant died, 21 (23%) were lost to follow-up despite repeated efforts by the study team to contact them, and one (1%) woman was withdrawn from the treatment programme because of a false pregnancy (study staff confirmed a negative urine pregnancy test despite the woman reporting pregnancy); therefore, 54 (60%) completed the study through the 24-week post-partum visit, and only data from the 90 (99%) women—excluding a woman who had a false pregnancy—were included in the study analysis.

The median overall age of the enrolled women was 31 years (IQR 25–34) and the median overall gestational age at enrolment was 19 weeks (15–22; table). Only one (1%) of 90 women was co-infected with HIV and HBV; she received a tenofovir disoproxil fumarate-based antiretroviral regimen. Of the 90 women, ten (11%) had a high-risk HBV infection; nine (90%) of ten were HBeAg positive and five (50%) had a high viral load. Of the ten

women with high-risk HBV infection, six (60%) were followed up to study completion, two (20%) voluntarily withdrew from the study (the first before initiation of tenofovir disoproxil fumarate and the second after delivery), one (10%) moved to another province in the Democratic Republic of the Congo after delivery, and one (10%) was lost to follow-up after the 10-week visit. Overall, women with high-risk HBV infection were younger and presented later in pregnancy. Few missing data were observed in the study population characteristics.

Enrolment and results across the care continuum are shown in figure 2. A total of 88 infants were born to the 90 enrolled women. Overall, 60 (68%) of 88 infants received a birth-dose monovalent HBV vaccine; of these infants, 46 (77%) received a timely birth-dose vaccine within 24 h of delivery. Among the 63 infants born at the two study facilities, 48 (76%) received a birth-dose vaccine; of whom, 41 (85%) were given timely birth-dose vaccines. Among 25 infants born at an outside facility, 12 (48%) received a birth-dose vaccine; of whom, 12 (42%) were given timely birth-dose vaccines. None of the infants were born outside of a health facility. Figure 2B shows the care continuum for infants, including reasons for missed or untimely vaccination. No adverse events were reported related to the birth-dose vaccine. Of the 53 infants tested at 24 weeks, none tested positive for HBsAg, consistent with no HBV mother-to-child transmission.

Nine (90%) of ten pregnant women with high-risk HBV infection received tenofovir disoproxil fumarate and one (10%) woman refused therapy and withdrew from the study. Five (56%) of the nine women achieved viral suppression (ie, <200 000 IU/mL) on tenofovir disoproxil fumarate therapy by the time of delivery (figure 2A); the remaining four (44%) women had decreased viral loads from enrolment to delivery, but not below 200 000 IU/mL (figure 3). Although all women taking tenofovir disoproxil fumarate returned empty pill bottles and reported full adherence per the exit survey, tenofovir diphosphate concentrations suggested low adherence. Three (33%) of nine women delivered within 28 days of initiation of tenofovir disoproxil fumarate therapy, so tenofovir diphosphate concentrations could not be interpreted. Of the remaining six women, three (50%) had tenofovir diphosphate concentrations below the limit of quantification—ie, were not detectable—and each of the other three (50%) women had tenofovir diphosphate concentrations reflecting taking less than 2 doses per week, 2–4 doses per week, and 4–7 doses per week, respectively. All three women with detectable tenofovir diphosphate concentrations who initiated tenofovir disoproxil fumarate therapy for more than 28 days before delivery were virally suppressed during childbirth.

No serious adverse events associated with tenofovir disoproxil fumarate treatment were reported. One (11%) of nine women reported dizziness during the course of medication; otherwise, no other side-effects were reported. Three (33%) of nine women developed rebound elevations of ALT (appendix 3 pp 5–7), and two (22%) developed corresponding elevations of HBV DNA viral loads after stopping tenofovir disoproxil fumarate at 12 weeks post partum. These women were referred to the study gastroenterologist for further management, but none attended their appointments.

All seven high-risk HBV-infected women who were followed up for 6 months reported that taking tenofovir disoproxil fumarate was very acceptable. 48 (89%) of 54 women followed-up post partum for 24 weeks reported that having their blood drawn was very acceptable, with only one (2%) reporting this procedure as very unacceptable and one (2%) reporting it as somewhat unacceptable (figure 4). One (2%) of 54 women reported the infant blood draw as very unacceptable and three (6%) reported the infant blood draw as somewhat unacceptable. Only one (2%) of 54 women reported vaccination of her infant as very unacceptable.

