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REVIEW ARTICLE

Seroprotection of Hepatitis B Vaccine and Need for Booster Dose: A Meta-Analysis

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Background and Aims: **The duration of protection provided by hepatitis B (HB) vaccine is still unknown but can be estimated indirectly by measuring the anamnestic immune response to booster doses of the vaccine.**
Methods: **We searched electronic databases and conference databases up to December 2008. We also screened reference lists of articles and contacted the authors and vaccine manufacturers for additional references. We included randomized and nonrandomized studies assessing the anamnestic immune response to the booster of HB vaccine in healthy participants 5 years or more after initial vaccination.**
Results: **The meta-analysis included 34 studies with 53 intervention groups and 4,479 individuals. The protective antibodies induced by initial vaccination waned over time; however, nonprotected vaccinees who had lost their antibodies to hepatitis B surface antigen (anti-HBs) over time responded strongly to the booster dose. The seroprotection rate of HB vaccine after the primary vaccination was 98.00% [95% confidence interval (CI): 95.32%, 99.52%] after 5 years, 96.88% [95% CI: 94.61%, 98.50%] after 6-10 years, 88.80% [95% CI: 79.84%, 95.08%] after 11-15 years, and 85.12% [95% CI: 82.18%, 88.20%] after 16-20 years.**
Conclusions: **According to these findings, the protection provided by HB vaccine is dependent on immune memory rather than anti-HBs titer; therefore, recommendations for booster doses should be based on immune memory instead of the persistence of antibody. In addition, a full course of HB vaccination can induce a long-term and strong serologic immunity against hepatitis B virus infection. Nonetheless, the decreasing trend of seroprotection during the first and second decades after immunization indicates that the long-term immunity induced by HB vaccine may diminish over time. This issue raises the possibility of the need for a booster dose, although universal revaccination does not seem necessary during the first and second decades after primary vaccination in healthy individuals with normal immune status who had fully responded to a complete course of the vaccine.**
Keywords: **Hepatitis B Vaccine, Immunization, Immunologic Memory, Immunity**

Introduction

The protection provided by hepatitis B (HB) vaccine has been well documented [1, 2]. Antibody to hepatitis B surface antigen (anti-HBs) concentrations ≥10 mIU/ml are generally considered protective against hepatitis B virus (HBV) infection [1, 3]. However, the protective antibodies induced by HB vaccination wane gradually over time and may reach very low or even undetectable levels [4, 5].

Some long-term follow-up studies have indicated that a 3-dose vaccination schedule provides immunity

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against HBV infection for as long as 15 years [2, 6]. In addition, immunologic studies have revealed that HB vaccine induces immunologic memory, so that memory B cells can proliferate, differentiate, and retain the capacity to generate a rapid and vigorous anamnestic immune response upon re-exposure to hepatitis B surface antigen (HBsAg), even if the anti-HBs titer falls below the protective level [7-9]. Hence, disappearance of the antibody does not necessarily imply loss of protection. Nonetheless, HBV breakthrough infection and chronic carriage state have been reported in some vaccinees especially in endemic regions [2, 6, 10]. Moreover, adults are less likely than infants to demonstrate an anamnestic response as they grow older [7], and the risk of HBV infection increases with sexual and occupational exposure during adulthood [11]. In the context of these relatively limited results, the duration of immunity provided by the complete course of the vaccine is unknown because vaccine protection is not parallel to anti-HB titer. Indeed, it is not clear whether a decline in serum anti-HB level indicates the need for a booster dose.

There is a practical approach to determining the duration of protection provided by HB vaccine. In this approach, we assumed that the response to the booster dose mimics the response to the wild virus. Therefore, through measuring the immune response after administration of a booster dose of the vaccine at definite time intervals from the initial vaccination, we indirectly assessed the presence of anamnestic immune response (AIR) and therefore the vaccine's long-term immunogenicity against HBV infection.

Because unnecessary HB revaccination is wasteful, none of the international guidelines recommend that booster doses be administered universally [1, 12-14]. Furthermore, the duration of protection provided by HB vaccine is important for public health authorities who have to plan immunization programs and formulate future booster policies. As a result, the seroprotection rate of HB vaccine still requires further investigation [12, 15, 16]. We found a few review articles [1, 15-17] but no meta-analysis addressing the booster dose of HB vaccine. In this meta-analysis, we took a practical approach to determine the "seroprotection rate" (SR) of HB vaccine and the need for a booster dose.

Materials and Methods

AIR is typically defined in two ways [8, 9, 18, 19]: a) experiencing a four-fold or greater rise in post-booster anti-HBs titer within 2 to 4 weeks of the booster dose administration for participants having detectable antibody or b) developing a post-booster anti-HBs level equal to or greater than 10 mIU/ml within 2 to 4 weeks of the booster dose administration for participants with no detectable antibody. In addition, protected participants are defined as vaccinees having an anti-HBs titer ≥10 mIU/ml, and nonprotected participants are defined as vaccinees having an anti-HBs titer <10 mIU/ml [1, 3].

