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Review

Long-term protection provided by hepatitis B vaccine and need for booster dose: A meta-analysis

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ABSTRACT

The duration of protection provided by hepatitis B vaccine is still unknown but can be estimated through long-term follow-up studies. Electronic databases and conference databases to December 2008 were searched. Reference lists of articles were screened and the studies authors and manufacturers were contacted for additional unpublished references. Randomized clinical trials and prospective cohort studies addressing the long-term protective effect of hepatitis B vaccine were included in this meta-analysis. We assessed 42 separate cohorts involving overall 11,090 subjects; 34 cohorts involving 9356 subjects were included in the final meta-analysis. Results indicate that the overall cumulative incidence of HBV breakthrough infection 5–20 years post-primary vaccination was 0.007 [95% CI: 0.005 to 0.010] with a variation among studies from 0 to 0.094. Available data do not allow us to exclude an increased risk for infection with time since vaccination. We conclude that the protection provided by three or four doses of monovalent HB vaccine persists for at least two decades in the great majority of immunocompetent individuals. Additional studies are needed for assessing vaccine efficacy for longer periods of time and the need of booster doses in different subgroups of population.

Contents

Abbreviations: HB, hepatitis B; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; Anti-HBs, antibody to hepatitis B surface antigen; Anti-HBc, antibody to hepatitis B core antigen; RV, recombinant vaccine; PDV, plasma-derived vaccine; HCWs, health care workers; CI, confidence interval; mIU/ml, milli international units per milliliter.

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1. Background

Hepatitis B (HB) immunization is now the most effective and cost-saving means to prevent hepatitis B virus (HBV) infection [1,2]. Antibody to hepatitis B surface antigen (anti-HBs) concentration equal to or greater than 10 mIU/ml is considered protective [1,2], however, anti-HBs titer decreases over time and may fall to below protective level [3,4]. Long-term immunogenicity induced by a 3-dose vaccination is well established [5–7], nonetheless, HBV breakthrough infection and chronic carriage are reported in some vaccinees [5,6,8]. Moreover, the risk of HBV infection increases by sexual and occupational exposures during adulthood [9]. Therefore, there is no worldwide consensus on the need for booster dose of HB vaccine [10].

A practical means to determine the long-term protection provided by HB vaccine against HBV infection is to estimate the cumulative incidence of chronic carrier state as well as breakthrough infection at different periods among previously vaccinated individuals.

To date, none of the international guidelines recommended booster doses for regular bases [1,11–13]. However, the duration of protection provided by HB vaccine is an important issue for future booster dose policies. In this meta-analysis, we aim to estimate long-term immunity induced by HB vaccine and the possible need for booster dose.

2. Methods

2.1. Definitions

The participants were considered to have HBV breakthrough infection if they had at least two consecutive serum specimens positive for hepatitis B core antigen (anti-HBc) and to be HBV chronic carriers if they had at least two consecutive serum specimens that were positive for hepatitis B surface antigen (HBsAg).

The regions where studies were conducted were classified into three different categories according to the prevalence of HBV infection: (1) regions with low endemicity where prevalence of HBV infection is <2%; (2) regions with intermediate endemicity where prevalence of HBV infection is 2–7%; and (3) regions with high endemicity where prevalence of HBV infection is >7% [1,14].

2.2. Criteria for including studies

We included both randomized clinical trials as well as prospective cohort studies addressing long-term (5 years follow-up or more) HB vaccine immunogenicity, irrespective of publication status or language. The short-term (less than 5 years) follow-up studies as well as cross-sectional and historical cohort studies were excluded.

We included immunocompetent participants of any age without history of previous HBV infection before admission into the study. The participants were excluded from the meta-analysis based on the following criteria: (a) were not screened for serologic markers of HBV infection (HBsAg and anti-HBc) before vaccination; (b) born to HBsAg carrier mothers; (c) had predisposing factors for immunodeficiency such as HIV positive or hemodialysis.

HB vaccine was administered in a 3-dose or a 4-dose schedule to assess the long-term protective effect of the vaccine, irrespective of type, dosage, route, or site of injection. We excluded other types of intervention, including less than 3 doses of HB vaccine, or hepatitis B vaccine plus immunoglobulin, or hepatitis B vaccine in fixed combination with other vaccines.

The primary outcome of interest was occurrence of HBV infection at maximum follow-up, including (a) chronic carrier state detected by the presence of HBsAg and (b) breakthrough infection detected by the presence of anti-HBc. To estimate 'cumulative incidence' of HBV breakthrough infection, we used all recruited participants at the start of follow-up as a denominator and the number of HBV breakthrough infections at the end of follow-up as a numerator.

