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RESEARCH PAPER

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Demonstration of durable hepatitis B immune memory in children vaccinated with a DTaP5-IPV-HepB-Hib infant-toddler series 7 to 8 years previously

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ABSTRACT

Vaccination against hepatitis B (HepB) provides long-term protection against infection. This is despite a reduction in HepB surface antibody (anti-HBs) concentrations over time to levels below the well-accepted correlate of protection of ≥ 10 mIU/mL. Continued evidence of immune memory and protection despite declined anti-HBs concentrations can be demonstrated by HepB virus surface antigen challenge studies. Long-term immune memory and protection against HepB infection has not been demonstrated previously for the pediatric hexavalent vaccine DTaP5-IPV-HepB-Hib. This phase 3, multicenter, single-group, open-label challenge study (NCT04490499; EudraCT: 2020-000126-26) evaluated immune memory against HepB infection in children who had received DTaP5-IPV-HepB-Hib at 2, 4, and 11–12 months of age, or at 2, 3, 4, and 12 months of age. At age 8–9 years, they were each challenged with 5 μ g of monovalent HepB vaccine. Anti-HBs levels were measured on pre-challenge day 1 and post-challenge day 30. At baseline, 45.4% (93 of 205) had anti-HBs levels ≥ 10 mIU/mL. On post-challenge day 30, 99.5% (201 of 202) had anti-HBs levels ≥ 10 mIU/mL, regardless of initial vaccination schedule. Post-challenge, geometric mean concentrations increased 71-fold over baseline and 96.0% of children had a ≥ 4 -fold rise in anti-HBs concentrations with similar results across both dosing schedules. The challenge dose was well tolerated. The robust anti-HBs responses after a single 5- μ g dose of HepB vaccine confirm the persistence of a HepB immune memory and demonstrate that DTaP5-IPV-HepB-Hib provides long-term protection against HepB.

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Introduction

Globally, hepatitis B virus (HBV) causes significant morbidity and mortality.¹ Vaccination is the primary means for preventing HBV infection and its complications.^{2,3} In 2015, 84% of infants worldwide received 3 doses of hepatitis B (HepB) vaccine. Widespread HepB vaccination, particularly in newborns, has helped reduce the global prevalence of HBV infection at 5 years of age from 4.7% to 1.3%.¹

A HepB surface antibody (anti-HBs) concentration of ≥ 10 mIU/mL, measured 1–2 months after a primary HepB vaccination series, is considered a reliable marker of long-term protection against HBV infection. After a 3-dose primary series of HepB vaccine, >95% of healthy infants, children, and young adults have protective antibody concentrations.^{4,5} However, levels of anti-HBs wane over time, and 15% to 50% of children who responded to the initial vaccination series will have low or undetectable anti-HBs levels by 5 to 15 years postvaccination.⁶ Despite reduced circulating anti-HBs levels, a high rate of protection is expected years after the primary series of HepB vaccinations⁷ owing to B- and T-cell immunologic memory.^{6,8–10} Immune memory is the key to ongoing protection against HBV infection, as booster vaccinations are not recommended for the general population.^{4,10,11}

Immunologic memory is commonly demonstrated through exposure to HepB surface antigen (ie, a challenge) using a HepB vaccine. This challenge serves as a surrogate for exposure to HBV. In the absence of pre-existing immune memory, a single 5 μ g HepB vaccination would not be expected to elicit an anti-HBs of ≥ 10 mIU/mL.^{12,13} Conversely, a 5- μ g HepB challenge dose in the presence of immune memory, should induce an anamnestic response, or rapid increase in antibody concentration to levels ≥ 10 mIU/mL within a short period (1–30 days). Long-term protective immunity against HepB has not heretofore been demonstrated after an infant-toddler vaccination series with DTaP5-IPV-HepB-Hib (Vaxelis™; MCM Vaccine B.V., Leiden, The Netherlands).

