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RESEARCH ARTICLE

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A phase 4, open-label study to evaluate the safety and immunogenicity of DTaP5-HBV-IPV-Hib in children previously vaccinated with DTaP2-HBV-IPV-Hib or DTaP5-HBV-IPV-Hib (V419-016)

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ABSTRACT

DTaP5-HBV-IPV-Hib (Vaxelis®) is a hexavalent combination vaccine (HV) indicated in infants and toddlers for the prevention of diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive disease due to *Haemophilus influenzae* type b. Switching between HVs during the childhood vaccination series is sometimes necessary due to, for example, vaccine availability, health-care provider preference, and/or tender awards. The purpose of this study was to describe the safety, tolerability, and immunogenicity of a booster dose of Vaxelis® in participants who previously received a primary infant series of either DTaP2-HBV-IPV-Hib (Hexyon®) or Vaxelis®. Healthy participants approximately 11–13 months of age who previously received a two-dose primary series of Hexyon® (HHV group) or Vaxelis® (VVV group) all received a Vaxelis® booster dose. Immunogenicity was evaluated by measuring antibody levels to individual vaccine antigens approximately 30 days following booster vaccination. Safety was evaluated as the proportion of participants with adverse events (AEs). The proportions of participants with antibody-specific responses for antigens contained in both Vaxelis® and Hexyon® at 30 days post-toddler-booster vaccination with Vaxelis® were comparable between groups, and higher in the VVV group for Vaxelis® antigens PRN and FIM2/3. The overall proportions of participants with AEs were generally comparable between groups. Following a booster dose of Vaxelis®, immune responses were comparable between groups for all shared antigens, and higher in the VVV group for antigens found only in Vaxelis®. The booster was well tolerated in both groups. These data support the use of Vaxelis® as a booster in mixed HV regimens.

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Introduction

Multivalent vaccines that include a combination of diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib), hepatitis B, and/or polio antigens have improved the delivery of life-saving vaccinations to infants and children in countries where they are routinely used. In particular, pentavalent and hexavalent combination vaccines (HVs) are valuable in reducing overall office visits and the number of vaccinations needed with the growing complexity of pediatric vaccination schedules. Combination vaccines have the associated benefits of simplifying vaccine transportation and storage and maintaining the timeliness of vaccination.[1,2] DTaP2-HBV-IPV-Hib (Hexyon®, Sanofi Pasteur), DTaP3-HBV-IPV/Hib (Infanrix® Hexa, GlaxoSmithKline), and DTaP5-HBV-IPV-Hib (Vaxelis®, MCM Vaccine B.V.) are HVs currently licensed in the European Union (EU).

Although the antigen composition of each HV is similar, there are some key differences with respect to the pertussis and Hib components. Vaxelis® contains five acellular pertussis antigens (detoxified pertussis toxin [PT], filamentous hemagglutinin [FHA], pertactin [PRN], and fimbriae types 2 and 3 [FIM2/3]), Infanrix® Hexa contains three pertussis antigens (PT, FHA, and PRN), and Hexyon® contains two pertussis antigens (PT and FHA). The Hib antigen polyribosylribitol phosphate (PRP) is conjugated to a meningococcal outer membrane protein complex (PRP-OMPC) in Vaxelis® and conjugated to a tetanus protein (PRP-T) in the others. See Table 1 for additional details of HVs licensed in the EU. Overall, these three HVs have comparable safety profiles[3–7] and can be concomitantly administered with other routine pediatric vaccines.[8–10] In addition, long-term vaccine-induced immunogenicity at different time points has been demonstrated for all three.[11–17]

Switching between HVs is sometimes required to complete the childhood vaccination series. This may occur due to vaccine availability, health-care provider preference, tender awards, schedule changes, and/or patient relocation. While some studies have

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Table 1. Characteristics of hexavalent combination vaccines.