Criteria for including studies

Types of studies: Both randomized and nonrandomized studies addressing AIR to booster doses of vaccines were included in this meta-analysis. We considered nonrandomized studies, because most studies exploring immune response to booster dose were nonrandomized in design (Fig. 1). We included studies irrespective of randomization, publication status, or language. We excluded short-

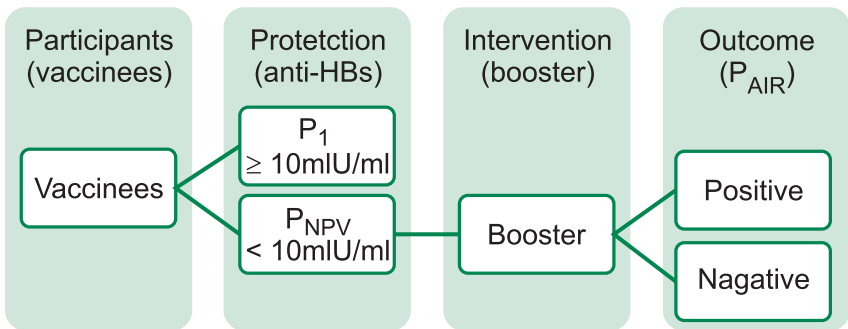

Figure 1. Design of the review for assessing the long-term seroprotection of HB vaccine

P_1: proportion of protected participants;
P_2: proportion of nonprotected participants;
P_{AIR}: proportion of anamnestic immune response in nonprotected participants.

term trials (fewer than 5 years follow-up from the initial vaccination).

Types of participants: We limited our investigation to apparently healthy participants, who had intact immune status, no previous HBV infection, and who had already received a complete course of HB vaccine. We excluded those studies whose participants a) were not screened for serologic markers of HBV infection before admission to the study; b) were born to carrier mothers; c) had no clear and reliable vaccination history; d) received an incomplete course of HB vaccine; e) received HB vaccine in fixed combination with other vaccines; f) received HB vaccine plus immunoglobulin; and g) had predisposing factors for immunodeficiency such as HIV or hemodialysis.

Types of intervention: The intervention of interest was administering a booster dose of HB vaccine to already immunized participants to assess the long-term presence (5 years or more) of AIR to the booster dose (Fig. 1). We assessed booster effect irrespective of type, dosage, injection route, and injection site.

Types of primary outcomes: We assessed two types of primary outcomes, including a) the proportion of protected participants at the end of the follow-up period (P) and b) the proportion of nonprotected participants with AIR to the booster dose (P_{AIR}).

Search methods

Electronic databases: 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 (Jan 1950 to Dec 2008), EMBASE (Jan 1980 to Dec 2008), and Science Citation Index Expanded (Jan 1945 to Dec 2008).

Other sources: We scanned the reference lists of all included studies for additional references. We also contacted the authors of the included studies as well as vaccine manufacturers for additional unpublished trials. In addition, the following conference databases were searched for unpublished data:

- Annual Meeting of the Infectious Diseases Society of America (IDSA), retrieved from *htttp://www.idsociety.org* ;
- European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), retrieved from *http://www.escmid.org* ; and
- Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) retrieved from *http://www.icaac.org* .

Data collection and analysis

Two authors independently made the decisions on which trials meet the inclusion criteria considered for this review. The two authors were not blinded to the names of the authors of the included studies, the journals, or the results. Any disagreements were resolved through discussion among the authors until a consensus was reached. Excluded trials were listed with the reasons for exclusion.

We extracted data regarding the Data Collection and Abstraction Form. In cases of missing data or need for clarification, the trial authors were contacted.

Three authors assessed the risk of bias in the included studies using a risk-of-bias tool. Any disagreements were resolved through discussion among the authors until a consensus was reached. The studies that had an adequate handling of incomplete outcome data, were free of selective reporting, included an adequate intervention description, had appropriate criteria for participant recruitment, and included an adequate outcome explanation were considered low-bias risk trials. The studies with one or more unclear or inadequate quality component were considered high-bias risk trials.

To handle withdrawals and dropouts in the analysis, we used an available-participant approach, meaning that we included data on only those participants whose results were known, using as a denominator the total number of people who had data recorded for AIR.