DTaP5-IPV-HepB-Hib is a pediatric hexavalent vaccine indicated for primary and booster vaccination against diphtheria, pertussis, tetanus, poliomyelitis, HepB, and invasive diseases caused by *Haemophilus influenzae* type b.^{14,15} It is the only pediatric hexavalent vaccine licensed in the US^{14,16} and is 1 of 3 approved in the EU.¹⁷ In two European studies of DTaP5-IPV-HepB-Hib administered as a 2-dose infant series and toddler dose (2 + 1) in Protocol V419-008¹⁸ or 3-dose infant series and toddler dose (3 + 1) in Protocol V419-007,¹⁹ 98.1% and 99.6% of participants, respectively, had anti-HBs concentrations ≥ 10 mIU/mL 1 month after receipt of the

toddler dose.^{18,19} In a follow-up study 3 to 4 years after the toddler dose, 65.8% and 70.2% of participants previously receiving DTaP5-IPV-HepB-Hib on a 2 + 1 (Protocol V419-008) and 3 + 1 schedule (Protocol V419-007), respectively, had anti-HBs levels ≥ 10 mIU/mL.²⁰ However, that follow-up study did not include an assessment of immune memory and continued protective immunity.

This clinical study aimed to evaluate the long-term durability of immune protection against HBV infection in a subset of children aged 8–9 years who were vaccinated with DTaP5-IPV-HepB-Hib on either a 2 + 1 or 3 + 1 schedule in the two previous clinical studies (Protocols V419-008 and V419-007, respectively). Ongoing protection was evaluated via a challenge dose study design in which anti-HBs levels were measured before and 30 days after a 5- μ g challenge dose of the monovalent HepB vaccine.

Methods

Study design

This study (Protocol V419-013; ClinicalTrials.gov identifier: NCT04490499; EudraCT: 2020-000126-26) was an open-label, phase 3, single-dose, challenge study conducted in 10 centers in Finland from 2 September 2020 to 29 December 2020 (Supplemental Table S1). This is an estimation study, and the sample size of approximately 200 participants was determined using the number of participants needed to allow the estimation of the 95% CI of the primary immunogenicity endpoint having a half width of 4.0 percentage points, assuming an underlying response rate of 95%. The calculation was based on the exact binomial method proposed by Clopper and Pearson.^{21,22} Eligible children were healthy, aged 8 to 10 years, who had previously received DTaP5-IPV-HepB-Hib administered as a 2 + 1 (aged 2, 4, and 11–12 months) or 3 + 1 (aged 2, 3, 4, and 12 months) infant series and toddler dose as part of participation in Protocol V419-008 and Protocol V419-007, respectively. Exclusion criteria included a diagnosis of HBV infection determined by clinical, serologic, or microbiologic methods; receipt of any dose of a HepB vaccine other than the vaccines used in the initial studies; receipt of blood transfusion or blood products, including immunoglobulins within 6 months of study participation; receipt of any licensed, non-live vaccine within the 14 days before receipt of the challenge vaccine; or scheduled to receive any licensed, non-live vaccine within 30 days after receipt of the challenge vaccine. Each child was administered a single 0.5-mL (5 μ g) dose of monovalent HepB vaccine (HBVAXPRO™; MSD, B.V., Haarlem, The Netherlands) as the challenge dose.

Scientists from Merck & Co., Inc., Rahway, NJ, USA, from MCM Vaccine B. V., Leiden, The Netherlands, and from Sanofi Pasteur, Swiftwater, PA, USA, contributed to the development of the study protocol and formulation of the statistical analysis plan. The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. Written informed consent was provided by a legally acceptable representative before study enrollment of each study participant.

