Risk of early horizontal transmission of hepatitis B virus in children of uninfected mothers in sub-Saharan Africa: a systematic review and meta-analysis

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Summary

Background Sub-Saharan Africa is highly endemic for hepatitis B virus (HBV); historically, most people were exposed during childhood through vertical or horizontal transmission. Although all African countries now provide a three-dose infant hepatitis B vaccination starting at age 6–8 weeks, only a third of African countries have introduced birth dose (HepB-BD) vaccine. Adding HepB-BD is fundamental to prevent vertical transmission, but its effectiveness in preventing horizontal transmission, compared with the three-dose infant vaccination alone, is unknown. We aimed to estimate the risk of early horizontal transmission in children of hepatitis B surface antigen (HBsAg)-negative mothers in sub-Saharan Africa stratified according to the vaccination schedule.

Methods In this systematic review and meta-analysis we searched MEDLINE, Global Health, Embase, African Index Medicus and African Journals Online from their inception to Oct 24, 2022, for studies reporting HBsAg or HBV DNA, or both, in children (aged 0–5 years) of HBsAg-negative mothers. We excluded studies if children were only tested at birth. Two reviewers independently screened the titles and abstracts of all articles and data were extracted using a standardised pre-piloted data extraction sheet, and authors were contacted if any important information was missing. The primary outcome was the risk of HBV infection in children of HBsAg-negative mothers, stratified by vaccination schedule (no vaccination, first dose at 6–8 weeks, or first dose at birth). We pooled the child risks of HBsAg or HBV DNA-positivity from the age of 0 years to 5 years via a random-effect meta-analysis using a generalised linear mixed model. The study was registered on PROSPERO, CRD42021236203.

Findings Of 8856 articles identified, 27 studies evaluating 10 003 children of HBsAg-negative mothers were included. The pooled risks of infection were 6·16% (95% CI 3·05–12·04; 155/1407) in the no vaccination group, 0·21% (0·04–1·15; 10/3425) in children who received their first dose at 6–8 weeks, and 0·05% (0·00–1·32; 3/2902) in children who received their first dose at birth. The difference was not statistically significant in children who received their first dose at 6–8 weeks and children who received their first dose at birth after adjusting for the study period, region, and maternal HIV status (test of moderators p=0·37).

Interpretation In children of HBsAg-negative mothers, the risk of infection might be minimal even with the vaccination starting at 6–8 weeks, without clear additional benefit from HepB-BD. When births take place at home and timely administration of HepB-BD is challenging, antenatal HBsAg screening and selective HepB-BD might allow efficient allocation of resources to mother and child pairs at high risk compared with universal HepB-BD.

Funding None.

Lancet Glob Health 2023; 11: e715–28

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

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Introduction

Sub-Saharan Africa has a disproportionately high burden of hepatitis B virus (HBV) infection. An estimated 80 million people live with chronic HBV infection, and HBV-related cirrhosis and hepatocellular carcinoma are leading causes of morbidity and mortality.[1] Before the widescale implementation of hepatitis B vaccination, most transmission in sub-Saharan Africa occurred during childhood, either through vertical or horizontal transmission.[2,3] Although the exact mechanisms of horizontal transmission during childhood are not firmly established, epidemiological studies in sub-Saharan Africa found that the majority of horizontal transmission occurs within a household, particularly from older children who often carry hepatitis B e antigen (HBeAg) and a high viral load.[4–6]

Since the 1990s, countries in sub-Saharan Africa have gradually introduced hepatitis B vaccines into the Expanded Programme on Immunization (EPI). To date, all these countries have adopted a three-dose infant vaccination series against HBV (HepB3) using a combined vaccine (DTP-HepB-Hib [pentavalent], or DTaP-IPV-HepB-Hib [hexavalent]) with doses scheduled at 6, 10, and 14 weeks or at 8, 12, and 16 weeks. The scale-up of HepB3 might have reduced horizontal transmission and thus decreased HBsAg prevalence among vaccinated

Research in context

Evidence before this study

An estimated 80 million people are living with chronic hepatitis B virus (HBV) infection in sub-Saharan Africa. Most of them were infected in the early years of life, primarily as a consequence of vertical transmission or horizontal transmission. To date, all African countries have incorporated three-dose infant hepatitis B vaccination, starting at 6–8 weeks of age, into their immunisation programmes. However, by 2021, only 14 (30%) of 47 countries in this region additionally provide birth dose vaccination (HepB-BD) despite WHO's recommendation of universal HepB-BD strategy, whereby every neonate should receive a vaccination dose within 24 h of birth, regardless of maternal HBV serological status. HepB-BD is fundamental to the prevention of vertical transmission in children born to HBsAg-positive mothers. Conversely, the additional benefit of HepB-BD in children born to HBsAg-negative mothers has been poorly studied and is likely to depend on early horizontal transmission risk. We searched PubMed for systematic reviews of studies evaluating the efficacy of HepB-BD in children born to HBsAg-negative mothers in sub-Saharan Africa, compared to no vaccine, placebo, or a vaccination schedule starting at 6–8 weeks of age, published from database inception up until Jan 16, 2023, using the terms "systematic review" AND "birth dose" AND "HBsAg-negative mothers" AND "sub-Saharan Africa". We did not identify any previous systematic review.

Added value of this study

This study is the first systematic review and meta-analysis to quantify the early horizontal transmission risk in children younger than 5 years in Africa according to different hepatitis B vaccination schedules. Through synthesising data from over 10 000 children of HBsAg-negative mothers we found that the pooled risk of infection was high at 6·2% in the absence of vaccination, and that this risk significantly decreased with vaccination. However, there was no statistically significant difference in the risk of infection between the groups who started hepatitis B vaccination series at birth and those who started at 6–8 weeks. This finding suggests that the vaccination schedule starting at 6–8 weeks might be sufficient in children born to HBsAg-negative mothers, without a clear benefit from the addition of HepB-BD.

Implications of all the available evidence

In many sub-Saharan African countries, institutional birth rate remains low and implementation of a universal HepB-BD policy is challenging. Alternatively, the coverage of antenatal care services is high. Scale-up of antenatal HBsAg screening in this region might allow efficient allocation of resources to mother and child pairs at high risk through (1) selective peripartum antiviral prophylaxis to HBV-infected pregnant women with high viremia (or positive hepatitis B e antigen), and (2) selective HepB-BD to children born to HBsAg-positive mothers. Further implementations research is needed to guide country-level choice of strategy.

cohorts in this region.[7] In contrast, currently only 14 (30%) of 47 countries in sub-Saharan Africa additionally provide birth dose monovalent hepatitis B vaccine (HepB-BD), due to a complex interplay of epidemiological, financial, and implementation challenges.[8]

Since 2009, WHO has recommended a universal HepB-BD strategy in addition to HepB3, whereby every neonate should be vaccinated within 24 h of birth regardless of maternal HBV serological status.[8] Of the 194 WHO member states, 143 have introduced HepB-BD by 2020 and most (110 [77%] of 143) adopted this universal approach. However, 33 (23%) countries, mostly in Europe, opted for a selective approach, whereby only infants born to HBsAg-positive women are given HepB-BD.[9]

See Online for appendix 2

One of the incremental benefits of a universal HepB-BD strategy compared with a selective one is that it might also protect children born to HBsAg-negative mothers from early horizontal transmission before receiving their first dose of HepB3 at the age of 6–8 weeks. However, the risk of infection for children born to HBsAg-negative mothers in this early period of life (ie, early horizontal transmission) has not been formally assessed. We therefore conducted a systematic review and meta-analysis to estimate the risk of HBV infection in children of HBsAg-negative mothers in sub-Saharan Africa, according to the different vaccination schedules.

