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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 10003 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 6-8 weeks, and 0.05% (0.00-1.32; 3/2902) 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 6-8 weeks and 0.05% (0.00-1.32; 3/2902) 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 6-8 weeks and children who received their first dose at 6-8 weeks and children who received their first dose at 6-8 weeks and children who received their first dose at 6-8 weeks at 6-8 weeks and children who received their first dose at 6-8 weeks at 6-8 weeks and children who received their first dose at 6-8 weeks at 6-8 weeks and 0.05% (0.00-1.32; 3/2902) in 0.00-1.00 their first dose at 6-8 weeks at 6-8 weeks and 0.00-1.00 their first dose at 6-8 weeks at 6-8

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.

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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 scaleup of HepB3 might have reduced horizontal transmission and thus decreased HBsAg prevalence among vaccinated



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

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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 HBsAq-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 "HBsAq-negative mothers" AND "sub-Saharan Africa". We did not identify any previous systematic review.

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

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.

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.

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

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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 collegues¹⁰ (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 < 0.05 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



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

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

	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 ch	ildren of m	others 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	80	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	х Х	N
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	R
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	R	NR
Woodruff et al (1986) ≇	NR	Sudan	Cohort	Haemagglutination assay	§62	62	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	R	The Gambia	Cohort	Haemagglutination assay	661§	630	12, 36, and 48 months	<1, ≥2, and9 months	Ň	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	R
										(Table 1	continues or	next page)

	Study period	Country	Study design	Maternal or child HBs Ag 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 (%)
tinued from previ et al (2008) ¹⁶ †	ious page) 2001–02	Côte d'Ivoire	Interventional	Enzyme immunoassay	1740 in BD group;§ 2001 in HepB3	1740 in BD group; 1771 in HepB3	0 and 9 months in BD group: 6–8 weeks and 9 months in HepB3 group	<24 h, 6 weeks, 24 h, 6 weeks, 10 weeks, and 14 weeks in BD group; 6, 10, and 14 weeks in 20, and	Median 26-1 years (IQR 14-53)‡	Prenatal (third trimester) in BD group; alongside index child aged 6-8 wooks in	NR NR	NR
oni et al (2009) ²²	2007	Côte d'Ivoire	Cross- sectional	Enzyme immunoassay	9100P3 756**	756**	12-59 months	14 weeks in HepB3 group 6 weeks, 10 weeks, 14 weeks, and	Mean 28.7 years (SD 6.7)‡	HepB3 group HepB3 group Alongside index child aged 12–59 months	NR	X
ido et al (2010) ⁴¹	2007-09	Burkina Faso	Cohort	Enzyme immunoassay	101	101	2–9 months	12 months 8, 12, and 14 weeks††	Mean 30.03 years (range 19–39)	Prenatal (<32 weeks)	101/101 (100%)	0/101 (0%)
uwa and Chika 2) 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
ewhor et al 3) ²⁰	NR	Nigeria	Cohort	lmmuno- 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
$t = (2015)^{25}$	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
nba et al 7) ²⁶	2012-14	Uganda	Cohort	lmmuno- 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
etal (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††	R	Alongside index child aged 0-60 months	36/36 (100%)	36/36 (100%)
o) 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	N	X
ti 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% Cl 31.1-32.5)‡	At delivery	282/282 (100%)	0/282 (0%)
ani 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 or	next page)

	Study period	Country	Study design	Maternal or child HBsAg assay	Number of children HBsAg- egative mothers chigible for chis review	Number of children used for primary outcome	Child age at assesment	Child vaccination schedule*	Maternal mean or median age	Timing of maternal HBsAg assesment	HIV- positive mother, n/N (%)	HIV- positive child, n/N (%)
(Continued from previo	us page)											
Studies evaluating chi	ldren of m	others with	n occult HBV infe	ction								
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	6	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‡‡	m	m	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. adherence to vaccination s Accrombessi et al [2020] ¹⁷ number of children tested defined as a HBsAg-positiv of infected children, [Stud ersted at last timepoint we accination as per the nativ	HBsAg=her cchedule. †T .). ‡Mean or at any time! <i>ie</i> test that r <i>is</i> not explic and immun seks. ‡‡Mate	batitis B surfa hree studies, median age c point as a pro emained pos mean age at itly reported isation progr	ec antigen. HepB-I examined two grout of all mothers incluo ball mothers incluo sitive on all subseques istive on all subseques tassessment we tra- tassessment we tra- tasses only. Heb attime assay only. Heb attime	BB-hepatitis B infant vaccina ups of children with distinct v ded in the study, irrespective e tested at various timepoints uent tests or last sample teste ansformed this into the rangi of study. For Osazuwa and CH is D virs DNA was seed as an	tion birth dos accination sch f from birth to sch For this ans e shown by ad negative as a p nika (2012), ⁴⁴ : marker of chilc	e. HepB3=hep hedules: HepB3=hep ey tested neg; 38 months. It ilysis we used ding 2 standa ding 2 standa although Hepl infectiol	atitis B infant vaccination v -BD group versus no vaccine ative or positive for HBsA n each time point only new. the first timepoint with recc radeviations above and bel g a 1:1 ratio of mothers.chil g-B-BD was part of the nation n, using APCR (candotti etc	vithout birth dose. Ni stroug (Yvonnet et al \$Number of children events were recorded orded infections (5–1: low the mean. **Nurr dren. ±1Vaccination vo al immunisation proc al 2007 ¹⁸) or COBAS	A=not reported. *See risk c 4 [1982]™) and HepB-BD g born to HBsAg-negativen 1 and infected children wer 2 months) as subsequent ther of children born to HB was not reported in these s gramme in Nigeria at the tT Tadman assay (Chasela et the 1 and an assay (Chasela et the 1 and an assay (Chasela et the 1 and 1 and	f bias table in appendix yroup versus HepB3 grou yroup versus HepB3 grou not here was not report re not counted in the ne timepoints might under 384 progrative mothers studies. We assumed the ime, coverage was low,	(2 (pp 11–14)) up (Ekra et al ed so we used ext period. Inf restimate the and number. a children reco so we assume nn et al [2014	for 2008] ¹⁶ and tthe largest proportion proportion ived d infants !***.

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 articles¹⁵⁻⁴³ 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, 15448 mothers (including pregnant women) were tested for HBsAg (1463 [9.5%] were positive and 13985 [90.5%] were negative). 10003 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 h20 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

	Number infected/ number assessed	Assessment age (months)	Events per 100 observations	Risk (95% CI)
No vaccine				
Ayoola et al (1981) ²⁸	0/15	8	P	0.00% (0.00-21.80)
Barin et al (1981) ²⁹	2/88	3-15	÷	2.27% (0.28-7.97)
Prince et al (1981) ³⁰	69/577	0-48		11.96% (9.42–14.89)
Yvonnet et al (1982)15	1/49	2-5	• •	2.04% (0.05-10.85)
Marinier et al (1985) ³¹	3/186	5-12	· · ·	1.61% (0.33-4.64)
Woodruff et al (1986) ³²	9/79	10-21		11.39% (5.34-20.53)
Ayoola and Johnson (1987) ³³	4/126	12		3.17% (0.87-7.93)
Tsega et al (1988) ³⁴	1/23	24		4.35% (0.11-21.95)
Vall Mayans et al (1990) ³⁵ †	55/202	6-60		27.23% (21.22-33.92)
Roingeard et al (1993) ³⁶	2/20	6-7		10.00% (1.23-31.70)
Menendez et al (1999) ³⁷	9/42	18		21.43% (10.30-36.81)
Pooled estimate			\sim	6.16% (3.05-12.04)
Heterogeneity: <i>I</i> ² =86%, τ ² =1·0807, p<0·001				
Vaccine starting at 6–8 weeks				
Ekra et al (2008)16	0/1771	9		0.00% (0.00-0.21)
Magoni et al (2009) ²²	2/756	12-59	+	0.26% (0.03-0.95)
Ilboudo et al (2010)41	0/101	2-9		0.00% (0.00-3.59)
Osazuwa and Chika (2012) ⁴²	3/217	6-42		1.38% (0.29–3.99)
Pirillo et al (2015) ²⁵	4/163	24		2.45% (0.67-6.16)
Seremba et al (2017) ²⁶	0/197	9		0.00% (0.00-1.86)
Kaba et al (2019) ⁴³	0/36	12-60		0.00% (0.00-9.74)
Accrombessi et al (2020)17	1/59	9	· · · · · · · · · · · · · · · · · · ·	1.69% (0.04–9.09)
Lingani et al (2020) ²⁷	0/125	12-60	—	0.00% (0.00-2.91)
Pooled estimate			Þ	0.21% (0.04–1.15)
Heterogeneity: I ² =0%, τ ² =2·8360, p=0·55				
Vaccine starting at birth				
Yvonnet et al (1982) ¹⁵	0/75	3		0.00% (0.00-4.80)
Coursaget et al (1983)18	0/41	14		0.00% (0.00-8.60)
Fortuin et al (1993) ¹⁹ †	1/630	48	+ +	0.16% (0.00-0.88)
Ekra et al (2008)16	0/1740	9	1	0.00% (0.00-0.21)
Onakewhor et al (2013) ²⁰	0/66	12		0.00% (0.00-5.44)
Accrombessi et al (2020)17	2/68	9	· · ·	2.94% (0.36-10.22)
Baruti et al (2020) ²¹	0/282	18	÷	0.00% (0.00-1.30)
Pooled estimate			>	0.05% (0.00–1.32)
Heterogeneity: <i>I</i> ² =0%, τ ² =5·2750, p=0·45				
Pooled estimate			⊳	0.65% (0.22-1.92)
Heterogeneity: <i>I</i> ² =84%, τ ² =5·5021, p<0·001				
Test for subgroup differences: χ^2_2 =19·49, df=	2 (p<0·0001)		<u> </u>	-
			0 10 20 30	40
			Risk of infection by vaccination schedule*	