Vaxelis®		Hexyon®		Infanrix® Hexa	
Antigen	Amount	Antigen	Amount	Antigen	Amount
Diphtheria toxoid	≥ 20IU	Diphtheria toxoid	≥ 20IU	Diphtheria toxoid	≥ 30IU
Tetanus toxoid	≥ 40IU	Tetanus toxoid	≥ 40IU	Tetanus toxoid	≥ 40IU
Bordetella pertussis antigens		Bordetella pertussis antigens		Bordetella pertussis antigens	
- Pertussis toxoid (PT)	20ug	- Pertussis toxoid (PT)		- Pertussis toxoid (PT)	
- Filamentous hemagglutinin (FHA)	20ug 3ug	- Filamentous hemagglutinin (FHA)	25ug 25ug	- Filamentous hemagglutinin (FHA)	25ug 25ug
- Pertactin (PRN)	5ug	- Pertactin (PRN)	Not in vaccine	- Pertactin (PRN)	8ug
- Fimbriae Types 2 and 3 (FIM2/3)		- Fimbriae Types 2 and 3 (FIM2/3)	Not in vaccine	- Fimbriae Types 2 and 3 (FIM2/3)	Not in vaccine
Hepatitis B surface antigen	10ug	Hepatitis B surface antigen	10ug	Hepatitis B surface antigen	10ug
Poliovirus (inactivated)	40 D antigen units	Poliovirus (inactivated)	40 D antigen units	Poliovirus (inactivated)	40 D antigen units
- Type 1 (Mahoney)	8 D antigen units	- Type 1 (Mahoney)	8 D antigen units	- Type 1 (Mahoney)	8 D antigen units
- Type 2 (MEF-1)	32 D antigen units	- Type 2 (MEF-1)	32 D antigen units	- Type 2 (MEF-1)	32 D antigen units
- Type 3 (Saukett)		- Type 3 (Saukett)		- Type 3 (Saukett)	
- Haemophilus influenzae type b polysaccharide		- Haemophilus influenzae type b polysaccharide	12ug 22-36ug	- Haemophilus influenzae type b polysaccharide-Polyribosylribitol phosphate (PRP) conjugated to tetanus protein	10ug 25ug
- Polyribosylribitol phosphate (PRP) conjugated to meningococcal protein	3ug 50ug	- Polyribosylribitol phosphate (PRP) conjugated to tetanus protein			

demonstrated that switching between HVs is well tolerated[3,18] and can be utilized effectively at the regional level,[19] further studies are needed to evaluate HV interchangeability in support of vaccination guidelines that often allow for such practice in order to maintain national vaccination coverage rates.

Vaxelis® can be used as a two- or three-dose primary series beginning at 6 weeks of age, followed by a booster dose, given at least 6 months after the primary series. While Vaxelis® is approved to be used for a mixed hexavalent/pentavalent/hexavalent combined vaccination schedule in the primary series,[20,21] to date there are no studies evaluating the interchangeability of Vaxelis® with other HVs at the booster dose. The goal of this study was to evaluate the safety and immunogenicity of Vaxelis® given as the booster dose after a two-dose primary series with another HV. Although both a two-dose and three-dose primary series are approved in the EU for all vaccines, the two-dose primary series (2 + 1 schedule) has been increasingly adopted by many countries and was chosen for the study.

Methods

Study design

This was a Phase 4, open-label, interventional, parallel, multicenter study to compare the safety, tolerability, and immunogenicity of a booster dose of Vaxelis® in healthy children previously vaccinated with a two-dose primary infant series of either Hexyon® (HHV group) or Vaxelis® (VVV group) (protocol V419-016). The study was conducted at 13 centers in three countries (Germany, Italy, and Spain) from March 2022 to August 2022 (clinicaltrials.gov NCT05289271 and EU at EudraCT 2021-004053-23).