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis we searched MEDLINE, Embase, Global Health, African Index Medicus, and African Journals Online from their inception to Oct 24, 2022, without any language restrictions. The search strategy used the following terms and their variations: "HBV" AND "mothers or children" AND "sub-Saharan Africa" (appendix 2 pp 2–3).

We included studies evaluating the HBV serological status in mother and child pairs in sub-Saharan Africa, in which mothers tested negative for HBsAg during pregnancy or up to 5 years postnatally, and children were tested for HBsAg or HBV DNA, or both, from 0 years to 5 years of age. We excluded studies if children were only tested at birth. Studies that exclusively enrolled mothers with occult HBV infection (defined as negative HBsAg and detectable HBV DNA) were eligible, but we reported this group separately from our main analysis. Child HBV infection was defined as positive HBsAg or HBV DNA, or both, between 0 years and 5 years of age. We included any study design except case-control studies.

After removal of duplicate articles, two reviewers (AA JPV) independently screened the titles and abstracts of all articles identified by the literature search, reviewed potentially eligible full-text articles, and extracted data

from included studies using a standardised pre-piloted data extraction sheet (appendix 2 pp 4–5). We evaluated the risk of bias using a framework adapted from Hoy and collegues[10] (appendix 2 pp 6–9). When multiple articles of the same study population were identified, we included them if the data differed by time of child HBV assessment. We extracted the following information from the articles: study design, settings, vaccination schedules, adherence to vaccination schedules, other preventive measures, type of serological or virological assay, maternal information, child age at assessment, and child outcomes. A third reviewer (YS or SN) verified all extracted data. We resolved any conflict through group discussion. Whenever important information was missing, we contacted corresponding authors. Of 16 authors contacted, nine replied and six provided additional numerical data. If studies did not explicitly report on whether hepatitis B vaccination was offered or not, the vaccination schedule for that country at the time of the study was ascertained using WHO or UNICEF reports and used as a proxy.[11]

The study protocol was pre-registered in PROSPERO (CRD42021236203) and is reported according to PRISMA guidelines.[12]

Data analysis

The primary outcome was the risk of HBV infection in children of HBsAg-negative mothers, stratified by vaccination schedule (no vaccination, first dose at 6–8 weeks, or first dose at birth). The secondary outcome was the risk of HBV infection in children of mothers with occult HBV infection. We defined the risk of infection as the number of children positive for HBsAg or HBV DNA divided by the total number assessed. To pool the risks, we performed a random-effects meta-analysis using a generalised linear mixed model with the logit link by the "metaprop" command in R (version 4.2.2). We presented the exact binomial confidence intervals for the individual studies. We assessed the proportion of variability attributable to heterogeneity between studies using the I^2 statistic and considered more than 50% as substantial. We assessed heterogeneity between subgroups using the meta-regression and test of moderators. We considered two-sided $p<0{\cdot}05$ to be statistically significant.

Because the administration of antiretroviral regimens that are effective against HBV to children might influence their risk of HBV infection, we conducted a sensitivity analysis by excluding these studies. We also performed the following subgroup analyses to explore the sources of between-study heterogeneity in the risk of HBV infection stratified by vaccination schedule: maternal HIV infection, type of child outcome assessed (HBsAg or HBV DNA), child age at assessment (birth, <12 months, 12–23 months, 24–35 months, 36–47 months, and 48–60 months), type of serological assay (moderately sensitive assays are radioimmunoassay, haemagglutination assay, and immunochromatography; highly sensitive assays are enzyme immunoassay and chemiluminescent immunoassay), sample size (above or below median), study region (western, central, eastern, or southern Africa), and study period (before or after the country introduced hepatitis B vaccine into the EPI). Additionally, we conducted a post-hoc multivariable meta-regression analysis to evaluate the association between the vaccination schedule and child HBV infection, accounting for the following covariates identified by directed acyclic graph:[13] region, period, and maternal HIV infection (appendix 2 p 10). We assessed small-study effects by plotting study size against the logarithm of the odds of risk.[14]

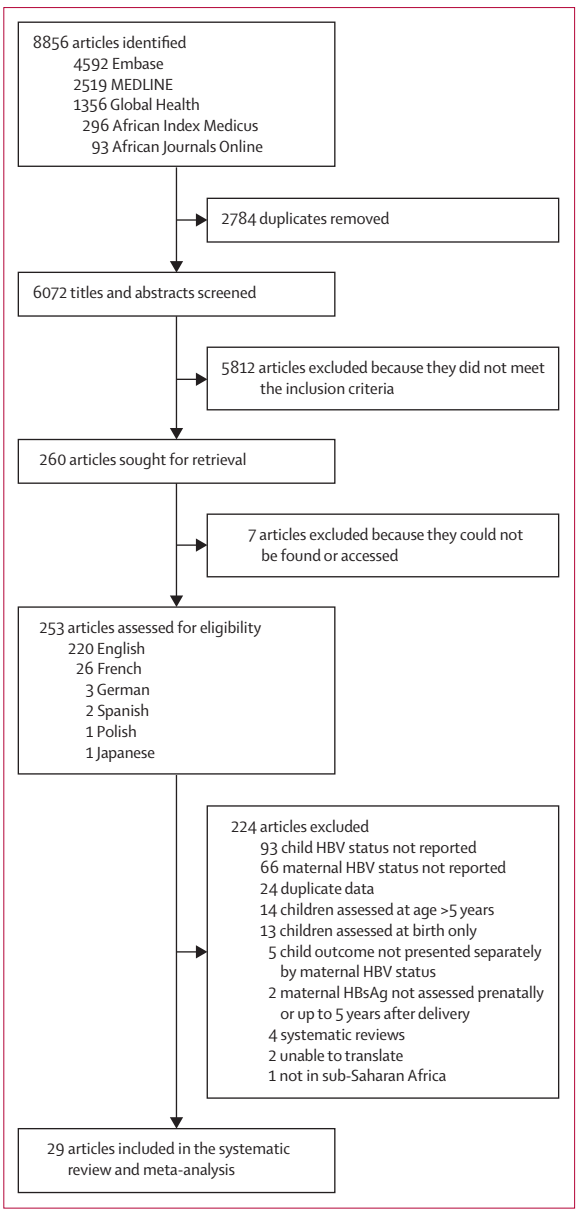


Figure 1: **PRISMA flow diagram showing study selection process**
HBsAg=hepatitis B surface antigen. HBV=hepatitis B virus.