Seroprotection rate

Vaccinated individuals having an anti-HBs level ≥10 mIU/ml are generally considered protected [1, 3], whereas vaccinated people with an anti-HBs level <10 mIU/ml may not be protected and are assessed in this review. Seroprotection rate (SR) determines the proportion of protective immunity provided by HB vaccine among vaccinated individuals. SR consists of the proportion of protected participants plus the proportion of nonprotected participants who responded to the booster. SR is calculated by the following formula [20]:

$$SR = [P_1 + (P_2 \times P_{AIR})] \times 100,$$

where P_1 is proportion of protected participants; P_2 is proportion of nonprotected participants; and P_{AIR} is the proportion of nonprotected participants with an anamnestic immune response.

Both Review Manager 5 [21] and Stata 9 were used for the data analysis. A meta-analysis was performed to obtain the summary measures P_2 and P_{AIR} using a random-effects model with a 95% confidence interval (CI). To explore statistical heterogeneity we used the chi-square (χ^2 or Chi^2) test at the 10% significance level ($P < 0.10$). We also used the I^2 statistic to quantify inconsistency in results across

studies. In addition, a funnel plot was employed for assessing publication bias.

Results

Description of studies

We retrieved 4,699 studies up to December 2008, including 2,208 studies by searching electronic databases, 2,467 studies by checking reference lists, and 24 studies through personal contact with study authors or searching conference databases. Of the 46 studies considered potentially eligible after screening, 34 [7-9, 18, 20, 22-50] were eventually included in the review and 12 studies were excluded [51-62].

Of the 34 included studies, 33 studies [7-9, 18, 20, 22-34, 36-50] were published in English, and one study was written in Chinese [35]. Thirty-three studies were published as full papers, and one study [45] was a poster presentation. All included studies were either randomized or nonrandomized in design. Randomized clinical trials included multiple parallel intervention groups without a control group. These parallel intervention groups varied by booster dosage, route or site of injection, vaccination schedule, age, and so on. Hence, there were 34 studies having 53 intervention groups overall. We considered each intervention group as a separate study for analysis.

There were 15 low-risk trials among the included studies, and the remaining 19 trials were high risk. Overall, adequate handling of incomplete outcome data was 88.2%. About 76.5% of the included trials were free of selective reporting. The intervention was well defined in all but one (97%) of the studies. The eligibility criteria for selection and recruitment of participants were addressed clearly in 79.4% of the trials. The definition of AIR was mentioned clearly in 55.9% of the included trials (Fig. 2).

Intervention effects

This meta-analysis included 34 studies with 53 intervention groups and 4,479 participants. The 53 intervention groups were divided into four different strata based on the duration of the last vaccination (Table 1). Stratum 1 included studies that assessed AIR to booster dose 5 years after the initial vaccination; Stratum 2 included studies that assessed AIR to booster dose 6 to 10 years after the initial vaccination; Stratum 3 included studies that assessed AIR to booster dose 11 to 15 years after the initial vaccination; and Stratum 4 included studies that assessed AIR to booster dose 16 to 20 years after the initial vaccination. Stratum 1 included 12 intervention groups with 480 participants; Stratum 2 included 27 intervention groups with 1,405 participants; Stratum 3 included 12 intervention groups with 1,883 participants; and Stratum 4 included 2 intervention groups with 711 participants.

The proportion of protected participants (P_1) was the complement of the proportion of nonprotected participants (P_2), and therefore P_1 (Fig. 3) decreased over time as P_2 increased. Furthermore, the proportion of AIR to the booster dose (P_{AIR}) (Fig. 4) and SR decreased, albeit more slowly over time (Fig. 5).

Because the follow-up period from booster injection to blood sampling was short (between 1 to 4 weeks), the amount of missing participants due to dropout was negligible (37 out of 4,479 participants).

We assessed reporting bias using the funnel plot, which was asymmetric for both P_2 and P_{AIR}. The Chi^2 test for heterogeneity was large, and thus the P value was low in all strata ($P < 0.001$), indicating that there was heterogeneity in the results across studies. The I^2 statistic also confirmed heterogeneity. To explore the reasons for heterogeneity across studies, we divided the data into subgroups according to the different variables under investigation and then performed the meta-analysis across subgroups.

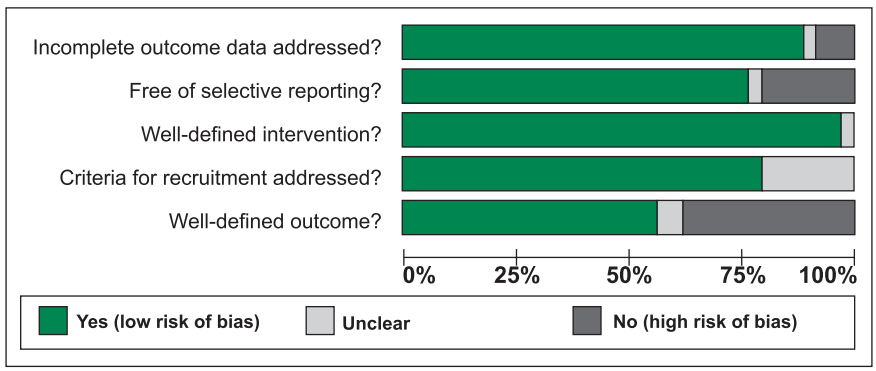

Figure 2. Methodological quality graph: review authors' judgments about each methodological quality item, presented as percentages across all included studies.