2.3. Search methods

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register (2008), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2008, Issue 3), MEDLINE (January 1950 to December 2008), EMBASE (January 1980 to December 2008), and Science Citation Index Expanded (January 1945 to December 2008). The conference databases were searched for unpublished data too.

We also scanned the reference lists of all included studies and pertinent reviews for additional references. We contacted the authors of included studies as well as vaccine manufacturers for additional unpublished studies.

2.4. Data collection and analysis

Two authors independently made the decision on which studies meet the inclusion criteria to objective of this meta-analysis. The authors were not blinded to the names of the studies authors, journals, and results. Any disagreements were resolved through discussion among the authors until consensus was reached.

We assessed the risk of bias in included studies using the risk of bias tool. To handle withdrawals and dropouts in the analysis, we used "*available-participant approach*" [15] and included data on only those participants whose results were known, using as the denominator total number of participants at baseline.

We explored statistical heterogeneity using the chi-square (χ^2 or Chi^2) test at the 10% significance level ($P < 0.10$). We quantified inconsistency across studies results using I^2 statistic [16]. We also estimated the between-study variance using tau-squared (τ^2 or Tau^2) statistic [15]. Publication bias was assessed using the funnel plot [15].

Both Review Manager 5 [17] and Stata 9 were employed for data analysis. Meta-analysis was performed to obtain summary measure of 'cumulative incidence' of HBV breakthrough infection (anti-HBc positivity) at maximum follow-up. Data were analyzed and the results were reported using a fixed effect model with 95% CI when the results of fixed and random effect models were the same [18].

3. Results

3.1. Results of the search

We conducted a meta-analysis and developed a search strategy to encompass both randomized clinical trials and prospective cohort studies. We retrieved 4699 references up to December 2008, including 2208 references through searching electronic databases, 2467 references through checking reference lists, and 24 references through personal contact with studies authors or searching conference databases. Of 112 references considered potentially eligible after screening, 81 studies were excluded and 22 studies were eventually included for meta-analysis [19–40].

Of 22 included studies, 20 studies were published in English and 2 studies in Chinese [31,35,37]. Twenty studies were published as full paper and 2 studies [24,32] as a poster presentation. Some studies had multiple intervention groups. The multiple intervention groups varied due to different types of vaccine or different dosage. Results of some long-term follow-up studies were reported periodically and thus were repeated in more than one stratum

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(see below). Based on what mentioned above, we divided the 22 included studies into 42 intervention cohorts for analysis.

Nine out of 22 studies (41%) were randomized in design, however, the method of sequence generation was specified in none but one [19]. Randomization was made in all but two studies in order to allocate the participants to the different interventions (vaccine) groups randomly without considering any control group. The reasons for dropouts were described in only four studies [20–22,30], hence, the overall adequate handling of incomplete outcome data was 18.2%. All but three (86.4%) of the studies [24,32,37] were free of selective reporting. The eligibility criteria for selection and recruitment of participants were addressed clearly in 86.4% of the studies.

3.2. Effect of intervention

We included in the meta-analysis 22 studies containing 42 independent cohorts with overall 11,090 participants. Two out of 42 cohorts were from the same study [19] and were followed for 22 years post-primary vaccination. These two cohorts were presented separately because of longer than 20 years follow-up.

Of the remaining 40 intervention cohorts, 33 were relevant to general population and 7 to health care workers (HCWs). We divided the 40 cohorts into 4 different strata based on duration from initial vaccination, including stratum 1 contained 5 years follow-up studies; stratum 2 contained 6–10 years follow-up studies; stratum 3 contained 11–15 years follow-up studies; and stratum 4 contained 16–20 years follow-up studies. Stratum 1 included 14 cohorts with 3400 participants; stratum 2 included 12 cohorts with 3422 participants; stratum 3 included 9 cohorts with 3449 participants; and stratum 4 included 5 cohorts with 611 participants (Table 1).

Forty-four percent of the participants (4929 out of 11,090) were <20 years old; 12% (1271 out of 11,090) were 20–39 years old; 3% (292 out of 11,090) were ≥40 years old; and the

Table 1
Summary of studies results.

