Immunogenicity and safety of a fully liquid DTaP-IPV-HB-PRP~T hexavalent vaccine compared with the standard of care in infants in the Republic of Korea

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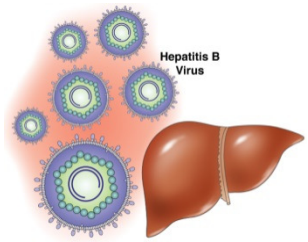
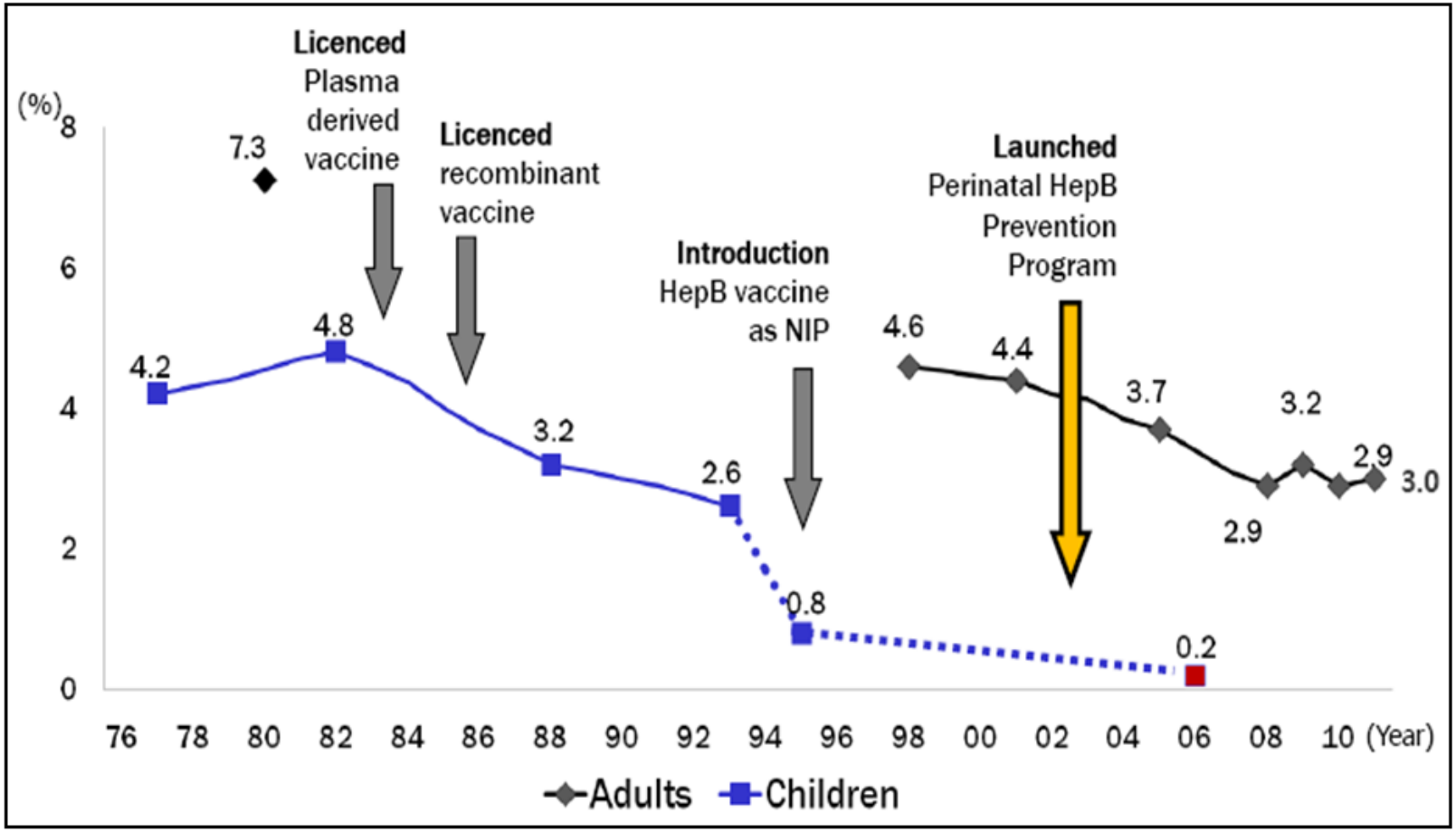


Background

- Hepatitis B (HB) prevalence is highest in the WHO Western Pacific Region where 6.2% of the adult population is infected.
- Mode of transmission in highly endemic areas
  - Vertical transmission from mother to child at birth (perinatal transmission)
  - Horizontal transmission: exposure to infected blood, from an infected child to an uninfected child during the first 5 years of life
- Therefore, vaccination against HB in children is important.
- Pediatric combination vaccines are crucial in maintaining protection against diphtheria (D), tetanus (T), pertussis, poliomyelitis, and *Haemophilus influenzae* type b (Hib) diseases.
- Tetra- and pentavalent vaccine such as DTaP-IPV and DTaP-IPV//PRP~T have been widely used.
- In this study, fully liquid hexavalent combination vaccine containing DTaP-IPV//PRP~T and hepatitis B (HB) was studied in Korean children.

