Determinants of Long-term Protection After Hepatitis B Vaccination in Infancy: A Meta-analysis

Katharina Schönberger, MSc, MPH,* Christina Riedel, MSc,* Simon Rückinger, PhD,*
Ulrich Mansmann, MSc,† Wolfgang Jilg, MD,‡ and Rüdiger v. Kries, MD, MPH*

Background: The duration of protection after hepatitis B vaccination in early infancy is unclear and may be related to vaccination schedule, dosage, vaccine type and population characteristics. Factors potentially influencing waning immunity were assessed.

Methods: A systematic review was performed. The main outcomes were prevalence of anti-hepatits B antibodies ≥ 10 mIU/mL after primary or booster vaccination. Factors potentially influencing protection were assessed in an adjusted random-effects meta-analysis model by age for both outcomes. Results of both meta-analyses were combined in a prognostic model.

Results: Forty-six studies reporting on the anti-hepatits B antibodies ≥ 10 mIU/mL 5 to 20 years after primary immunization and 29 on booster response were identified. The adjusted meta-analyses identified maternal carrier status (odds ratio [OR]: 2.37 [1.11; 5.08]), lower vaccine dosage than presently recommended (OR: 0.14 [0.06; 0.30]) and gap time between last and preceding dose of the primary vaccine series (OR: 0.44 [0.22; 0.86]) as determinants for persistence of anti-hepatits B antibodies ≥ 10. A lower vaccine dosage was also associated with failure to respond to booster (OR: 0.20 [0.10; 0.38]). The prognostic model predicted long-term protection of 90% [77%; 100%] at the age of 17 years for offspring of noncarrier mothers vaccinated with a presently recommended dose and vaccination schedule.

Conclusions: Based on meta-analyses, predictors of waning immunity after hepatitis B vaccination in infancy could be identified. A prognostic model for long-term protection after hepatitis B vaccination in infancy was developed.

Key Words: hepatitis B, infant vaccination, booster, long-term protection, determinants of protection

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Although hepatitis B vaccination is highly effective, vaccination failures leading to acute[1–5] and sometimes chronic infection[5–8] have been observed. Although infections occurring within a short time interval after vaccination are likely to reflect primary

vaccination failure[1,4] due to nonresponse, those occurring after decades are likely to reflect secondary vaccination failure due to waning immunity. Anti-hepatits B antibodies [anti-HBs] ≥ 10 mIU/mL either after primary vaccination or as response to booster if the antibody concentrations have fallen below are widely accepted marker of protection after hepatitis B vaccination.[9–11] Immunity against hepatitis B gives protection against infection and protection against disease.[12–14] Protection against infection is based on the presence of anti-HBs ≥ 10 mIU/mL. After vaccination against hepatitis B, the proportion of individuals with anti-HBs ≥10 mIU/mL is highly dependent on the time elapsed since primary vaccination. Individuals whose anti-HBs concentrations dropped below a level of 10 mIU/mL are not protected any more against infection with hepatitis B virus. However, they are not at risk of hepatic disease as long as they have hepatitis B surface antigen (HBsAg)-specific immune memory. Memory persists beyond the time during which anti-HBs is present and protects against clinically relevant disease.[12–14] In case of hepatitis B virus exposure, memory rapidly leads to a vigorous anamnestic response, which prevents acute disease, prolonged viremia and chronic infection. Specific memory after hepatitis B vaccination is demonstrated by an anamnestic anti-HBs response after vaccination with an additional vaccine dose.[15] This dose acts as a booster leading to a rapid increase in anti-HBs in most of individuals who had successfully responded to the initial series of vaccinations. Persistence of immune memory is appeared to be related also to the time after primary vaccination.[16]

In most countries with universal hepatitis B vaccination, vaccine is given in infancy.[17] We, therefore, focused our study on the duration of protection after infant immunization. Although quite a number of studies exist dealing with the persistence of anti-HBs after primary immunization or analyzing the response to a booster dose after anti-HBs has dropped below 10 mIU/mL[18–26], there is no systematic investigation assessing determinants for waning immunity.