Immunogenicity

Anti-HBs levels were analyzed on serum from blood samples taken on day 1, prior to challenge, and 30 days post-challenge. The primary endpoint was the proportion of children with anti-HBs levels ≥ 10 mIU/mL on day 30 post-challenge. The secondary immunogenicity endpoint was anti-HBs geometric mean concentrations (GMC) on day 1 pre-challenge and on day 30 post-challenge. Additional exploratory endpoints included the proportion of children with anti-HBs levels ≥ 10 mIU/mL on day 1 and the proportion of participants with a ≥ 4 -fold rise in anti-HBs levels from day 1 to 30 days post-challenge. A ≥ 4 -fold rise in anti-HBs levels is a commonly accepted marker of robust anamnestic response.¹⁰ The immunogenicity analyses were conducted using the per-protocol population, which included all enrolled children without protocol deviations that could have substantially affected the results of the immunogenicity endpoints. For subgroup analyses, the immunogenicity endpoints were also estimated and descriptively summarized by prior 2 + 1 and 3 + 1 dosing schedules to confirm the overall immunogenicity response was consistent across the dosing schedules. Quantification of anti-HBs was performed using a HepB-enhanced chemiluminescence assay (Q² Solutions Vaccines, San Juan Capistrano, CA), which is a solid phase antigen sandwich enzyme-labeled immunoassay. Three internally prepared control serum pools—consisting of a high-positive, low-positive, and negative control—were used to monitor the performance of the assay. These pools were each prepared from four individual human immune sera obtained from an external vendor (Valley Biomedical, Winchester, VA). The 10-mIU/mL World Health Organization international standard concentration was also run as a control. The lower limit of quantitation of the assay was 5 mIU/mL, and the upper limit of quantitation of the assay was 1000 mIU/mL.

Safety

As specified in the protocol, adverse events (AE) resulting in study discontinuation and serious AEs were collected. The safety analysis population included all children who received the monovalent HepB vaccine challenge dose.

Statistical analysis

No statistical hypothesis testing was performed for immunogenicity analyses in this study. The point estimates for the proportion of participants with an anti-HBs level of ≥ 10 mIU/mL on pre-challenge day 1 and 30 days post-challenge were calculated, along with their 95% CIs using the Clopper–Pearson method.²¹ The point estimates for anti-HBs GMC pre-challenge on day 1 and post-challenge on day 30 were calculated by exponentiating the estimates of the mean of the natural log values; 95% CIs were derived by exponentiating the bounds of the CIs of the mean of the natural log values based on the *t*-distribution. Reverse cumulative distribution (RCD) curves for anti-HBs GMC on day 30 post-challenge were plotted for the per-protocol population and by prior 2 + 1 and 3 + 1 dosing schedules.²³ Displaying results by RCD curves allows for the

visual assessment and rapid comparison between distributions.²³ The point estimates for the proportion of participants with a ≥ 4 -fold rise in anti-HBs levels from day 1 to day 30 post-challenge were provided with 95% CIs calculated using the Clopper–Pearson method.²¹ The proportion of children with AEs resulting in discontinuation from the study and any serious AEs were summarized descriptively. All analyses and results were generated with SAS version 9.4.