Table 1. Summary of results from the included studies

Trial	Follow-up	Participants	Vaccine	MA (yr)	N	P_1	P_2	P_{AIR}
Belloni 2000 [22]	5	GP	RV	5	51	0.71	0.29	1
Da Villa 1996 [23]	5	GP	Mixed	5	27	0.93	0.07	0.96
Dahifar 2008 [24]	5	GP	RV	6.5	4	0.94	0.06	1
Gilca 2008 [25]	5	GP	RV	15.5	36	0.87	0.13	0.94
Milne 1992a [26]	5	GP	PDV	6.1	55	0.83	0.17	0.82
Petersen 2004 [27]	5	GP	RV	5.2	71	0.13	0.87	0.85
Williams 2003 [18]	5	GP	RV	5.3	44	0.37	0.63	0.93
Duval 2005 [28]	5	GP	RV	15.1	38	0.87	0.13	0.92
Duval 2005 [28]	5	GP	RV	15.1	50	0.82	0.18	0.96
Milne 1992b [29]	5	GP	RV	18	8	0.89	0.11	1
Bucher 1994 [30]	5	HCWs	PDV	40.9	49	0.83	0.17	0.80
Bucher 1994 [30]	5	HCWs	PDV	40.4	47	*	*	0.89
Li 1998 [31]	6	GP	PDV	6-7	65	0.55	0.45	0.77
Samandari 2007 [7]	6	GP	RV	5.9	116	0.29	0.71	0.97
Seto 2002 [32]	6	GP	RV	6.1	34	0.19	0.81	1
Floreani 2004 [33]	6	HCWs	PDV	28.8	7	0.90	0.10	1
Floreani 2004 [33]	6	HCWs	RV	31.4	11	0.68	0.32	0.45
Trivello 1995 [34]	6	HCWs	PDV	30.8	99	0.67	0.33	0.92
Trivello 1995 [34]	6	HCWs	PDV	29.8	40	0.94	0.06	0.88
Li 1996 [35]	7	GP	PDV	8-11	26	0.66	0.34	1
Petersen 2004 [27]	7	GP	RV	7.5	14	*	*	1
Petersen 2004 [27]	7	GP	RV	7.4	21	0	1	0.86
Davidson 1986 [36]	7	HCWs	PDV	43	16	0.48	0.52	0.81
Petersen 2004 [27]	8	GP	RV	8.1	63	*	*	0.95
Milne 1994 [37]	9	GP	RV	11-12	17	0.86	0.14	0.94
Petersen 2004 [27]	9	GP	PDV	9.1	25	*	*	0.52
Williams 2003 [18]	9	GP	PDV	9.25	25	0.39	0.61	0.88
Williams 2001 [38]	9	HCWs	RV	46.7	13	*	*	1
Williams 2001 [38]	9	HCWs	RV	46.7	15	0.74	0.26	1
Da Villa 1996 [23]	10	GP	PDV	10	147	0.69	0.31	0.96
Petersen 2004 [27]	10	GP	PDV	10.4	29	0.41	0.59	0.69
Saffar 2004 [39]	10	GP	RV	10.7	52	*	*	0.88
Saffar 2004 [39]	10	GP	RV	10.7	57	0.58	0.42	0.95
Saffar 2004 [39]	10	GP	RV	10.7	56	*	*	0.79
Zanetti 2005 [40]	10	GP	RV	10.9	342	0.64	0.36	0.97
Gilca 2008 [25]	10	GP	RV	20.3	42	0.85	0.15	1
Zanetti 2005 [40]	10	GP	RV	21.8	48	0.89	0.11	0.96
Chadha 2000 [41]	10	HCWs	RV	37.3	10	0.19	0.81	0.8
Durlach 2003 [42]	10	HCWs	RV	44.3	15	0.87	0.13	0.8
Gabbuti 2007 [43]	11	GP	RV	23	12	0.91	0.09	0.92
Xueliang 2000 [44]	11	GP	PDV	16-20	31	*	*	0.78
Petersen 2004 [27]	12	GP	PDV	12.6	12	0.24	0.76	0.67
Samandari 2007 [7]	12	GP	RV	11.8	118	0.14	0.86	0.81
Lu 2008a [45]	13	GP	RV	13-14	522	0.31	0.69	0.74
Watson 2001 [9]	13	GP	RV	14-23	3	0.83	0.17	1
Watson 2001 [9]	13	GP	RV	43-67	2	0.71	0.29	1
Samandari 2007 [7]	14	GP	PDV	14	58	0.22	0.78	0.60
Hammitt 2007 [46]	15	GP	RV	14.6	37	*	*	0.62
LU 2004 [47]	15	GP	PDV	15	68	0.38	0.62	0.96
Lu 2008b[48]	15	GP	PDV	15-17	872	0.37	0.63	0.71
van der Sande 2007 [8]	15	GP	PDV	14.9	148	0.34	0.66	0.95
Wang 2007 [20]	16	GP	PDV	15.9	395	*	*	0.77
Su 2007 [49]	20	GP	PDV	18.7	316	0.38	0.62	0.75