Persistence of anti-HBs ≥ 10 mIU/mL and response to booster vaccination[19,21,23] may be related to vaccine dosage,[27–30] beginning of the primary vaccine regime (at birth or later in infancy),[22,28,29,31–33] timing of the last vaccination of the primary series (ie, the gap time between last and preceding dose),[4,33] numbers of vaccine doses given as primary vaccine series[4] and use of plasma-derived or recombinant vaccines.[4,8,11,19,28,31–37] Finally, both parameters may also be influenced by the prevalence of hepatitis B infection in the population and the HBsAg carrier status of the mothers in the country.[6,7,11,21,22,28–33,35,37,38] All these studies, however, are difficult to compare because results are influenced by a mixture of causes as well as by different follow-up periods.

Based on a systematic review on studies providing information on the duration of anti-HBs ≥ 10 mIU/mL persistence after hepatitis B vaccination started within the first 6 months of life and on the response to booster vaccination in individuals with anti-HBs concentrations <10 mIU/mL, we performed meta-analyses to identify relevant factors for duration of protection. A prognostic model to predict the proportion of vaccinated individuals likely to be protected is presented.

METHODS

Case Definitions

Proportion of children/adolescents with anti-HBs titers ≥ 10 mIU/mL; proportion of children/adolescents with a response to booster vaccination (anti-HBs titers ≥ 10 mIU/mL among those with prior anti-HBs titers < 10 mIU/mL).

Description of Search Strategy

Studies were identified through searches of the 3 databases MEDLINE, EMBASE and Cochrane Library of Clinical Trials and additionally by hand search in relevant publications in September 2011. Any study published in English was eligible if reporting data on children who were vaccinated with a hepatitis B vaccine and had their first dose before an age of 6 months. The search syntax was: (Hepatitis B [All Fields]) AND (Vaccine OR vaccination OR immunization [All Fields]) AND (Immunogenicity OR immunity OR antibody OR waning [All Fields]) AND (Infants OR children OR adolescents OR toddler OR newborn OR birth OR cohort [All Fields]).

Data Extraction

Two independent reviewers read the titles and abstracts of all retrieved articles according to the inclusion criteria. Disagreement regarding the relevance of specific articles prompted second review of the titles/abstracts and was resolved by consensus.

Data collected were name of authors, name of journal, country of the study, age of the subjects at follow-up, HBsAg carrier status of mothers, response to primary immunization, vaccination schedule, types of vaccines used, dosage, number of children tested and number and percentage of children with detectable anti-HBs, type and dosage of booster dose if applicable. In case of missing data, the corresponding study authors were contacted.

Any observational studies (cross-sectional or cohort studies) reporting proportions of anti-HBs titers ≥ 10 mIU/mL with or without information on response to a booster dose in subjects who had been vaccinated against hepatitis B in infancy were considered. We excluded all studies if the 1st vaccination was given later than 6 months of age, if the follow-up was shorter than 5 years, if not all children were vaccinated in the reported (sub-) populations or if the age range within reported age groups was ≥ 5 years. Furthermore studies were not included if a booster dose was given between completed infant vaccination schedule and age at follow-up or if the vaccine was not given by intramuscular injection. Additionally, we did not include studies with inconsistent data or not reporting original data (review or editorial letter).

Determinants considered to assess the decrease of anti-HBs ≥ 10 mIU/mL were responder status (anti-HBs antibody titers ≥ 10 mIU/mL after primary vaccination), maternal carrier status (HBsAg positive versus negative), prevalence of chronic hepatitis B infection (as outlined in [39]) in the study country, vaccine type (recombinant or plasma derived), timing of first vaccination and vaccination schedules (number of vaccine doses; gap time between last and preceding dose of hepatitis vaccination <6 months, 6 to 8 or > 8 months). The booster response was defined by antibody titers ≥ 10 mIU/mL 1 week after the booster administration or later.

Statistical Analyses

We calculated multivariate random-effects models to control for study-specific uncertainties on a binary outcome (proportions of individuals with anti-HBs ≥ or < 10 mIU/mL) applying generalized mixed effects models with a random intercept allowing for adjustment for potential protective or risk factors as previously applied in meta-analyses of observational and registry bases studies.[40,41] Variables supposed to be associated with protection by hepatitis B vaccination in univariate analyses ($P < 0.05$) were included in the multivariate random-effects models by backward selection. Applying this approach allows to include all studies irrespective of the vaccinees' age at follow-up and to adjust for confounding by a number of different study characteristics.