Discussion

We showed the feasibility of implementing a programme to prevent mother-to-child transmission of HBV in the Democratic Republic of the Congo, using the existing HIV prevention of mother-to-child transmission and Expanded Programme on Immunisation infrastructure. We took a two-pronged approach: screening and treatment of HBV-positive pregnant women at high-risk for mother-to-child transmission, and provision of a birth-dose vaccine to HBV-exposed infants. Of the 53 HBV-exposed infants followed up for 24 weeks, none were positive for HBV infection, supporting no vertical transmission. Even with vaccination, the estimated risk of mother-to-child transmission among infants born to women with high-risk HBV infection ranges from 20% in Asia to 32% in Africa, compared with less than 1% for vaccinated infants born to Asian and African women without high-risk features.[18] These results prompted WHO to revise HBV guidelines for the prevention of mother-to-child transmission in 2020 by adding antiviral prophylaxis to the recommended three-dose vaccination programme, with the first dose within 24 h of life.[3] Our successful integration of HBV screening of pregnant women and provision of tenofovir disoproxil fumarate prophylaxis within an existing HIV prevention of mother-to-child transmission programme in the two busiest maternity centres in Kinshasa supports the feasibility of this WHO recommendation, even in the most resourcelimited settings.

The prevalence of HBV infection among pregnant women was in line with similar studies in African settings.[18,19] We found that 11% of HBV-positive women met the eligibility criteria for tenofovir disoproxil fumarate therapy based on the detection of a high viral load or HBeAg positivity, or both, a percentage that is similar to other reports in sub-Saharan Africa.[19–21] The assessment of high-risk HBV infection and the administration of tenofovir disoproxil fumarate was feasible within this study's framework, but without reliable point-of-care tests for HBV DNA quantification or HBeAg testing, scale-up will be a challenge. Until such infrastructure is in place, HBV birth-dose vaccines should be prioritised as a prevention tool to reduce the risk of mother-to-child transmission.[22–24]

Birth-dose vaccination was feasible in two high-volume maternity centres in urban Kinshasa, and was largely acceptable to mothers. Although we did not achieve vaccination within 24 h of birth for all infants, we showed that a high standard-of-care with adoption of a universal birth-dose vaccine is within reach in the Democratic Republic of the Congo. We identified several barriers to timely administration of the birth-dose vaccine that must be overcome as the country moves toward universal birth-dose vaccination. First, many women delivered at facilities other than at one of the two study facilities. Potential reasons

for delivering at other facilities include personal preference, cost, quality of care received, or the need for caesarean section delivery, which was not possible at either maternity hospital in our study. With the adoption of a universal HBV birth-dose vaccine, all infants at all facilities would have access, such that maternal preference of delivery site would not preclude infant vaccination. To bridge this implementation gap, further scale-up studies will be needed, followed by inclusion of birth-dose vaccine in the national immunisation schedule. Second, baseline knowledge of HBV was inadequate among mothers in our study (unpublished data), and dropouts along the care cascade were high. Our team has previously shown that a mother's perception of HIV risk to her infant was a key determinant of her retention in the HIV prevention of mother-to-child transmission care cascade.[25] Third, reliable cold chains are needed. With support from Gavi and the Democratic Republic of the Congo's Expanded Programme on Immunisation, established cold chains for other routine vaccines could be used for HBV birth-dose vaccines. At the same time, sentinel studies have already evaluated storage of HBV birth-dose vaccines outside of the cold chain.[26] Finally, many births occur outside of health facilities in the Democratic Republic of the Congo and throughout sub-Saharan Africa. Initial rollout of such immunisation programmes to health centres could be followed by decentralised vaccination after home birth, although the logistics of this strategy are more complex. Nonetheless, with small investments of resources to strengthen the existing infrastructure of the Expanded Programme on Immunisation in the Democratic Republic of the Congo, timely delivery of the HBV birth-dose vaccine is possible alongside other birth-dose vaccinations.[27]

We observed a discordance between verbally reported adherence to tenofovir disoproxil fumarate therapy and adherence as measured by dried blood spot assay tenofovir diphosphate concentrations. Only three (33%) of nine women had tenofovir diphosphate concentrations suggesting that they took at least two doses per week; all of these women had viral load suppression at delivery. This finding is in contrast with the nearly 100% adherence reported on the exit surveys and via pill counts. Changes in viral load and serum creatinine concentrations among women taking tenofovir disoproxil fumarate can be used as proxy measures of adherence but do not fully explain the discordance. Further studies should investigate drivers of poor adherence.

