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Review

Hepatitis B surface antigen prevalence and the rates of mother-to-child transmission of hepatitis B virus after the introduction of infant vaccination programs in South East Asia and Western Pacific regions: a systematic review

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ABSTRACT

Objectives: Infant vaccination against the hepatitis B virus began in the World Health Organization South East Asia Region and the Western Pacific Region between 1983 and 2016. This systematic review examined the seroprevalence of hepatitis B surface antigen (HBsAg) in children and the rate of mother-to-child transmission (MTCT) in these regions between 1990 and 2020.

Methods: MEDLINE and EMBASE were searched for articles published between January 1990 and September 2020, which reported seroprevalence of HBsAg in children aged 0-15 years and/or the rate of MTCT in the South East Asia Region and Western Pacific Region. A pragmatic review identified supporting information. This review was registered in the International Prospective Register of Systematic Reviews (#CRD42020211707).

Results: Of 115 included studies, 77 (24 countries) reported HBsAg prevalence, and 38 (nine countries) reported MTCT. The seroprevalence of HBsAg ranged between 0.0% and 27.4%, with a decreasing trend over time in each country. MTCT rates were 0.0-5.2% in infants of mothers who are hepatitis B e antigen-negative and 2.7-53.0% in infants of mothers who are hepatitis B e antigen-positive.

Conclusion: After the introduction of infant hepatitis B virus vaccination programs, the countries in South East Asia Region and Western Pacific Region observed a reduction in HBsAg seroprevalence in children. Nevertheless, the risk of MTCT persists, emphasizing the importance of antenatal screening to identify high-risk pregnancies.

Introduction

Hepatitis B virus (HBV) infection incurs a substantial burden worldwide due to the associated cost of prevention, diagnosis, and treatment (Zampino *et al.*, 2015). Global HBV seroprevalence in 2016 was estimated to be 3.9%, with approximately 296 million people living with chronic HBV infection in 2019 and 1.5 million new infections annually (CDA Foundation Polaris Observatory, 2020; World Health Organization, 2017; 2021). In highly endemic countries, mother-to-child transmission (MTCT) accounts for most new cases (Gentile and Borgia, 2014).

Abbreviations: HBeAg, Hepatitis B e antigen; HBsAg, Hepatitis B surface antigen; HBIG, Hepatitis B immunoglobulin; HBV, Hepatitis B virus; MTCT, Mother-to-child transmission; SEAR, South East Asia Region; WHO, World Health Organization; WPR, Western Pacific Region.

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In 2016, the World Health Assembly endorsed the 'Global Health Sector Strategy on Viral Hepatitis 2016-2021'. One goal is to reduce the incidence of chronic HBV infections worldwide, with a target of <0.1% prevalence of hepatitis B surface antigen (HBsAg) carriage in children aged 5 years by the year 2030 (World Health Organization, 2016). Estimating the current seroprevalence of HBsAg in children and evaluating the progress toward this target is critical because this may reflect the impact of vaccination programs and be a future indicator of the burden of chronic HBV infection in adults.

The composition of the HBV vaccine has evolved from a monovalent vaccine to being a component of pentavalent and hexavalent vaccines. Pentavalent vaccines provide immunization against HBV plus four other pathogens: diphtheria, tetanus, and pertussis (DTP) and either *Haemophilus influenzae* type B (Hib) or inactivated polio virus (IPV); hexavalent vaccines provide immunization against all six. Compared with monovalent HBV vaccines, combination vaccines may be advantageous because they simplify the immunization schedule and increase opportunities to vaccinate (Dodd, 2003), improving vaccination coverage rates, particularly for Hib and HBV (Bairwa *et al.*, 2012). The evolution of vaccine development has, in part, led to changes in the infant HBV vaccination schedules used worldwide. To prevent MTCT, the World Health Organization (WHO) recommends that the first dose of HBV vaccine is administered immediately after birth (i.e., birth dose) as a monovalent vaccine. A subsequent dose given at 6-8 weeks aligns with the schedule recommended for the administration of the DTP vaccines, components of pentavalent and hexavalent formulations.

This systematic review aimed to examine the seroprevalence of HBsAg carriage in children over time and the MTCT rate in infants between 1990 and 2020 in two WHO regions: the South East Asia Region (SEAR) and the Western Pacific Region (WPR).

A secondary objective was to evaluate the impact of a change in the timing of the second HBV vaccine dose from 1 month to 2 months of age on the seroprevalence of HBsAg in children.

Methods

Search strategy

The study protocol was preregistered in the International Prospective Register of Systematic Reviews (#CRD42020211707). The study was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (Supplementary Table S1) (Moher *et al.*, 2009). The following electronic databases were systematically searched for articles published from January 1, 1990 to September 11, 2020: Ovid MEDLINE, MEDLINE In-Process Citations & Daily Update, and EMBASE. The detailed search strategy is available in Supplementary Table S2. A manual search of references in published systematic reviews and websites of health authorities was also conducted.

Eligibility criteria

The search included observational studies (cohort and cross-sectional studies) published in any language from 1990 onwards that reported: (i) the seroprevalence of HBsAg in children aged between 0 and 15 years or (ii) the rate of MTCT of HBV. For studies published between 1990 and 2017, only full-text articles were included; for those more recently published (2018-2020), both full-text articles and conference abstracts were included. Studies were excluded if they restricted participants to only healthy individuals or included only selective high-risk populations.

The countries of interest were

SEAR: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, and Timor-Leste.