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 colleagues²³ provided children with a 7-day prophylactic course of HIV and HBV-active drugs (lamivudine) starting at birth, while another study by Hoffmann and colleagues²⁴ 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;^{21,25,4,43} of these, Kaba and colleagues⁴³ 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.^{15,18,20,23–26,28,29,33,43,6,37,41} The follow-up rate was high (\geq 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 hepat	titis B vaccin	ie (n=11)		Hepatitis	s B vaccine s	starting at 6–8 v	veeks (n=9)	Hepatitis	B vaccine s	tarting 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%	0.00-2.09		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 88<="" of="" sample="" size="" td=""><td>6</td><td>7.51%</td><td>3.25-16.41</td><td></td><td>2</td><td>1.05%</td><td>0.15-7.09</td><td></td><td>4</td><td>0.47%</td><td>0.02-11.07</td><td></td></median>	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 HBsAgnegative mothers stratified by vaccination schedule differed significantly across the three groups (p<0.0001); $6\cdot16\%$ (95% CI $3\cdot05-12\cdot04$; 155/1407) in the no vaccination group, $0\cdot21\%$ ($0\cdot04-1\cdot15$; 10/3425) in children who received their first dose at 6-8 weeks, and $0\cdot05\%$ ($0\cdot00-1\cdot32$; 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 therapy⁴³ 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'Ivoire¹⁶ (0% [0·00–0·21], 0/1771 vs 0% [0·00–0·21], 0/1740) and in Benin¹⁷ (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%