P_1: proportion of protected participants
P_2: proportion of nonprotected participants
PAIR: proportion of anamnestic immune response
N: sample size
RV: recombinant vaccine
PDV: plasma derived vaccine
MA: mean age
GP: general population
HCWs: health care workers
* In these studies, the booster dose was administered to nonprotected participants, but the proportion with protected and nonprotected participants was not specified.

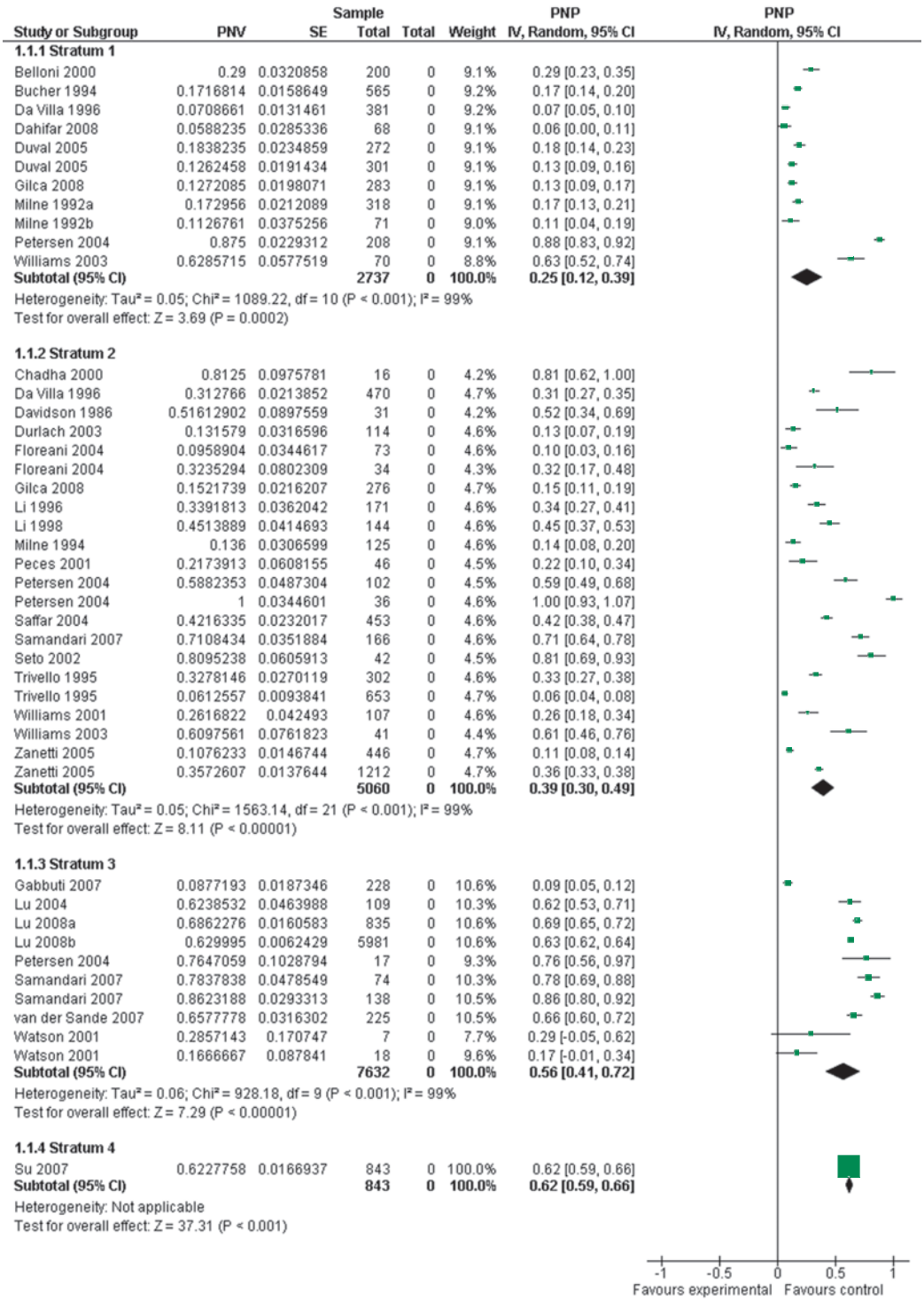

Figure 3. Forest plot of proportion of nonprotected participants (PNP) across different strata.