WPR: Australia, Brunei Darussalam, Cambodia, China, Cook Islands, Fiji, Hong Kong, Japan, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia, Mongolia, Nauru, New Zealand, Palau, Papua New Guinea, Philippines, Republic of Korea, Singapore, Solomon Islands, Taiwan, Tonga, Tuvalu, Vanuatu, and Vietnam.

Screening and data extraction

Two reviewers (ZM and CW) independently screened titles and abstracts of all publications identified through the electronic database search and independently reviewed potentially eligible full-text articles. Any disagreement was resolved by discussion.

To examine time trends in HBsAg seroprevalence, the following data were extracted: HBsAg seroprevalence; the age range of included children; the data collection period; and whether studies were representative of the entire country, a region, or a single city. For studies reporting MTCT rates, the estimates were stratified by maternal hepatitis B e antigen (HBeAg) seropositivity. When reported, the following data were also extracted: the number of doses and administration schedule for hepatitis B immunoglobulin (HBIG) and the timing of HBV vaccination.

The seroprevalence of HBsAg was recorded as the percentage of children who are HBsAg-positive in the population. The rate of MTCT of HBV was defined as the percentage of infants born to mothers infected with HBV who were HBsAg-positive at age 6-12 months.

Risk of bias and quality assessment

The risk of bias was assessed using a modified Newcastle-Ottawa scale for quality assessment of cross-sectional and cohort studies (Wells *et al.*, 2013) in two domains: (i) selection of study groups and (ii) ascertainment of outcomes of interest (Supplementary File S3).

Pragmatic review

A pragmatic review identified information on the history of HBV vaccination, vaccine type, schedules, and vaccination coverage rates in each country. This process included a combination of electronic searches and free-text searching of databases and government websites.

Results

The pragmatic search identified HBV vaccination schedules across 38 countries in the WHO SEAR and WPR, including the year that infant HBV vaccination was reported to begin (for any population), the year that nationwide vaccination for all infants began, and the year an HBV birth dose was introduced. The World Bank income level for each country is also reported (Table 1, Supplementary Table S7).

Hepatitis B (HepB) infant vaccination was introduced nationwide between 1992 and 2011 in the SEAR, with unclear information for two of the 11 countries, and between 1983 and 2016 in the 27 countries in the WPR. Four countries in the SEAR and 21 countries in the WPR had introduced nationwide HBV vaccination before the year 2000 (Table 1, Supplementary Table S7).

Table 1
Summary of HepB vaccination in South East Asia and Western Pacific Regions.

Country or territory	World Bank income group[a]	Year infant HepB vaccination started	Year infant HepB vaccination introduced nationwide	Year HepB birth dose introduced	Current (2020) infant HepB vaccines in national vaccination programme[b]	Current (2020) national HepB vaccination schedule
South East Asia						
Bangladesh	Lower middle	2003	2005	No birth dose	DTwP-Hib-HepB	6, 10, 14 weeks
Bhutan	Lower middle	1997	1997	2012	DTaP-Hib-HepB	0, 6, 10, 14 weeks
Democratic People's Republic of Korea	Low	2003	Unclear, by at least 2013	2004	DTwP-Hib-HepB	0, 6, 10, 14 weeks
India	Lower middle	2002	2011-2012	2011 - 2012	DTwP-Hib-HepB	0, 6, 10, 14 weeks
Indonesia	Upper middle	1997	1997	1999, all islands 2002	DTwP-Hib-HepB	0, 2, 3, 4 months
Maldives	Upper middle	1993	1993	2000	DTwP-Hib-HepB	0, 2, 4, 6 months
Myanmar	Lower middle	2003	Unclear, by at least 2012	2003 – 2009 2016	DTwP-Hib-HepB	0, 2, 4, 6 months
Nepal	Lower middle	2002	2002	No birth dose	DTwP-Hib-HepB	6, 10, 14 weeks
Sri Lanka	Lower middle	2003	2003	No birth dose	DTwP-Hib-HepB	2, 4, 6 months
Thailand	Upper middle	1992	1992	1992	DTwP-Hib-HepB	0, 2, 4, 6 months
Timor-Leste	Lower middle	2007	2007	2016	DTwP-Hib-HepB	0, 6, 10, 14 weeks
Western Pacific						
Australia	High	1986	2000	1986	DTaP-IPV-Hib-HepB	0, 2, 4, 6 months
Brunei Darussalam	High	1988	1988	1988	DTaP-IPV-Hib-HepB	0, 2, 4,6 months
Cambodia	Lower middle	2001	2005	2005	DTwP-Hib-HepB	0, 6, 10, 14 weeks
China	Upper middle	1992	1992	1992	HepB	0, 1, 6 months
Cook Islands	NR	1989	1989	Unclear, before 2013	DTaP-Hib-HepB	0, 6 weeks, 3, 5 months
Fiji	Upper middle	1989	1995	1989	DTwP-Hib-HepB	0, 6, 10, 14 weeks
Hong Kong	High	1982	1988	1988	HepB	0, 1, 6 months
Japan	High	1986	2016	2015, only if mother HBsAg[c]	HepB	2, 3, 7 months
Kiribati	Lower middle	1989	1995	1990	DTwP-Hib-HepB	0, 6, 10, 14 weeks
Lao PDR	Lower middle	2001	2004	2004 - 2006	DTwP-Hib-HepB	0, 6, 10, 14 weeks
Malaysia	Upper middle	1989	1989	1989	DTaP-IPV-Hib-HepB	0, 2, 3, 5 months
Marshall Islands	Upper middle	1993	1993	1998/ 2003	DTaP-IPV-HepB	0, 2, 4, 6 months
Micronesia	Lower middle	1988	1988	1988	DTaP-IPV-HepB	0, 2, 4, 6 months
Mongolia	Lower middle	1991	1991	1991	DTwP-Hib-HepB	0, 2, 3, 4 months
Nauru	High	1983	1983	Unclear, before 1987	DTwP-Hib-HepB	0, 6, 10, 14 weeks
New Zealand	High	1985	1988	1987, only if mother HBsAg+	DTaP-IPV-Hib-HepB	6 weeks, 3, 5 months
Palau	High	1989	1989	1989	DTaP-IPV-HepB	0, 2, 6 months
Papua New Guinea	Lower middle	1989	1989	2002	DTwP-Hib-HepB	0, 1, 2, 3 months
Philippines	Lower middle	1991	1992	2007	DTwP-Hib-HepB	0, 6, 10, 14 weeks
Republic of Korea	High	1983	1995	1983	HepB	0, 1, 6 months
Singapore	High	1983	1987	1987	DTaP-IPV-Hib-HepB	0, 2, 6 months
Solomon Islands	Lower middle	1990	1990	1990	DTwP-Hib-HepB	0, 6, 10, 14 weeks
Taiwan	High	1984	1986	1984	HepB	0, 1, 6 months
Tonga	Upper middle	1988	1988	1988	DTwP-Hib-HepB	0, 6, 10, 14 weeks
Tuvalu	Upper middle	1993	1993	1993	DTwP-Hib-HepB	0, 6, 10, 14 weeks
Vanuatu	Lower middle	1989-1993[c]	1989-1993[c]	1993	DTwP-Hib-HepB	0, 6, 10, 14 weeks
Vietnam	Lower middle	1997	2002	2003	DTwP-Hib-HepB	0, 2, 3, 4 months