Results

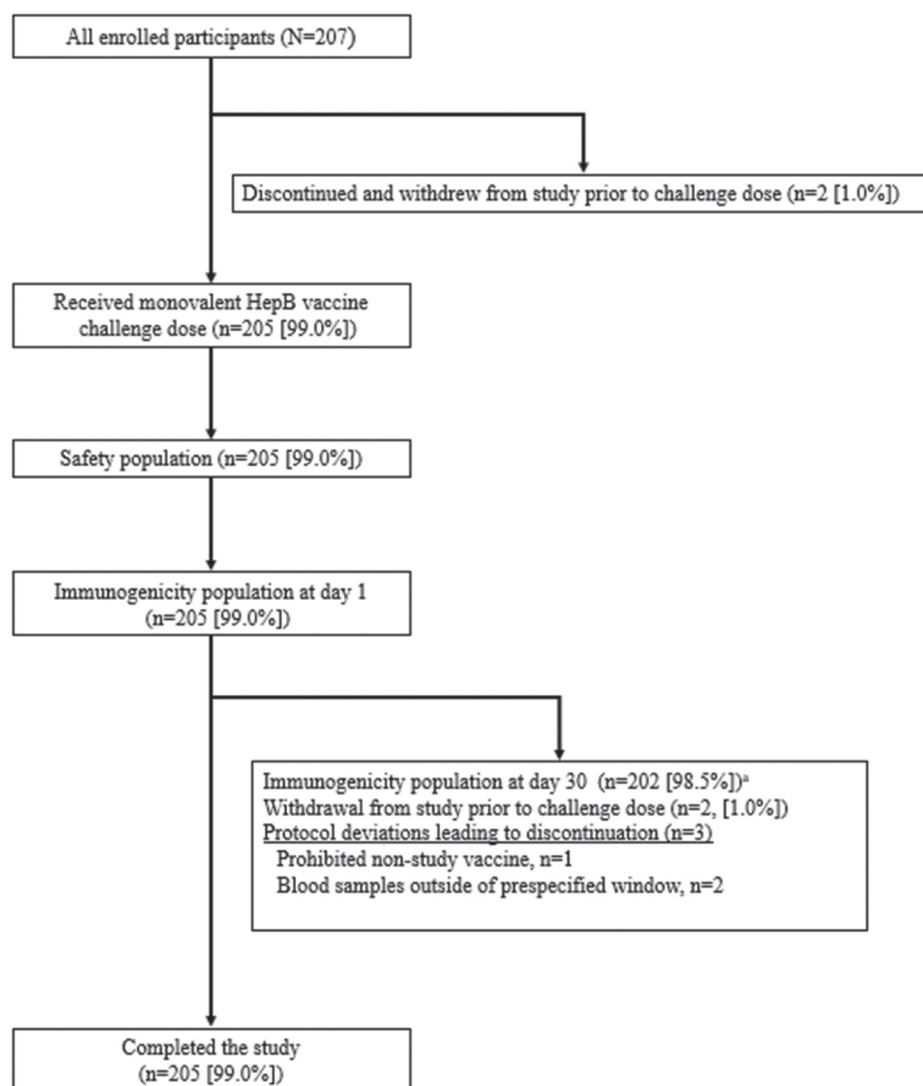
Study participants

A total of 207 healthy children were enrolled in the study and 205 were vaccinated with monovalent HepB vaccine; 2 children withdrew from the study before receiving study vaccination (1 child experienced syncope after phlebotomy and 1 withdrew per a physician decision) (Figure 1). Three protocol deviations were considered clinically important, and those data points (day 30 post-challenge immunogenicity) were excluded from

the immunogenicity per-protocol analyses. These deviations were administration of prohibited non-study live or non-live vaccine during the 30 days after receipt of the study vaccine ($n = 1$) and blood samples drawn outside of the prespecified analysis window for the time point ($n = 2$). Eligible participants for this challenge-dose study were children 8–10 years of age. However, the age range of enrolled participants was 8–9 years, with a mean age of 8.4 years (Table 1).

Immunogenicity

At baseline, 45.4% ($n = 93/205$) of children in the per-protocol study population had anti-HBs levels of ≥ 10 mIU/mL. These percentages were 40.9% and 49.1% among children who had received the DTaP5-IPV-HepB-Hib vaccine on a 2 + 1 and 3 + 1 schedule, respectively. Thirty days after receiving the monovalent HepB vaccine challenge dose, 99.5% ($n = 201/202$) of children in the immunogenicity analysis achieved anti-HBs levels of ≥ 10 mIU/mL (Table 2). When stratified according to



^aPercentage derived from safety population.

Figure 1. Disposition of participants.

Table 1. Demographics of the all enrolled population.

Parameter	N = 207
Male, n (%)	110 (53.1)
Age, y, mean (range)	8.4 (8–9 years)
Race, n (%)	
White	205 (99.0)
Other	2 (1.0)
Ethnicity, n (%)	
Not Hispanic or Latino	205 (99.0)
Hispanic or Latino	2 (1.0)

N, the number of children enrolled.

Table 2. Response rate at baseline and day 30 after the challenge dose with monovalent hepatitis B vaccine in the per-protocol population and in children stratified by 2 + 1 and 3 + 1 dosing DTaP5-IPV-HepB-Hib schedules.

Analysis population	Participants with anti-HBs ≥ 10 mIU/mL	
	n (%) ^a	95% CI ^b
<i>Baseline</i>		
Per-protocol population	93/205 (45.4)	38.4, 52.5
2 + 1 dosing	38/93 (40.9)	30.8, 51.5
3 + 1 dosing	55/112 (49.1)	39.5, 58.7
<i>Day 30 post-challenge</i>		
Per-protocol population ^c	201/202 (99.5)	97.3, 100.0
2 + 1 dosing	93/93 (100.0)	96.1, 100.0
3 + 1 dosing ^d	108/109 (99.1)	95.0, 100.0

^aResponse rate is the percentage of children with an anti-HBs level of ≥ 10 mIU/mL.