The logarithmized random-effects models were calculated with the underlying formula p = exp(η)/(1 + exp[η]). For model estimation, the independent variable age was centered (subtracting the mean age from age of each case). For all analyses a significance level of 0.05 was applied. The final models were selected by p-level based backward selection.

In order to identify the population of individuals protected by either anti-HBs ≥ 10 mIU/mL or response to booster, we combined the results of the respective meta-analyses. The proportion of individuals likely to be protected was calculated as $\text{proportion}_{\text{protected}} = \text{proportion}_{\text{with anti-HBs titers} \geq 10 \text{ mIU/mL}} + \text{propotion}_{\text{with anti-HBs titers} < 10 \text{ mIU/mL}} \times \text{proportion}_{\text{with response to booster}}$.

Sensitivity analyses were conducted for both meta-analyses based on the methodological quality of the included studies (vaccination status of population, age at assessment, losses to follow-up) according to the GATE statement (Graphic Appraisal Tool for Epidemiological Studies).[42] Calculations were performed with R 2.13.0 by using glmer (package lme4, Vienna, Austria).

RESULTS

An overview of the literature search strategy is depicted in Figure, Supplemental Digital Content 1, http://links.lww.com/INF/B407. Table, Supplemental Digital Content 2, http://links.lww.com/INF/B408, summarizes all studies reporting anti-HBs ≥ 10 mIU/mL in 5 to 20 years old vaccinees. Because several studies reported on >1 subpopulation, all relevant subpopulations are listed separately. Measurement of the same individuals at different time points reported in 12 subpopulations was given a supplemental identifier in the random effects model. The analysis was confined to studies with full information on potential confounders leaving 55 subpopulations on 28,329 individuals, 15,944 (56.3%) with anti-HBs ≥ 10 mIU/mL at the respective time of measurement.

Figure 1 shows the proportions of individuals with anti-HBs ≥ 10 mIU/mL by size of study population and age of the individuals which decrease by age. Although most big studies were close to the estimated waning curve, the smaller studies scattered more widely and equally above and below.

In 13 subpopulations[1,2,28,29,32,33] on 982 individuals aged between 5 and 17.7 years reporting proportions of anti-HBs ≥ 10 mIU/mL were <25%. Three characteristics were shared by most of these subpopulations: gap time between last and preceding dose of primary vaccination series <6 month, first dose of vaccine was given at birth and vaccination with a lower than the presently recommended dose.

Subpopulations with proportions of anti-HBs ≥ 10 mIU/mL >90% until the age of 13 years or >60% thereafter had been vaccinated with a normal dose, with a gap time between last and preceding dose of primary vaccination >6 months and included offspring of carrier mothers. In 605 of them reported repetitive measurements in the same individuals at different time points.[30]

Risk factors for the decrease in proportions of individuals with anti-HBs ≥ 10 mIU/mL were assessed in univariate and multivariate analyses (Table 1). We did not include the child's responder status after the primary immunization in the analyses because responder status was only defined in 359 of 28,329 individuals. In univariate analyses, significant associations were observed with maternal carrier status, vaccine dosage, gap time between last and preceding dose of primary vaccination series <6 months and the number of vaccine doses. After mutual adjustment, only a gap
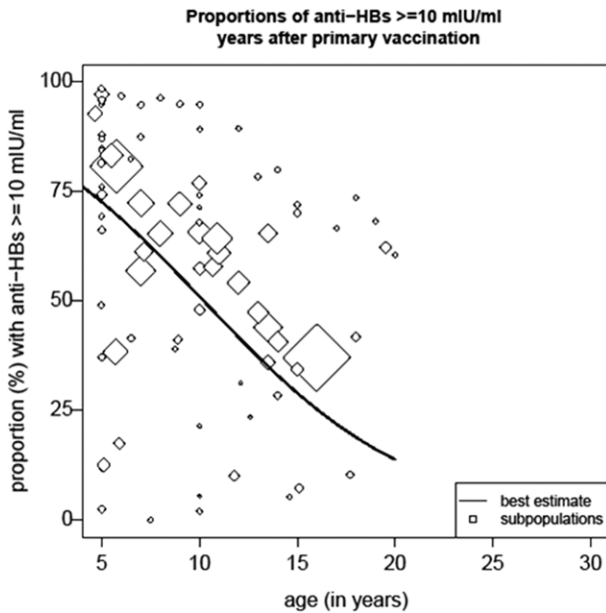
FIGURE 1. Overall description of proportions of anti-HBs ≥ 10 mIU/mL 5 to 20 years after the primary childhood vaccination. The line represents the marginal fixed effect estimate for the waning curve of anti-HBs ≥ 10 mIU/mL based on the random effects model for children vaccinated with hepatitis B vaccine in infancy. The boxes represent the size of the study population.