aP, acellular pertussis; DT, diphtheria, tetanus; HBsAg, hepatitis B surface antigen; HepB, Hepatitis B; Hib, Haemophilus influenzae type B; NR, not reported; PDR, People's Democratic Republic; wP, whole-cell pertussis.
[a] World bank income group, June 2020.
[b] Monovalent HepB vaccine for birth dose when recommended.
[c] Conflicting reports.

At the time of the introduction of HBV vaccines into national immunization programs, most countries exclusively used monovalent HBV vaccines. Pentavalent whole-cell pertussis (wP) DTwP-Hib-HepB vaccines were gradually introduced in the SEAR and WPR, followed by hexavalent acellular pertussis (aP) DTaP-IPV-HepB-Hib vaccines in five countries, all in the WPR (Australia, Brunei Darussalam, Malaysia, New Zealand, and Singapore). Three countries (Marshall Islands, Micronesia, and Palau) currently administer a DTaP-IPV-HepB pentavalent vaccine.

Bangladesh, Nepal, and Sri Lanka (SEAR) do not administer a birth dose of the HBV vaccine. Japan and New Zealand (WPR) have opted for a selective birth dose, given to infants of mothers who are HBsAg-positive only. All other included countries had introduced a universal birth dose of the HBV vaccine by 2016.

All countries give at least three HBV vaccination doses to all infants, irrespective of maternal HBV status, with differing schedules. A vaccination schedule of 0, 1, and 6 months is currently in use in countries and territories which continue to exclusively administer a monovalent HBV vaccine. Countries that have integrated combination vaccines into their infant vaccination regimen generally administer a birth dose of monovalent HBV vaccine followed by three doses of HBV-containing pentavalent or hexavalent vaccines in the first 6 months of life. The most common schedules currently in use are 0, 6, 10 and 14 weeks (n = 14 countries), 0, 2, 4 and 6 months (n = 7), and 0, 1 and 6 months (n = 4).

Estimated vaccination coverage for HBV vaccine birth dose in 2019 was <90% in 13 countries: eight of 24 reporting countries in the WPR and five of eight reporting countries in the SEAR. The vaccination coverage rate for HBV third dose was <90% in eight countries in 2019: six in the WPR and two in the SEAR (UNICEF, 2020).

These countries have varied income levels, with one country in the low-income group, 17 lower-middle, nine upper-middle, and 10 in the high-income group. All 10 high-income countries are in the WPR (Table 1) (World Bank, 2020).

The systematic literature review identified a total of 7148 articles after deduplication. After title and abstract screening, 466 articles were evaluated for full-text review, and three additional articles were identified through hand searching; a total of 115 studies met inclusion criteria (Figure 1). A list of the studies excluded at full-text screening and the reasons for exclusion are in Supplementary Table S4. Risk of bias assessment of the 77 cross-sectional studies identified 25 with a high risk, 48 with medium risk, and four with low risk of bias. Of the 38 cohort studies, 14 had high risk, 13 had medium risk, and 11 had low risk of bias; results for all studies are presented in Supplementary Tables S5 and S6.

A total of 77 studies from 24 countries reported HBsAg prevalence in children, and 38 studies from nine countries reported HBV MTCT rates. The majority of reported data were from national studies, with only Indonesia, Japan, Marshall Islands, and Micronesia reporting results solely from single-city or regional studies. No studies were identified from Brunei Darussalam, Democratic People's Republic of Korea, Maldives, Myanmar, Nauru, New Zealand, Palau, Singapore, Sri Lanka, Timor-Leste, or Tuvalu.