	Study period	Country	Study design	Maternal or child HBsAg assay	Number of children born to HBsAg-negative mothers eligible for this review	Number of children used for primary outcome	Child age at assessment	Child vaccination schedule*	Maternal mean or median age	Timing of maternal HBsAg assessment	HIV-positive mother, n/N (%)	HIV-positive child, n/N (%)
Studies evaluating children of mothers with negative HBsAg												
Ayoola et al (1981)[28]	NR	Nigeria	Cohort	Haemagglutination assay	15	15	0, 6 weeks, 4 months, and 8 months	None	NR	Prenatal	NR	NR
Barin et al (1981)[29]	NR	Senegal	Cohort	Radioimmunoassay	349	88	0 and 3–15 months	None	NR	Prenatal	NR	NR
Prince et al (1981)[30]	1978–79	Liberia	Cross-sectional	Radioimmunoassay	577	577	0–48 months (0–6, 7–12, 13–24, 25–36, and 37–48 months)	None	NR	Alongside index child aged 0–48 months	NR	NR
Yvonnet et al (1982)[15]†	1981	Senegal	Interventional	Radioimmunoassay	106 in BD group; 49 in no vaccine group	75 in BD group; 49 in no vaccine group	0 and 3 months in BD group; 1–5 days and 2–5 months in no vaccine group	<24 h, 1 month, and 2 months in BD group; none in no vaccine group	Mean 25 years (range 15–41) in BD group;‡ NR in no vaccine group	At delivery	NR	NR
Coursaget et al (1983)[18]	NR	Senegal	Cohort	Radioimmunoassay	49	41	3, 12, and 14 months	<24 h, 1 month, 2 months, and 12 months	NR	At delivery	NR	NR
Marinier et al (1985)[31]	1977–80	Senegal	Cohort	Haemagglutination assay	1221§	186	0, 1 week–5 months, 5–12 months, 12–24 months, and 24–38 months¶	None	NR	At delivery	NR	NR
Woodruff et al (1986)[32]	NR	Sudan	Cohort	Haemagglutination assay	79§	79	10–21 months‖	None	NR	Alongside index child aged 10–21 months	NR	NR
Ayoola and Johnson (1987)[33]	NR	Nigeria	Cohort	Radioimmunoassay	137	126	0, 1, 3, 6, and 12 months	None	NR	Prenatal	NR	NR
Tsega et al (1988)[34]	1983–85	Ethiopia	Cohort	Radioimmunoassay	29	23	0, 6, 12, and 24 months	None	Mean 27·6 years (range 17–36)	At delivery	NR	NR
The Gambia Hepatitis Intervention Study: Hall et al (1989),[39] Chotard et al (1992),[40] and Fortuin et al (1993)[19]	NR	The Gambia	Cohort	Haemagglutination assay	661§	630	12, 36, and 48 months	<1, ≥2 , ≥4, and 9 months	NR	Alongside index child aged <1 month	NR	NR
Vall Mayans et al (1990)[35]	NR	The Gambia	Cross-sectional	Haemagglutination assay	202§	202	6–60 months	None	NR	Alongside index child aged 6 months–5 years	NR	NR
Roingeard et al (1993)[36]	NR	Senegal	Cohort	Enzyme immunoassay	134	20	0 and 6–7 months	None	Median 27 years (±6)	Prenatal (third to sixth trimester)	NR	NR
Menendez et al (1999)[37]	1995	Tanzania	Cohort	Enzyme immunoassay	42	42	8 and 18 months	None	Mean 24·5 years (SD 6·2; range 15–50)‡	At delivery	NR	NR

(Table 1 continues on next page)

	Study period	Country	Study design	Maternal or child HBsAg assay	Number of children born to HBsAg-negative mothers eligible for this review	Number of children used for primary outcome	Child age at assessment	Child vaccination schedule*	Maternal mean or median age	Timing of maternal HBsAg assessment	HIV-positive mother, n/N (%)	HIV-positive child, n/N (%)
(Continued from previous page)												
Ekra et al (2008)[16]†	2001–02	Côte d'Ivoire	Interventional	Enzyme immunoassay	1740 in BD group;§ 2001 in HepB3 group§	1740 in BD group; 1771 in HepB3 group	0 and 9 months in BD group; 6–8 weeks and 9 months in HepB3 group	<24 h, 6 weeks, 10 weeks, and 14 weeks in BD group; 6, 10, and 14 weeks in HepB3 group	Median 26·1 years (IQR 14–53)‡	Prenatal (third trimester) in BD group; alongside index child aged 6–8 weeks in HepB3 group	NR	NR
Magoni et al (2009)[22]	2007	Côte d'Ivoire	Cross-sectional	Enzyme immunoassay	756**	756**	12–59 months	6 weeks, 10 weeks, 14 weeks, and 12 months	Mean 28·7 years (SD 6·7)‡	Alongside index child aged 12–59 months	NR	NR
Ilboudo et al (2010)[41]	2007–09	Burkina Faso	Cohort	Enzyme immunoassay	101	101	2–9 months	8, 12, and 14 weeks††	Mean 30·03 years (range 19–39)	Prenatal (<32 weeks)	101/101 (100%)	0/101 (0%)
Osazuwa and Chika (2012)[42]	2011	Nigeria	Cross-sectional	Enzyme immunoassay	217**	217**	6–42 months	6, 10, and 14 weeks††	Range 18–45 years‡	Alongside index child aged 6 months–3·5 years	NR	NR
Onakewhor et al (2013)[20]	NR	Nigeria	Cohort	Immuno-chromatography	66	66	12 months	<12 h, 4 weeks, and 6 months	Mean 38·613 years (SD 2·25; range 26–41)	Prenatal	NR	NR
Pirillo et al (2015)[25]	2008–11	Malawi	Cohort	Enzyme immunoassay	272	163	12, 18, and 24 months	6, 10, and 14 weeks	Mean 27 years (IQR 23–30)	At delivery	282/282 (100%)	NR
Seremba et al (2017)[26]	2012–14	Uganda	Cohort	Immuno-chromatography	566	197	6 weeks and 9 months	6, 10, and 14 weeks	Mean 23 years (range 20–27)	Alongside index child aged 6 weeks	71/549 (13%)	NR
Kaba et al (2019)[43]	2017	Guinea	Cross-sectional	Immuno-chromatography	36	36	12–60 months (12–23, 24–35, 36–47, and 48–60 months)	6, 10, and 14 weeks††	NR	Alongside index child aged 0–60 months	36/36 (100%)	36/36 (100%)
Accrombessi et al (2020)[17]†	2017	Benin	Cross-sectional	Enzyme immunoassay	68 in BD group; 59 in HepB3 group	68 in BD group; 59 in HepB3 group	9 months in BD group; 9 months in HepB3 group	<24 h, 6 weeks, 10 weeks, and 14 weeks in BD group; 6, 10, and 14 weeks in HepB3 group	Mean 28·8 years (SD 4·7) in BD group;‡ mean 28·6 years (SD 4·9)‡	Alongside index child aged 0–60 months	NR	NR
Baruti et al (2020)[21]	2011–13	Botswana	Cross-sectional	Enzyme immunoassay	282	282	18 months	<24 h, 2 months, 3 months, and 4 months	Mean 31·8 years (95% CI 31·1–32·5)‡	At delivery	282/282 (100%)	0/282 (0%)
Lingani et al (2020)[27]	NR	Burkina Faso	Cross-sectional	Immuno-chromatography	125	125	12–60 months (12–23, 24–35, 36–47, and 48–60 months)	2, 3, and 4 months	Mean 33·2 years (SD 7·8)‡	Alongside index child aged 12–60 months	NR	NR

(Table 1 continues on next page)