Birch Apoola et al (1981)¹⁰ 0/15 0 000% (000-128) 000% (000-128) 000% (000-128) 000% (000-200) 000% (000-200) 000% (000-200) 000% (000-200) 000% (000-218) 000% (000-218) 000% (000-218) 000% (000-218) 000% (000-218) 000% (000-266) 000% (000-218) 000% (100-218) 000% (100-219) <	A	Number infected/ number assessed	Assessment age (months)	Events per 100 observations	Risk (95% CI)
Ayoola at al (1981) ¹⁹ 0/349 0 Bain et al (1982) ¹⁹ 0/349 0 Ocores (1987) ¹⁹ 0/349 0 Ocores (1987) ¹⁹ 0/349 0 Ocores (1987) ¹⁹ 0/37 Ocores (1987) ¹⁰ 0/37 Noola at al (1993) ¹⁸ 0/137 0 Freq at al (1993) ¹⁸ 2/134 0 Ocores (1993) ¹⁸ 2/134 0 Ocores (1993) ¹⁸ 2/134 0 Ocores (1993) ¹⁹ 0/15 8 Ayoola at al (1993) ¹⁹ 0/15 8 Ayoola at al (1981) ¹⁹ 0/15 8 Ayoola at al (1981) ¹⁹ 1/15 8 Ayoola at al (1982) ¹⁹ 1/42 0 Ocores (1987) ¹⁰ 1/15 8 Ayoola at al (1982) ¹⁹ 1/49 2-5 Ayoola at al (1982) ¹⁹ 1/49 2-5 Ayoola at al (1983) ¹⁸ 2/137 6 Freq at al (1981) ¹⁹ 1/147 6 Dece at (1981) ¹⁹ 1/147 8 Ayoola at al (1993) ¹⁸ 2/20 6-7 Heterogenetic, <i>F</i> =0%, r ⁺ 0, p=0.65 12-23 Month Frince at al (1981) ¹⁹ 1/142 8 Ayoola fraid (1993) ¹⁹ 1/142 8 12-33 Ayoola and Johnson (1987) ¹¹ 4/126 1 12-33 months Frince at al (1981) ¹⁹ 1/127 7-12 Ayoon (1987) ¹¹ 4/126 1 12-33 Ayoola and Johnson (1987) ¹¹ 4/126 1 12-33 months Frince at al (1981) ¹⁹ 1/123 12 12-3 Ayoola and Johnson (1987) ¹¹ 4/126 1 12-3 months Frince at al (1981) ¹⁹ 1/118 13-24 13-34 (1988) ¹⁴ 1/23 12 14-4 4/35% (011-2195) Frince at al (1981) ¹⁹ 1/118 13-24 14-4 4/35% (011-2195) Frince at al (1981) ¹⁹ 1/119 Frince at al (1981) ¹⁹ 1/119 Frinc	Birth				
Define at al (1981) ¹⁹ 0/349 0 000% (000-105) Vonnet et al (1985) ¹⁹ 0/1221 0 000% (000-26) Avoita and Johnson (1987) ¹⁰ 0/137 0 000% (000-26) Toge at al (1988) ¹⁴ 0/23 0 000% (000-35) Probled stimate 002% (000-324) 000% (000-324) Heterogenetic, P-0%, c+8-0066, p=1-00 002% (000-324) Less than 12 months 002% (000-324) Avoolat al (1981) ¹⁸ 0/15 8 Prince et al (1981) ¹⁸ 0/15 8 Prince et al (1982) ¹⁵ 1/49 2-5 Avoolat al (1983) ¹⁸ 0/12 6 Spooland Johnson (1987) ¹⁹ 2/137 6 Vonnet et al (1983) ¹⁸ 0/23 6 Spooland Johnson (1987) ¹⁹ 2/137 6 Vooland Johnson (1987) ¹⁹ 2/137 6 Pooled estimate 23% (00-6-257 Letrogenetic, P'-0%, c+0, p-0.65 227% (0.28-797) Log 1981) ¹⁹ 1/127 7-12 Neminde et al (1981) ¹⁹ 1/126 12 Letrogenetic, P'-0%, c+0, p-0.21 37% (2.62-10.70 <td>Ayoola et al (1981)²⁸</td> <td>0/15</td> <td>0</td> <td></td> <td>0.00% (0.00-21.80)</td>	Ayoola et al (1981) ²⁸	0/15	0		0.00% (0.00-21.80)
Yonnet et al (1987) ¹⁶ 0/49 0 000% (000-725) Marinier et al (1985) ¹¹ 0/137 0 000% (000-735) Stoppola and Johnson (1987) ¹⁸ 0/137 0 000% (000-245) Stoppola and Johnson (1987) ¹⁸ 0/137 0 000% (000-245) Stoppola and Johnson (1987) ¹⁸ 0/13 0 000% (000-245) Stoppola and Johnson (1987) ¹⁸ 0/15 8 0.00% (000-2180 Pooled estimate 0.02% (000-2180 312% (066-824) Vonnet et al (1981) ¹⁹ 1/49 2-5 2.04% (0.05-10.85 Yoonnet et al (1981) ¹⁹ 1/49 2-5 2.04% (0.05-10.85 Stoppat and Johnson (1987) ¹⁹ 1/137 6 0.00% (0.00-44.82 Nonendez et al (1993) ¹⁹ 2/137 6 0.00% (0.00-44.82 Prince et al (1993) ¹⁹ 1/128 3-6 0.00% (0.00-44.82 Noola and Johnson (1987) ¹⁹ 1/128 3-15 2.04% (0.05-10.85 2.23month 2/20 6-7 1.000% (1.23-87.97) Prince et al (1980) ¹⁹ 10/127 7-12 7.87% (3.84-	Barin et al (1981) ²⁹	0/349	0		0.00% (0.00-1.05)
Marine et al (1987) ¹⁶ 0/1221 0 Ayola and Johnson (1987) ¹³ 0/137 0 Ersage at al (1988) ¹⁴ 0/23 0 Pooled estimate Heterogeneity: F-0%, t ⁻ e.80066, p-100 Less than 12 months Ayoola at al (1983) ¹⁶ 0/15 8 Ayoola at al (1981) ¹⁷ 1/18 0 Sampa et al (1981) ¹⁸ 0/15 8 Ayoola at al (1981) ¹⁸ 1/128 0-6 Monnet at al (1981) ¹⁸ 1/127 7-12 Monnet at al (1981) ¹⁸ 1/126 12 Monnet at al (1981) ¹⁸ 1/126 12 Monnet at al (1981) ¹⁸ 1/126 12 Monnet at al (1983) ¹⁸ 1/123 12 Monnet at al (1983) ¹⁸ 1/123 12 Monnet at al (1983) ¹⁸ 1/23 24 Meterogeneity: F-77%, t ⁻ -0.7227, p-0.001 Z+35 months Phine et al (1981) ¹⁸ 1/118 13-24 Heterogeneity: F-75%, t ⁺ -0, p-0.21 S-47 months Phine et al (1981) ¹⁸ 1/23 2/4 Mondet at al (1981) ¹⁸ 1/23 2/4 Mondet at al (1981) ¹⁸ 1/23 2/4 Meterogeneity: F-15%, t ⁺ -0, p-0.27 To follow Minus et al (1991) ¹⁹ 5/202 6-60 Z-23% (10.00-246 Z-36% (10.00-246 Z-3	Yvonnet et al (1982) ¹⁵	0/49	0		0.00% (0.00-7.25)
Ayoola and Johnson (1987) ¹⁰ 0/137 0 Srega et al (1988) ¹⁰ 0/33 0 Pooled estimate Heterogeneity: $f=0$, $t=0$ Less than 12 months Ayoola and Johnson (1987) ¹⁰ 2/137 6 Sega et al (1981) ¹⁰ 1/49 2-5 Ayoola and Johnson (1987) ¹¹ 2/137 6 Sega et al (1981) ¹⁰ 1/49 2-5 Ayoola and Johnson (1987) ¹¹ 2/137 6 Sega et al (1981) ¹⁰ 1/49 2-5 Ayoola and Johnson (1987) ¹¹ 2/137 6 Sega et al (1981) ¹⁰ 1/49 2-5 Pooled estimate Heterogeneity: $f=0$, $t=0$, $p=0.65$ L227% ($0.28-791$) Thice et al (1981) ¹⁰ 1/42 8 Barin et al (1981) ¹⁰ 1/42 8 Ayoola and Johnson (1987) ¹¹ 2/137 7 Pooled estimate Heterogeneity: $f=0$, $t=0$, $p=0.65$ L227% ($0.28-791$) Thice et al (1981) ¹⁰ 1/127 7-12 Mariner et al (1985) ¹¹ 1/13 L238 months Pooled estimate Heterogeneity: $f=0$, $t=0$, $p=0.65$ L227% ($0.28-791$) Menendez et al (1981) ¹⁰ 1/13 L238 ($0.06-12.57$ Pooled estimate Heterogeneity: $f=0$, $t=0$, $p=0.65$ L237% ($0.28-791$) Menendez et al (1981) ¹⁰ 1/13 L238 ($0.06-12.57$ L238 ($0.08-7.91$) L238 ($0.03-36$ 4 L238 ($0.03-36$ 4 L238 ($0.03-36$ 4 L238 ($0.03-36$ 4 L238 ($0.03-246$ 4 L238 ($0.03-246$ 2 L238 ($0.12-12.59$ L238 ($0.12-12.59$	Marinier et al (1985) ³¹	0/1221	0		0.00% (0.00-0.30)
Tagga et al (1988) ¹⁴ 0/23 0 000% (0.00-14.82 Roingard et al (1993) ¹⁶ 2/134 0 0.00% (0.00-8.24) Pooled estimate 0.00% (0.00-8.24) 0.00% (0.00-8.24) Heterogeneity: $F = 0\%$, $r = 8.0066$, $p = 1.00$ 0.00% (0.00-21.80 0.00% (0.00-21.80 Less than 12 months 0.00% (0.00-21.80 0.00% (0.00-21.80 0.00% (0.00-21.80 Ayoola at al (1981) ¹⁶ 4/128 0.6 3.12% (0.86-7.81) 0.00% (0.00-21.80 Ayoola at al (1982) ¹⁵ 1/49 2-5 0.00% (0.00-21.80 0.00% (0.00-21.80 Ayoola at al (1983) ¹⁶ 0/13 6 0.00% (0.00-21.80 0.00% (0.00-21.80 Ayoola at al (1983) ¹⁶ 0/23 6 0.00% (0.00-21.80 0.00% (0.00-21.80 Brin et al (1983) ¹⁶ 0/23 6 0.00% (0.00-21.80 0.00% (0.00-21.80 0.00% (0.00-21.80 0.00% (0.00-21.80 0.00% (0.00-21.80 0.00% (0.00-21.80 0.00% (0.00-21.80 0.00% (0.00-21.80 0.00% (0.00-21.80 0.00% (0.00-24.82 0.00% (0.00-24.82 0.00% (0.00-24.82 0.00% (0.00-24.82 0.00% (0.00-24.82 0.00% (0.00-24.82 0.00% (0.00-24.82 0.00% (0.00-24.82 0.00% (0.00-24.82 0.00% (0.00-24.82 <td>Ayoola and Johnson (1987)³³</td> <td>0/137</td> <td>0</td> <td>_</td> <td>0.00% (0.00-2.66)</td>	Ayoola and Johnson (1987) ³³	0/137	0	_	0.00% (0.00-2.66)