The strength of this study lies in its pragmatic, comprehensive approach. In line with recent WHO guide lines for preventing HBV mother-to-child transmission, we integrated HBsAg screening into an existing HIV prevention of mother-to-child transmission programme, leveraged laboratory infrastructure to identify and treat pregnant women with high-risk HBV infection, and leveraged the existing Expanded Programme on Immunisation cold-chain infrastructure to deliver birth-dose vaccination. This package of interventions is delivered routinely in high resource settings, but infrequently across Africa. Integration of activities into existing HIV prevention of mother-to-child transmission and Expanded Programme on Immunisation infra structure distinguishes our approach from a recently published feasibility study of an antenatal HBV programme in Burkina Faso,[8] and our study yielded a higher uptake of HBV screening at the first antenatal visit. We longitudinally followed up HBV-infected women and their exposed infants to document adherence to the care cascade, side-effects of birth-dose vaccine and tenofovir disoproxil fumarate, and the incidence of mother-to-child transmission. Although most studies of HBV mother-to-child transmission

in Africa published to date focus on HBV–HIV co-infection, our cohort of mainly HBV mono-infected pregnant women is generalisable to settings in Africa where HIV prevalence is low.

This study had limitations. First, the sample size was relatively small. Yet, to the best of our knowledge, this is the largest study of HBV prevention of mother-to-child transmission among mono-infected pregnant women in sub-Saharan Africa done to date. Second, we observed a high rate of women lost to follow-up in this study. Although the loss to follow-up negatively affects our ability to determine the incidence of mother-to-child transmission, it is an expected feature of pragmatic feasibility studies and consistent with postnatal follow-up patterns in the Democratic Republic of the Congo.[17] The high rate of women lost to follow-up also affected our ability to fully ascertain the overall acceptability of the study's procedure; our Kinshasa-based study team worked diligently to re-engage these participants lost to follow-up but many did not have working telephone numbers or had moved away from their reported physical addresses. Third, since respondents were asked about the acceptability of study procedures at the time of the exit survey at 24 weeks post partum, self-reporting and recall bias might have affected their responses. Fourth, an ongoing pragmatic randomised clinical trial of continuous quality improvement interventions to improve HIV prevention of mother-to-child transmission across Kinshasa province might have had beneficial spill over effects that affected the generalisability of our HBV prevention of mother-to-child transmission efforts. Fifth, supply chain disruption prevented us from completing planned laboratory comparisons of HBeAg and viral load testing on dried blood spot samples versus venous blood samples in the Democratic Republic of the Congo, and will be an ongoing challenge with similar programmes. Finally, the measurement of tenofovir diphosphate concentrations from dried blood spot samples might not accurately depict adherence to tenofovir disoproxil fumarate therapy. Tenofovir diphosphate is not sensitive for behavioural changes, as it represents an average of adherence over several months. Furthermore, we cannot exclude the possibility of tenofovir diphosphate degradation during dried blood spot sample preparation or transportation from the Democratic Republic of the Congo, where ambient temperatures and humidity are high. No clear threshold was reported for how much tenofovir disoproxil fumarate is required to prevent HBV mother-to-child transmission, but decreases in maternal HBV DNA before delivery are associated with decreased risk of HBV mother-to-child transmission.[6,7] Despite variable tenofovir diphosphate concentrations, most women did have a decline in HBV DNA viral loads. Even with these limitations, we successfully implemented HBV prevention of mother-to-child transmission measures.

In conclusion, this study provides strong evidence that WHO-recommended measures to prevent motherto-infant HBV transmission can be implemented in resource-constrained settings such as the Democratic Republic of the Congo by building upon HIV prevention of mother-to-child transmission and Expanded Programme on Immunisation platforms. Lessons learned from HIV prevention of mother-to-child transmission, including how to improve retention and adherence to prophylaxis, can be leveraged to address similar challenges in the HBV prevention of motherto-child transmission programme. We showed the feasibility of implementing proven HBV mother-to-child transmission prevention measures during routine care at two high-volume maternity hospitals in Kinshasa. A