	Study period	Country	Study design	Maternal or child HBsAg assay	Number of children born to HBsAg-negative mothers eligible for this review	Number of children used for primary outcome	Child age at assessment	Child vaccination schedule*	Maternal mean or median age	Timing of maternal HBsAg assessment	HIV-positive mother, n/N (%)	HIV-positive child, n/N (%)
(Continued from previous page)												
Studies evaluating children of mothers with occult HBV infection												
Candotti et al (2007)[38]	NR	Ghana	Cross-sectional	Enzyme immunoassay‡‡	10	10	2 weeks	None	Median 27 years (range 15–48)	At delivery	0/10 (0%)	NR
Chasela et al (2014)[23]	2007	Malawi	Cohort	Chemiluminescent immunoassay ‡‡	16	9	2 and 48 weeks	6, 10, and 14 weeks	Median 25 years(IQR 22–29)	Prenatal (second to third trimesters)	16/16 (100%)	0/16 (0%)
Hoffmann et al (2014)[24]	2014	South Africa	Cohort	Radioimmunoassay‡‡	3	3	12 months	6, 10, and 14 weeks	Mean 29 years (IQR 16–31)	Prenatal	3/3 (100%)	0/3 (0%)

BD=hepatitis B birth dose. HBsAg=hepatitis B surface antigen. HepB-BD=hepatitis B infant vaccination birth dose. HepB3=hepatitis B infant vaccination without birth dose. NR=not reported. *See risk of bias table in appendix 2 (pp 11–14) for adherence to vaccination schedule. †Three studies examined two groups of children with distinct vaccination schedules: HepB-BD group versus no vaccine group (Yvonnet et al [1982][15]) and HepB-BD group versus HepB3 group (Ekra et al [2008][16] and Accrombessi et al [2020][17]). ‡Mean or median age of all mothers included in the study, irrespective of whether they tested negative or positive for HBsAg. §Number of children born to HBsAg-negative mothers was not reported so we used the largest number of children tested at any timepoint as a proxy. ¶Children were tested at various timepoints from birth to 38 months. In each time point only new events were recorded and infected children were not counted in the next period. Infection was defined as a HBsAg-positive test that remained positive on all subsequent tests or last sample tested. For this analysis we used the first timepoint with recorded infections (5–12 months) as subsequent timepoints might underestimate the proportion of infected children. ‖Study presented mean age at assessment; we transformed this into the range shown by adding 2 standard deviations above and below the mean. **Number of children born to HBsAg-negative mothers and number of children tested at last timepoint was not explicitly reported so we used number of mothers testing HBsAg-negative as a proxy assuming a 1:1 ratio of mothers:children. ††Vaccination was not reported in these studies. We assumed the children received vaccination as per the national immunisation programme at the time of study. For Osazuwa and Chika (2012),[42] although HepB-BD was part of the national immunisation programme in Nigeria at the time, coverage was low, so we assumed infants started vaccination at 6 weeks. ‡‡Maternal HBsAg assay only. Hepatitis B virus DNA was used as a marker of child HBV infection, using qPCR (Candotti et al [2007][38]) or COBAS Taqman assay (Chasela et al [2014][23] and Hoffmann et al [2014][24]).

Table 1: **Characteristics of 27 included studies from 29 published articles**

If a study had multiple intervention groups, a separate cohort was created for each intervention. If a longitudinal study reported children's outcomes at two or more time points between the age of 0 years and 5 years, we only used the latest timepoint for the primary outcome. In contrast, for the subgroup analysis by child age at assessment, we used age-specific infection rates reported at multiple timepoints from the same cohort.

Role of the funding source

There was no funding source for this study.

Results

Of 8856 articles identified, 29 articles[15–43] describing 27 distinct studies from 16 countries met our inclusion criteria, and were included in the systematic review and meta-analysis (figure 1; table 1). Across all the included studies, 15 448 mothers (including pregnant women) were tested for HBsAg (1463 [9·5%] were positive and 13 985 [90·5%] were negative). 10 003 children born to these HBsAg-negative women were eligible for this review, and 7690 children were included in the primary outcome. 24 studies reported HBsAg positivity as a child outcome and three used HBV DNA detection. The studies were conducted in western (n=19), eastern (n=4) and southern Africa (n=4). There were 16 cohort studies, nine cross-sectional studies, and two non-randomised intervention studies.

In terms of vaccination schedule, three studies provided two distinct paediatric cohorts: one study evaluated a no vaccination group and a group starting a vaccination series at birth,[15] and two evaluated a birth dose group and a group starting vaccination at 6–8 weeks.[16,17] 21 studies had the same vaccination schedule for all children: first dose starting at birth (n=4),[18–21] at 6–8 weeks (n=6),[22–27] and no vaccine (n=11).[28–38] Of four studies of children starting HBV vaccination at birth, one aimed to immunise within 12 h[20] and two within 24 h.[18,21] The fourth, The Gambia Hepatitis Intervention Study,[19,39,40] aimed to vaccinate children as soon as possible after birth, but allowed the administration of the first dose up to 4 weeks of life. Three studies did not explicitly provide the child vaccination schedule;[41–43] we referred to the national immunisation schedule at the time of these studies—ie, vaccination schedule starting at 6–8 weeks.[11] Although HepB-BD was the national policy in Nigeria during the study period of the study by Osazuwa and Chika,[42] the coverage was low (29% in 2011).[44] Therefore, we categorised children in this study as having received their first dose at 6–8 weeks.

The timing of maternal HBsAg evaluation varied widely among the studies: prenatally in eight studies,[20,23,24,28,29,33,36,41] at the time of delivery in eight studies,[15,18,21,25,31,34,37,38] after birth of the index child in ten studies,[17,19,22,26,27,30,32,35,42,43] and mixed in one study.[16] Three studies exclusively recruited mothers with occult HBV infection;[23,24,38] in two of these, mothers were also