Rongeard et al (1993) ¹⁶ 2/134 0 Pooled stimate Heterogeneity: $F = 0\%$, $r = 8.20066$, $p = 1.00$ Less than 12 months Aycola at al (1981) ¹⁹ 0/15 8 Aycola at al (1981) ¹⁹ 1/137 6 Trege at al (1981) ¹⁹ 1/137 6 Rongeard et al (1982) ¹⁸ 1/49 2-5 Aycola and Johnson (1987) ¹⁰ 2/137 6 Rongeard et al (1983) ¹⁸ 1/42 8 Pooled stimate Heterogeneity: $F = 0\%$, $r = 0$, $p = 0.65$ L22% ($0.28.797$) Menendez et al (1983) ¹⁹ 1/127 7-12 Rarine et al (1985) ¹⁹ 1/126 12 Trege at al (1985) ¹⁹ 1/126 12 Rongeard et al (1985) ¹⁹ 1/126 12 Rongeard (1985) ¹⁹ 1/126 12 Rongeard (1985) ¹⁹ 1/126 12 Rongeard et al (1985) ¹⁹ 1/128 13-24 Rongeard (1985) ¹⁹ 1/128 3/26 Pooled stimate Heterogeneity: $F = 7\%$, $r = 0.727$, $p = 0.001$ Z4-35 months Prince et al (1981) ¹⁹ 1/118 13-24 Rongeard (1988) ¹⁶ 1/23 2/4 Pooled stimate Heterogeneity: $F = 7\%$, $r = 0.727$, $p = 0.001$ Z4-35 months Prince et al (1981) ¹⁹ 1/118 13-24 Rongeard (1988) ¹⁶ 1/23 2/4 Pooled stimate Heterogeneity: $F = 7\%$, $r = 0.727$, $p = 0.001$ Z4-35 months Prince et al (1981) ¹⁹ 2/094 37-48 Vall Mayns et al (1990) ¹⁹ 5/5/202 6-60 Prince et al (1981) ¹⁹ 2/094 37-48 Vall Mayns et al (1990) ¹⁹ 5/5/202 6-60 Pooled stimate Heterogeneity: $F = 16\%$, $r = 0$, $p = 0.27$ Test for subgroup differences: $r = 75$ -29, dif-5 ($p = 0.001$) Bel di infertion Prince et al (1981) ¹⁹ 2/094 37-48 Vall Mayns et al (1990) ¹⁹ 5/5/202 6-60 Pooled stimate Heterogeneity: $F = 16\%$, $r = 0$, $p = 0.27$ Test for subgroup differences: $r = 75$ -29, dif-5 ($p = 0.001$) Prince et al (1981) ¹⁹ 2/094 37-48 Vall Mayns et al (1990) ¹⁹ 5/5/202 6-60 Pooled stimate Heterogeneity: $F = 16\%$, $r = 0$, $p = 0.27$ Test for subgroup differences: $r = 75$ -29, dif-5 ($p = 0.001$) Prince te al (1981) ¹⁹ 2/094 37-48 Vall Mayns et al (1990) ¹⁹ 5/5/202 6-60 Prince et al (1981) ¹⁹ 2/094 37-48 Vall Mayns et al (1990) ¹⁹ 5/5/202 6-60 Prince et al (1981) ¹⁹ 2/094 37-48 Vall Mayns et al (1990) ¹⁹ 5/5/202 6-60 Prince et al (1980) ¹⁰ 1/118	Tsega et al (1988) ³⁴	0/23	0		0.00% (0.00-14.82)
Pooled estimate 0-02% (0-00-3:4) Heterogeneity: $f=0\%$, $t^2=0.0066$, $p=1.00$ 0-00% (0-00-21:80 Lest than 12 months 0-06 Ayoola et al (1981) ¹⁹ 0/15 8 Prince et al (1981) ¹⁹ 1/128 0-6 Synonet et al (1982) ³ 1/49 2-5 Ayoola and Johnson (1987) ³¹ 2/137 6 Singeadt et al (1983) ³¹ 0/23 6 Songeadt et al (1993) ³¹ 2/20 6-7 Songeadt et al (1993) ³¹ 1/42 8 Pooled estimate 2.24% (0.06-12.57 Pooled estimate 2.24% (0.28-7.97) Heterogeneity: $F=0\%$, $t^2=0$, $p=0.65$ 2.27% (0.28-7.97) Pince et al (1981) ³¹ 10/127 7-12 Pooled estimate 2.27% (0.28-7.97) Pince et al (1981) ³¹ 10/127 7-12 Ayoola and Johnson (1987) ³¹ 4/126 12 Pooled estimate 11.39% (5.34-20.53 11.39% (5.34-20.53 Pooled estimate 14.31% (6.36-22.06 12.35% (0.11.21.95) Pooled estimate 14.31% (6.36-22.06 12.35% (0.11.21.95) Pooled estimate 12.37% (5.11.21	Roingeard et al (1993) ³⁶	2/134	0	-	1.49% (0.18-5.29)
Heterogeneity: f^{-0} %, τ^{-8} -80066, p=1.00 Lest han 12 months Prince et al (1981) ⁹ 0/15 8 Prince et al (1982) ⁵ 1/49 2-5 Prince et al (1982) ⁵ 1/49 2-5 Prince et al (1983) ⁹ 0/123 6 Roingeard et al (1993) ⁹ 2/137 6 Roingeard et al (1993) ⁹ 2/23 6 Roingeard et al (1993) ⁹ 1/42 8 Pooled estimate Heterogeneity: f^{-7} %, τ^{-6} 0, p=0.65 L2-23 months Prince et al (1981) ⁹ 10/127 7-12 Roingeard al (1983) ¹⁸ 10/127 7-12 Roingeard al (1983) ¹⁹ 10/127 7-13 Roingeard al (1983) ¹⁹ 10/128 2-3 Roingeard al (1983) ¹⁹ 10/128 2-3 Roing	Pooled estimate			\geq	0.02% (0.00-8.24)
Less than 1 p moths Aycola at 21 (1981) ¹⁶ 0/15 8 Prince et al (1982) ¹⁶ 1/128 0-6 Younet et al (1982) ¹⁵ 1/49 2-5 Aycola and Johnson (1987) ¹⁷ 2/137 6 Taga et al (1988) ¹⁴ 0/23 6 Roingeard et al (1993) ¹⁶ 2/20 6-7 Pooled estimate 12-23 moths Barin et al (1981) ¹⁹ 2/88 3-15 Prince et al (1981) ¹⁹ 10/127 7-12 Prince et al (1981) ¹⁹ 10/126 12 Prince et al (1981) ¹⁹ 17/118 13-24 Heterogeneity: <i>F</i> -375%, <i>x</i> ² =0, p=0.21 36-47 months Prince et al (1981) ¹⁹ 18/110 25-36 43-50 months Prince et al (1981) ¹⁹ 18/110 25-36 43-60 months Prince et al (1981) ¹⁹ 10/127 3-24 537% (262-1070 Heterogeneity: <i>F</i> -375%, <i>x</i> ² =0, p=0.21 36-47 months Prince et al (1991) ¹⁹ 20/94 37-48 Vall Maynes et al (1990) ¹⁵ 55/202 6-60 Prince et al (1991) ¹⁹ 20/94 37-48 Vall Maynes et al (1990) ¹⁵ 55/202 6-60 Prince et al (1991) ¹⁹ 20/94 37-48 Vall Maynes et al (1990) ¹⁵ 55/202 6-60 Prince et al (1991) ¹⁹ 20/94 37-48 Prince et al (1	Heterogeneity: $l^2 = 0\%$, $\tau^2 = 8.0066$,	p=1.00			· · · · · · · · · · · · · · · · · · ·
Ayola et al (1981) ²⁸ 0/15 8 Prince et al (1981) ²⁹ 4/128 0-6 Yonnet et al (1982) ¹⁵ 1/49 2-5 Ayola and Johnson (1987) ¹³ 2/137 6 Ayola and Johnson (1987) ¹³ 2/137 6 Ayola and Johnson (1987) ¹³ 2/137 6 At (1983) ²⁶ 0/23 6 Ayola and Johnson (1987) ¹³ 2/137 6 Brine et al (1993) ²⁶ 1/22 6 Pooled estimate Heterogeneity: $F=0\%$, $t^2=0$, $p=0.65$ 12-23 months Barin et al (1981) ²⁶ 0/127 7-12 Pooled estimate Pooled estimate Prince et al (1981) ²⁶ 1/23 12 Menendez et al (1985) ²⁶ 1/23 12 Menendez et al (1981) ²⁶ 1/21 123 24 Meterogeneity: $F=37\%$, $t^2=0$, $p=0.21$ 36-47 months Prince et al (1981) ²⁶ 20/94 37-48 Vall Maynes et al (1990) ³⁵ 5/202 6-60 Pooled estimate Heterogeneity: $F=15\%$, $t^2=0$, $p=0.21$ 36-47 months Prince et al (1981) ²⁶ 20/94 37-48 Meterogeneity: $F=15\%$, $t^2=0$, $p=0.27$ Test for subgroup differences: $g^2=752$, $g^4=5$ ($p=0.0001$) Else finiferion	Less than 12 months				
Prince et al $(1981)^{59}$ 4/128 0-6 Wonnet et al $(1982)^{55}$ 1/49 2-5 Ayoola and Johnson $(1987)^{73}$ 2/137 6 Trege at al $(1983)^{56}$ 2/20 6-7 Nenendez et al $(1993)^{57}$ 2/20 6-7 Poloid estimate Heterogeneity: $P=0\%$, $t^*=0$, $p=0.65$ 12-23 months Barin et al $(1981)^{59}$ 2/88 3-15 Prince et al $(1981)^{59}$ 10/127 7-12 Heterogeneity: $P=0\%$, $t^*=0$, $p=0.65$ 12-23 months Prince et al $(1981)^{59}$ 10/127 7-12 Heterogeneity: $P=7\%$, $t^*=0$, $p=0.27$ Prince et al $(1981)^{59}$ 10/127 7-12 Heterogeneity: $P=7\%$, $t^*=0$, $p=0.27$ Prince et al $(1981)^{59}$ 10/128 Prince et al $(1981)^{59}$ 10/127 7-12 Heterogeneity: $P=7\%$, $t^*=0$, $p=0.27$ Prince et al $(1981)^{59}$ 10/127 Prince et al $(1981)^{59}$ 10/128 Prince et al $(1981)^{59}$ 10/118 Prince et al $(1981)^{59}$ 10/118 Prince et al $(1981)^{59}$ 10/118 Prince et al $(1981)^{59}$ 10/118 Prince et al $(1981)^{59}$ 18/110 25-36 Prince et al $(1981)^{59}$ 20/94 37-48 Prince et al $(1991)^{59}$ 20/94 37-48 Prince et al	Avoola et al (1981) ²⁸	0/15	8		0.00% (0.00-21.80)
Yvonnet et al $(1982)^{15}$ $1/49$ 2-5 Aycola and Johnson $(1987)^{13}$ $2/137$ 6 Bain et al $(1988)^{14}$ $0/23$ 6 Nonendez et al $(1993)^{16}$ $2/20$ 6-7 Pooled estimate 238% $(0.06-12.57)$ Heterogeneity: $F-05$, $\tau=0$, $p=0.65$ 242% $(13.0-4.43)$ Nondari et al $(1981)^{19}$ $10/127$ 7-12 Marine et al $(1981)^{19}$ $10/127$ 7-12 Marine et al $(1985)^{13}$ $3/186$ 5-12 Yoola ad Johnson $(1987)^{13}$ $4/126$ 12 Mooduly et al $(1986)^{12}$ $9/79$ 10-21 Aycola and Johnson $(1987)^{13}$ $4/126$ 12 Marine et al $(1980)^{19}$ $9/79$ 10-21 Aycola and Johnson $(1987)^{13}$ $4/126$ 12 Marine et al $(1980)^{19}$ $1/138$ 12-4 Poile destimate 537% (2.62-10.70) Heterogeneity: $F-35\%$, $\tau=0$, $p=0.21$ $36-47$ $36-47$ months $1/2332$ $2/4$ Prince et al $(1981)^{19}$ $18/110$ $25-36$ $43-60$ months 12.28% ($13.51-30.92$	Prince et al (1981) ³⁰	4/128	0-6	·	3.12% (0.86-7.81)