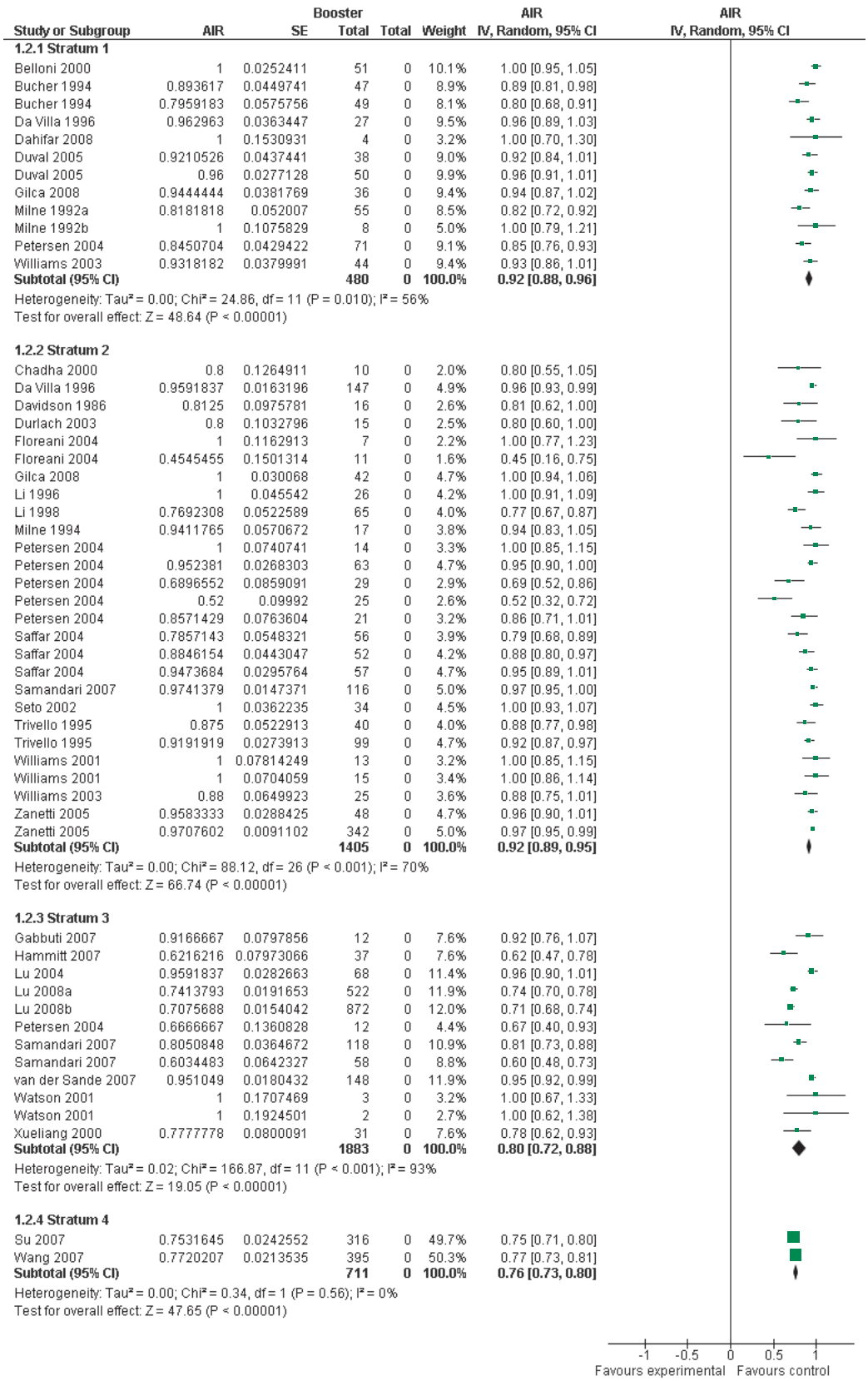

Figure 4. Forest plot of anamnestic immune response (AIR) to booster dose in nonprotected participants across different strata.