The study was designed to enroll 160 participants who had previously received two doses of either Hexyon® or Vaxelis® at approximately two and four months of age as part of their standard care, in a 1:1 ratio (80 in each group) to receive a booster dose of Vaxelis®. The Vaxelis® booster dose was administered to participants at approximately 11 months of age. Because the study was open label, the study vaccine was prepared and/or dispensed by unblinded study site staff who were not involved in subsequent study-related assessments. The study was conducted in accordance with the principles of Good Clinical Practice (GCP) and local and/or national regulations, International Conference on Harmonization GCP, and the ethical principles that have their origin in the Declaration of Helsinki regarding independent ethics committee review, informed consent, and the protection of human participants in biomedical research.

Participants

Participants were healthy infants 11–13 months of age (≥327 to ≤396 days inclusive) at the time of informed consent. Written informed consent was obtained from parents (or legally acceptable representatives) prior to any study procedure.

Key exclusion criteria included: impaired immunological function due to congenital or acquired immunodeficiency, or had received or was expected to receive immunosuppressive agents; had a history of Hib, hepatitis B, diphtheria, tetanus, pertussis, or poliovirus infection; had hypersensitivity to any component of the study vaccine; had a febrile illness within 72 hr of receipt of the study vaccine; received any licensed, non-live vaccine within 14 days of receipt of study vaccine or prior to Visit 2 blood draw, or live vaccine within 30 days of receipt of study vaccine or prior to Visit 2 blood draw; or had a health or developmental disorder that, based on the clinical judgment of the investigator, could affect evaluation of the vaccine. The study permitted administration of non-study, non-live routine childhood vaccines according to the pediatric vaccination schedule on the same day as the study vaccine. History of pertussis vaccination during pregnancy was collected during the first visit.

Study vaccine and administration

Vaxelis® is a pediatric combination vaccine. Each 0.5 mL intramuscular dose contains ≥20IU diphtheria toxoid (DT), ≥40IU tetanus toxoid (TT), acellular pertussis antigens (20 µg PT, 20 µg FHA, 3 µg PRN, 5 µg FIM 2/3), inactivated polioviruses (40 D-antigen units [DU] Type 1 [Mahoney], 8 DU Type 2 [MEF-1], 32 DU Type 3 [Saukett]), 3 µg PRP of Hib covalently bound to 50 µg of the outer membrane protein complex of *Neisseria meningitidis* serogroup B, and 10 µg hepatitis B surface antigen (HBsAg). Each 0.5 mL dose contains 319 µg aluminum from aluminum salts used as adjuvant. Participants were observed by study staff for 15 min following vaccination for immediate reactions.

Safety and immunogenicity assessments

Participants were followed for solicited injection-site (erythema, swelling, pain) and systemic (decreased appetite, somnolence, irritability, and vomiting) adverse events (AEs) from Day 1 through Day 5 postvaccination and for unsolicited AEs from Day 1 through Day 15 postvaccination. Serious AEs (SAEs) and deaths were collected from time of informed consent to the end of the study. Daily maximum body temperature measurements were additionally recorded from Day 1 through Day 5 postvaccination. A vaccination report card (VRC) was used by parents to record AEs, complaints, daily temperature measurements, concomitant medications, and non-study vaccinations. VRC records were subsequently assessed by study investigators to confirm that AE criteria were met and to assess causality and intensity.

The booster dose of Vaxelis® was administered to all participants at Day 1. Blood samples were drawn for immunogenicity endpoints before vaccination at Day 1 and at Day 30 (30 days after the booster dose of Vaxelis®) for measurement of antibodies against Vaxelis® antigens. DT, TT, and pertussis (PT, FHA, PRN, FIM 2/3) antibodies were tested using a multiplexed electrochemiluminescence assay (Meso Scale Discovery). Hib PRP antibodies were tested using ELISA (Binding Site). Antibodies to HBsAg were tested using an enhanced chemiluminescence assay. Poliovirus 1, 2, and 3 antibodies were tested using a poliovirus neutralization assay.