Ayoola and Johnson (1987) ¹³ 2/137 6 Ayoola and Johnson (1987) ¹³ 2/137 6 Roingeard et al (1993) ¹⁶ 0/23 6 Roingeard et al (1993) ¹⁶ 2/20 6-7 Meendez et al (1993) ¹⁶ 1/42 8 Pooled estimate Heterogeneity: $P=0\%$, $r^2=0$, $p=0.65$ 1 .2-23 Pooled estimate Heterogeneity: $P=0\%$, $r^2=0$, $p=0.65$ 1 .2-37 Pooled estimate Heterogeneity: $P=0\%$, $r^2=0$, $p=0.65$ 1 .2-23 Pooled estimate Heterogeneity: $P=0\%$, $r^2=0$, $p=0.27$ Pooled estimate 1 .237 Pooled estimate 1 .237 1 .247 1 .247 1 .237 1 .247 1 .247 1 .237 1 .247 1 .247 1 .247 1 .237 1 .247 1 .247 1 .237 1 .247 1 .247 1 .237 1 .247 1 .247 1 .247 1 .237 1 .247 1 .257 1 .277 1 .	Yvonnet et al (1982) ¹⁵	1/49	2-5		2.04% (0.05-10.85)
Targe at al (1988) ³⁴ 0/23 6 000% (0.00-1452 Reingeard et al (1993) ³⁶ 2/20 6-7 10.00% (1.23-31.70) Menendez et al (1993) ³⁶ 2/20 6-7 10.00% (1.23-31.70) Menendez et al (1993) ³⁶ 2/20 6-7 10.00% (1.23-31.70) Pooled estimate 2.38% (0.06-12.57) 2.42% (1.30-4.43) Heterogeneity: $P=0\%$, $r^2=0$, $p=0.65$ 2.27% (0.28-797) 7-12 Barin et al (1981) ³⁰ 10/127 7-12 7-87% (3.84-14.00) Marinier et al (1981) ³⁰ 10/127 7-12 7-87% (3.84-14.00) Moodruff et al (1981) ³⁰ 4/126 12 317% (0.87-793) Yoola ad (bhoson (19.87) ³¹ 4/126 12 317% (0.87-793) Yoola estimate 537% (2.62-10.70) 11.39% (5.34-20.53) 11.39% (5.34-20.53) Pooled estimate 122 4.35% (0.11-21.95) 11.43% (0.86-22.06) 137% (0.87-793) Heterogeneity: $r^2-77\%$, $r^2=0.7227$, $p<0.001$ 24-35 14.41% (0.86-2-2.06) 14.35% (0.11-21.95) Prince et al (1981) ³⁰ 18/110 25-36 16.36% (10.00-24.6 27.23% (2.2-3.92) Pooled estimate 21.28% (13.51-	Avoola and Johnson (1987)33	2/137	6 -	_	1.46% (0.18-5.17)
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Tsega et al (1988) ³⁴	0/23	6 +		0.00% (0.00-14.82)
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Roingeard et al (1993) ³⁶	2/20	6-7		10.00% (1.23-31.70)
Pooled estimate 2.42% $(130-443)$ Heterogeneity: $l^2 = 0\%$, $t^2 = 0$, $p = 0.65$ 2.27% $(0.28-797)$ 12-23 months 2.27% $(0.28-797)$ Barin et al $(1981)^{19}$ 2/88 3-15 Prince et al $(1985)^{11}$ 0/127 7-12 Marinier et al $(1985)^{12}$ 9/79 10-21 7.67% $(3.84-14.00)$ Woodriff et al $(1986)^{12}$ 9/79 10-21 11.39% $(5.34-20.53)$ Ayoola and Johnson $(1987)^{13}$ 4/126 12 31.7% $(0.87-793)$ Seqa et al $(1988)^{14}$ 1/23 12 4.35% $(0.11-21-95)$ Meterogeneity: $l^2 = 77\%$, $t^2 = 0.7227$, $p < 0.001$ 24-35 months 14.41% $(8.62-22.06)$ Prince et al $(1981)^{10}$ 17/118 13-24 14.41% $(8.62-22.06)$ Z4-35 months 12.23 24 4.35% $(0.11-21-95)$ Pooled estimate 12.23 24 4.35% $(0.11-21-95)$ Actionate al $(1981)^{10}$ 18/110 25-36 16.36% $(10-00-24.66)$ Valid Mayans et al $(1981)^{10}$ 20/94 37-48 21.28% $(13.51-30.92)$ 27.23% $(21.22-33.92)$ Prince et al $(1981)^{10}$ 20/94 37-48 21.28% $(13.51-30.92)$ <	Menendez et al (1999) ³⁷	1/42	8		2.38% (0.06-12.57)
Heterogeneity: $P=0\%$, $t^{2}=0$, $p=0.65$ 12-23 months Barin et al (1981) ³⁰ 2/88 3-15 Prince et al (1985) ³¹ 3/186 5-12 Modurif et al (1985) ³¹ 3/186 5-12 Modurif et al (1985) ³¹ 3/186 5-12 Modurif et al (1985) ³² 9/79 10-21 Ayoola and Johnson (1987) ³³ 4/126 12 Heterogeneity: $P=77\%$, $t^{2}=0.7227$, $p<0.001$ 24-35 months Prince et al (1981) ³⁰ 17/118 13-24 Heterogeneity: $P=35\%$, $t^{2}=0$, $p=0.27$ Frince et al (1981) ³⁰ 20/94 37-48 Heterogeneity: $P=16\%$, $t^{2}=0$, $p=0.27$ Test for subgroup differences: $t_{c}^{2}=75\cdot29$, df=5 ($p<0.0001$) Exit of infertion	Pooled estimate			\diamond	2.42% (1.30-4.43)
12-23 months Barin et al (1981) ³⁰ 10/127 7-12 Marinier et al (1981) ³⁰ 10/127 7-12 Marinier et al (1985) ³¹ 3/186 5-12 Moodruff et al (1986) ³² 9/79 10-21 Ayoola and Johnson (1987) ³³ 4/126 11-39% (5-34-20-53) Ayoola and Johnson (1987) ³³ 4/126 12 Tsega et al (1988) ³⁴ 1/23 12 Menedez et al (1999) ³⁷ 9/42 18 Pooled estimate 5-37% (2-62-10-70) Peterogeneity: $P=77\%$, $r^2=0.7227$, p<0-001	Heterogeneity: $l^2=0\%$, $\tau^2=0$, $p=0.6^{10}$	5			
Barin et al $(1981)^{39}$ 2/88 3-15 Prince et al $(1981)^{30}$ 10/127 7-12 Marinier et al $(1985)^{31}$ 3/186 5-12 Woodruff et al $(1986)^{32}$ 9/79 10-21 Ayoola and Johnson $(1987)^{33}$ 4/126 12 Tseg at al $(1988)^{34}$ 1/23 12 Menendez et al $(1999)^{37}$ 9/42 18 Pooled estimate Prince et al $(1981)^{30}$ 17/118 13-24 Tseg at al $(1981)^{30}$ 18/110 25-36 Poled estimate Prince et al $(1981)^{30}$ 18/110 25-36 Prince et al $(1981)^{30}$ 20/94 37-48 Prince et al $(1981)^{30}$ 20/94 37-48 Prince et al $(1990)^{35}$ 55/202 6-60 Poled estimate Heterogeneity: l^2 -16%, t^2 =0, p=0.27 Tset for subgroup differences: χ_c^2 =75:29, df-5 (p<0.0001) Bick of infertion Bick of infertion	12-23 months				
Prince et al $(1981)^{30}$ 10/127 7-12 Marinier et al $(1985)^{31}$ 3/186 5-12 Modulf et al $(1985)^{31}$ 3/186 5-12 Modulf et al $(1985)^{32}$ 9/79 10-21 11.39% $(534-20.53)^{33}$ Ayoola and Johnson $(1987)^{33}$ 4/126 12 31.7% $(0.877-73)$ Tsega et al $(1988)^{34}$ 1/23 12 Menendez et al $(1998)^{37}$ 9/42 18 Poled estimate Heterogeneity: $P=77\%$, $t^2=0.7227$, p<0.001 24-35 months Prince et al $(1981)^{30}$ 17/118 13-24 Tsega et al $(1988)^{34}$ 1/23 24 Poled estimate Heterogeneity: $P=35\%$, $t^2=0$, p=0.21 36-47 months Prince et al $(1981)^{30}$ 18/110 25-36 48-60 months Prince et al $(1981)^{30}$ 20/94 37-48 Vall Mayans et al $(1990)^{35}$ 55/202 6-60 Poled estimate Heterogeneity: $P=16\%$, $t^2=0$, p=0.27 Test for subgroup differences: $t_{s}^2=75.29$, df=5 (p<0.0001) Bisk of infertion	Barin et al (1981) ²⁹	2/88	3-15	•	2.27% (0.28-7.97)
Marinier et al $(1985)^{31}$ $3/186$ 5-12 Woodruff et al $(1985)^{32}$ $9/79$ 10-21 Ayoola and Johnson $(1987)^{33}$ $4/126$ 12 Tsega et al $(1988)^{34}$ $1/23$ 12 Menedez et al $(1999)^{37}$ $9/42$ 18 Pooled estimate Heterogeneity: l^2 =77%, τ^2 =0.7227, p<0.001 24-35 months Prince et al $(1981)^{30}$ $17/118$ 13-24 Tsega et al $(1988)^{34}$ $1/23$ 24 Pooled estimate Heterogeneity: l^2 =35%, τ^2 =0, p=0.21 36-47 months Prince et al $(1981)^{30}$ $18/110$ 25-36 48-60 months Prince et al $(1981)^{30}$ $20/94$ $37-48$ Vall Mayans et al $(1990)^{35}$ $55/202$ $6-60$ Pooled estimate Heterogeneity: l^2 =16%, τ^2 =0, p=0.27 Test for subgroup differences: χ^2_5 =75-29, df=5 (p<0.0001) Bick of infection	Prince et al (1981) ³⁰	10/127	7-12		7.87% (3.84–14.00)
Woodruff et al $(1986)^{32}$ 9/79 10-21 Ayoola and Johnson $(1987)^{33}$ 4/126 12 Tsega et al $(1998)^{34}$ 1/23 12 Menendez et al $(1999)^{37}$ 9/42 18 Pooled estimate 5.37% (2.62-10.70) Heterogeneity: $l^2=77\%$, $t^2=0.7227$, p<0.001	Marinier et al (1985) ³¹	3/186	5-12	-	1.61% (0.33-4.64)
Ayoola and Johnson (1987) ³³ 4/126 12 Tsega et al (1988) ³⁴ 1/23 12 Menendez et al (1999) ³⁷ 9/42 18 Pooled estimate Heterogeneity: l^2 =77%, t^2 =0.7227, p<0.001 24-35 months Prince et al (1981) ³⁰ 17/118 13-24 Heterogeneity: l^2 =35%, t^2 =0, p=0.21 36-47 months Prince et al (1981) ³⁰ 18/110 25-36 48-60 months Prince et al (1981) ³⁰ 20/94 37-48 Vall Mayans et al (1990) ³⁵ 55/202 6-60 Pooled estimate Heterogeneity: l^2 =16%, t^2 =0, p=0.27 Test for subgroup differences: χ_2^2 =75-29, df=5 (p<0.0001) Pick of infertion Pick of infertion	Woodruff et al (1986) ³²	9/79	10-21		11.39% (5.34-20.53)