Stratum	Study	Fu (year)	Design	Part	Age (year)	Region	Vaccine	*N*	NF	CCS	HBsAg+	Anti-HBc+
1	But [19]	5	RCT	GP	1–11	High	RV	104	63	0	0	0
	But [19]	5	RCT	GP	1–11	High	PDV	104	64	0	0	0
	Chadha [20]	5	Cohort	HCW	37.5	Inter	PDV	18	18	0	0	0
	Durlach [21]	5	Cohort	HCW	22–55	Low	RV	292	175	0	0	0
	Gilca [22]	5	Cohort	GP	8–10	Low	RV	377	283	0	0	0
	Goh [23]	5	Cohort	HCW	19–21	High	PDV	240	100	0	0	1
	Joshi [24]	5	Cohort	HCW	21–40	Inter	RV	78	65	0	0	No data
	Lai [25]	5	RCT	GP	1–11	High	RV	106	63	0	0	0
	Lai [25]	5	RCT	GP	1–11	High	PDV	107	64	0	0	0
	Mintai [26]	5	Cohort	GP	13–15	High	PDV	95	95	0	0	9
	Wainwright [27]	5	Cohort	GP	1–65+	High	PDV	1581	1114	0	0	4
	Yuen [28]	5	RCT	GP	1–11	High	RV	99	63	0	0	0
	Yuen [28]	5	RCT	GP	1–11	High	PDV	104	64	0	0	0
	Zhang [29]	5	Cohort	GP	13–15	High	PDV	95	85	0	0	9
Total	–	5	–	–	–	–	–	3400	2316	0	0	23
2	Goh [23]	6	Cohort	GP	18–21	High	PDV	293	190	0	2	4
	Van Herck [30]	8	Cohort	GP	23.3	Low	RV	132	40	0	0	0
	Xu [31][a]	9	RCT	GP	5–9	High	PDV	126	101	0	1	16
	But [19]	10	RCT	GP	1–11	High	RV	104	55	0	0	1
	But [19]	10	RCT	GP	1–11	High	PDV	104	56	0	0	0
	Chadha [20]	10	Cohort	HCW	37.3	Inter	RV	18	16	0	0	0
	Durlach [21]	10	Cohort	HCW	33–40	Low	RV	292	114	0	0	2
	Gilca [22]	10	Cohort	GP	8–10	Low	RV	377	277	0	0	0
	Patel [32]	10	Cohort	GP	Infants	High	PDV	192	192	0	0	14
	Wainwright [33]	10	Cohort	GP	1–65+	High	PDV	1581	1059	0	2	13
	Yuen [28]	10	RCT	GP	1–11	High	RV	99	55	0	0	1
	Yuen [28]	10	RCT	GP	1–11	High	PDV	104	56	0	0	0
Total	–	6–10	–	–	–	–	–	3422	2211	0	5	51
3	Gabbuti [34]	11	Cohort	GP	12	Low	RV	480	228	0	0	0
	Xu [35][a]	11	RCT	GP	5–9	High	PDV	126	84	0	1	28
	Liu [36]	12	Cohort	GP	Infants	High	PDV	688	424	0	5	No data
	But [19]	15	RCT	GP	1–11	High	RV	104	37	0	0	1
	But [19]	15	RCT	GP	1–11	High	PDV	104	36	0	0	0
	Liao [37]	15	RCT	GP	1–3	High	PDV	308	52	1	1	No data
	McMahon [38]	15	Cohort	GP	1–65+	High	PDV	1436	783	0	6	16
	Yuen [39]	15	RCT	GP	1–11	High	RV	99	37	0	0	1
	Yuen [39]	15	RCT	GP	1–11	High	PDV	104	36	0	0	0
Total	–	11–15	–	–	–	–	–	3449	1717	1	13	46
4	Alavian [40][a]	16	Cohort	HCW	19–49	Inter	RV	200	113	0	0	30
	Yuen [39]	18	RCT	GP	1–11	High	RV	99	30	0	0	1
	Yuen [39]	18	RCT	GP	1–11	High	PDV	104	33	0	0	1
	But [19]	20	RCT	GP	1–11	High	RV	104	22	0	0	1
	But [19]	20	RCT	GP	1–11	High	PDV	104	24	0	0	1
Total	–	16–20	–	–	–	–	–	611	222	0	0	34

FU: follow-up; Part: participants; *N*: number of participants at start of follow-up; NF: number of participants at final follow-up; CCS: chronic carrier state; RCT: randomized clinical trial; GP: general population HCW: health care worker; Low: low endemicity; Inter: intermediate endemicity; High: high endemicity; RV: recombinant vaccine; PDV: plasma-derived vaccine.

[a] Outlier.