Study endpoints and statistical methods

The primary safety objective was to evaluate the safety and tolerability of a booster dose of Vaxelis® with respect to the proportions of participants with AEs. Estimated 95% confidence intervals (CIs) were calculated based on the exact binomial method proposed by Clopper and Pearson.[22]

The primary immunogenicity objective was to describe the response rates of antigens contained in both Vaxelis® and Hexyon® following a booster dose of Vaxelis®. The endpoints used to evaluate the immune response rates are consistent with established protective and acceptable antibody levels.[23,24] For pertussis, there are no benchmark antibody concentrations that are widely accepted as correlates of protection; therefore, the pertussis antibody endpoints are based on adaptations of previously published standards.[25]

Other objectives included to describe the response rates of pertussis antigens found only in Vaxelis® (PRN, FIM 2/3) following a booster dose of Vaxelis®; the antigen-specific geometric mean concentrations (GMCs) before and 30 days following a booster dose of Vaxelis®; and the proportion of participants with a ≥4-fold rise in antibody from before to 30 days following a booster dose with Vaxelis®, for each antigen contained in Vaxelis®. Evidence of possible blunting of the immune response to pertussis antigens due to pertussis vaccination during pregnancy was assessed in the infant.[26] For the continuous endpoints, the within-group 95% CIs were obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. For the dichotomous endpoints, the within-group 95% CIs were based on the exact binomial method proposed by Clopper and Pearson.[22]

The study was descriptive, and there was no formal hypothesis testing. All analyses were performed using SAS© software, version 9.4, of the SAS System for Unix (Copyright 2012 SAS Institute Inc., Cary, NC, USA).

Results

Participants

The study enrolled 168 participants, 167 of which (85 in the VVV group, 82 in the HHV group) received a single booster

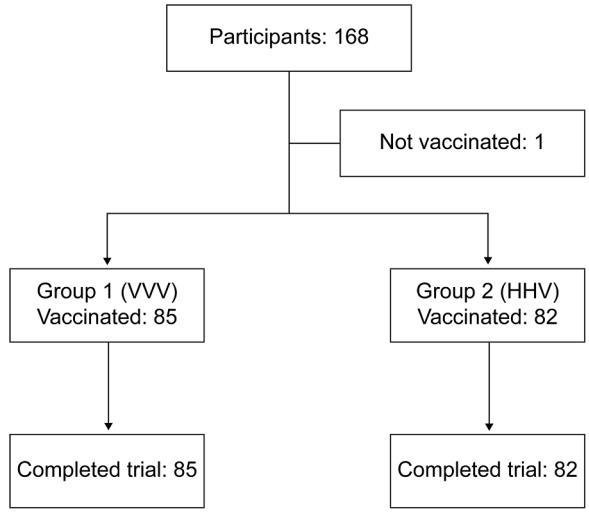

Figure 1. Participant disposition.

Table 2. Participant characteristics.

	VVV $n = 85$	HHV $n = 82$
Sex – n (%)		
– Male	41 (48.2)	49 (59.8)
– Female	44 (51.8)	33 (40.2)
Age in days – mean (SD)	348.3 (18.2)	344.7 (16.4)
Race – n (%)		
– White	84 (98.8)	82 (100.0)
– Asian	1 (1.2)	0 (0.0)
History of maternal pertussis vaccination during pregnancy		
– Yes	66 (77.6)	66 (80.5)
– No	16 (18.8)	15 (18.3)
– Unknown	3 (3.5)	1 (1.2)

vaccination with Vaxelis®. All vaccinated participants completed the study (Figure 1). Participants were approximately 1 year of age at the time of vaccination (Table 2). The majority of participants (77.6% in the VVV group, 80.5% in the HHV group) had a history of maternal pertussis vaccination during pregnancy.