The seroprevalence of HBsAg in children aged 0-15 years reported from 1990 to 2000 in the 24 countries ranged from 0.0 to 27.4% (Table 2). Full seroprevalence data from all studies are presented in Supplementary Table S8. Countries with the highest levels of HBsAg seroprevalence since 1990 were all part of the WPR and included China (24.2%), Kiribati (27.4%), Mongolia (9.3%), Tonga (11.1%), and Vanuatu (16.3%) (Davaalkham *et al.*, 2007a; Li *et al.*, 1998; Wilson *et al.*, 2000). A decreasing trend in seroprevalence was observed in 10 studies that compared seroprevalence in children at multiple timepoints; seven studies from China; and one each from Japan, Malaysia, and Taiwan (Cui *et al.*, 2017; Hsu *et al.*, 1999; Kang *et al.*, 2017a; Liu *et al.*, 2017; Ng *et al.*, 2005; Noto *et al.*, 2003; Tao *et al.*, 2018; Wang *et al.*, 2017a, 2017c; Zhou *et al.*, 2017). Lower seroprevalence was also consistently reported in younger children than in older children (Supplementary Table S8).

Studies with the objective of comparing HBsAg seroprevalence in cohorts of children born before and after the nationwide introduction of HBV vaccination were reported from Bangladesh, China, Fiji, Kiribati, Nepal, Thailand, Tonga, and Vanuatu (Figure 2). A study in 1998 of infants aged 12-24 months and children aged 10-13 years (born before the vaccination era) in Fiji, Kiribati, Tonga, and Vanuatu demonstrated lower seroprevalence in the 12-24 month-old age group (0.7% vs 6.9% in Fiji, 3.8% vs 27.4% in Kiribati, 3.8% vs 11.1% in Tonga, and 3.0% vs 16.3% in Vanuatu) (Wilson *et al.*, 2000). Similar results were found in China (0.64% in 2014 vs 10.5% in 1992) (Wang *et al.*, 2017a).

HBV MTCT rates were reported by 38 studies; 26 from China (Chen *et al.*, 2018; Choi *et al.*, 2019; Ding *et al.*, 2013; Evans *et al.*, 2015; Guo *et al.*, 2010; Hu *et al.*, 2019; Kang *et al.*, 2014; Kang *et al.*, 2017b; Liu *et al.*, 2019; Peng *et al.*, 2019; Li *et al.*, 2012; Peng *et al.*, 2019; Qiao *et al.*, 2019; Shao *et al.*, 2011; Su *et al.*, 2013; Wang *et al.*, 2015, 2017d; Wang *et al.*, 2003; Yin *et al.*, 2013; Yin *et al.*, 2019; Yonghao *et al.*, 2017; Zhang *et al.*, 2014a, 2014b, 2014c, 2016; Zhang *et al.*, 2017); three from Japan (Sasagawa *et al.*, 2019; Shirakawa *et al.*, 2018; Sugiyama *et al.*, 2017); two from Lao People's Democratic Republic (Jutavijittum *et al.*, 2005; Latthaphasavang *et al.*, 2019); two from Hong Kong (Cheung *et al.*, 2018; Tse *et al.*, 2006); and one study each from Australia (Wiseman *et al.*, 2009), Indonesia (Vranckx *et al.*, 1999), Republic of Korea (Kim *et al.*, 2014), Taiwan (Chen *et al.*, 2012), and Vietnam (Khue *et al.*, 2020). When reported, 81-100% of infants in these studies received HBV vaccination, and some also benefited from HBIG. MTCT rates from all included studies, irrespective of maternal HBeAg status, are presented in Supplementary Table S9. In 23 studies, HBV transmission rates reported in infants of mothers who are HBeAg-positive ranged from 2.7-53.0% (Supplementary Table S10). In 18 studies, transmission rates reported in infants of mothers who are HBsAg-positive and HBeAg-negative ranged from 0.0-5.2% (Supplementary Table S11). In seven studies with 100% coverage for both HBV vaccinations, including a birth dose and HBIG, no MTCT was observed from mothers who are HBsAg-positive and HBeAg-negative (Cheung *et al.*, 2018; Liu *et al.*, 2019; Zhang *et al.*, 2014a, 2014b, 2014c). Because there were very few MTCT studies identified outside China, and there was large heterogeneity between studies in terms of data collection period, vaccination coverage, HBIG coverage, and child age at assessment, a meta-analysis to pool the MTCT rates was not performed.

The percentage of mothers who are HBeAg-positive included in the studies of HBV MTCT ranged from 22.1-67.1% (Supplementary Table S9). There was considerable heterogeneity in the study populations and data collection period, and few nationally representative studies were reported.

The pragmatic search identified eight countries that changed vaccination schedules from a 1-month interval between the birth dose and the second dose (0-1 months) to a 2-month interval (0-2 months). Three of these countries, Australia, Brunei Darussalam, and Malaysia, changed the schedule when the hexavalent vaccine DTaP-IPV-HepB-Hib was introduced into the national vaccination program. The remaining five countries (Maldives, Marshall Islands, Mongolia, Myanmar, and Vietnam) altered the schedule when a DTwP-HepB-Hib pentavalent vaccine was introduced. The systematic review did not identify any study reporting HBsAg seroprevalence in children born after the change in vaccination schedule from 0-1 to 0-2 months in these countries.

Discussion

This review presents a comprehensive overview of the seroprevalence of HBsAg in children in the SEAR and WPR regions over the last 30 years. In the 17 countries with temporal studies or comparisons of different age groups, prevalence of HBV in children tended to decline over time, irrespective of the timing of HBV vaccination programs. A comparison of pre and postvaccine-era cohorts of children, as reported by eight countries, all showed a lower prevalence of HBsAg in the postvaccine-era cohorts than the prevaccine-era cohorts, independent of the HBV vaccination schedule. Similarly, studies assessing change of HBsAg prevalence over time demonstrated a decreasing trend over time, and stratification of children by age or age groups nearly always demonstrated a decrease in younger children. A total of 45 studies reporting HBsAg prevalence in children were identified from China. A clear decrease

Table 2
Summary of HBsAg prevalence in children aged 0-15 years, by country or territory.