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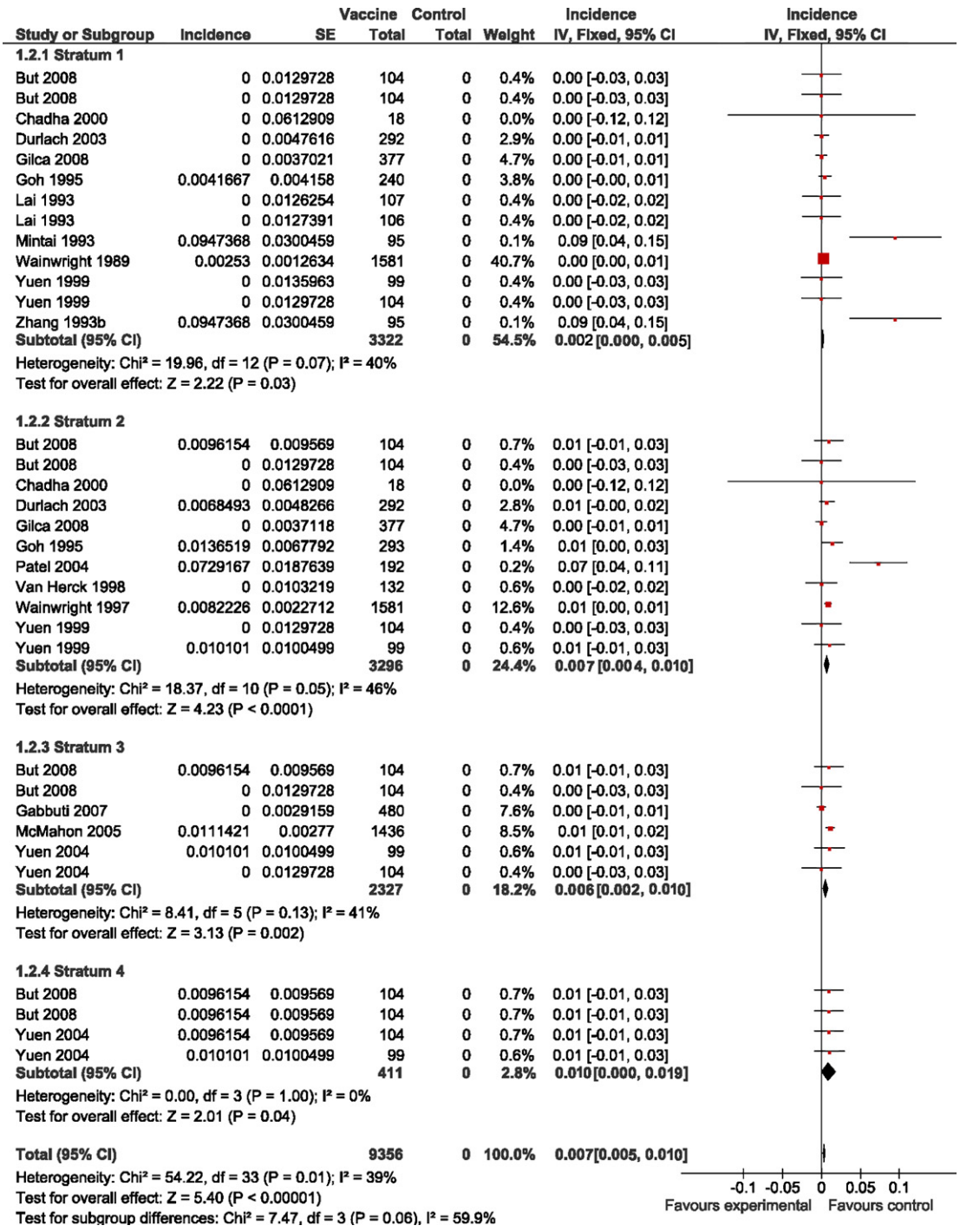

Fig. 1. Forest plot of incidence risk of HBV breakthrough infection.

remaining 41% (4598 out of 11,090) included all age groups (Table 1).

We summarized and listed the incidence of chronic carrier state (HBsAg+) and breakthrough infection (anti-HBc+) reported by 40 cohorts (Table 1). Eight transient HBsAg seroconversions occurred among 11,090 participants in different periods of post-vaccination follow-up but no one became chronic carrier. The only chronic carrier state in these individuals occurred 6 months after the first dose of vaccine suggesting that the infection was present before protective effect of HB vaccine could be established [37].