Changes of HBsAg positive rate in Republic of Korea



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Vaccination schedules 2018 in Republic of Korea

Immunization schedule

Disease	Vaccine Name/brand	Birth	≤4w	1m	2m	4m	6m	12m	15m	18m	19-23m	24-35m	4Y	6Y	11Y	12Y
HepB	Hepavax, Euvax	1st		2nd			3rd									
BCG	Danish (ID), Tokyo (PC)		1st													
DTaP	DTaP, DTaP-IPV, DTaP-IPV-Hib				1st	2nd	3rd		4th				5th		Tdap	
Polio	IPV				1st	2nd	3rd						4th			
PCV, Hib	PCV13 or PCV10 / Hib (LG)				1st	2nd	3rd	4th								
Rotavirus	Rotateq, Rotarix				1st	2nd	3rd									
MMR								1st					2nd			
VZ								1st								
Flu							yearly									
HepA								1st AND 2nd								
JE	Cell culture							1st AND 2nd				3rd		4th		5th
JE (live)	Chundu, SanofiPasteur							1st				2nd				
HPV	HPV2, HPV4 or HPV9														1st AND 2nd	

National Immunization Program
Private sector

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Objectives

- Primary objective
  - To demonstrate non-inferiority of the investigational vaccine compared to the control vaccines
    - at 1 month post-third dose
    - seroprotection (SP) rates (anti-D, anti-T, anti-polio 1, 2, 3, anti-PRP, anti-HB)
    - seroconversion (SC) rates (anti-PT and anti-FHA)

- Secondary objectives
  - To describe the immune responses to anti-D, anti-PT and anti-FHA, and anti-HB pre-first dose, all antigens post-third dose
  - Safety profile in each group

Method (I)

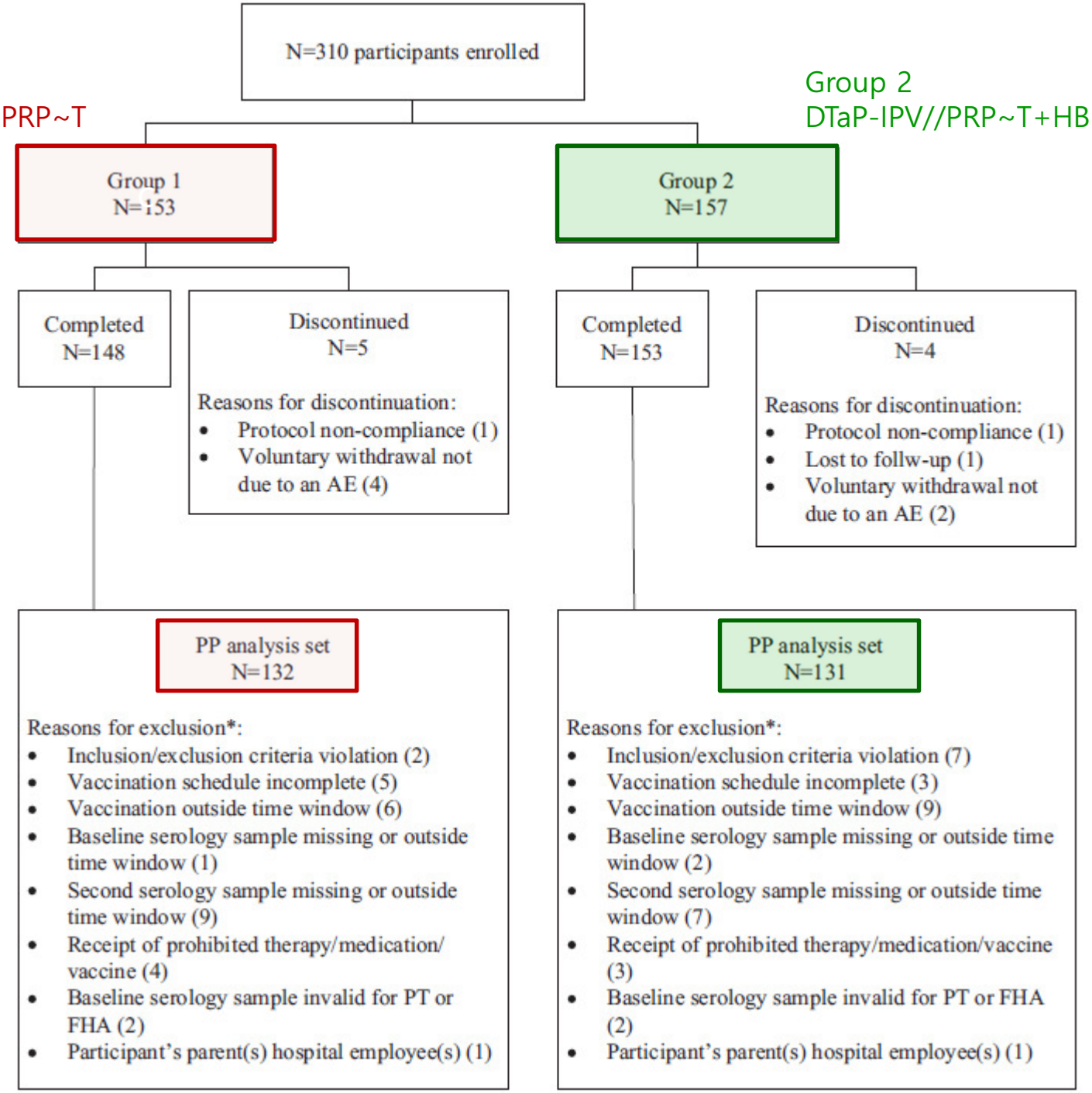
- A phase III, randomized, active-controlled, open-label study at 18 sites in Korea
- WHO Universal Trial Number U1111-1127-6896, ClinicalTrials.gov identifier NCT02094833
- Study period: from March 2014 to April 2016
- **Inclusion:**
  - Healthy infants ages 30-40 days, born at full-term (≥37 weeks) with birth weight ≥2.5 kg, who received one dose of HB vaccine at birth
- **Exclusion:**
  - current or planned participation in another clinical trial or non-study vaccination during or in the 4 weeks pre-study (except for BCG vaccine) or any planned non-study vaccination in the 8 days post-any trial vaccination
  - any prior vaccination against D, T, P, poliomyelitis, HB (except the birth dose of HB vaccine), Hib, or any history of these infections
  - receipt of blood products or of any immune-modifying treatment for more than two consecutive weeks
  - personal/maternal history of HIV or hepatitis C seropositivity
  - known hypersensitivity to any study vaccine component
  - history of seizures
  - bleeding disorder contraindicating intramuscular (IM) injection
  - chronic or acute illness that could interfere with study conduct/completion
  - a child of anyone directly involved in the study