^bFor the dichotomous endpoints, the within-group 95% CIs are based on the exact binomial method proposed by Clopper and Pearson.²¹

^c202 children contributed to the day 30 post-challenge analysis out of the 205 enrolled.

^d109 children contributed to the day 30 post-challenge analysis out of the 112 enrolled.

Anti-HBs, hepatitis B surface antibody; n, the number of children enrolled, vaccinated, and contributed to the analysis.

a prior 2 + 1 and 3 + 1 dosing schedule, a similarly high percentage of children, 100% and 99.1%, respectively, achieved an anti-HBs level of ≥ 10 mIU/mL (Table 2), indicating similar responses across the two dosing schedules.

A 71-fold increase in anti-HBs GMCs was observed from baseline to day 30 post-challenge in the per-protocol population, with increases observed when the population was stratified by prior 2 + 1 (83-fold increase) or 3 + 1 (63-fold increase) dosing of DTaP5-IPV-HepB-Hib (Table 3). In the per-protocol population, 96.0% (n = 194/202) of children had a ≥ 4 -fold rise in anti-HBs levels from baseline to day 30 post-challenge, with similar results across the 2 + 1 and 3 + 1 dosing schedules (Table 4).

Table 4. Percentage of children with at least a 4-fold rise in anti-HBs concentration after monovalent hepatitis B vaccine challenge in the per-protocol population and in children stratified by Prior 2 + 1 and 3 + 1 dosing DTaP5-IPV-HepB-Hib schedules.

Analysis population	Participants with ≥ 4 -fold rise (%)	
	n (%)	95% CI ^a
<i>Day 30 post-challenge</i>		
Per-protocol population ^b	194/202 (96.0)	92.3, 98.3
2 + 1 dosing	92/93 (98.9)	94.2, 100.0
3 + 1 dosing ^c	102/109 (93.6)	87.2, 97.4

^aFor the dichotomous endpoints, the within-group 95% CIs are based on the exact binomial method proposed by Clopper and Pearson.²¹

^bA total of 202 children contributed to the analysis out of the 205 enrolled.

^cA total of 109 children contributed to the analysis out of the 112 enrolled.

Anti-HBs; hepatitis B surface antibody.

Table 3. Geometric mean concentrations (Anti-HBs) at baseline and day 30 after monovalent hepatitis B vaccine challenge in the per-protocol population and in children stratified by prior 2 + 1 and 3 + 1 dosing DTaP5-IPV-HepB-Hib schedules.

Analysis population	n	Geometric mean concentration of anti-HBs, mIU/mL (95% CI) ^a
<i>Baseline</i>		
Per-protocol population	205	9.6 (7.9, 11.8)
2 + 1 dosing	93	7.9 (6.0, 10.5)
3 + 1 dosing	112	11.3 (8.5, 15.0)
<i>Day 30 post-challenge</i>		
Per-protocol population ^b	202	685.8 (605.7, 776.6)
2 + 1 dosing	93	657.5 (549.1, 787.2)
3 + 1 dosing ^c	109	711.0 (597.4, 846.1)

^aFor the continuous endpoints, the within-group 95% CIs are obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

^bA total of 202 children contributed to the day 30 post-challenge analysis out of the 205 enrolled.

^cA total of 109 children contributed to the day 30 post-challenge analysis out of the 112 enrolled.

Anti-HBs; hepatitis B surface antibody; n, the number of children enrolled, vaccinated, and contributed to the analysis.

All but one child reached the seroprotective anti-HBs level of ≥ 10 mIU/mL at day 30 postchallenge in the per-protocol population and when stratified by 2 + 1 and 3 + 1 dosing of DTaP5-IPV-HepB-Hib (Table 2). As seen in the RCD curve for the per-protocol populations, a high percentage of children (94.0% [n = 189/202]) reached anti-HBs levels of ≥ 100 mIU/mL and many (75.0% [n = 152/202]) exceeded the upper limit of quantitation and reached anti-HBs levels ≥ 1000 mIU/mL at day 30 post-challenge; the distribution of anti-HBs was consistent across 2 + 1 and 3 + 1 dosing schedules (Figure 2).