two-pronged maternal screening plus treatment and infant birth-dose vaccination approach was acceptable to most mothers, and no cases of HBV mother-to-child transmission were observed among those retained in our care. Although obstacles must be overcome before a rollout of antiviral prophylaxis for pregnant women at high-risk of HBV mother-to-child transmission, universal birth-dose HBV vaccination is a proven measure that should be implemented in the Democratic Republic of the Congo. To meet WHO's elimination goals by 2030,[28] countries with endemic HBV infections such as the Democratic Republic of the Congo should adopt and implement WHO guidelines that establish pathways for HBV prevention of mother-to-child transmission,[3] and should prioritise issues that affect all aspects of the programme, including birth-dose vaccination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Declaration of interests

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Research in context

Evidence before this study

We searched PubMed for articles in any language through March 13, 2021, using the following search terms: ("hepatitis B") AND ("Africa") AND ("mother-to-child transmission" OR "vertical transmission"). Among the 70 manuscripts identified, no studies of combined maternal antiviral prophylaxis and birth-dose vaccination in hepatitis B virus (HBV) mono-infected pregnant women in Africa were identified. Upon further literature review, a single pilot study in Burkina Faso was identified that evaluated the feasibility of an HBV prevention programme—including antiviral prophylaxis for pregnant women and birth-dose vaccination for infants—as part of antenatal screening. In countries where a birth-dose of HBV vaccine has been introduced, studies have shown its effectiveness in preventing mother-to-child transmission; however, transmission did occur in some infants born to women with high viral loads because birth-dose vaccine was not coupled with maternal antiviral prophylaxis. In its 2020 guidelines on HBV prevention of mother-to-child transmission, WHO recommends that HBV-infected women with high-risk HBV infection receive antiviral prophylaxis from the 28th week of pregnancy to delivery or beyond in order to prevent breakthrough mother-to-child transmission in addition to infant vaccination (including a birth-dose vaccine), but no published study to date has evaluated a dual approach to preventing HBV mother-to-child transmission within an HIV framework in Africa.

Added value of this study

HBV prevention of mother-to-child transmission measures are not part of routine maternal and child health care throughout most of sub-Saharan Africa, where HBV infection is endemic. We leveraged the HIV prevention of mother-to-child transmission infrastructure at two large-volume maternity centres in Kinshasa (the Democratic Republic of the Congo) to identify and treat HBV-infected pregnant women. Alongside screening and treatment of mothers, we also leveraged the vaccination programme infrastructure to provide a birth-dose vaccine to HBV-exposed infants. Our cohort was unique in that most women were HBV mono-infected, with only one HIV–HBV co-infected woman. We showed that it is feasible to integrate HBV screening and provision of antiviral prophylaxis into a current HIV prevention of mother-to-child transmission programme, and that the current Expanded Programme on Immunisation system can be leveraged to administer birth-dose vaccines to infants in health facilities. However, we uncovered implementation challenges in providing timely vaccination (within 24 h of birth) that must be overcome to enable widespread adoption of a birth-dose vaccine.

Implications of all the available evidence

Our two-pronged prevention approach of birth-dose vaccination as well as screening and treatment of pregnant women was not only feasible in a low-resource setting, but was also potentially effective in preventing breakthrough HBV mother-to-child transmission. Our results support the feasibility of WHO's 2020 guidelines even in the most resourcechallenged settings, especially when integrated into existing HIV prevention of mother-to-child transmission programme infrastructure. With widespread