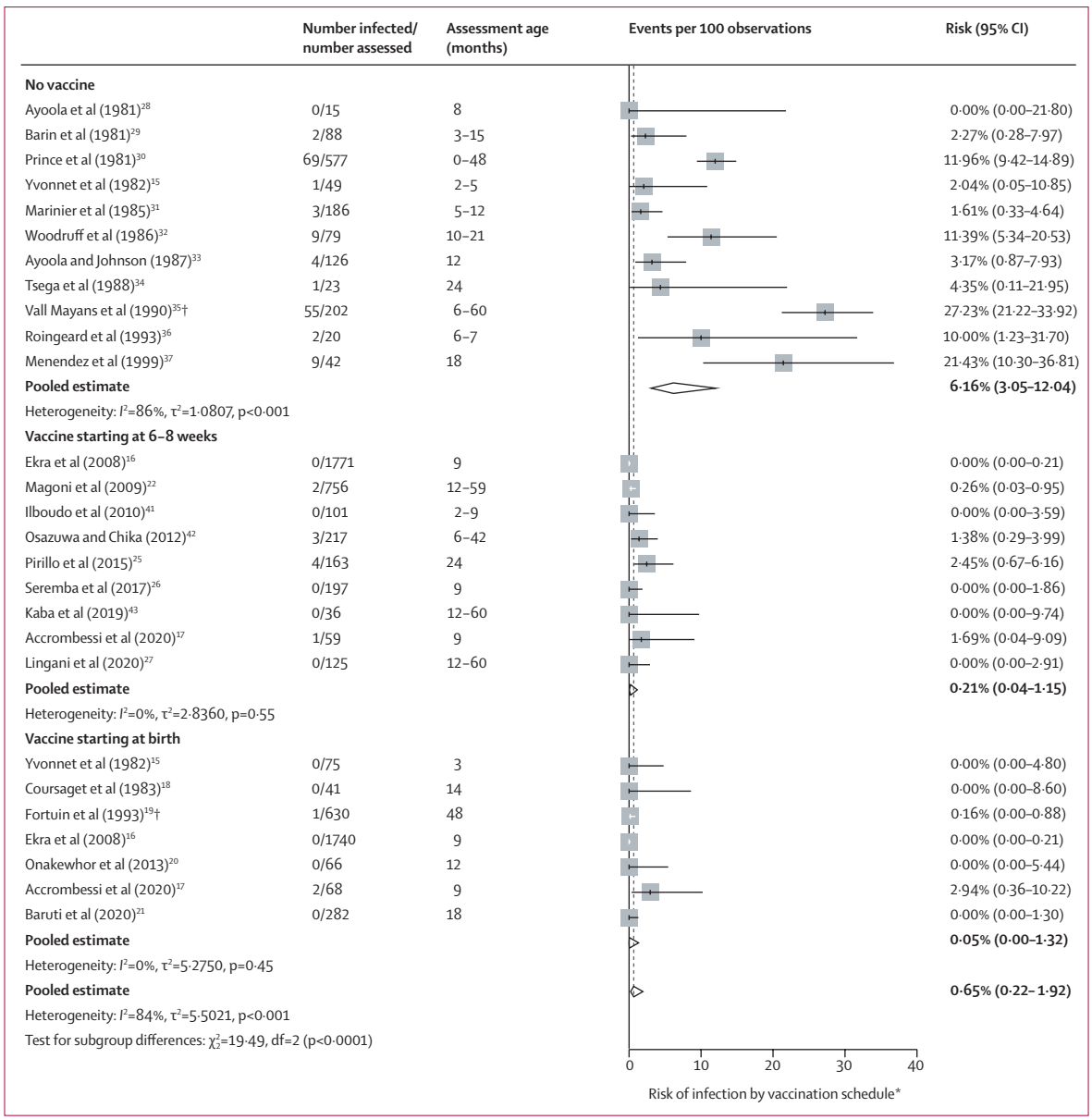


Figure 2: **Risk of hepatitis B virus infection in children of HBsAg-negative mothers by vaccination schedule**
HBsAg=hepatitis B surface antigen. *See risk of bias table in appendix 2 (pp 11–14) for data on adherence to vaccination schedules. †Infection was defined as HBsAg positivity confirmed twice, 6 months apart.

co-infected with HIV.[23,24] One study by Chasela and colleagues[23] provided children with a 7-day prophylactic course of HIV and HBV-active drugs (lamivudine) starting at birth, while another study by Hoffmann and colleagues[24] did not provide any HIV and HBV active drugs to children. In addition to these two studies of mothers co-infected with HIV and occult HBV infection, there were four studies that exclusively included mothers who were HIV-positive;[21,25,41,43] of these, Kaba and colleagues[43] exclusively studied children infected with HIV on antiretroviral treatment, all receiving a regimen active against HBV (lamivudine or tenofovir disoproxil fumarate).

The risk of bias is summarised in appendix 2 (pp 11–14). In 18 studies[15,16,18–20,23–26,28,29,31–34,36,37,41] assessing 20 distinct cohorts in which children were prospectively followed-up from the point of enrolment to the last timepoint, we were able to estimate the rate of follow-up from 15 cohorts.[15,18,20,23–26,28,29,33,34,36,37,41] The follow-up rate was high (≥75%) in nine cohorts[15,18,20,24,28,33,34,37,41] and poor in (<75%) six cohorts.[15,23,25,26,29,36] Of 13 studies[15–27] that provided hepatitis B vaccination and explicitly reported its schedule, seven[15,17–20,26,27] provided data on the number of doses actually administered to children. In all seven

	No hepatitis B vaccine (n=11)				Hepatitis B vaccine starting at 6–8 weeks (n=9)				Hepatitis B vaccine starting at birth (n=7)			
	Number of studies	Pooled estimate	95% CI	p value (test of moderators)	Number of studies	Pooled estimate	95% CI	p value (test of moderators)	Number of studies	Pooled estimate	95% CI	p value (test of moderators)
Maternal HIV infection	..	..	..	NA	..	..	..	0·44	..	..	..	1·00
<100% of mothers HIV infected	11	6·16%	3·05–12·04	..	6	0·16%	0·02–1·05	..	6	0·07%	0·00–1·58	..
100% of mothers HIV infected	0	NA	NA	..	3	0·95%	0·09–9·74	..	1	0·00%	0·00–1·30	..
Child age at assessment	..	..	..	<0·0001	..	..	..	0·0051	..	..	..	0·99
Birth	7	0·02%	0·00–8·24	..	0	NA	NA	..	2	0·00%	0·00–0·10	..
<12 months	7	2·42%	1·30–4·43	..	4	0·02%	0·00–5·09	..	4	0·02%	0·00–16·16	..
12–23 months	7	5·37%	2·62–10·70	..	3	0·00%	0·00–100·00	..	4	0·19%	0·05–0·76	..
24–35 months	2	12·77%	8·19–19·35	..	3	2·08%	0·78–5·42	..	0	NA	NA	..
36–47 months	1	16·36%	10·00–24·62	..	3	1·11%	0·36–3·37	..	1	0·33%	0·04–1·19	..
48–60 months	2	25·34%	20·71–30·60	..	3	0·25%	0·06–0·99	..	1	0·16%	0·00–0·88	..
Assay type	..	..	..	0·19	..	..	..	0·78	..	..	..	0·74
Moderately sensitive*	9	4·96%	2·19–10·85	..	4	0·26%	0·01–6·37	..	4	0·12%	0·02–0·87	..
Highly sensitive†	2	17·74%	10·11–29·27	..	5	0·23%	0·03–1·83	..	3	0·03%	0·00–13·23	..
Sample size	..	..	..	0·87	..	..	..	0·59	..	..	..	0·051
<median sample size of 88	6	7·51%	3·25–16·41	..	2	1·05%	0·15–7·09	..	4	0·47%	0·02–11·07	..
≥median sample size of 88	5	5·67%	1·92–15·58	..	7	0·15%	0·02–1·35	..	3	0·04%	0·00–0·43	..
Region	..	..	..	0·26	..	..	..	0·23	..	..	..	1·00
Western Africa	8	4·73%	1·92–11·20	..	7	0·17%	0·03–1·02	..	6	0·07%	0·00–1·58	..
Eastern Africa	3	13·07%	7·93–20·80	..	1	0·00%	0·00–1·86	..	0	NA	NA	..
Southern Africa	0	NA	NA	..	1	2·45%	0·67–6·16	..	1	0·00%	0·00–1·30	..
Period	..	..	..	NA	..	..	..	NA	..	..	..	0·91
Before EPI	11	6·16%	3·05–12·04	..	0	NA	NA	..	3	0·13%	0·02–0·95	..
After EPI	0	NA	NA	..	9	0·21%	0·04–1·15	..	4	0·02%	0·00–13·24	..