time <6 months and a lower vaccine dosage were related with lower proportions of anti-HBs ≥ 10 mIU/mL. Maternal carrier status was associated with higher proportions of anti-HBs ≥ 10 mIU/mL.

Table, Supplemental Digital Content 3, http://links.lww.com/INF/B409, summarizes included studies on response to booster. All relevant subpopulation are listed separately. As in the meta-analysis on vaccinees showing anti-HBs ≥ 10 mIU/mL 5 to 20 years after infant vaccination, we only included studies with full information on potential predictors. Thus, we analyzed 42 subpopulations with 3,235 individuals of whom 2,663 (82.3 %) responded to the booster vaccination.

Figure 2 shows the subpopulations reporting booster response by age (5 to 17.7 years). The distribution of the boxes scatters around the estimated waning curve with small studies equally distributed above and below. Three studies reported particularly low response to booster (67%)[22] in 5-year-old children, 52%[32] in 9-year-old children and 44% in 15-year-old children.[1] In 2 of these studies,[1,32] children had received a lower than the presently recommended vaccine dose at vaccination in infancy. The third study[22] was based on 3 children only vaccinated with a normal vaccine dose.

In univariate analyses, response to booster vaccination in children with anti-HBs < 10 mIU/mL was significantly associated to primary vaccination with a lower than the presently recommended dose and the number of doses at primary immunization. These variables were considered in the multivariate meta-analyses. In the adjusted final model—in addition to age—only the lower dose remained significantly associated with a lower response to the booster dose (Table 2).

Prediction of our model for subpopulations to be protected at different ages by risk status was compared with a major European study reporting anti-HBs ≥ 10 mIU/mL and response to booster.[24] The point estimated for protection rate in this study was 98% after 10 years as compared with 97% (95% confidence interval: 92%; 100%) estimated in the prognostic model. Modeled protection rates up to an age of 17 years for offspring of non-HBsAg carrier mothers for different scenarios are shown in Table 3. Among offspring of noncarrier mothers vaccinated with a recommended dose and a

TABLE 1. Stratified and Adjusted Analyses of Determinants Potentially Influencing the Decrease of Anti-HBs ≥ 10 mIU/mL 5 to 20 Years After the Primary Vaccination

Factors With a Potentially Influence	Values	N	Univariate (Stratified)		Multivariate (Adjusted)	
			OR	95% CI	OR	95% CI
Age at follow-up	Metric variable	28329	**0.83**	**[0.81; 0.85]**	**0.84**	**[0.82; 0.85]**
Mothers HBsAg carrier status*	Unspecified	21601	1.68	[0.71; 3.96]	1.33	[0.73; 2.40]
	Positive	2142	**4.14**	**[1.59; 10.75]**	**2.37**	**[1.11; 5.08]**
	Negative	4586	Ref		Ref	
Endemicity	Endemic (intermediate and high)	24006	0.44	[0.19; 1.05]	†	†
	Nonendemic (low)	4323	Ref		†	†
Vaccine type (infancy vaccination)	Recombinant	12158	0.50	[0.23; 1.09]	†	†
	Plasma derived	16171	Ref		†	†
Dosage of infancy vaccination (compared to present recommendation)	Normal/high	27308	Ref		Ref	
	Lower dose	1021	**0.06**	**[0.03; 0.15]**	**0.14**	**[0.06; 0.30]**
Time point of first vaccine dose	At birth	24331	Ref		†	†
	Second month of life or later	3998	2.06	[0.77; 5.52]	†	†
Vaccination schedule of infancy vaccination	Gap time between last and preceding dose <6 mo	3867	**0.27**	**[0.12; 0.59]**	**0.44**	**[0.22; 0.86]**
	Gap time between last and preceding dose between 6 and 8 mo	8176	Ref		Ref	
	Gap time between last and preceding dose >8 mo	16286	1.91	[0.80; 4.59]	1.19	[0.54; 2.63]
Numbers of vaccine doses	3 doses	11719	Ref			
	4 doses	16610	**3.79**	**[1.68; 8.55]**	1.02	[0.32; 3.27]