scale-up of birth-dose vaccination as well as screening and treatment of pregnant women, elimination of HBV mother-to-child transmission is possible in the Democratic Republic of the Congo and throughout sub-Saharan Africa.
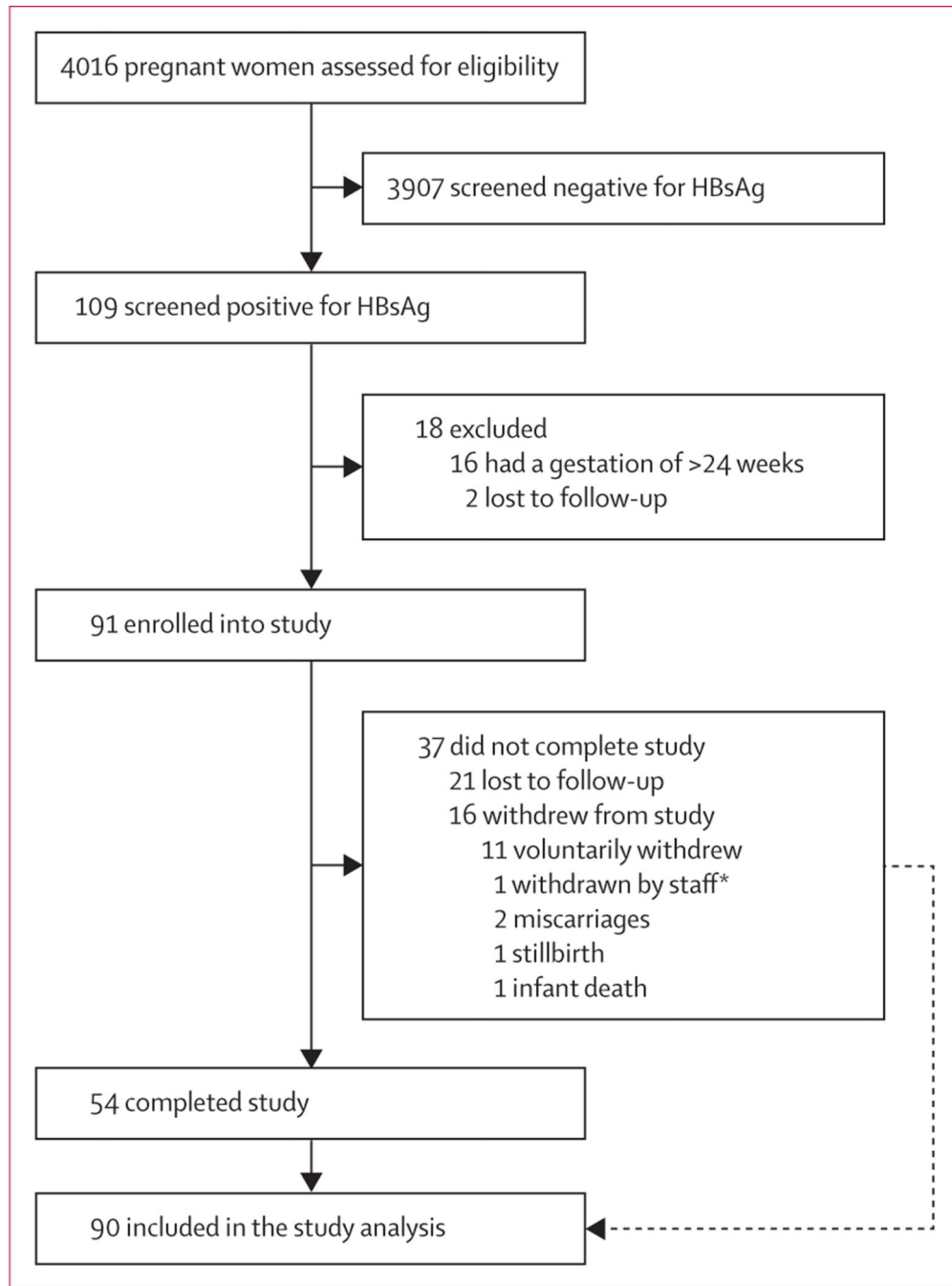
Figure 1: Study profile
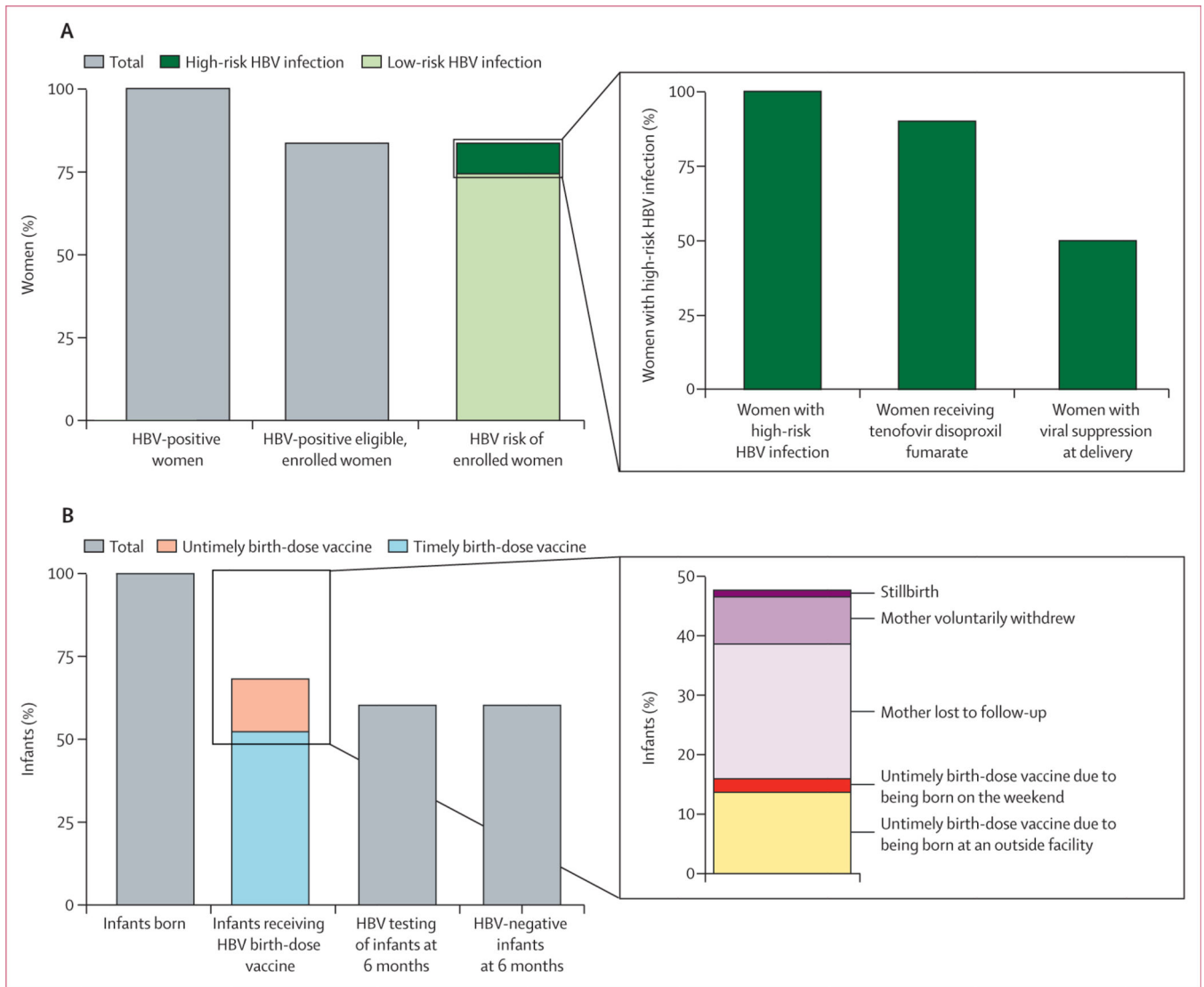*Not pregnant and therefore not included in the study analysis.