Tsega et al $(1988)^{34}$ 1/23 12 Menendez et al $(1999)^{37}$ 9/42 18 Pooled estimate 5·37% (2·62-10·70) 24-35 months 5·37% (2·62-10·70) Prince et al $(1981)^{30}$ 17/118 13-24 Pooled estimate 5·37% (2·62-10·70) Heterogeneity: $l^2=77\%$, $t^2=0.7227$, $p<0.001$ 24 Prince et al $(1981)^{30}$ 17/118 13-24 Pooled estimate 12·27% (8·19-19)-35 Heterogeneity: $l^2=35\%$, $t^2=0$, $p=0.21$ 36-47 months Prince et al $(1981)^{30}$ 18/110 25-36 Prince et al $(1981)^{30}$ 20/94 37-48 Vall Mayans et al $(1990)^{35}$ 55/202 6-60 Pooled estimate 25-36 16·36% (10·00-24·6 Heterogeneity: $l^2=16\%$, $t^2=0$, $p=0.27$ 25·34% (20·71-30·6) Vall Mayans et al $(1990)^{35}$ 55/202 6-60 Pooled estimate 25·34% (20·71-30·6) Heterogeneity: $l^2=16\%$, $t^2=0$, $p=0.27$ 0 10 20 30 40 Pick of infertion 10 20 30 40 Pick of infertion Pick of infertion	Ayoola and Johnson (1987) ³³	4/126	12 -	•	3.17% (0.87-7.93)
Menendez et al $(1999)^{37}$ 9/42 18 Pooled estimate 5:37% (2:62-10:70) Heterogeneity: l^2 =77%, t^2 =0.7227, p<0:001	Tsega et al (1988) ³⁴	1/23	12		4.35% (0.11-21.95)
Pooled estimate Heterogeneity: l^2 =77%, τ^2 =0.7227, p<0.001 24-35 months 17/118 13-24 Prince et al (1981) ³⁰ 17/118 13-24 Stage et al (1988) ³⁴ 1/23 24 Pooled estimate 12.77% (8.19-19.35) Heterogeneity: l^2 =35%, τ^2 =0, p=0.21 36-47 months Prince et al (1981) ³⁰ 18/110 25-36 Prince et al (1981) ³⁰ 18/110 25-36 Vall Mayans et al (1990) ³⁵ 55/202 6-60 Pooled estimate 25-34% (20.71-30.6) Heterogeneity: l^2 =16%, τ^2 =0, p=0.27 25.34% (20.71-30.6) Prince et al (1981) ³⁰ 20/94 37-48 Vall Mayans et al (1990) ³⁵ 55/202 6-60 Pooled estimate 25.34% (20.71-30.6) Heterogeneity: l^2 =16%, τ^2 =0, p=0.27 72.23, 92.23, 92.23, 93.23,	Menendez et al (1999) ³⁷	9/42	18	-	21.43% (10.30-36.81)
Heterogeneity: $P=77\%$, $t^2=0.7227$, p<0.001 24-35 months Prince et al (1981) ³⁰ 17/118 13-24 Tsega et al (1988) ³⁴ 1/23 24 Poole estimate Heterogeneity: $P=35\%$, $t^2=0$, p=0-21 36-47 months Prince et al (1981) ³⁰ 18/110 25-36 48-60 months Prince et al (1981) ³⁰ 20/94 37-48 Vall Mayans et al (1990) ³⁵ 55/202 6-60 Poole estimate Heterogeneity: $P=16\%$, $t^2=0$, p=0-27 Test for subgroup differences: $\chi_2^2=75-29$, df=5 (p<0.0001) Risk of infertion	Pooled estimate			\Leftrightarrow	5.37% (2.62-10.70)
24-35 moths Prince et al $(1981)^{30}$ 17/118 13-24 Tsega et al $(1988)^{34}$ 1/23 24 Pooled estimate 12.77% (8.19-19.35) Heterogeneity: $l^2=35\%$, $\tau^2=0$, p=0.21 36-47 months Prince et al $(1981)^{30}$ 18/110 25-36 Prince et al $(1981)^{30}$ 18/110 25-36 Vall Mayans et al $(1990)^{35}$ 55/202 6-60 Pooled estimate 21.28% (13.51-30.92) Vall Mayans et al $(1990)^{35}$ 55/202 6-60 Pooled estimate 25.34% (20.71-30.62) Heterogeneity: $l^2=16\%$, $\tau^2=0$, p=0.27 0 10 20 30 40 Risk of infection Risk of infection 0 10 20 30 40	Heterogeneity: <i>l</i> ² =77%, τ ² =0·7227,	p<0.001			
Prince et al $(1981)^{30}$ 17/118 13-24 Test for subgroup differences: $\chi_c^2 = 75 \cdot 29$, df =5 (p<0.0001) 13-24 14.41% (8.62-22.06 13-24 14.41% (8.62-22.06 14.41% (8.62-22.06 14.45% (0.11-21.95) 12.77% (8.19-19.35 12.77% (8.19-19.35 16.36% (10.00-24.6 16.36% (10.00-24.6 27.23% (21.22-33.92 25.34% (20.71-30.6 0 10 20 30 40 Risk of infection	24-35 months				
Tsega et al $(1988)^{34}$ 1/23 24 4-35% (0.11-21.95) Pooled estimate 12.77% (8.19-19.35) 12.77% (8.19-19.35) Heterogeneity: $l^2=35\%$, $\tau^2=0$, $p=0.21$ 36-47 months 16.36% (10.00-24.6) Prince et al (1981) ³⁰ 18/110 25-36 16.36% (10.00-24.6) 48-60 months 7.48 21.28% (13.51-30.9) Vall Mayans et al (1990) ³⁵ 55/202 6-60 Pooled estimate 25.34% (20.71-30.6) Heterogeneity: $l^2=16\%$, $\tau^2=0$, $p=0.27$ 0 10 20 30 40 Risk of infection Risk of infection 10 20 30 40	Prince et al (1981) ³⁰	17/118	13-24		14-41% (8-62-22-06)
Pooled estimate 12.77% (8.19-19.35 Heterogeneity: $P=35\%$, $\tau^2=0$, $p=0.21$ 36-47 months Prince et al (1981) ³⁰ 18/110 25-36 48-60 months 16.36% (10.00-24.6 Prince et al (1981) ³⁰ 20/94 37-48 Vall Mayans et al (1990) ³⁵ 55/202 6-60 Pooled estimate 25.36% (20.71-30.6% Heterogeneity: $P=16\%$, $\tau^2=0$, $p=0.27$ 0 10 20 30 40 Risk of infection Risk of infection 10 20 30 40	Tsega et al (1988) ³⁴	1/23	24		4.35% (0.11-21.95)
Heterogeneity: P^{2} =35%, τ^{2} =0, p=0.21 36-47 months Prince et al (1981) ³⁰ 18/110 25-36 48-60 months Prince et al (1981) ³⁰ 20/94 37-48 Vall Mayans et al (1990) ³⁵ 55/202 6-60 Poole estimate Heterogeneity: P^{2} =16%, τ^{2} =0, p=0.27 Test for subgroup differences: χ^{2}_{c} =75-29, df=5 (p<0.0001) Risk of infection	Pooled estimate			\sim	12.77% (8.19-19.35)
36-47 months Prince et al (1981) ³⁰ 18/110 25-36 48-60 months Prince et al (1981) ³⁰ 20/94 37-48 Vall Mayans et al (1990) ³⁵ 55/202 6-60 Poole estimate 25-36 Heterogeneity: l^2 =16%, τ^2 =0, p =0-27 25-34% (20-71-30-6) Test for subgroup differences: χ^2_5 =75-29, df=5 (p<0-0001)	Heterogeneity: $l^2 = 35\%$, $\tau^2 = 0$, p=0.2	21			
Prince et al $(1981)^{30}$ 18/110 25-36 16.36% (10.00-24.6 48-60 months 21.28% (13.51-30.9) Prince et al $(1981)^{30}$ 20/94 37-48 21.28% (13.51-30.9) Vall Mayans et al $(1990)^{35}$ 55/202 6-60 27.23% (21.22-33.9) Poole estimate 25.34% (20.71-30.6) Heterogeneity: l²=16%, τ²=0, p = 0.27 0 10 20 30 40 Risk of infection	36-47 months				
48-60 months Prince et al $(1981)^{30}$ $20/94$ $37-48$ Vall Mayans et al $(1990)^{35}$ $55/202$ $6-60$ Pooled estimate $27\cdot23\% (21\cdot22-33\cdot92)$ Heterogeneity: $l^2=16\%$, $\tau^2=0$, p = 0·27 $25\cdot34\%$ (20·71-30·60) Test for subgroup differences: $\chi_3^2=75\cdot29$, df=5 (p<0·0001)	Prince et al (1981) ³⁰	18/110	25-36		16.36% (10.00-24.62)
Prince et al $(1981)^{30}$ 20/94 $37-48$ 21.28% $(13.51-30.92)$ Vall Mayans et al $(1990)^{35}$ 55/202 6-60 27.23% $(21.22-33.92)$ Pooled estimate 25.34% $(20.71-30.62)$ 25.34% $(20.71-30.62)$ Heterogeneity: $l^2=16\%$, $\tau^2=0$, p = 0.27 0 10 20 30 40 Risk of infection Risk of infection 21.28% $(13.51-30.92)$ 10 20.28% $(20.71-30.62)$	48-60 months			_	
Vall Mayans et al (1990) ³⁵ 55/202 6-60 27.23% (21.22-33.92 Pooled estimate 25.34% (20.71-30.62 Heterogeneity: l^2 =16%, τ^2 =0, p =0.27 25.34% (20.71-30.62 Test for subgroup differences: χ^2_5 =75-29, df=5 (p<0.0001)	Prince et al (1981) ³⁰	20/94	37-48		21.28% (13.51-30.93)
Pooled estimate 25:34% (20:71-30:6 Heterogeneity: P=16%, τ²=0, p=0:27 0 10 20 30 40 Test for subgroup differences: χ²=75:29, df=5 (p<0:0001)	Vall Mayans et al (1990) ³⁵	55/202	6-60		27.23% (21.22-33.92)
Heterogeneity: <i>l</i> ² =16%, τ ² =0, p =0-27 Test for subgroup differences: χ ² ₅ =75-29, df=5 (p<0-0001) Risk of infection	Pooled estimate			\sim	25.34% (20.71-30.60
Test for subgroup differences: χ^2_s =75-29, df=5 (p<0.0001) Risk of infection	Heterogeneity: $l^2=16\%$, $\tau^2=0$, p =0.	27			
Risk of infection	Test for subgroup differences: v2=7	′5·29, df=5 (p<0·0001)	0	10 20 30 40	
	λ	5 5, 5 (p)		Risk of infection	