Significant results were printed in bold.
*1423 of 2142 (66%) offspring of documented carrier mothers received immunoglobulin in conjunction with the first dose of hepatitis B vaccination.
†Not included in multivariate model (no significant influence after the univariate/stratified analyses).
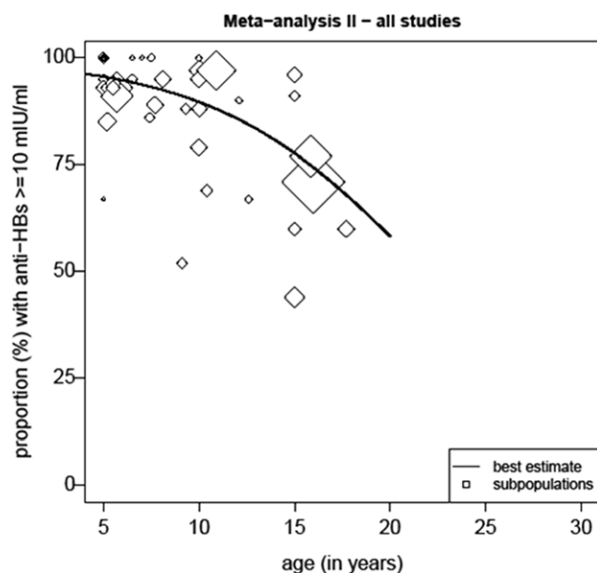OR indicates odds ratio; CI, confidence interval.

FIGURE 2. Overall description of the booster response in children with proportions of anti-HBs < 10 mIU/mL 5 to 17.7 years after the primary childhood vaccination. The line represents the marginal fixed effect estimate for the waning curve for booster response based on the random effects model for children vaccinated with hepatitis B vaccine in infancy. The boxes represent the size of the study population.

gap time between last and preceding dose of 6–8 months, for example, 92% (95% confidence interval: 0.82; 1.00) were likely to be protected after 15 years. The proportion of individual likely to be protected was slightly reduced by a shorter gap time and considerably reduced if a lower than recommended dose had been given for primary vaccination.

Failure to report losses to follow-up and potentially flawed or insufficient documentation of the vaccination status were considered as potential sources of bias.[42] Excluding these studies accounted for only marginal changes of the effect estimates in the multivariate analyses (data not shown).

DISCUSSION

The proportion of individuals with anti-HBs ≥ 10 mIU/mL decreased by age confirming what is well known since many years. Consistently lower proportions were observed in children vaccinated with a lower than presently recommended dose. A gap time between last and preceding dose of primary vaccination series of <6 months was associated with a lower proportion of individuals with protective anti-HBs. Significantly higher estimates in offspring of carrier mothers were observed. The response to booster similarly decreased by age. The decrease was accelerated by vaccination with a lower vaccine dose than presently recommended given at primary vaccination. We developed a prognostic model on long-term protection after primary hepatitis B vaccination in infancy.

A negative impact of vaccination with lower than presently recommended vaccine doses seems to be biological plausible and has been reported,[29,30,43] whereas a higher dosage was related to higher and longer lasting anti-HBs concentrations.[27,29,30]

In offspring of carrier mothers, the proportion of individuals with anti-HBs ≥ 10 mIU/mL was more than twice as high compared with noncarrier mothers, whereas maternal carrier status was not related to the booster response. Natural boosting by close contact to the carrier mother during infancy is believed to be instrumental.[7,11,21,22,29–32,35,37,38]

The association between longer gap time between the last and preceding dose of primary vaccination has been discussed in several other studies.[29,33,44–46] This may be explained by a more mature immune system in older infants[31,33] and maturation of the immune memory during the longer interval between the last 2 doses as shown for polio, hepatitis B and hepatitis A vaccine in children and adults.[44–46]