Figure 2: Enrolment and results across the care continuum
(A) Care continuum of women. (B) Care continuum of infants. HBV=hepatitis B virus.
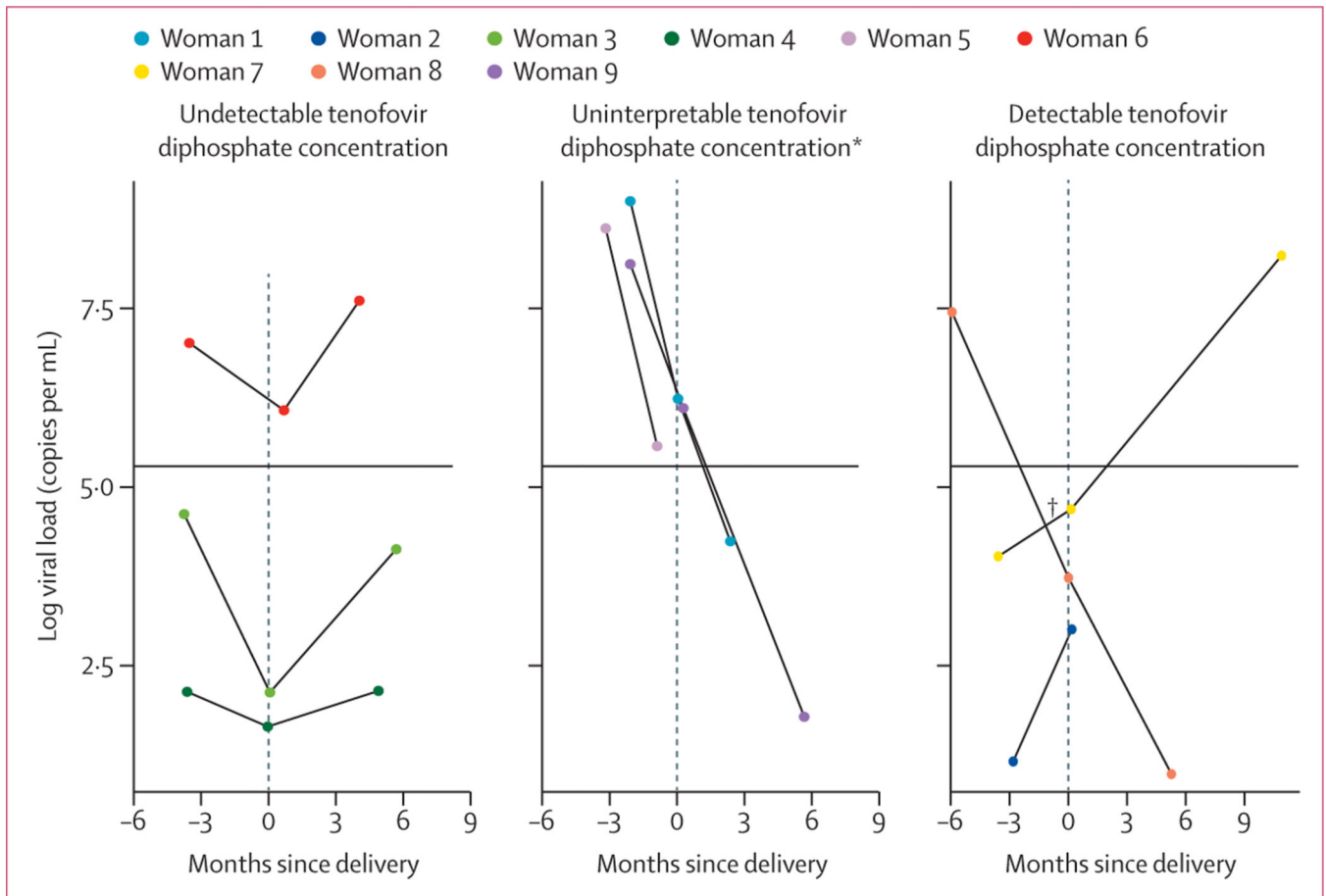
Figure 3: Viral loads of pregnant women with high-risk HBV infection across study timepoints, by tenofovir diphosphate level