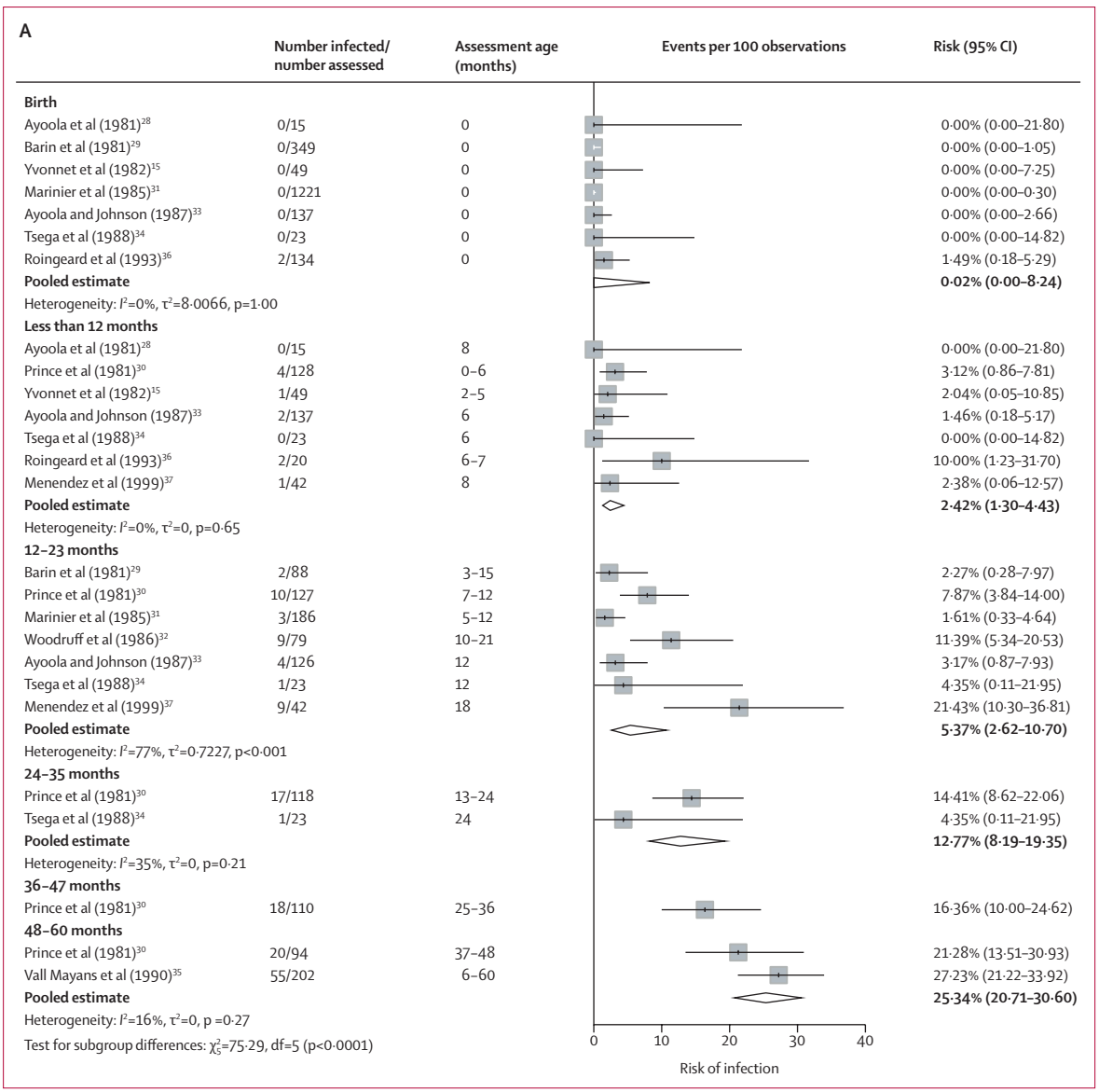
EPI=Expanded Programme on Immunization. HBsAg=hepatitis B surface antigen. NA=not applicable. *Moderately sensitive assays are radioimmunoassay, haemagglutination assay, and immunochromatography. †Highly sensitivity assays are enzyme immunoassay and chemiluminescent immunoassay.

Table 2: **Subgroup analysis for the risk of hepatitis B virus infection in children of HBsAg–negative mothers by vaccination schedule**

studies, 75% or more of children received all required doses of hepatitis B vaccination as per the study protocol. Of seven cohorts of children starting vaccination series at birth, three reported that 75% or more of children received it within 24 hours of birth.[15,17,21] Three studies did not provide data on timeliness of birth dose,[16,18,20] and in The Gambia Hepatitis Intervention Study, the median age at which children received the birth dose was 3 weeks.[40] The adapted funnel plots showed asymmetry because of two outliers in terms of sample size (HepB-BD cohort and HepB3 cohort in the study by Ekra and colleagues;[16] appendix 2 p 15).

The pooled risk of infection in children of HBsAg-negative mothers stratified by vaccination schedule differed significantly across the three groups (p<0·0001); 6·16% (95% CI 3·05–12·04; 155/1407) in the no vaccination group, 0·21% (0·04–1·15; 10/3425) in children who received their first dose at 6–8 weeks, and 0·05% (0·00–1·32; 3/2902; figure 2) in children who started the vaccination series at birth. Heterogeneity was high among studies with no vaccination (I^2=86%), and low in those starting vaccination at 6–8 weeks (I^2=0%) and at birth (I^2=0%). A study of HIV-infected children on HBV-active antiretroviral therapy[43] did not observe any HBV infection when children started vaccination at 6 weeks (0% [95% CI 0·00–9·74], 0/36). A sensitivity analysis excluding this study did not alter the pooled risk of the group with first dose of vaccination at 6–8 weeks (0·22% [0·04–1·22], 10/3389; appendix 2 p 16). In two studies that directly compared two different vaccination schedules, the risk was similar between those starting at 6–8 weeks versus at birth in Côte d'Ivoire[16] (0% [0·00–0·21], 0/1771 *vs* 0% [0·00–0·21], 0/1740) and in Benin[17] (2% [0·04–9·09], 1/59 *vs* 3% [0·36–10·22], 2/68).

In the subgroup analysis, the risk of HBV infection by vaccination schedule was further stratified according to the predefined sources of heterogeneity (table 2; appendix 2 pp 17–31). Child age at assessment was significantly associated with the prevalence of HBsAg in the unvaccinated group: the pooled risk was 0·02%



(Figure 3 continues on next page)

(95% CI 0·00–8·24; 2/1928) at birth, 2·42% (1·30–4·43; 10/414) at younger than 12 months, and 5·37% (2·62–10·70; 38/671) at 12–23 months (p<0·0001; figure 3A; table 2). In contrast, in the 6–8 weeks group and the birth dose group, the risks remained low throughout the different age groups (figure 3B–C). In the unvaccinated group, the risk of HBV infection was lower in studies using less sensitive HBsAg assays (radioimmunoassay, haemagglutination assay, or immunochromatography; 4·96% [95% CI 2·19–10·85], 144/1345) than those using highly sensitive assays (enzyme immunoassay or chemiluminescent immunoassay; 17·74% [10·11–29·27], 11/62), although the difference was not statistically significant and there were only two studies in the group using highly sensitive assays.