Country or territory	Number of studies identified	Age range of children in studies	HBsAg prevalence		
			%	Data period	Study coverage
South East Asia					
Bangladesh	1 (Paul *et al.*, 2018)	4–7 years	0.1%	2011–2012	National
		8–11 years	1.2%		
Bhutan	1 (Tshering *et al.*, 2020)	1–4 years	0.0%	2017	National
India	1 (Murhekar *et al.*, 2020)	5–10 years	0.7%	2017	National
Indonesia	2 (Achwan *et al.*, 2007; Purwono *et al.*, 2016)	1–15 years	0.0%	2005	City
		1–5 years (min/max)	2.1%/4.2%	2012	City
		6–12 years (min/max)	0.0%/5.9%		
Nepal	1 (Upreti *et al.*, 2014)	5–6 years	0.1%	2012	National
		10–12 years	0.3%		
Thailand	3 (Chunsuttiwat *et al.*, 1997; Jutavijittum *et al.*, 2005; Posuwan *et al.*, 2016)	7 months–5 years	2.9%	1991	Regional
			0.8%	1993	
		4–5 years	0.4%	1998–2000	Regional
		6–7 years	0.9%		
		8–9 years	2.2%		
		0.5–5 years	0.1%	2014	National
		5–10 years	0.3%		
Western Pacific					
Australia	2 (Burgess *et al.*, 1993; O'Sullivan *et al.*, 2004)	11–12 years	1.9%	1990–1991	City
		1–9 years	0.0%	1996–1999	National
		10–14 years	0.2%		
Cambodia	5 (Ko *et al.*, 2020; Mao *et al.*, 2013; Ork *et al.*, 2019; Soeung *et al.*, 2009; Tanaka *et al.*, 2018)	5–7 years	0.5-0.8%	NR	National
		5 years	3.5%	2006	National
		4–5 years	0.33%	2011	City
		5–7 years	0.52%	2017	National
		5–7 years	0.56%	2017	National
China[a]	45 (Cheng *et al.*, 2013; Cui *et al.*, 2017; Dong *et al.*, 2009; Du *et al.*, 2009; Gao *et al.*, 2016; Gong *et al.*, 2003, 2005; Huang *et al.*, 2015; Ji *et al.*, 2014; Kang *et al.*, 2017a; Li *et al.*, 1998, 2009; Li X *et al.*, 2012; Liang *et al.*, 2009a, 2009b, 2005; Liu *et al.*, 2017; Liu *et al.*, 2018; Lu *et al.*, 2009a, 2009b; Shao *et al.*, 2015; Su *et al.*, 2017; Tao *et al.*, 2018; Wang *et al.*, 2018a; Wang *et al.*, 2018b; Wang *et al.*, 2017a, 2017b; Wang *et al.*, 2013; Wang *et al.*, 2002,2017c; Wu *et al.*, 2007 Wu *et al.*, 2015; Xi *et al.*, 2017; Xia *et al.*, 1996; Xiao *et al.*, 2012; Yonghao *et al.*, 2015; Zeng *et al.*, 2016; Zhai *et al.*, 2010; Zhang *et al.*, 2016; Zhang T *et al.*, 2012; Zhang XC *et al.*, 2012; Zhou *et al.*, 2009; Zhou *et al.*, 2017; Zhang *et al.*, 2010; Zhuo *et al.*, 2000)	1–14 years	10.39%	1992	National
		3–4 years	3.11	2002	National
		5–9 years	4.83%		
		10–14 years	7.09%		
		1–14 years	2.1%	2006	National
		<5 years	1.16%	2007	National
		1–4 years	0.31%	2014	National
		1–12 years	10.5%	1992	National
			0.64%	2014	
		<15 years	10.5%	1992	National
			10.5%	2014	
Cook Islands	1 (Patel *et al.*, 2016)	6–7 years	0.0%	2012–2015	National
Fiji	1 (Wilson *et al.*, 2000)	12–24 months	0.7%	1998	National
		10–13 years	6.9%		
Japan	1 (Noto *et al.*, 2003)	7–12 years	0.3%	1990	Regional
			0.0%	2000	
		13–15 years	0.04%	1990	
			0.0%	2000	
Kiribati	2 (Patel *et al.*, 2016; Wilson *et al.*, 2000)	12–24 months	3.8%	1998	National
		10–13 years	27.4%		
		5–6 years	3.3%	2012–2015	National
Lao People's Democratic Republic	3 (Black *et al.*, 2014; Komada *et al.*, 2015; Xeuatvongsa *et al.*, 2014)	9–16 months	0.5%	2011–2013	National
		5–9 years	2.1%	2011	Regional
		5–9 years	1.7%	2012	National
Malaysia	1 (Ng *et al.*, 2005)	7–12 years	1.6%	1997	National
			0.3%	2003	
Marshall Islands	1 (Bialek *et al.*, 2010)	5–9 years	1.8%	2007	Regional
Micronesia	1 (Bialek *et al.*, 2010)	2–6 years	2.5%	2000	Regional
		2–9 years	1.5%	2005	
Mongolia	3 (Davaalkham *et al.*, 2007a, 2007b; Ochirbat *et al.*, 2008)	7–12 years	5.2%	2004	National
		5–10 years	1.1%	2006	City
Papua New Guinea	1 (Kitau *et al.*, 2015)	4–6 years	1.4%	2012–2013	National
Philippines	1 (Lopez *et al.*, 2018)	4–5 years	0.5%	2013	National
		5–6 years	1.2%		
Solomon Islands	1 (Breakwell *et al.*, 2020)	6–7 years	3.1%	2016	National
Taiwan	1 (Hsu *et al.*, 1999)	6 years	6.3%	1991	National
			1.7%	1993	
Tonga	1 (Wilson *et al.*, 2000)	12–24 months	3.8%	1998	National
		10–13 years	11.1%		
Vanuatu	1 (Wilson *et al.*, 2000)	12–24 months	3.0%	1998	National
		10–13 years	16.3%		
Vietnam	1 (Nguyen *et al.*, 2014)	3–4 years	1.6%	2011	National
		5–7 years	2.1%		
		8–11 years	3.6%		