The grey lines connecting each datapoint represent the change in viral load over time. The solid horizontal line represents the level that corresponds to viral suppression at delivery (200 000 IU/mL), which is a log viral load of 5·3. *Tenofovir disoproxil fumarate initiated within 28 days of delivery, before tenofovir diphosphate steady state is expected. †Imputed viral load from dried blood spot assay.

Figure 4:
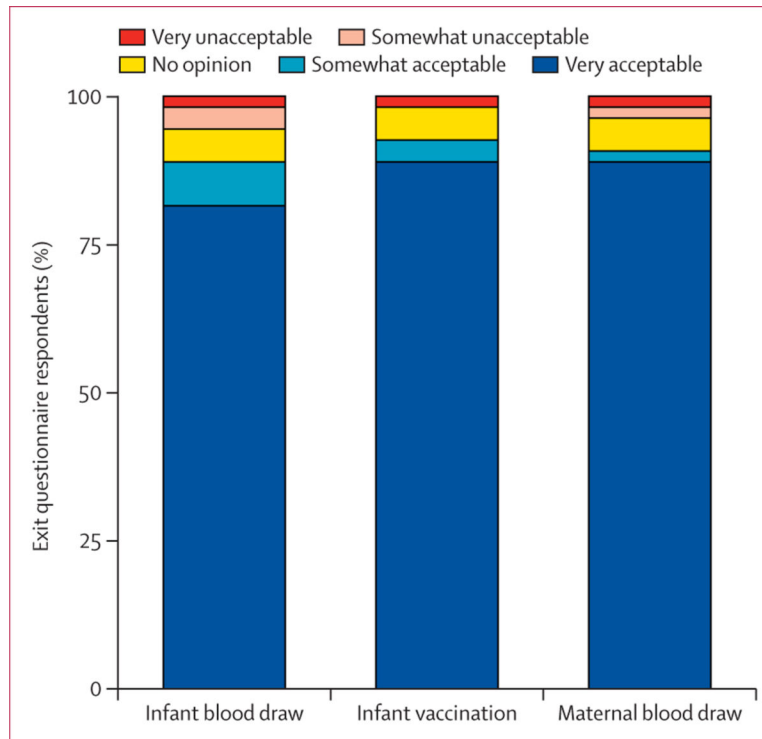Acceptability of clinical study components assessed at 6-month follow-up visit (n=54)