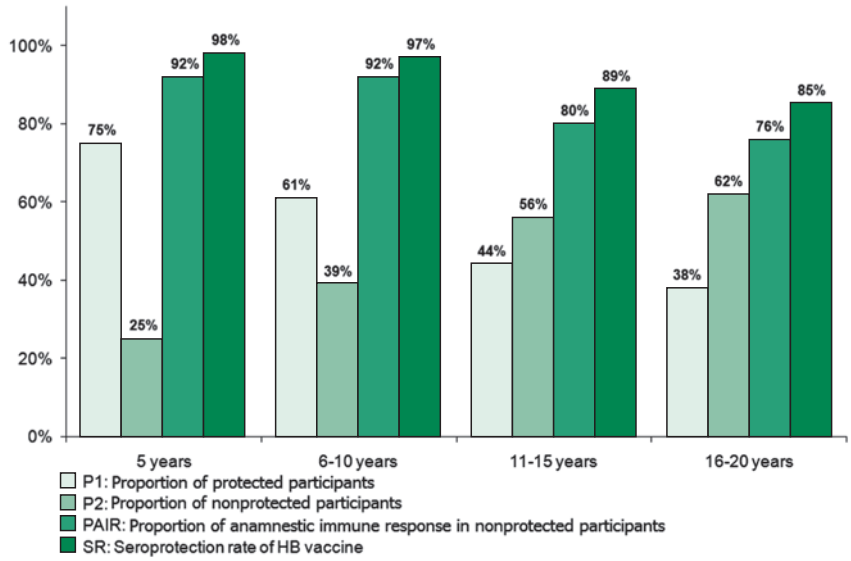

Figure 5. Proportion of protected and nonprotected participants, proportion of anamnestic immune response to booster dose among nonprotected participants, and the seroprotection rate of HB vaccine in different periods after primary vaccination.

Subgroup analysis

To assess the effect of various variables on the seroprotection rate of HB vaccine, we ignored the strata and performed the 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 the methodological quality of the studies, types of participants, and types of vaccine.

There were 15 low-risk and 19 high-risk trials among the included studies. The subgroup analysis indicated that SR was 96.08% [95% CI: 93.10% to 98.21%] for the low-risk studies and 94.29% [95% CI: 90.01% to 97.36%] for the high risk studies ($P < 0.438$).

The age range of participants varied from 5 to over 60 years. Nonetheless, 93% (4,155 out of 4,479) of participants were 5 to 24 years old. Therefore, due to sparse data, it was impossible to perform a subgroup analysis across different age groups.

Of the 53 intervention groups, 42 groups comprised the general population, whereas the remaining 11 intervention groups comprised health care workers (HCWs). The subgroup analysis revealed that SR was 94.74% [95% CI: 91.75% to 97.11%] in the general population, whereas it was 96.83% [95% CI: 93.88% to 98.87%] among HCWs ($P < 0.266$).

For the primary vaccination, a recombinant vaccine (RV) was used for 32 intervention groups, a plasma-derived vaccine (PDV) was used for 21 groups, and a mixed RV/PDV combination was used for 1 group. The subgroup analysis indicated that SR was 96.72% [95% CI: 94.10% to 98.59%] among RV recipients and 92.11% [95% CI: 86.41% to 96.27%] among PDV recipients ($P < 0.104$).

HB vaccine had been administered in a 3-dose schedule for 44 intervention groups, in a 4-dose schedule for 7 groups, and in a mixed schedule for the remaining 3 groups. However, the number of subgroups across strata was not enough to perform a subgroup analysis.

Most of the intervention groups (49 out of 53) had received a booster of RV, and 2 groups had received PDV. The type of booster was not specified in the remaining 2 groups; hence, there were not enough data to perform a subgroup-analysis across different types of booster. In addition, participants had received different booster doses for various types of RV, including Engerix-B, Recombivax HB, Genhevac B, Euvax B, and Hevac. Because the antigen contents of recombinant vaccines differ and the recommended vaccine doses vary across products from different manufacturers, assessing the dose-response relationship across intervention groups was not reasonable.

We calculated the fold rise in geometric mean titer (GMT) from the baseline to assess the strength of the immune response to the booster in different

strata. GMT rose 2,243-fold in Stratum 1, 284-fold in Stratum 2, 20-fold in Stratum 3, and 112-fold in Stratum 4. Furthermore, to determine the best time to measure GMT after the booster dose, we compared the results of 7 trials in which GMT was measured sequentially 3 times during the first, second, and fourth weeks after the booster dose. GMT increased 18-fold during the first week, reached 512-fold in the second week, and then decreased to 356-fold during the fourth week.

Discussion

We found that the protective anti-HBs induced by initial vaccination waned over time, and thus the proportion of nonprotected vaccinees increased over time. Nonetheless, a considerable proportion of nonprotected participants who had lost anti-HBs over time responded vigorously to the booster dose. Therefore, according to these findings, the protection provided by a complete course of HB vaccine is dependent on immune memory rather than anti-HBs titer.