The cumulative incidence of HBV breakthrough infection was not reported in 3 out of 40 cohorts, one [24] in stratum 1 and two [36,37] in stratum 3 (Table 1). By exclusion of these cohorts from the analysis, total number of participants decreased from 3400 to 3322 in stratum 1 and from 3449 to 2453 in stratum 3. Then we performed a meta-analysis to obtain a summary of cumulative incidence of HBV breakthrough infection in vaccinated participants. Results of meta-analysis indicated that cumulative incidence of HBV breakthrough infection was 0.002 [95% CI: 0.000 to 0.005] in stratum 1; 0.007 [95% CI: 0.004 to 0.010] in stratum 2; 0.006 [95% CI: 0.002 to 0.010] in stratum 3; and 0.010 [95% CI: 0.000 to 0.019] in stratum 4. Based on 34 cohorts with 9356 participants in all strata, the overall cumulative incidence of HBV breakthrough infection 5 to 20 years post-primary vaccination was 0.007 [95% CI: 0.005 to 0.010]. The Chi^2 test for subgroup differences revealed no statistically significant differences between cumulative incidence among

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strata ($P = 0.06$), although it was close to statistically significant level (Fig. 1).

According to results of But et al. study, including 2 independent cohorts with 208 participants, the cumulative incidence of HBV breakthrough infection 22 years post-primary vaccination was 0.010 [95% CI: 0.001 to 0.034].

3.3. Heterogeneity and publication bias

There was no considerable heterogeneity among the included studies so that the results of Chi^2 test for heterogeneity was significant in no strata (Fig. 1). In addition, the I^2 and τ^2 (Tau^2) statistics confirmed this issue (Fig. 1).

There were two extreme values (outliers) among the studies results. The first outlier which was repeated in stratum 2 [31] and 3 [35] consisted of a cohort of 126 children 5–9 years old vaccinated with a local produced plasma-derived vaccine in a 3-dose schedule and followed for 9–11 years. The cumulative incidence of HBV breakthrough infection in this cohort was 0.127 [95% CI: 0.074 to 0.198] 9 years post-primary vaccination and reached 0.222 [95% CI: 0.153 to 0.305] after 11 years. The second outlier [39] which was included in the stratum 4 consisted of a single cohort involving 200 HCWs 19–49 years old vaccinated in a 3-dose schedule of recombinant vaccine and followed for 16 years. The cumulative incidence of HBV breakthrough infection in this cohort was 0.150 [95% CI: 0.104 to 0.207].

To establish homogeneity among the studies, we excluded these outliers [31,35,39] from the meta-analysis. By exclusion of the outliers from the analysis the total number of participants decreased in stratum 2 to 3296, in stratum 3 to 2327, and in stratum 4 to 411 (Fig. 1). The cumulative incidence of HBV breakthrough infection without exclusion of outliers was 0.007 [95% CI: 0.004 to 0.010] in stratum 2; 0.006 [95% CI: 0.003 to 0.010] in stratum 3; and 0.015 [95% CI: 0.005 to 0.024] in stratum 4. However, in comparison with the results mentioned previously, the estimated cumulative incidence with and without excluded outliers was not statistically significant in no strata ($P = 1.00$ for strata 2 and 3 and $P = 0.897$ for strata 4).

We assessed publication bias using the funnel plot. Since the risk cannot be negative; therefore, all studies were distributed on the right side of the vertical line but mostly at the narrower side of the funnel with some studies out of 95% pseudo confidence interval lines. There was one outlier among the studies which were omitted to allow a better representation of the remaining data (Fig. 2).

3.4. Subgroup analysis

To assess the effect of various variables on cumulative incidence of HBV infection at maximum follow-up, we ignored the strata and performed subgroup analysis of all studies together to enhance sample sizes across different levels of variables to obtain more precise estimates. The variables under investigation included: studies design, types of vaccine, various endemic regions, types of participants, and age groups.

The cumulative incidence of HBV infection was 0.019 [95% CI: 0.000 to 0.040] based on randomized clinical trials and 0.014 [95% CI: 0.006 to 0.021] based on prospective cohort studies ($P = 0.44$).

The cumulative incidence of HBV infection was 0.009 [95% CI: 0.000 to 0.019] among participants receiving recombinant vaccine (RV) and 0.020 [95% CI: 0.010 to 0.030] among participants receiving plasma-derived vaccine (PDV) ($P = 0.003$).

The cumulative incidence of HBV infection was 0.001 [95% CI: 0.000 to 0.005] for regions with low endemicity, 0.061 [95% CI: 0.000 to 0.177] for regions with intermediate endemicity and 0.017 [95% CI: 0.008 to 0.025] for regions with high endemicity ($P < 0.001$). We should remember that the cumulative incidence for regions with intermediate endemicity was estimated based on only 2 studies involving 218 participants.