Immunogenicity

At 30 days following the Vaxelis® booster dose, the proportions of participants meeting specified responses to antigens contained in both Vaxelis® and Hexyon® (primary endpoint) were comparable between groups (Table 3). For the antigens contained only in Vaxelis® (PRN and FIM 2/3), an immune response was elicited in both groups; however, response rates were higher in Group 1 (VVV). The proportions of participants meeting Vaxelis® pertussis antigen responses at 30 days postvaccination were similar comparing participants with a history of maternal pertussis vaccination during pregnancy and those without (Supplemental Table S1). At 30 days following the Vaxelis® booster dose, IgG GMCs to each individual antigen were several-fold higher than pre-booster measurements in both groups (Table 4).

At Day 1 prior to the booster dose, the proportion of participants with a short-term protective concentration of anti-PRP antibodies (≥0.15 µg/mL) was higher in participants who received a Vaxelis® infant series compared to Hexyon® (87.3%

Table 3. Proportions of participants meeting specified antigen responses at Day 30.

		Group 1 (VVV)		Group 2 (HHV)	
Antigen	Endpoint	Observed % (m/n)	95% CI	Observed % (m/n)	95% CI
Hib-PRP	% ≥1.0 µg/mL	89.0 (65/73)	(79.5, 95.1)	90.8 (69/76)	(81.9, 96.2)
HBsAg	% ≥10 mIU/mL	100.0 (56/56)	(93.6, 100.0)	94.2 (65/69)	(85.8, 98.4)
Diphtheria toxoid	% ≥0.1 IU/mL	100.0 (69/69)	(94.8, 100.0)	98.6 (73/74)	(92.7, 100.0)
Tetanus toxoid	% ≥0.1 IU/mL	98.6 (68/69)	(92.2, 100.0)	98.6 (73/74)	(92.7, 100.0)
Pertussis – PT	% vaccine response[a]	98.4 (63/64)	(91.6, 100.0)	94.4 (67/71)	(86.2, 98.4)
Pertussis – FHA	% vaccine response[a]	98.4 (63/64)	(91.6, 100.0)	90.1 (64/71)	(80.7, 95.9)
Pertussis – PRN[b]	% vaccine response[a]	92.2 (59/64)	(82.7, 97.4)	22.5 (16/71)	(13.5, 34.0)
Pertussis – FIM 2/3[b]	% vaccine response[a]	95.3 (61/64)	(86.9, 99.0)	69.0 (49/71)	(56.9, 79.5)
Poliovirus 1	% Nab ≥ 1:8 dilution	100.0 (66/66)	(94.6, 100.0)	95.7 (66/69)	(87.8, 99.1)
Poliovirus 2	% Nab ≥ 1:8 dilution	100.0 (66/66)	(94.6, 100.0)	100.0 (69/69)	(94.8, 100.0)
Poliovirus 3	% Nab ≥ 1:8 dilution	97.0 (64/66)	(89.5, 99.6)	100.0 (69/69)	(94.8, 100.0)

[a]The pertussis vaccine response is defined as follows.
1) If prevaccination <LLOQ, then postvaccination should be ≥4 times the LLOQ.
2) If prevaccination ≥LLOQ but <2 times the LLOQ, then postvaccination should achieve a 4-fold rise (postvaccination/prevaccination ≥4).
3) If prevaccination ≥ 2 times the LLOQ, then postvaccination should achieve a 2-fold response (postvaccination/prevaccination ≥2)
[b]Antigen contained only in Vaxelis®.
H = Hexyon®; V = Vaxelis®.
N = number of participants randomized and vaccinated; *n* = number of participants contributing to the analysis; *m* = number of participants with the indicated response
CI = confidence interval; IU = international unit; PT = pertussis toxin; FHA = filamentous hemagglutinin; Hib = Haemophilus influenzae type b; PRP = polyribosylribitol phosphate; HBsAg = hepatitis B surface antigen; Nab = neutralizing antibodies; FIM 2/3 = fimbriae types 2 and 3; PRN = pertactin.

Table 4. IgG GMCs for all antigens at Day 1 and Day 30.