[a] Only prevalence data from nationally representative studies are presented due to the large number of included studies from China. All studies are presented in Supplementary Table S8. HBsAg, hepatitis B surface antigen.

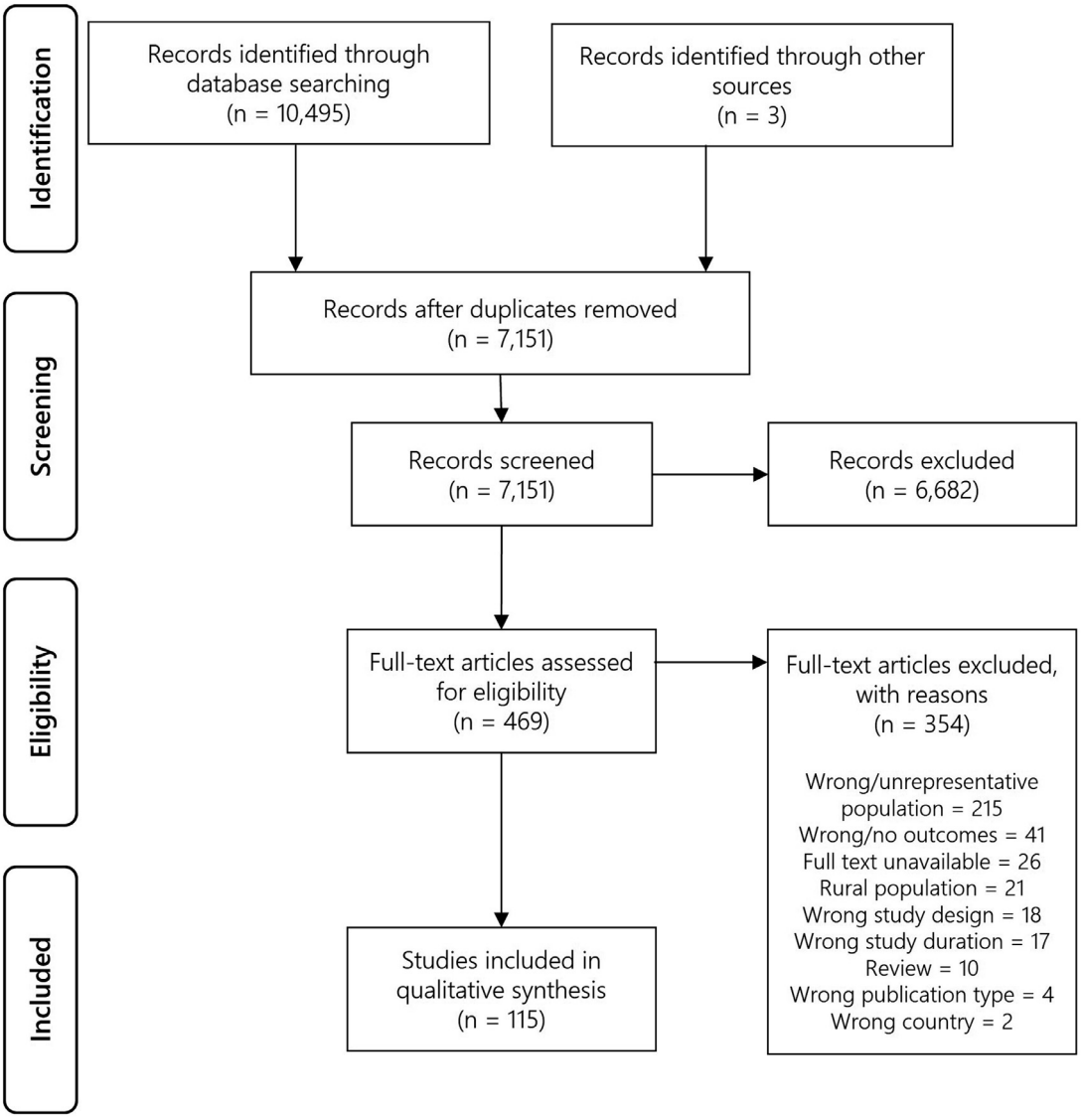


Figure 1. Flow of information through the different phases of the systematic review, adapted from Moher *et al.* (2009).