The multivariable meta-regression analysis, accounted for covariates identified by directed acyclic graph (appendix 2 p 10), found that the association between vaccination schedule and child HBV infection remained statistically significant (table 3). After adjusting for the study period, study region, and maternal HIV status, vaccination schedule remained significantly associated with the risk of infection; compared to no vaccination, coefficients were –3·46 (95% CI –7·16 to –0·24) for vaccination starting at 6–8 weeks and –4·46 (–7·40 to –1·53) for vaccination starting at birth (p=0·0081). Compared with the vaccination at birth as a reference, there was no significant difference in the effect size for the vaccination starting at 6–8 weeks (1·01 [–1·21 to 3·2], p=0·37).

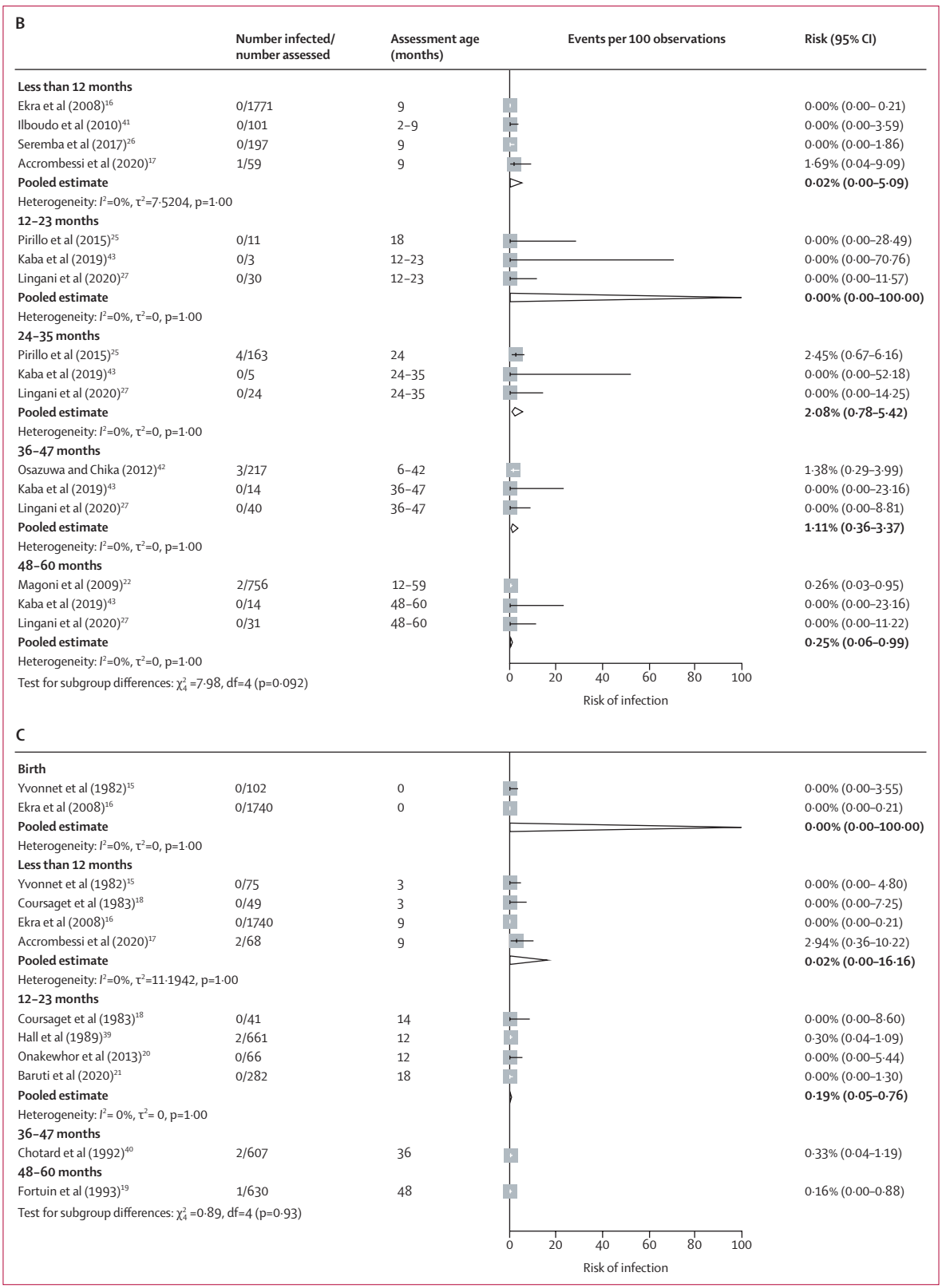


Figure 3: **Risk of hepatitis B virus infection in children of HBsAg-negative mothers by vaccination schedule and child age at assessment**
No vaccination (A), vaccination starting at 6–8 weeks (B), and vaccination starting at birth (C). HBsAg=hepatitis B surface antigen.

	Number of estimates*	Univariable analysis		Multivariable analysis†	
		Coefficient (95% CI)	p value	Coefficient (95% CI)	p value
Vaccination schedule					
No vaccine	15	0 (ref)	<0·0001	0 (ref)	0·0081
Vaccine starting at 6–8 weeks	15	−3·36 (−4·65 to −2·07)	..	−3·46 (−7·16 to −0·24)	..
Vaccine starting at birth	7	−4·28 (−6·02 to −2·54)	..	−4·46 (−7·40 to −1·53)	..
Maternal HIV infection					
<100% of mothers HIV infected or not reported	30	0 (ref)	0·13	0 (ref)	1·00
100% of mothers HIV infected	7	−2·39 (−5·50 to 0·71)	..	−15·76 (−9109·58 to 9078·06)	..
Region					
Western Africa	31	0 (ref)	0·43	0 (ref)	0·94
Eastern Africa	4	1·49 (−1·02 to 4·01)	..	0·27 (−1·19– 1·72)	..
Southern Africa	2	−0·86 (−4·51 to 2·78)	..	17·09 (−9076·73 to 9110·91)	..
Period					
Before EPI	18	0 (ref)	<0·0001	0 (ref)	0·98
After EPI	19	−3·29 (−4·74 to −1·85)	..	0·04 (−3·49 to 3·57)	..

EPI=Expanded Programme on Immunization. *For longitudinal studies that followed a cohort of children multiple times, we only considered the estimates obtained at the latest timepoint. For cross-sectional studies that reported multiple age-specific estimates, we considered each age-specific estimate independently. †A minimally sufficient set of covariates to include in the multivariable model was selected by using directed acyclic graph (appendix 2 p 10).

Table 3: **Univariable and multivariable meta-regression analyses to assess the association between vaccination schedule and child hepatitis B virus infection**

As a secondary outcome, we estimated that children born to mothers with occult HBV infection had an infection risk of 2·92% (95% CI 0·05–62·89, 1/22). However, there were only three studies which tested a total of 22 mother and child pairs, and 12 children were born to HIV-positive mothers (appendix 2 p 32).

Discussion

This systematic review and meta-analysis found that the risk of HBV infection in children of HBsAg-negative mothers in sub-Saharan Africa was 6·16% (95% CI 3·05–12·04; 155/1407) without vaccination and decreased to 0·21% (0·04–1·15; 10/3425) when the first vaccination dose was given at 6–8 weeks, and to 0·05% (0·00–1·32; 3/2902) when the vaccination was started at birth. To our knowledge, this is the first study to quantify the early horizontal transmission risk by vaccination schedule in children of HBsAg-negative mothers.