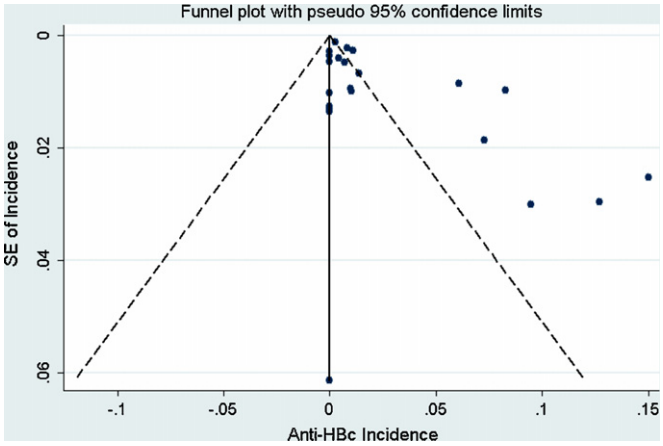

Fig. 2. Funnel plot of included studies.

The cumulative incidence of HBV infection obtained for general population was 0.013 [95% CI: 0.005 to 0.020] and that of health care workers (HCWs) was 0.030 [95% CI: 0.002 to 0.058] ($P = 0.92$).

To perform subgroup analysis across different age groups, at first, we divided the participants into 10-year age groups but there were sparse data in age groups above 20 years. Then we had to divide the participants into 20-year age groups in order to cumulate sparse age groups above 20 years. However, there were still spare data for age groups above 40 years. Based on the available data, the cumulative incidence of HBV infection was 0.021 [95% CI: 0.008 to 0.034] among those participants aged 1–19 years and 0.027 [95% CI: 0.000 to 0.053] among those participants aged 20–39 years ($P = 0.24$).

4. Discussion

The results of this meta-analysis indicated that transient HBsAg seroconversion may occur sparsely among the previously vaccinated individuals but chronic carrier state may not occur. Our findings revealed that cumulative incidence of HBV breakthrough infection is less than 0.01 during 5–20 years post-primary vaccination. In addition, 95% confidence interval of cumulative incidence includes zero in strata 1 and 4. This means that even this very low cumulative incidence is not statistically significant at conventional level ($P < 0.05$) in these strata.

The stratum 4 included only 2 studies with 4 independent cohorts involving 411 participants. The data in this stratum come from children who were close relatives of HBV carriers. Thus, it is expected that risk of HBV infection to be greater in these individuals than general population, although the Chi^2 test revealed no statistically significant differences between cumulative incidence among strata ($P = 0.06$). However, due to insufficient studies and participants in stratum 4, it is difficult to extrapolate confidentially the cumulative incidence extracted form these data to general population.

In 15 out of 44 independent cohorts under investigation, the non-respondents to primary vaccination were excluded from follow-up. This approach might contribute to the overestimation of actual vaccine efficacy against HBV infection.

The observed dynamics of HBsAg positive by strata are very interesting and merit a special attention because of its increasing trend. The cumulative incidence of HBsAg was zero (0/3400) in 5 years period post-vaccination; 0.0006 (2/3422) in 6–10 years post-vaccination; and 0.002 (6/3449) in 11–15 years post-vaccination. The result of stratum 4 does not seem robust enough due to insuffi-

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cient studies. However, attention should focus on this trend. If the observed increase in HBsAg positivity with time since vaccination is confirmed in longer follow-up studies a revision of the present immunization strategies might be needed. Fortunately these positive HBsAg seroconversions are transient and may rarely develop to chronic carrier state during the first 20 years post-primary vaccination in general population.

We excluded the outliers [31,35,39] from the meta-analysis in order to establish homogeneity among the studies. However, the exclusion of outliers did not change the results in strata 2 and 3 because of large sample sizes in these strata. The exclusion of the outlier in stratum 4 changed the results a little but it was not statistically significant.

There were a lot of dropouts due to very long-term follow-up, including 31.9% (1084 out of 3400) in stratum 1; 38.3% (1311 out of 3422) in stratum 2; 50.2% (1732 out of 3449) in stratum 3; and 63.7% (389 out of 611) in stratum 4. The reasons for dropouts were described in only 4 studies (16.7%). Of course, such amount of dropouts usually occurs during long-term periods of 5–20 years follow-up. To handle the dropouts and withdrawals for whom no outcome data were obtained, it was not reasonable to perform a sensitivity analysis based on consideration of the "best scenario" (assuming all missing participants did not experience the event or infection) versus "worst scenario" (assuming all missing participants experienced the event or infection). We estimated "cumulative incidence" so that dropouts were not introduced in the calculation while some of the dropouts might be infected. This issue raises the possibility of selection bias.