Differences in the protective effect of plasma versus recombinant vaccines have been under debate for a while.[4,8,11,19,28,34,35,37,47] Comparison of plasma and recombinant vaccines needs to take account of age at follow-up time, vaccination schedules and dosage. In our analysis, we did account for these confounding factors and could not identify differences between plasma and recombinant vaccines. Previously reported differences are therefore might reflect differences in setting, vaccination protocol and ages at follow-up or chance.[4,8,28]

The endemic status of the country was neither associated with a difference in waning proportions of individuals with anti-HBs ≥ 10 mIU/mL nor with the booster response. Some of the unexpected findings regarding, for example, the seemingly lower vaccine effects in intermediate endemic countries must be interpreted in context with the vaccination protocols in the reported studies and possibly use of measures to prevent reexposure such as safer injections, blood supply and availability of barrier methods would prevent reexposure also. So higher penetration of interventions to secure these might reflect still high endemicity (for years to come), but low transmission. In several studies from intermediate endemic countries, Alaska in particular, vaccination programs were performed with a lower than the presently recommended vaccination dose.[28,29,32,33]

Some authors reported lower proportions of individuals with anti-HBs ≥ 10 mIU/mL if the first vaccine dose had been given directly after birth,[22,29,32] whereas Mele et al[48] failed to confirm such an association. Our meta-analyses are in accordance with the observations by Mele at al. Therefore, a first dose at birth does not appear to be related to lower proportions of individuals with anti-HBs ≥ 10 mIU/mL, supporting the use of vaccination schedules starting at birth in order to attain higher vaccination rates and timely vaccination.

In the adjusted analyses, the number of doses given at primary immunization was neither significantly associated to the persistence of anti-HBs ≥ 10 mIU/mL nor to response to booster. Previous reports on the associations to the beginning of immunization and the number of administered doses might reflect confounding, for example, by a gap time <6 months between the last and the preceding dose of the vaccination series.[29,30,32]

To our knowledge, this is the first systematic review and meta-analysis on the long-term impact of factors influencing the duration of protection and on the response to a booster dose in individuals vaccinated against hepatitis B in infancy.[42,49] The sensitivity analyses did not identify aspects of study quality, which might be relevant for the analyses. Since we could not assess publication bias in a funnel plot, because funnel plot assessment cannot take account of differences in follow-up time, which is a major determinant for waning immunity, we scrutinized the distribution of small studies around the overall estimate of the waning curve. Absence of potential publication bias is suggested in Figures 1 and 2: at any given age, the individual studies scatter equally around the best estimate as indicated by the waning curves. Scattering is evidently not related to the size of the boxes. Heterogeneity was considered in the random-effects model by the intercept for study population and the covariates.[50] Current methods

TABLE 2. Stratified and Adjusted Analyses of Determinants Potentially Influencing the Response to Booster Vaccination in Children With Anti-HBs < 10 mIU/mL 5 to 17.7 Years After the Primary Vaccination

Factors With a Potentially Influence	Values	n	Univariate OR	Univariate 95% CI	Multivariate (Adjusted) OR	Multivariate (Adjusted) 95% CI
Age at follow-up	Metric variable	3235	**0.83**	**[0.76; 0.91]**	**0.91**	**[0.85; 0.98]**
Child's responder status after primary vaccination	Yes	287	1.39	[0.61; 3.14]	†	†
	Unspecified	2948	Ref		†	†
Mothers HBsAg carrier status*	Unspecified	1776	1.04	[0.47; 2.30]	†	†
	Positive	80	3.87	[0.89; 16.73]	†	†
	Negative	1379	Ref		†	†
Endemicity	Endemic (intermediate and high)	2037	0.49	[0.23; 1.06]	†	†
	Nonendemic (low)	1198	Ref		†	†
Vaccine type (infancy vaccination)	Recombinant	1655	0.99	[0.45; 2.18]	†	†
	Plasma derived	1580	Ref		†	†
Dosage of infancy vaccination (compared with present recommendation)	Normal/high	2975	Ref		Ref	†
	Lower dose	260	**0.20**	**[0.10; 0.38]**	**0.20**	**[0.10; 0.38]**
Time point of first vaccine dose	At birth	2091	Ref		†	†
	>1 mo of life	1144	1.69	[0.78; 3.69]	†	†
Vaccination schedule of infancy vaccination	Gap time between last and preceding dose <6 mo	574	0.52	[0.26; 1.06]	†	†
	Gap time between last and preceding dose between 6 and 8 mo	1189	Ref		†	†
	Gap time between last and preceding dose >8 mo	1472	1.34	[0.53; 3.38]	†	†
Numbers of vaccine doses at vaccination in infancy	3 doses	1766	Ref		Ref	
	4 doses	1469	**2.50**	**[1.04; 5.99]**	0.79	[0.35; 1.81]
Vaccine type (booster vaccination)	Recombinant	3232	10.45	[0.52; 208.97]	†	†
	Plasma derived	3	Ref		†	†
Dosage of booster vaccination (compared with present recommendation)	Normal/high	2526	Ref		†	†
	Lower dose	709	0.68	[0.32; 1.45]	†	†