(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).

В				
	Number infected/ number assessed	Assessment age (months)	Events per 100 observations	Risk (95% CI)
Less than 12 months				
Ekra et al (2008) ¹⁶	0/1771	9	b	0.00% (0.00-0.21)
Ilboudo et al (2010)41	0/101	2-9	-	0.00% (0.00-3.59)
Seremba et al (2017) ²⁶	0/197	9	F	0.00% (0.00-1.86)
Accrombessi et al (2020)17	1/59	9	T	1.69% (0.04-9.09)
Pooled estimate			\triangleright	0.02% (0.00-5.09)
Heterogeneity: I ² =0%, τ ² =7·5204, p=1	·00			
12-23 months				
Pirillo et al (2015) ²⁵	0/11	18		0.00% (0.00-28.49)
Kaba et al (2019) ⁴³	0/3	12-23		0.00% (0.00-70.76)
Lingani et al (2020)27	0/30	12-23	•	0.00% (0.00-11.57)
Pooled estimate				0.00% (0.00-100.00)
Heterogeneity: <i>l</i> ² =0%, τ ² =0, p=1·00				
24–35 months				
Pirillo et al (2015) ²⁵	4/163	24	+	2.45% (0.67-6.16)
Kaba et al (2019) ⁴³	0/5	24-35	<u> </u>	0.00% (0.00-52.18)
Lingani et al (2020) ²⁷	0/24	24-35		0.00% (0.00-14.25)
Pooled estimate			\diamond	2.08% (0.78-5.42)
Heterogeneity: I²=0%, τ²=0, p=1·00				
36–47 months				
Osazuwa and Chika (2012) ⁴²	3/217	6-42	H	1.38% (0.29–3.99)
Kaba et al (2019) ⁴³	0/14	36-47		0.00% (0.00-23.16)
Lingani et al (2020) ²⁷	0/40	36-47	—	0.00% (0.00-8.81)
Pooled estimate			\diamond	1.11% (0.36-3.37)
Heterogeneity: I ² =0%, τ ² =0, p=1·00				
48–60 months				
Magoni et al (2009) ²²	2/756	12-59		0.26% (0.03–0.95)
Kaba et al (2019) ⁴³	0/14	48-60		0.00% (0.00–23.16)
Lingani et al (2020) ²⁷	0/31	48-60		0.00% (0.00–11.22)
Pooled estimate			þ	0·25% (0·06–0·99)
Heterogeneity: <i>l</i> ² =0%, τ ² =0, p=1·00				
Test for subgroup differences: $\chi_4^2 = 7.98$	8, df=4 (p=0·092)		0 20 40 80 80 100	
			Risk of infection	
С				
Birth	0/400	<u>^</u>	1	0.00% (0.00.2.55)
Yvonnet et al (1982) ¹⁵	0/102	0		0.00% (0.00-3.55)
Ekra et al (2008) ¹⁰	0/1/40	0		0.00% (0.00-0.21)
Pooled estimate				0.00% (0.00-100.00)
Heterogeneity: I=0%, t=0, p=1.00				
Vuonnot et al (1082) ¹⁵	0/75	2		0.00% (0.00 4.80)
Courses at al $(1902)^{18}$	0/75	2		0.00% (0.00 7.25)
Ekra at al (2008) ¹⁶	0/49	5		0.00% (0.00-7.25)
Accromosci et al (2020) ¹⁷	2/68	9		0.00% (0.00-0.21)
Pooled estimate	2/00	9		2.94% (0.30-10.22)
Heterogeneity: $l^2 = 0\% t^2 = 11.1042 training$	1.00			0.02%(0.00=10.10)
12_22 months	1.00			
(0)	0/41	14		0.00% (0.00-8.60)
Hall et al (1980) ³⁹	2/661	14		0.20% (0.04-1.00)
Onakewhor et al $(2013)^{20}$	0/66	12		0.00% (0.00-5.44)
Baruti et al (2020) ²¹	0/282	18	Ⅰ	0.00% (0.00–1.30)
Pooled estimate	5,202	10	T	0.19% (0.05-0.76)
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 1.00$				0_ 0 0 0 0 0
36-47 months				
Chotard et al (1992) ⁴⁰	2/607	36		0.33% (0.04–1.19)
48-60 months		2	Т	
Fortuin et al (1993) ¹⁹	1/630	48		0.16% (0.00-0.88)
Test for subgroup differences: $v^2 = 0.81$	9. df=4 (p=0.93)		Т	
	(CC > 4) +			
			o 20 40 60 80 100	
			Risk of infection	