The funnel plot, a bivariate scatter plot of standard error against intervention effect, was reasonably asymmetric. Although the funnel plot asymmetry may raise the possibility of publication bias but it is not proof of it [40]. For instance, differences in methodological quality among the studies are considered an important potential source of funnel plot asymmetry as was the case in our meta-analysis because of using both randomized clinical trials as well as prospective cohort studies [16].

Based on the results of this meta-analysis, recombinant vaccine (RV) is more effective than plasma derive vaccine (PDV) to establish long-term protection against HBV infection. However, it is to note that recombinant vaccines were used in all but one study conducted in hypoendemic regions and that plasma derived vaccines were used in all studies conducted in hyperendemic regions. Hence, we can not exclude that the observed difference is due to different level of risk for infection.

Our study encompassed all different age groups and thus the result of this meta-analysis can be generalized to the general population. However, we assessed cumulative incidence of HBV infection among immunocompetent people who received either three doses or four doses of HB vaccine. Hence we can generalize the results of this meta-analysis neither to immunocompromised individuals nor to vaccinees who received less than three doses of vaccine.

We developed a wide search strategy to encompass as many studies as possible. We screened 4699 retrieved references and included 22 eligible studies in the meta-analysis involving 11,090 participants. Hence the amount of studies and body of evidence identified allow a robust conclusion regarding the objective of the study for estimating long-term protection provided by HB vaccine against HBV infection.

There were a few limitations and potential biases in this meta-analysis, including: (a) 9 studies seemed potentially eligible to be included in our meta-analysis but the full texts were not accessible. This issue may raise the possibility of selection bias. (b) There were considerable number of dropouts (37%) among the participants due to very long period of follow-up which might introduce selection bias in our results. (c) Some studies were conducted more than one decade ago and we could not manage to contact the authors in cases of missing data or need for clarification. This issue may raise the possibility of information bias. (d) The incidence of HBV breakthrough infection and hence its standard error was zero in some studies. To solve this problem for using meta-analysis we added 2 to the numerator and 4 to the denominator [41].

This meta-analysis indicated that long-term protection provided by HB vaccine is sufficient enough to prevent HBV infection in immunocompetent people for at least 20 years. Furthermore individuals adequately vaccinated in a 3-dose or 4-dose schedule do not require additional booster dose. Our findings are confirmed by other reviews. A review article revealed that development of HBsAg positive is a rare and transient event in vaccinated individuals even if anti-HBs titer decreases to very low or undetectable level. Anti-HBc seroconversion may occur but never develop to HBV carrier state [7]. Another review indicated that long-term protection against HBV infection depends on immunological memory which elicits a vigorous anamnestic immune response to HBV antigen. The immune memory persists for at least 15 years in immunocompetent persons. According to the results of this review, there are no data to support the need for booster doses of HB vaccine in individuals immunized with at least 3 doses of vaccine [10]. A third review stated that adults who responded to HB vaccination are protected from chronic HBV infection for at least 20 years even if lose detectable anti-HBs at the time of an exposure. According to the results of this review, the immunocompetent persons who responded to HB vaccination successfully do not need additional booster dose [1].

Meta-analysis was not conducted in the reviews mentioned above. In addition, our work brought some new information about HB vaccine efficacy, including (a) longer period of follow-up; (b) consolidation of the data to obtain summary measure of HBV infection for different periods since vaccination; (c) indication of potential trend in breakthrough infection with time since vaccination; (d) the possibility of HBsAg seroconversion and occurrence of rare chronic carriage state in previously immunized individuals; and (e) the impact of various variables on vaccine efficacy such as regional endemicity, different subgroups of the population and various types of vaccine.

5. Conclusions

The results of this meta-analysis show that protection provided by HB vaccine persists for at least two decades in the great majority of immunocompetent adequately vaccinated individuals. Transient HBsAg seroconversion and HBV breakthrough infection may rarely occur in individuals who received at least 3 doses of monovalent HB vaccine. Based on these findings, we conclude that 3 doses of HB vaccine ensure a good protection against infection for up to 20 years. However, additional longer-term studies should be conducted to explore vaccine efficacy and the need of booster doses in different subgroups of the population.

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Appendix A.

See Tables A.1–A.3.

Table A.1
Inclusion–exclusion criteria.

Criteria	Included	Excluded
Types of studies		
Was the study a randomized trial or a prospective cohort in design?	Yes	No
Has the trial been followed up as long as 5 years or more?	Yes	No
Types of participants		
Were the participants apparently healthy individuals without previous HBV infection?	Yes	No
Were the participants free of predisposing factors for immunodeficiency?	Yes	No
Were the participants screened for serologic markers of HBV infection before vaccination?	Yes	No
Types of interventions		
Was the administered vaccine a monovalent RV or PDV without immunoglobulin or additional dose?	Yes	No
Primary outcomes		
Has occurrence of HBV infection (either HBsAg or anti-HBc) at maximum follow-up been investigated?	Yes	No

Table A.2
Search strategies.