Significant results were printed in bold.
*70 of 80 (88%) offspring of documented carrier mothers received immunoglobulin in conjunction with the first dose of hepatitis B vaccination.
†Not included in multivariate model (no significant influence in univariate/stratified analyses).
OR indicates odds ratio; CI, confidence interval.

for meta-analysis still leave a number of unresolved issues, such as the choice between fixed- and random-effects models, the choice of population distribution in a random-effects analysis, the treatment of small studies and extreme results, and incorporation of study-specific covariates. These problems are all met in our systematic review. Smith et al[51] describe how likelihood-based or bayesian analyses can deal with these and other issues in a natural way. This technique is now well established and often used.[52] A good model fit could be seen by variance reduction of the random effect in our analyses. The variance in the analysis of anti-HBs ≥ 10 mIU/mL decreased from 2.33 in the empty model to 0.79 in the final model (adjusting for carrier status, vaccination dose and time gap between last and preceding dose) and in the analysis of the response to booster from 1.23 in the empty model to 0.34 in the final model (adjusting for vaccination dose). This means that a large part of the variation is explained by the predictors identified.

There is clear evidence from high-risk populations that the risk for breakthrough infections increases with time since vaccination.[53] Peak anti-HBs titer correlate quite well with anti-HBs concentrations after 10 to 20 years, which are inversely correlated to the frequency of seroconversion to anti-HBs indicating that protection against infection is a function of anti-HBs.[9–11] Anti-HBs concentrations ≥ 10 mIU/mL and booster response are widely used markers for protection against infection or disease.[12,44,54] Therefore, the proposed prognostic model, which allows for adjustment for risk and protective factors for waning immunity, is likely to reflect the increasing risk for infection after vaccination in infancy by age.

TABLE 3. Proportions of Offspring of Noncarrier Mothers Likely to be Protected Against Hepatitis After Primary Vaccination in Infancy

Hepatitis B Vaccination in Infancy		Proportion of Individuals Protected After Vaccination by Age At 5 yr (95% CI)	At 10 yr (95% CI)	At 15 yr (95% CI)	At 17 yr (95% CI)
Estimation irrespective of dose and vaccination schedule		0.99 [0.97; 1.01]	0.95 [0.88; 1.02]	0.84 [0.65; 1.04]	0.77 [0.51; 1.03]
Dosage	Vaccination Schedule	At 5 yr (95% CI)	At 10 yr (95% CI)	At 15 yr (95% CI)	At 17 yr (95% CI)
Adequate	Gap time <6	0.98 [0.95; 1.01]	0.95 [0.89; 1.01]	0.90 [0.78; 1.02]	0.87 [0.72; 1.03]
Adequate	Gap time 6–8	0.99 [0.97; 1.00]	0.97 [0.92; 1.01]	0.92 [0.82; 1.02]	0.90 [0.77; 1.02]
Lower	Gap time <6	0.82 [0.74; 0.90]	0.71 [0.60; 0.83]	0.59 [0.46; 0.73]	0.54 [0.40; 0.68]
Lower	Gap time 6–8	0.85 [0.71; 1.00]	0.74 [0.52; 0.96]	0.61 [0.33; 0.88]	0.55 [0.27; 0.84]

CI indicates confidence interval of the prediction.

CONCLUSIONS

Based on these 2 meta-analyses, relevant factors influencing the duration of protection after hepatitis B vaccination in infancy could be identified. A prognostic model for long-term protection after hepatitis B vaccination in infancy was developed.

ACKNOWLEDGMENTS

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