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 $6 \cdot 16\%$ (95% CI $3 \cdot 05-12 \cdot 04$; 155/1407) without vaccination and decreased to $0 \cdot 21\%$ ($0 \cdot 04-1 \cdot 15$; 10/3425) when the first vaccination dose was given at 6–8 weeks, and to $0 \cdot 05\%$ ($0 \cdot 00-1 \cdot 32$; 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 HBsAgnegative 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 noninferior 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 200000, 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 (≥200000 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 nonrandomised 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.

References

- Razavi-Shearer D, Gamkrelidze I, Nguyen MH, et al. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol* 2018; 3: 383–403.
- 2 Edmunds WJ, Medley GF, Nokes DJ, O'Callaghan CJ, Whittle HC, Hall AJ. Epidemiological patterns of hepatitis B virus (HBV) in highly endemic areas. *Epidemiol Infect* 1996; 117: 313–25.
- 3 Nayagam S, Thursz M, Sicuri E, et al. Requirements for global elimination of hepatitis B: a modelling study. *Lancet Infect Dis* 2016; 16: 1399–408.
- 4 Whittle H, Inskip H, Bradley AK, et al. The pattern of childhood hepatitis B infection in two Gambian villages. J Infect Dis 1990; 161: 1112–15.
- 5 Martinson FE, Weigle KA, Royce RA, Weber DJ, Suchindran CM, Lemon SM. Risk factors for horizontal transmission of hepatitis B virus in a rural district in Ghana. *Am J Epidemiol* 1998; 147: 478–87.
- 6 Dumpis U, Holmes EC, Mendy M, et al. Transmission of hepatitis B virus infection in Gambian families revealed by phylogenetic analysis. *J Hepatol* 2001; **35**: 99–104.
- 7 Burnett RJ, Kramvis A, Dochez C, Meheus A. An update after 16 years of hepatitis B vaccination in South Africa. *Vaccine* 2012; 30 (suppl 3): C45–51.
- 8 de Villiers MJ, Nayagam S, Hallett TB. The impact of the timely birth dose vaccine on the global elimination of hepatitis B. *Nat Commun* 2021; **12**: 6223.
- 9 Khetsuriani N, Lesi O, Desai S, Armstrong PA, Tohme RA. Progress toward the elimination of mother-to-child transmission of hepatitis B virus—worldwide, 2016–2021. MMWR Morb Mortal Wkly Rep 2022; 71: 958–63.
- 10 Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol 2012; 65: 934–39.
- 11 WHO. Hepatitis B vaccination coverage. https://immunizationdata. who.int/pages/coverage/hepb.html (accessed June 18, 2022).
- 12 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71.
- 13 Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999; 10: 37–48.
- 14 Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. *J Clin Epidemiol* 2014; 67: 897–903.
- 15 Yvonnet B, Digoutte P, Denis F, Correa P. Prevention de la transmission mere-enfant du virus l'hepatite B par la vaccination du nouvea-ne. *Med Afr Noire* 1982; 29: 721–31.
- 16 Ekra D, Herbinger K-H, Konate S, et al. A non-randomized vaccine effectiveness trial of accelerated infant hepatitis B immunization schedules with a first dose at birth or age 6 weeks in Côte d'Ivoire. *Vaccine* 2008; 26: 2753–61.
- 17 Accrombessi M, Adetola CV, Bacharou S, et al. Assessment of the anti-HBs antibody response in Beninese infants following 4 doses of HBV vaccine, including administration at birth, compared to the standard 3 doses regime; a cross-sectional survey. *Vaccine* 2020; 38: 1787–93.
- 18 Coursaget P, Chiron JP, Barin F, et al. Hepatitis B vaccine: immunization of children and newborns in an endemic area (Senegal). *Dev Biol Stand* 1983; 54: 245–57.
- 19 Fortuin M, Chotard J, Jack AD, et al. Efficacy of hepatitis B vaccine in the Gambian expanded programme on immunisation. *Lancet* 1993; 341: 1129–31.

- 20 Onakewhor JUE, Charurat M, Matthew O, Osagie E, Asemota MO, Omoigberale A. Immunologic pattern of hepatitis B infection among exposed and non-exposed babies in a PMTCT program in low resource setting: does every exposed newborn require 200 IU of hepatitis B immunoglobulin? J Vaccines Vaccin 2013; 4: 207.
- 21 Baruti K, Lentz K, Anderson M, et al. Hepatitis B virus prevalence and vaccine antibody titers in children HIV exposed but uninfected in Botswana. *PLoS One* 2020; 15: e0237252.
- 22 Magoni M, Ekra KD, Aka LN, Sita KS, Kanga K. Effectiveness of hepatitis-B vaccination in Ivory Coast: the case of the Grand Bassam health district. Ann Trop Med Parasitol 2009; 103: 519–27.
- 23 Chasela CS, Kourtis AP, Wall P, et al. Hepatitis B virus infection among HIV-infected pregnant women in Malawi and transmission to infants. J Hepatol 2014; 60: 508–14.
- 24 Hoffmann CJ, Mashabela F, Cohn S, et al. Maternal hepatitis B and infant infection among pregnant women living with HIV in South Africa. J Int AIDS Soc 2014; 17: 18871.
- 25 Pirillo MF, Scarcella P, Andreotti M, et al. Hepatitis B virus motherto-child transmission among HIV-infected women receiving lamivudine-containing antiretroviral regimens during pregnancy and breastfeeding. J Viral Hepat 2015; 22: 289–96.
- 26 Seremba E, Van Geertruyden JP, Ssenyonga R, et al. Early childhood transmission of hepatitis B prior to the first hepatitis B vaccine dose is rare among babies born to HIV-infected and non-HIV infected mothers in Gulu, Uganda. *Vaccine* 2017; 35: 2937–42.
- 27 Lingani M, Akita T, Ouoba S, et al. The changing epidemiology of hepatitis B and C infections in Nanoro, rural Burkina Faso: a random sampling survey. *BMC Infect Dis* 2020; 20: 46.
- 28 Ayoola EA, Ogunbode O, Odelola HA. Congenital transmission of hepatitis B antigen in Nigerians. Arch Virol 1981; 67: 97–99.
- 29 Barin F, Perrin J, Chotard J, et al. Cross-sectional and longitudinal epidemiology of hepatitis B in Senegal. *Prog Med Virol* 1981; 27: 148–62.
- 30 Prince AM, White T, Pollock N, Riddle J, Brotman B, Richardson L. Epidemiology of hepatitis B infection in Liberian infants. *Infect Immun* 1981; 32: 675–80.
- 31 Marinier E, Barrois V, Larouze B, et al. Lack of perinatal transmission of hepatitis B virus infection in Senegal, west Africa. *J Pediatr* 1985; 106: 843–49.
- 32 Woodruff AW, Adamson EA, el Suni A, Maughan TS, Kaku M, Bundru W. Children in Juba, southern Sudan: the second and third years of life. *Lancet* 1986; **2**: 615–18.
- 33 Ayoola EA, Johnson AO. Hepatitis B vaccine in pregnancy: immunogenicity, safety and transfer of antibodies to infants. Int J Gynaecol Obstet 1987; 25: 297–301.
- 34 Tsega E, Tsega M, Mengesha B, Nordenfelt E, Hansson BG, Lindberg J. Transmission of hepatitis B virus infection in Ethiopia with emphasis on the importance of vertical transmission. *Int J Epidemiol* 1988; 17: 874–79.
- 35 Vall Mayans M, Hall AJ, Inskip HM, et al. Risk factors for transmission of hepatitis B virus to Gambian children. *Lancet* 1990; 336: 1107–09.
- 36 Roingeard P, Diouf A, Sankale JL, et al. Perinatal transmission of hepatitis B virus in Senegal, west Africa. *Viral Immunol* 1993; 6: 65–73.
- 37 Menendez C, Sanchez-Tapias JM, Kahigwa E, et al. Prevalence and mother-to-infant transmission of hepatitis viruses B, C, and E in Southern Tanzania. J Med Virol 1999; 58: 215–20.
- 38 Candotti D, Danso K, Allain J-P. Maternofetal transmission of hepatitis B virus genotype E in Ghana, west Africa. J Gen Virol 2007; 88: 2686–95.
- 39 Hall A, Inskip H, Loik F, Chotard J, Jawara M, Vall Mayans M. Hepatitis B vaccine in the expanded programme of immunisation: The Gambian experience. *Lancet* 1989; 1: 1057–59.
- 40 Chotard J, Inskip HM, Hall AJ, et al. The Gambia Hepatitis Intervention Study: follow-up of a cohort of children vaccinated against hepatitis B. J Infect Dis 1992; 166: 764–68.
- H Ilboudo D, Simpore J, Ouermi D, et al. Towards the complete eradication of mother-to-child HIV/HBV coinfection at Saint Camille Medical Centre in Burkina Faso, Africa. *Braz J Infect Dis* 2010; 14: 219–24.
- 42 Osazuwa F and Chika AH. Risk of mother to child transmision of hepatitis B among children. Int J Trop Med 2012; 7: 34–37.

- 43 Kaba D, Bangoura MA, Sylla MM, et al. Prevalence and factors associated with hepatitis B in a cohort of HIV-infected children in the Pediatric Department at Donka National Hospital, Guinea. *Pan Afr Med J* 2019; 34: 182.
- 44 WHO. Hepatitis B vaccination coverage in Nigeria 2000–21. https://immunizationdata.who.int/pages/coverage/hepb. html?CODE=NGA&ANTIGEN=HEPB_BD+HEPB3&YEAR= (accessed Nov 26, 2022).
- 45 Dionne-Odom J, Njei B, Tita ATN. Elimination of vertical transmission of hepatitis B in Africa: a review of available tools and new opportunities. *Clin Ther* 2018; 40: 1255–67.
- 46 Hagan JE, Carvalho E, Souza V, et al. Selective Hepatitis B birth-dose vaccination in São Tomé and Príncipe: a program assessment and cost-effectiveness study. Am J Trop Med Hyg 2019; 101: 891–98.
- 47 WHO. Interim guidance for country validation of viral hepatitis elimination. 2021. https://www.who.int/publicationsdetail-redirect/9789240028395 (accessed June 19, 2022).
- Shimakawa Y, Veillon P, Birguel J, et al. Residual risk of mother-tochild transmission of hepatitis B virus infection despite timely birth-dose vaccination in Cameroon (ANRS 12303): a single-centre, longitudinal observational study. *Lancet Glob Health* 2022; 10: e521–29.
- 49 WHO. Prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy. 2020. https://www.who.int/publications-detail-redirect/978-92-4-000270-8 (accessed June 19, 2022).
- 50 Shimakawa Y, Lemoine M, Njai HF, et al. Natural history of chronic HBV infection in west Africa: a longitudinal population-based study from The Gambia. *Gut* 2016; 65: 2007–16.
- 51 Song E, Kew MC, Hwang LY, Beasley RP. Epidemiology of hepatitis B virus infection in South African Chinese. *Am J Epidemiol* 1988; 128: 828–38.