The observed dynamic of SR by strata is interesting and merits special attention because of its decreasing trend. The SR for HB vaccine was relatively high in the first 5 years after primary vaccination and decreased a little during the first decade. However SR decreased much more during the second decade and reached 85% 16 to 20 years after immunization. Therefore, attention should focus on this decreasing trend, which may indicate a certain fragility of the long-term immunity induced by HB vaccine. This raises the possibility of the need for a booster dose after the second decade, although revaccination does not seem necessary during the first or second decade after primary vaccination.

We developed a wide search strategy to encompass as many studies as possible. We screened 4,699 retrieved references and included 34 eligible studies involving 4,479 participants. Therefore, the amount of studies and the body of evidence identified allowed for a robust conclusion regarding the long-term seroprotection rate of HB vaccine. Although the number of actual participants may have been adequate in Stratum 4, the number of studies may not have been sufficient to confidently address the long-term protection provided by HB vaccine for as long as 16-20 years post initial vaccination. In addition, 93% of the participants aged 5 to 24 years and all of the participants in this review were apparently immunocompetent. Therefore, we cannot confidently generalize the results of this review to adults aged >25 years or to the immunocompromised population.

We calculated the multiplicative rise in GMT from the baseline to assess the strength of the immune response to the booster in different strata. GMT rose 2,243-fold in Stratum 1, 284-fold in Stratum 2, 20-fold in Stratum 3, and 112-fold in Stratum 4. Furthermore, to determine the best time of measuring GMT post booster dose, we compared the results of 7 trials in which GMT was measured sequentially 3 times during the first, second, and fourth weeks after the booster dose. GMT increased 18-fold during the first week, reached 512-fold in the second week, and then decreased to 356-fold during the fourth week.

According to the results of this meta-analysis, GMT increased during the first and second weeks after booster injection and then decreased thereafter. Therefore, the best time for measuring immune response to a booster dose is at the end of second week after the administration of the booster.

Although the amount of included studies seems sufficient, the funnel plot was asymmetric. The methodological quality of the included studies differed, which itself may be an important potential source of funnel plot asymmetry. In addition, the heterogeneity in the results of the included studies may have also led to the funnel plot asymmetry in our review. Moreover, the exclusion of short-term booster studies (those with fewer than 5 years of follow-up) from our meta-analysis may have been another reason for funnel plot asymmetry.

There was evidence of heterogeneity (small P value and large I^2 statistic) among the results of the included studies. However, care must be taken in the interpretation of tests of heterogeneity. The importance of the observed value of I^2 depends on a) the magnitude and direction of the effects and b) the strength of evidence for heterogeneity (*e.g.,* P value from the Chi^2 test) [63]. In addition, the Chi^2 test has low power when the sample size is small. Inversely, the statistic has high power in detecting a small amount of heterogeneity that may be clinically unimportant when there are many studies in a meta-analysis [63], as was the case in our review. Therefore, we can attribute the observed heterogeneity to many studies being included in the meta-analysis as well as large sample sizes.

In this review, we revealed that the protection provided by HB vaccine is dependent on immune memory, rather than anti-HB titer, and furthermore that the seroprotection rate against HBV infection is sufficient in people who responded to a complete course of the vaccine. Thus, booster doses are unnecessary in immunocompetent persons for at least 20 years after primary vaccination. Our findings

are confirmed by other reviews. For instance, one review revealed that protection was independent on antibody titer and indicated that following a complete course of vaccination, booster doses are unnecessary in immunocompetent persons [17]. Another review found that immune response to the vaccine after 10 years was powerful in vaccinees whose antibody titer decreased to below the protective level [16]. A third review revealed that immune memory lasted for at least 15 years in immunocompetent individuals and emphasized that there are no data to support the need for booster doses of HB vaccine in immunocompetent individuals who have responded to a primary course [15]. Finally, Mast *et al.* claimed that substantial evidence suggests that adults who respond to HB vaccination are protected from chronic HBV infection for at least 20 years, even if vaccinees lack detectable anti-HBs levels at the time of exposure [1].

Conclusions

We found that the protection provided by HB vaccine is dependent on immune memory rather than anti-HB titer; hence, recommendations for booster doses should be based on immune memory instead of persistence of the antibody. We also revealed that, following a full course of immunization, HB vaccine will induce a long-term and strong serologic immunity against HBV infection during the first and second decades after primary vaccination. However, SR decreased during the first decade and then decreased even faster in the second decade. This trend may indicate a degree of frailty in the long-term immunity induced by HB vaccine and raises the possibility of the need for a booster dose after the second decade. Still, universal revaccination does not seem necessary during the first and second decades after primary vaccination in healthy individuals with intact immune status who had fully responded to a complete course of the vaccine.

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