			Group 1 (VVV) (*N* = 85)			Group 2 (HHV) (*N* = 82)		
	Endpoint	Timepoint	n	Observed Response	95% CI	n	Observed Response	95% CI
Hib-PRP	GMC	Day 1	79	1.25	(0.92, 1.70)	81	0.11	(0.10, 0.13)
		Day 30	73	5.85	(4.28, 8.00)	76	5.12	(3.88, 6.76)
HBsAg	GMC	Day 1	69	30.88	(21.55, 44.23)	73	32.38	(21.21, 49.44)
		Day 30	56	1111.50	(784.67, 1574.46)	69	470.60	(292.00, 758.43)
Diphtheria toxoid	GMC	Day 1	73	0.08	(0.06, 0.11)	79	0.08	(0.07, 0.10)
		Day 30	69	3.24	(2.69, 3.89)	74	1.93	(1.55, 2.39)
Tetanus toxoid	GMC	Day 1	73	0.17	(0.14, 0.23)	79	0.14	(0.12, 0.17)
		Day 30	69	7.73	(5.88, 10.16)	74	3.92	(3.07, 4.99)
Pertussis – PT	GMC	Day 1	73	6.91	(5.35, 8.93)	79	7.15	(5.86, 8.72)
		Day 30	69	172.27	(138.99, 213.53)	74	59.41	(48.58, 72.67)
Pertussis – FHA	GMC	Day 1	73	8.39	(6.70, 10.49)	79	29.52	(24.90, 35.00)
		Day 30	69	99.01	(80.89, 121.20)	74	147.03	(124.94, 173.02)
Pertussis – PRN	GMC	Day 1	73	2.68	(2.08, 3.45)	79	1.39	(1.20, 1.61)
		Day 30	69	115.88	(84.02, 159.83)	74	3.21	(2.49, 4.14)
Pertussis – FIM 2/3	GMC	Day 1	73	18.01	(13.47, 24.06)	79	1.21	(1.08, 1.37)
		Day 30	69	337.60	(250.90, 454.27)	74	13.50	(10.75, 16.96)
Poliovirus 1	GMC	Day 1	62	38.94	(24.12, 62.86)	78	31.86	(21.29, 47.68)
		Day 30	66	2135.80	(1448.73, 3148.73)	69	1569.33	(958.73, 2568.81)
Poliovirus 2	GMC	Day 1	62	57.90	(37.28, 89.92)	78	53.12	(33.76, 83.60)
		Day 30	66	3020.62	(2162.92, 4218.44)	69	3470.29	(2441.36, 4932.86)
Poliovirus 3	GMC	Day 1	62	30.28	(18.87, 48.57)	78	33.78	(23.10, 49.39)
		Day 30	66	1161.50	(687.73, 1961.64)	69	2554.44	(1704.39, 3828.46)

N, number of participants allocated and vaccinated; n, number of participants contributing to the analysis.

and 27.2%, respectively, Supplemental Table S2). This was also true for the proportion of participants with a long-term protective concentration of anti-PRP antibodies (≥1.0 μg/mL) (64.6% in VVV group and 1.2% in HHV group).[24] Other shared antigen responses were generally comparable between groups (Supplemental Table S3). Anti-PRP IgG GMCs were also higher at Day 1 in the VVV group (Table 4).

The proportions of participants achieving a ≥4-fold increase in antibody level from pre- to post-booster dose (Supplemental Table S4) were generally high in both groups for the shared antigens and when antibody levels were analyzed by reverse cumulative distribution curves (Supplemental Figure S1).