Safety

No study discontinuations due to an AE or serious AEs were reported for children in the safety population. No deaths occurred during the study.

Discussion

This study demonstrated robust anti-HBs anamnestic responses after a monovalent HepB vaccine challenge dose in children 8–9 years who in the earlier studies had been vaccinated with DTaP5-IPV-HepB-Hib on either a 2 + 1 or 3 + 1 infant-toddler schedule. These findings confirm the presence of immune memory and durable protection against HepB among children who had received DTaP5-IPV-HepB-Hib.

The challenge dose elicited a 71-fold increase in anti-HBs GMCs, and this response was demonstrated in >99.0% of participating children, irrespective of anti-HBs levels at baseline. The percentage of responders after challenge was high for both dosing schedules (100% and 99.1%, respectively). The percentage of children with a ≥ 4 -fold rise in anti-HBs was high (96.0%) and was similar across participants who had received 2 + 1 and 3 + 1 DTaP5-IPV-HepB-Hib schedules. Furthermore, a high percentage (94.0%) of children in the per-protocol population achieved an anti-HBs level ≥ 100 mIU/mL, and many (75.0%) achieved an anti-HBs level ≥ 1000 mIU/mL

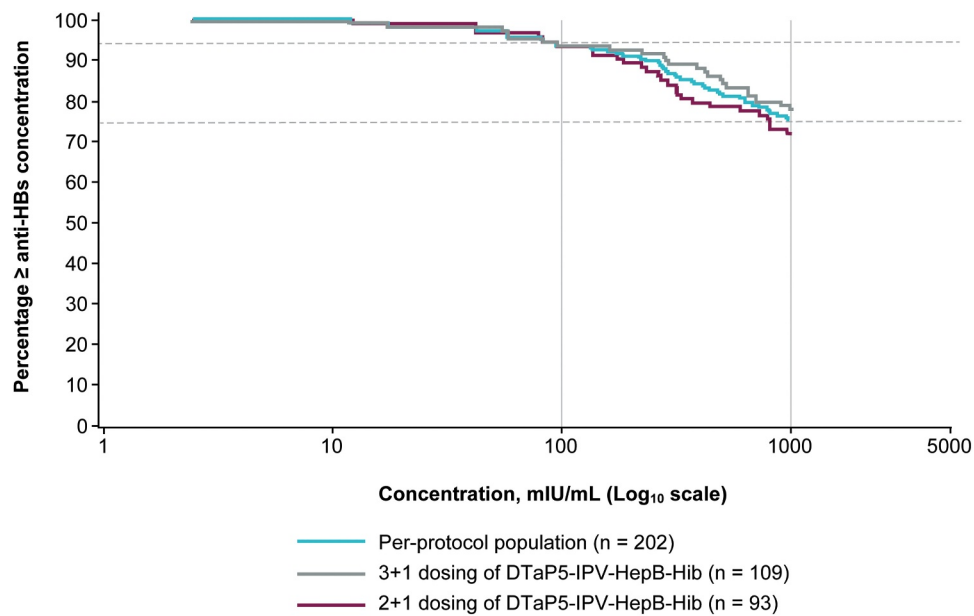


Figure 2. Reverse cumulative distribution curves of anti-HBs concentrations at day 30 post-challenge for the per-protocol population and for children stratified by a 2 + 1 dosing (V419–008) and 3 + 1 dosing (V419–007) of DTaP5-IPV-HepB-Hib. At day 30 post-challenge, anti-HBs levels of ≥ 100 mIU/mL (right solid vertical line) were achieved in 94% of children (upper dashed horizontal line) and anti-HBs levels of ≥ 1000 mIU/mL (left solid vertical line) were reached in 75% of children (lower dashed horizontal line). Anti-HBs, hepatitis B surface antibody.

at day 30 after the challenge dose. These vigorous responses would not be expected from a single 5- μ g dose of HepB vaccine challenge without the presence of immune memory.^{12,13}