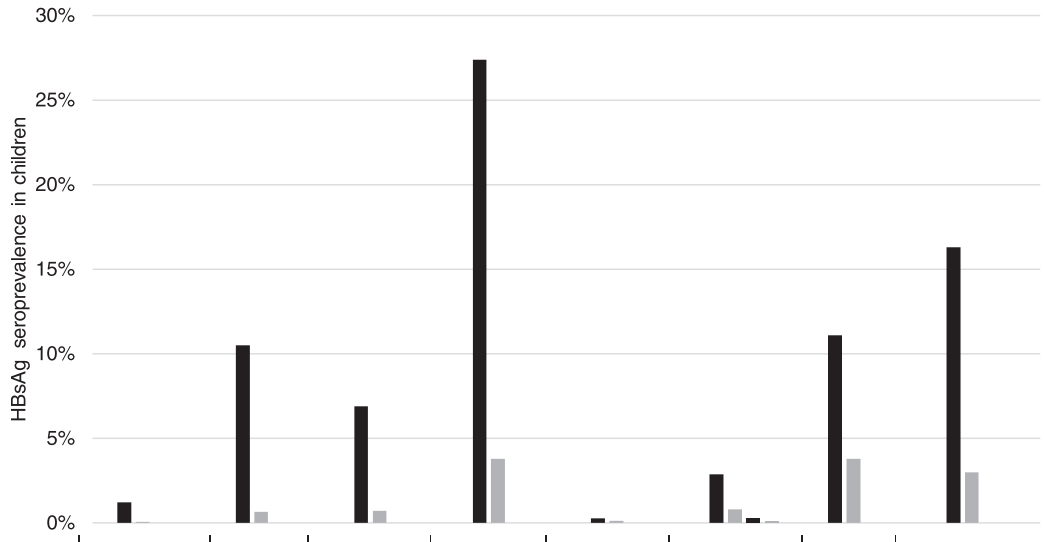
from high to low prevalence was observed in the included studies; in nationally representative studies, seroprevalence in children aged 1-15 years decreased from 10.4% in 1992 (Xia *et al.*, 1996) to 0.8% in 2014 (Cui *et al.*, 2017).

It can be assumed that infant vaccination programs have largely driven this decrease in HBV infection; over the time period assessed by this review, estimates of HBV vaccination coverage rates, including that of the birth dose, have increased (UNICEF, 2020). These findings imply that the successful implementation of HBV vaccination is key to effectively reducing the HBsAg seroprevalence in children, which should lead to achieving the WHO's global HBV elimination goals by 2030.

Chronic HBV infection has been largely preventable by vaccination since 1982 (World Health Organization, 2017). Vaccines currently in use include monovalent, DTaP and DTwP pentavalent, and DTaP hexavalent vaccines; the latter two enable synchronization of the HBV vaccination schedule with the infant vaccination schedule for other childhood diseases. The availability of combination vaccines has led to increased vaccination coverage rates, fewer health care worker visits, and fewer injections required by children to achieve timely immunity to common childhood diseases (Dolhain *et al.*, 2020). A study on the integration of the HBV vaccine into the 'Expanded Programme on Immunization' in Thailand demonstrated that HBV immunization can be successfully integrated without an adverse effect on coverage rates of other antigens and resulted in a marked reduction in the rate of chronic carriage of HBV in preschool age children (Chunsuttiwat *et al.*, 1997).

Differences between the two WHO regions were apparent. Nationwide immunization was introduced earlier in the WPR, with 21 of 27 countries having a program in place before the year 2000. This region also includes all 10 high-income countries in the study. Countries that do not routinely administer an HBV vaccine birth dose are all in the SEAR. A greater proportion of countries in the SEAR have vaccination coverage rates below 90% for both birth-dose and third-dose HBV vaccination.

A secondary objective of this review was to explore whether a change in vaccination schedule from an HBV vaccine dose at birth and at 1 month to a schedule of a dose at birth and another at 2 months had any impact on HBsAg seroprevalence in children. Although vaccination schedules in some countries have changed to align with the DTP schedule, this review did not identify any study in those countries that included children born after the schedule change and therefore, no comparison in seroprevalence could be made.



	Bangladesh (Paul 2018)	China (Wang 2017d)	Fiji (Wilson 2000)	Kiribati (Wilson 2000)	Nepal (Upreti 2014)	Thailand (Posuwan 2016, Chunsuttiwat 1997)	Tonga (Wilson 2000)	Vanuatu (Wilson 2000)
Pre-vaccine era								
Age	4-7 years	1-12 years	10-13 years	10-13 years	10-12 years	7 months-5 years (Chunsuttiwat 1997) 5-10 years (Posuwan 2016)	10-13 years	10-13 years
Study period	2011-2012	1992	1998	1998	2012	1991 (Chunsuttiwat 1997) 2014 (Posuwan 2016)	1998	1998
Post-vaccine era								
Age	8-11 years	1-12 years	12-24 months	12-24 months	5-6 years	7 months-5 years (Chunsuttiwat 1997) 0.5-4 years (Posuwan 2016)	12-24 months	12-24 months
Study period	2011-2012	2014	1998	1998	2012	1993 (Chunsuttiwat 1997) 2014 (Posuwan 2016)	1998	1998

Figure 2. Hepatitis B surface antigen seroprevalence in children, in studies comparing pre- and postvaccine era cohort.

There is very little published literature comparing HBV vaccination schedules. In a study conducted in infants born from HBsAg-positive mothers of Asian-American ethnicity receiving different types of HBV vaccines with HBIG in different schedules, there was no evidence that the risk of immunoprophylaxis failure was higher with the 0-2 months regimen than with the 0-1 months regimen (odds ratio 0.77, 95% confidence interval 0.39-1.51) (Stevens *et al.*, 2017). A 2016 WHO systematic review assessed the impact of different intervals between doses on the rate of seroprotection in children. The review did not identify any study specifically comparing the interval between the birth dose and the second dose; however, for other intervals, it did not identify any evidence that different intervals affect the seroprotection rates in children (e.g., 0, 1, and 2 months vs 0, 1, and 6 months). Nevertheless, care must be taken to interpret these results because of a high level of uncertainty owing to the limited number of studies and the high risk of bias in the studies (The Cochrane Collaboration, 2016).