Table:

Characteristics of the study population

	Total (n=90)	Low-risk HBV infection (n=80)	High-risk HBV infection (n=10)	p value
Age, years	31 (25–34)	31 (26–34)	24 (20–25)	0·003
Gestational age, weeks	19 (15–22)	19 (13–20)	21 (20–23)	0·025
Previous HBV diagnosis				0·59
No	82 (91%)	72 (90%)	10 (100%)	0·59
Yes	8 (9%)	8 (10%)	0	··
Total number of pregnancies				0·31
1	16 (18%)	14 (18%)	2 (20%)	0·31
2	18 (20%)	13 (16%)	5 (50%)	··
3	18 (20%)	17 (21%)	1 (10%)	··
4	14 (16%)	13 (16%)	1 (10%)	··
5	10 (11%)	10 (13%)	0	··
6	14 (16%)	13 (16%)	1 (10%)	··
Number of living children				0·099
0	28 (31%)	21 (26%)	7 (70%)	0·099
1	16 (18%)	15 (19%)	1 (10%)	··
2	18 (20%)	18 (23%)	0	··
3	12 (13%)	11 (14%)	1 (10%)	··
4	16 (18%)	15 (19%)	1 (10%)	··
Number of adults in household				0·77
0	2 (2%)	2 (3%)	0	0·77
1	24 (27%)	22 (28%)	2 (20%)	··
2	31 (34%)	26 (33%)	5 (50%)	··
3–4	25 (28%)	22 (28%)	3 (30%)	··
5	8 (9%)	8 (10%)	0	··
Number of children in household				0·22
0	22 (24%)	17 (21%)	5 (50%)	0·22
1–2	32 (36%)	31 (39%)	1 (10%)	··
3–4	25 (28%)	22 (28%)	3 (30%)	··
5–10	10 (11%)	9 (11%)	1 (10%)	··

	Total (n=90)	Low-risk HBV infection (n=80)	High-risk HBV infection (n=10)	p value
>10	1 (1%)	1 (1%)	0	..
Marital status				
Married or cohabiting	83 (92%)	74 (93%)	9 (90%)	0·35
Separated	1 (1%)	1 (1%)	0	..
Divorced	1 (1%)	1 (1%)	0	..
Never married	4 (4%)	4 (5%)	0	..
Missing	1 (1%)	0	1 (10%)	..
Highest schooling				
Never attended school	4 (4%)	4 (5%)	0	0·29
Primary	2 (2%)	1 (1%)	1 (10%)	..
Secondary	64 (71%)	58 (73%)	6 (60%)	..
Higher education	20 (22%)	17 (21%)	3 (30%)	..
Wealth quartile				
Lowest	23 (26%)	22 (28%)	1 (10%)	0·098
Lower-to-middle	22 (24%)	20 (25%)	2 (20%)	..
Upper-to-middle	22 (24%)	21 (26%)	1 (10%)	..
Highest	23 (26%)	17 (21%)	6 (60%)	..
Occupation				
Market or street trader	37 (41%)	35 (44%)	2 (20%)	0·25
Seamstress	5 (6%)	4 (5%)	1 (10%)	..
Hairdresser	6 (7%)	5 (6%)	1 (10%)	..
Salaried	10 (11%)	10 (3%)	0	..
Other	1 (1%)	1 (1%)	0	..
Not currently employed	31 (34%)	25 (31%)	6 (60%)	..
Employer status				
Employed by someone else	13 (14%)	12 (15%)	1 (10%)	0·24
Self-employed	46 (51%)	43 (54%)	3 (30%)	..
Not currently employed	31 (34%)	25 (31%)	6 (60%)	..

Data are median (IQR) or n (%), unless otherwise specified. HBV=hepatitis B virus.