An anamnestic response after challenge with monovalent HepB vaccine has been observed in other studies of children previously vaccinated with a hexavalent vaccine during infancy. This anamnestic response has also been demonstrated in adults who received a series with the monovalent HepB vaccine component included in the multivalent vaccine evaluated in this study.²⁴ In a head-to-head study of DTaP2-IPV-HB-Hib (Hexyon[®]; Sanofi Pasteur, Lyon, France) and DTaP3-IPV-HB/Hib (Infanrix hexa[™]; GlaxoSmithKline, Rixensart, Belgium) in children aged 9–10 years, who had received a dose of HepB vaccine at birth, followed by the hexavalent vaccine at 2, 4, and 6 months of age; 92.8% and 98.7%, respectively, achieved anti-HBs levels ≥ 10 mIU/mL at day 30 post-challenge.⁹ Other pediatric studies of DTaP3-IPV-HB/Hib vaccine were conducted and obtained similar results.^{25–28} However, this is the first demonstration of ongoing immune memory and protection against HepB in children who received an infant-toddler series of DTaP5-IPV-HepB-Hib. The subgroup analyses showed that the 2 + 1 and 3 + 1 dosing schedules presented similar point estimates and clearly overlapping 95% CIs for the immunogenicity endpoints, and very similar distribution patterns on the RCD curves. This indicates an overall immune response that is consistent across the two dosing schedules, which is particularly pertinent in Western Europe where 2 + 1 dosing has become the dominant schedule. It is noteworthy that DTaP5-IPV-HepB-Hib administered with a 2 + 1 dosing schedule at 2, 4, and 11–12 months of age provided ongoing excellent responses despite the 2-month age at first vaccine administration and the 2 dose infant series.

Although the study demonstrated the long-term protection provided by DTaP5-IPV-HepB-Hib through a challenge study, certain limitations should be considered when evaluating these results. In addition to being an open-label study, the study was limited to children in Finland, who had participated in the initial infant studies. T-cell responses were not directly analyzed because of substantial heterogeneity and lack of standardization in the methods used for assessment; therefore, no direct observations can be made about the T-cell functions in this study. The measurement of antibody concentrations, however, does provide a well-established standardized platform for the assessment of B-cell function. Furthermore, T-cell activity and support are required to enhance B-cell function and subsequent antibody production; thus, the high IgG concentration in this setting of remote infant-toddler vaccination does reflect the complex interactions that occur between B and T cells.^{8,10,29,30} Total hepatitis B core antibody and hepatitis B surface antigen levels were not tested prior to study entry and, given the time between the toddler booster dose and the challenge dose, it is not possible to rule out natural exposure to HBV. However, children with a history of a clinical or serologic diagnosis of HBV were excluded from study participation. Furthermore, a 2017 publication showed a low annual rate of acute HBV infection in Finland (1.67 per 100,000 per year), and the 2 most common routes of transmission are sexual contact and intravenous drug use.³¹ Children 1–11 years of age diagnosed with acute HBV were all foreign born, and the estimated incidence of acute infection in this age group was 0.55 per 100,000 per year.³¹ Our study participants were composed of preadolescent children who were previously enrolled as infants in Finland in the V419–007 and V419–008 studies, both of which excluded participants born to mothers with evidence

or history of chronic HBV infection. Therefore, the participants in the current study are considered extremely low risk for undiagnosed HBV infection.³¹

Despite these limitations, our study clearly demonstrated long-term immune memory and impressive rebounds in anti-HBs in children who had received DTaP5-IPV-HepB-Hib for their infant-toddler doses.

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Disclosure statement

DG, JL, TM, MBW, and YZ are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA. DRJ is an employee of Sanofi Pasteur, Swiftwater, PA, USA, who may own stock and/or stock options from Sanofi S.A., Paris, France. AA has nothing to disclose.

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Contributors/authorship

All authors are responsible for the work described in this paper. All authors were involved in at least one of the following: [conception, design of work or acquisition, analysis, interpretation of data] and [drafting the manuscript and/or revising/reviewing the manuscript for important intellectual content]. All authors provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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