Safety

Most participants experienced one or more non-solicited or solicited AEs during the study and the proportions of participants experiencing AEs were generally comparable between groups (Table 5). Solicited AEs included injection-site pain, erythema, and swelling, as well as decreased appetite, irritability, somnolence, and vomiting. The most frequently reported AEs were irritability, injection-site pain, and somnolence in the VVV group and irritability, injection-site pain, and injection-site erythema in the HHV group (Supplemental Table S5). The majority of the solicited AEs were of mild-to-moderate intensity or of size ≤1 inch (for injection-site erythema and swelling). One SAE of adenovirus gastroenteritis occurred in the HHV group that was determined not related to the study vaccine. No other SAEs or deaths occurred for the duration of the study, and no participant discontinued the study due to an AE. The majority of participants in both groups had maximum temperature measurements of less than 39.0°C (102.2°F) within 5 days of receiving Vaxelis®, and a low number of participants in both groups (three in VVV group, four in HHV group) recorded a maximum temperature ≥40.0°C (104.0°F) (Supplemental Table S6).

Discussion

Current hexavalent combination vaccines target the same diseases but have important differences in their formulation, the antigens included (as well as the amount of each antigen), and the conjugation of antigens. While the World Health Organization recommends that the same vaccine be used to complete the infant-toddler vaccination series where possible, real-world situations arise when the use of a mixed vaccine series is required.[9,19] No data regarding the interchangeability of hexavalent vaccines with differing Hib antigen conjugation were previously available. Given the vaccine differences, it is important to explore interchangeability between the vaccines with the purpose of increased vaccine access and subsequent completion of the vaccination series for all children.

This study is the first to evaluate the safety, tolerability, and immunogenicity of Vaxelis® given as a booster dose after another HV is given for the primary series. Hexyon® was chosen as the comparator in the primary series given its similarities to Infanrix® Hexa (both have PRP conjugated to a tetanus protein), but with fewer pertussis antigens. This makes the Hexyon® two-dose primary a more rigorous comparator arm, allowing extrapolation to other HVs that contain more pertussis antigens.

Overall, the proportions of participants with antigen-specific responses and IgG GMCs for antigens shared between Vaxelis® and Hexyon® were generally comparable between groups at 30 days following the booster dose. Responses were higher in the VVV group for pertussis antigens contained only in Vaxelis® (*i.e.*, PRN and FIM 2/3), suggesting the generation of immune memory following a two-dose primary series of Vaxelis®.

Achievement of a robust immune response to HVs after the primary series is critical to protect children in their vulnerable first year of life, before a booster dose is administered. With the

Table 5. Safety summary.

	VVV (*n* = 85)		HHV (*n* = 82)	
	n (%)	95% CI	n (%)	95% CI
≥1 AE	83 (97.6)	91.8, 99.7	76 (92.7)	84.8, 97.3
– Injection-site AEs	71 (83.5)		62 (75.6)	
– Systemic AEs	79 (92.9)		69 (84.1)	
Vaccine-related AEs[a]	83 (97.6)	91.8, 99.7	76 (92.7)	84.8, 97.3
– Injection-site AEs	71 (83.5)		62 (75.6)	
– Systemic AEs	79 (92.9)		68 (82.9)	
Serious AEs	0 (0.0)	0.0, 4.2	1 (1.2)	0.0, 6.6
– Serious vaccine-related AEs	0 (0.0)	0.0, 4.2	0 (0.0)	0.0, 4.4
Deaths	0 (0.0)	0.0, 4.2	0 (0.0)	0.0, 4.4
Solicited injection-site AEs	71 (83.5)	73.9, 90.7	62 (75.6)	64.9, 84.4
– Injection-site erythema	45 (52.9)	41.8, 63.9	41 (50.0)	38.7, 61.3
– Injection-site pain	63 (74.1)	63.5, 83.0	46 (56.1)	44.7, 67.0
– Injection-site swelling	45 (52.9)	41.8, 63.9	33 (40.2)	29.6, 51.7
Solicited systemic AEs	78 (91.8)	83.8, 96.6	57 (69.5)	58.4, 79.2
– Decreased appetite	37 (43.5)	32.8, 54.7	30 (36.6)	26.2, 48.0
– Irritability	66 (77.6)	67.3, 86.0	48 (58.5)	47.1, 69.3
– Somnolence	55 (64.7)	53.6, 74.8	39 (47.6)	36.4, 58.9
– Vomiting	3 (3.5)	0.7, 10.0	7 (8.5)	3.5, 16.8