The national HBV surveillance in Australia reveals that the prevalence of HBsAg in children has continued to decline since the introduction of HBV vaccination through changes in its schedule from 0, 1, 6 months to 0, 2, 4, 6 months in 2000, and the introduction of a hexavalent DTaP-Hib-HepB-IPV vaccine in 2009 (Supplementary Figure 1).

HBV MTCT has been defined as HBsAg or viral HepB DNA seropositivity at age 6-12 months in an infant born to an infected mother (Gentile and Borgia, 2014); although, it is more commonly recommended that this screening is performed no earlier than 9 months to avoid detection of passive antigenemia due to recent vaccination or HBIG (Mast *et al.*, 2005; Schillie *et al.*, 2015).

Perinatal MTCT is currently the main mode of HBV transmission worldwide (Gentile and Borgia, 2014; Mavilia and Wu, 2017; Nayagam *et al.*, 2016). Identification of pregnant women who are HBsAg-positive and risk stratification by HBeAg-positivity or viral HepB DNA levels to determine the women's eligibility for antenatal

antiviral prophylaxis is key to further reducing MTCT (Boucheron *et al.*, 2021; Funk *et al.*, 2021). Comparison of MTCT rates between countries with different vaccination schedules was not possible due to the low number of studies from countries with 0 and 2-month or 0 and 6-week schedules to compare against those with a 0 and 1-month schedule. High heterogeneity between studies, particularly regarding the vaccination status of children and the use of HBIG in newborns, would also limit any comparison.

In this review, it was observed that there is a substantial risk of MTCT in children born to mothers who are HBeAg-positive. This indicates the need for additional preventive strategies, such as antenatal antiviral prophylaxis, as recently recommended by the WHO (World Health Organization, 2020).

This systematic review has various limitations. The nationally representative studies of HBsAg seroprevalence in children and MTCT were not available for many countries, and wide geographical differences mean that the identified seroprevalence and MTCT rates are not reflective of the entire country. A comparison between pre and postvaccination child HBsAg prevalence in one country might be susceptible to the following confounding factors that could not be adequately addressed in our study: a change in maternal HBsAg prevalence over time, an increase in maternal age at first childbirth, leading to decrease in the risk of MTCT (Moutchia *et al.*, 2022), the impact of migrants from countries highly endemic for HBV, and the change in prevalence of HIV infection and the proportion treated with antiretroviral therapy effective against HBV.

The exclusion of studies where the population was entirely rural or of studies exclusively of tribal or indigenous populations from this review means that HBV seroprevalence may be underestimated for some countries. The prevalence of chronic HBV infection is often higher in these populations than the national average, with higher seroprevalence and lower vaccination coverage rates due to geographical remoteness, lack of access to health care services, and low socioeconomic status.

Conclusion

This systematic review examined HBsAg seroprevalence and the risk of MTCT in 38 countries in the SEAR and WPR. We found a decreasing trend in HBsAg seroprevalence in children over time in those studies assessing temporal or age trends, regardless of the vaccination type or schedule used. MTCT of HBV can be effectively prevented by infant immunoprophylaxis; although, the residual higher risk of transmission from mothers who are HBeAg-positive emphasizes the importance of screening to identify high-risk pregnant women who may benefit from antenatal antiviral treatment, as well as their children, who would benefit from receiving neonatal HBIG and HBV vaccine.

The systematic review did not identify any study allowing us to evaluate whether the risk of HBV infection differs when the second dose after the birth dose was given at the age of 1 month or 2 months. Because of the potential benefits of a combination vaccine synchronized to the DTP schedule to improve vaccination coverage with an efficient use of resources, compared with the historical schedule using monovalent vaccines only at 0, 1, and 6 months, a study directly comparing the risk of HBV infection and the kinetics of the immune response between these two vaccination intervals is highly warranted.

Countries are encouraged to carry out a comprehensive, prospective collection of HBV seroprevalence data of infants at age 9 months or 2-3 months after completion of vaccination to provide an accurate reflection of the efficacy of HBV vaccination, especially if there has been a change in vaccination schedule. This information can also be used to fine tune the local policy to optimize an HBV eradication program, including incorporation of antiviral treatment for highly viremic women, to achieve the WHO global HBV elimination goals by 2030.

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Ethical approval

Concerning ethical aspects, this study was conducted through a literature review, without subject identification, ensuring individual confidentiality and anonymity.

Author contributions

ZM, NP, EV, and JCVZ conceived and designed this study. NP, ZM, and CW performed initial screening, a review of full texts for eligibility and extracted the data. ZM, NP, and CW conducted the data analysis. ZM, NP, JCZV, EV, CW, YS, and KC conducted the data interpretation. ZM and CW drafted the final manuscript and prepared the tables and figures. YS, KC, JCZV, and EV provided critical analysis and made revisions of the manuscript and important intellectual contributions. All authors reviewed the manuscript before final submission.

Data sharing

Data is available upon reasonable request to the corresponding author.

Declaration of competing interests

KC declares no competing interests. YS received research grants from Gilead Sciences. ZM, NP, and CW received consulting fees from Sanofi. JCVZ and EV are Sanofi employees, a manufacturer, and distributor of many hepatitis B-containing combination vaccines and may hold shares and/or stock options in the company.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.09.003.

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