Our findings highlight the importance of infant vaccination starting at 6–8 weeks of life for children born to HBsAg-negative mothers and support the existing national recommendations for infant hepatitis B immunisation in all sub-Saharan African countries using a combined vaccine. This finding is consistent with existing data on the effectiveness of infant HBV vaccination starting at 6–8 weeks of age in reducing HBsAg prevalence in children.[7]

In addition to the combined vaccination series starting at 6–8 weeks, WHO also recommends the timely administration of monovalent hepatitis B vaccine to all neonates at birth, irrespective of maternal HBV infection, to close the gap in immunity between birth and 6–8 weeks. One of the benefits of HepB-BD vaccination, beyond the standard EPI schedule, pivots around the risk of transmission during that early period of life among children born to HBsAg-negative mothers, which, until now, has not been systematically quantified. We found that there is little horizontal transmission occurring before 6–8 weeks of life among children of HBsAg-negative mothers, and there is no significant difference in infection risk between the groups starting vaccination at birth and those starting at 6–8 weeks (p=0·37). The exact mechanism of horizontal transmission in children is not well understood. However, several studies in sub-Saharan Africa have shown that the majority of such transmissions occur within a household, particularly from older siblings, by percutaneous exposure to small quantities of blood through cuts or abrasions, or even by sharing objects such as chewing gum or toothbrushes.[4–6] These events are more probable when children become mobile and more interactive with household members other than their mothers, which might explain why we found little horizontal transmission occurring in this early window of life. Indeed, our subgroup analysis of unvaccinated children found that the prevalence of HBsAg increases steeply with age, particularly after the child's first birthday. These findings have important public health implications. First, for children born to HBsAg-negative mothers, a pentavalent or hexavalent vaccination starting at 6–8 weeks might be sufficient to prevent early horizontal transmission. Second, a selective HepB-BD strategy might be non-inferior to a universal HepB-BD strategy in terms of its effectiveness and therefore has the potential to be more cost-effective through achieving the equivalent impact for a lower cost.

However, there are other considerations beyond early horizontal transmission risk that should guide optimal choice of strategy. These considerations include local HBV epidemiology, uptake of antenatal care services, institutional delivery rate, and the availability and affordability of antenatal screening for HBsAg, which a selective strategy is dependent on. Furthermore, there might be some additional benefit of a HepB-BD vaccination for children who might miss subsequent EPI doses. Proponents of universal vaccination strategies also advocate for the ease of national scale-up compared to targeted strategies.[45]

A recent cost-effectiveness analysis in São Tomé and Príncipe in central Africa found that a universal HepB-BD strategy without maternal screening was cost-saving compared with the existing selective HepB-BD strategy, largely due to the cost of maternal screening.[46] However, the case of São Tomé and Príncipe might not be generalisable to other settings in Africa given its small population size of 200 000, high percentage of individuals born in health-care facilities (91%), and high baseline coverage of timely HepB-BD vaccination (92%). Moreover, the static model used for this cost-effectiveness analysis might not be able to fully capture the transmission benefits. Further economic analysis, incorporating the intervention-specific horizontal transmission risks obtained in our meta-analysis, would be strongly warranted to better guide decision-making.

WHO now considers ending HBV vertical transmission to be a priority for achieving global hepatitis elimination targets.[47] Because there is a residual risk of HBV vertical transmission in children born to pregnant women at high risk despite timely administration of the birth dose,[48] in 2020, WHO recommended peripartum antiviral prophylaxis for HBsAg-positive women with high viremia (≥200 000 IU/mL) or positive HBeAg, in addition to universal HepB-BD.[49] This approach requires antenatal screening for HBsAg, followed by HBV DNA or HBeAg testing for HBsAg-positive women, which generates three categories of pregnant women in terms of vertical transmission risk: high-risk (HBsAg-positive and high viremia or positive HBeAg), low-risk (HBsAg-positive and low viremia or negative HBeAg), and no-risk (HBsAg-negative). In such a context, selective peripartum antiviral prophylaxis combined with selective HepB-BD might become a more pragmatic option, which also optimises health-care resources and personalises prevention of vertical transmission interventions to meet each individual's risk, compared with the current WHO recommendation of selective peripartum antiviral prophylaxis with universal HepB-BD.

This study has limitations. First, a subset of studies (n=10) determined maternal HBV serostatus postpartum. This approach allows for the possibility of including children born to HBsAg-positive pregnant women who later seroconverted to HBsAg-negative, although the frequency of spontaneous HBsAg loss is low (1% per year) in people with chronic HBV infection in sub-Saharan Africa.[50] Second, three studies did not explicitly report the hepatitis B vaccination schedule and thus we had to assume that children in these studies followed the national recommendation at the time of the study. Of 13 studies that did report a vaccination schedule, six did not document whether children received all required doses in accordance with the protocol. Additionally, one of the seven birth dose studies allowed administration of the first dose of vaccine up to as late as 4 weeks of life,[19] therefore there might be some misclassification of children according to intervention groups. However, when it was not clear we took a conservative approach in terms of vaccine efficacy as to which group to classify the study into; this approach suggests that the genuine risk of infection in vaccinated groups should be far lower than what we reported here if the doses were administered as per protocol. Third, care must be taken when interpreting the difference in HBV risk between vaccination schedules. Although there were two non-randomised studies with a control group,[15,16] we did not identify any randomised controlled trial directly comparing different vaccination schedules and the estimates based on observational studies are prone to confounding factors. For example, all studies starting vaccination at 6–8 weeks were conducted post-EPI, whereas all of the no vaccine studies were conducted pre-EPI. This finding limits our ability to compare the risk of infection because the force of HBV infection has probably decreased over time in sub-Saharan Africa through an increase in scale-up of infant hepatitis B vaccination, but also by the reductions in sibling size and improved hygiene.[51] Nevertheless, multivariable meta-regression found that the association between the vaccination schedule and child HBV infection remained statistically significant after adjusting for the study period.

Substantial improvements in interventions to prevent HBV vertical transmission are required in Africa to reach the WHO elimination targets. Consequently, innovative strategies are urgently needed to direct interventions to where they have the most impact and provide the best value for money. Our study provides new epidemiological insights and quantifies the early horizontal transmission of HBV infection in Africa, suggesting that the current infant vaccination schedule starting at 6–8 weeks might be sufficient in children born to HBsAg-negative mothers. This finding has the potential to pave the way for antenatal HBsAg screening coupled with selective peripartum antiviral prophylaxis and selective HepB-BD in sub-Saharan Africa, which might be more feasible, sustainable, and cost-effective than the universal HepB-BD strategy.

Contributors

SN conceived the study. SN and YS developed the study protocol and supervised the study. AA and JPV screened the articles. AA performed the search. AA and JPV extracted and SN, LM, and YS verified the data. JPV and AA performed the statistical analysis under the supervision of

YS. AA, SN, and YS wrote the first draft of the manuscript. All authors had full access to all the data in the study, read and approved the final version of the manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

YS has received a research grant from Gilead and research materials from Abbott Laboratories and Fujirebio. All other authors declare no competing interests.

Data sharing

The full search strategy and key results used to generate data that inform the conclusion of this systematic review can be found in appendix 2.

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