[a]Determined by the investigator to be related to the vaccine.
Reported AEs include non-serious AEs days 1–15 after vaccination and serious AEs from enrollment to study completion

exception of anti-Hib responses (i.e. anti-PRP), baseline levels (prior to the booster dose) of IgG GMCs for the shared antigens were variable, but overall relatively high in both groups. However, anti-PRP IgG GMCs and response rates were noticeably higher after the infant series of Vaxelis®. This finding is consistent with previous results reported in Vaxelis® Phase 3 studies showing earlier and more robust anti-PRP responses pre-toddler booster dose compared with PRP-T conjugate containing combination vaccines.[5,6,27–29] This is a well-described characteristic of the PRP-OMPC conjugate vaccine and was seen in the early studies of the monovalent PRP-OMPC conjugated Hib vaccine (PedvaxHIB).[30,31] This response translated into earlier protection against invasive Hib disease and resulted in a preferential recommendation for PedvaxHIB in some high-risk infant populations.[32,33] These data suggest that Vaxelis® may have added value due to robust antibody responses prior to the toddler booster.

Vaxelis® was well tolerated following a two-dose Hexyon® primary series, with a safety profile generally comparable to a three-dose series of Vaxelis®. No new or unexpected AEs were observed during the study, and no vaccine-related SAEs, discontinuations, or deaths occurred. Some individual solicited AEs showed numerical differences between groups, but the majority of the experienced AEs were of mild-to-moderate intensity, suggesting no change in the characterization of the AEs between groups. Therefore, it is anticipated that any numerical differences observed are of limited clinical significance.

This study has limitations. This was a descriptive study and, therefore, was not powered for formal hypothesis testing between groups. The non-randomized primary series prior to study entry, and the open-label nature of the study, limit the interpretation of safety findings. The long-term immunogenicity of vaccine-induced antibodies following the mixed HV schedule was not evaluated in the study.

In conclusion, study results demonstrate that interchangeability of Hexyon® and Vaxelis® is well tolerated and is consistent with other published interchangeability studies of penta- and hexavalent combination vaccines[3,18] Data further support the interchangeability of a Vaxelis® booster with other HVs during the pediatric vaccination series.

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Disclosure statement

A.G., C.L., Z.C., J.L., and M.W. are employees of MSD and may hold stock in Merck & Co., Inc., Rahway, NJ, USA. F.M.-T. has received honoraria from Astra Zeneca, GSK, Pfizer Inc, Sanofi, MSD, Seqirus, Moderna, Novavax, Biofabri, and Janssen for taking part in advisory boards and expert meetings and for acting as a speaker in congresses outside the scope of the submitted work. F.M.-T. has also acted as principal investigator in randomized controlled trials of the above-mentioned companies as well as Ablynx, Gilead, Regeneron, Roche, Abbott, and MedImmune, with honoraria paid to his institution. T.M. is an employee of MCM Vaccine B.V. D.J. is a full-time employee of Sanofi Vaccines, and annually receives Sanofi stock options. All other authors have no relevant conflicts of interest to disclose.

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Author contributions

A.G., C.L., T.M., D.J., and M.W. contributed to the conception, design, or planning of the study. A.G., C.C., F.M.-T., S.W., and J.L. contributed to acquisition of the data. A.G., Z.C., and J.L. contributed to data analysis. A.G., C.C., F.M-T., S.W., T.M., D.J., and M.W. contributed to the interpretation of the results. All authors contributed to manuscript drafting and/or critically reviewing and revising the manuscript for important intellectual content and approved the final version.

Data sharing statement

The data sharing policy, including restrictions, of MSD, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the Engage Zone site or via e-mail to the Data Access mailbox.

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