Databases	Time of searches	Search terms
CHBG-CTR[a]	Time of review	vaccin* AND 'hepatitis B' AND boost*
CENTRAL[b]	Issue 3 2008	#1 MeSH descriptor 'Hepatitis B' explode all trees #2 MeSH descriptor 'Vaccines' explode all trees #3 MeSH descriptor 'Vaccination' explode all trees #4 MeSH descriptor 'Immunization' explode all trees #5 (#2 OR #3 OR #4) #6 (#1 AND #5)
MEDLINE	1950 to December 2008	#1 MeSH descriptor 'Hepatitis B' explode all trees #2 MeSH descriptor 'Vaccines' explode all trees #3 MeSH descriptor 'Vaccination' explode all trees #4 MeSH descriptor 'Immunization' explode all trees #5 (#2 OR #3 OR #4) #6 (#1 AND #5) #7 #6 NOT animal #8 random* OR blind* OR placebo* OR meta-analys* #9 Cohort studies #10 #8 OR #9 #11 #7 AND #10
EMBASE	1980 to December 2008	#1 MeSH descriptor 'Hepatitis B' explode all trees #2 MeSH descriptor 'Vaccines' explode all trees #3 MeSH descriptor 'Vaccination' explode all trees #4 MeSH descriptor 'Immunization' explode all trees #5 (#2 OR #3 OR #4) #6 (#1 AND #5) #7 #6 NOT animal #8 random* OR blind* OR placebo* OR meta-analys* #9 Cohort studies OR concurrent studies #10 #8 OR #9 #11 #7 AND #10
SCIE[c]	1945 to December 2008	#1 TS = vaccin* #2 TS = 'hepatitis B' #3 #1 AND #2 #4 TS = (boost* OR follow-up OR add* OR supplem*) #5 #3 AND #4 #6 TS = (random* OR blind* OR placebo* OR mask* OR meta-analys*) #7 Cohort studies OR concurrent studies #8 #6 OR #7 #9 #5 AND #8

[a] The Cochrane Hepato-Biliary Group Controlled Trials Register.
[b] Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library.
[c] Science Citation Index Expanded (http://portal.isiknowledge.com/portal.cgi?DestApp=WOS&Func=Frame).

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Table A.3
Assessment of risk of bias in included studies.

Item	Judgment		
Sequence generation?	Yes	Unclear	No
Yes, adequate			
Sequence generation was achieved using computer random number generation or a random number table.			
Drawing lots, tossing a coin, shuffling cards and throwing dice are adequate if performed by an independent adjudicator.			
Unclear			
The trial is described as randomized but the method of sequence generation was not specified.			
No, inadequate			
The sequence generation method is not, or may not be, random.			
Quasi-randomized studies, those using dates, names, or admittance numbers in order to allocate participants are inadequate.			
Incomplete outcome data addressed?	Yes	Unclear	No
Yes, adequate			
The numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.			
Unclear			
The report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.			
No, inadequate			
The number or reasons for dropouts and withdrawals were not described.			
Free of selective reporting?	Yes	Unclear	No
Yes, adequate			
Pre-defined, or clinically relevant and reasonably expected outcomes are reported.			
Unclear			
Not all pre-defined, or clinically relevant and reasonably expected outcomes are reported fully, or it is unclear whether data on these outcomes were recorded or not.			
No, inadequate			
One or more clinically relevant and reasonably expected outcomes were not reported.			
Free of other bias?	Yes	Unclear	No
Yes, adequate			
The trial appears to be free of other components that could put it at risk of bias.			
Unclear			
The trial may or may not be free of other components that could put it at risk of bias.			
No, inadequate			
There are other factors in the trial that could put it at risk of bias, e.g., no sample size calculation made, early stopping, industry involvement, or an extreme baseline imbalance.			
Criteria for recruitment addressed?	Yes	Unclear	No
Yes, adequate			
Well defined eligibility criteria for selection and recruitment of participants, including prescreened for HBV infection markers, a reliable history of receiving a complete course of HB vaccine, no history of receiving additional dose or HB immunoglobulin, not born to HBsAg carrier mothers, no evidence of immunosuppression at the time of study recruitment.			
Unclear			
The criteria for selection and recruitment of participants are not reported fully, or it is unclear whether data on history of participants' immunization or immune status were reliable.			
No, inadequate			
The eligibility criteria for selection and recruitment of participants were not explained.			

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