Method (II)

- Following HB vaccination at birth
- Group 1: Hexavalent vaccine (DTaP-IPV//PRP~T and HB, Hexaxim™ by Sanofi Pasteur) at 2, 4, 6 months of age
  - Four consecutive doses of HB-containing vaccine in the hexavalent group (i.e. birth, 2, 4, 6 months)
- Group 2: Pentavalent vaccine (DTaP-IPV-PRP~T, Pentaxim™, Sanofi Pasteur) at 2, 4, 6 months and a standalone HB (Euvax B®) vaccine at 1 and 6 months
  - Three HB-containing vaccine doses in the pentavalent and HB group (i.e. birth, 1, 6 months)
- This study was a pre-licensure requirement of the Ministry of Food and Drug Safety of Korea and designed to establish non-inferiority for immunogenicity of hexavalent antigens versus its predecessor vaccine, pentavalent vaccine coadministered with HB.

Group 1
DTaP-IPV-HB-PRP~T

Group 2
DTaP-IPV//PRP~T+HB



*A participant could have had more than one reason for exclusion from the PP analysis set

N=number of subjects in population

AE=adverse event
PP=per protocol
PT=pertussis toxin
FHA=filamentous hemagglutinin

Per protocol analysis

Summary of demography

	Group 1 DTaP-IPV-HB-PRP~T (N = 132)	Group 2 DTaP-IPV//PRP~T + HB (N = 131)	All (N = 263)
Sex n (%)			
Male	77 (58.3)	66 (50.4)	143 (54.4)
Female	55 (41.7)	65 (49.6)	120 (45.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Sex ratio: M/F	1.40	1.02	1.19
Age (days)			
Mean (SD)	33.8 (2.8)	33.8 (2.6)	33.8 (2.7)
Median	33.0	34.0	34.0
Min; Max	30.0; 40.0	30.0; 40.0	30.0; 40.0
Q1; Q3	32.0; 35.5	31.0; 36.0	31.0; 36.0
Weight (kg)			
Mean (SD)	4.7 (0.5)	4.7 (0.6)	4.7 (0.5)
Median	4.7	4.7	4.7
Min; Max	3.1; 5.8	3.0; 6.5	3.0; 6.5
Q1; Q3	4.4; 5.0	4.3; 5.1	4.4; 5.1

N = number of subjects in group. n: number of subjects.
SD = standard deviation. Q1; Q3: first quartile; third quartile.

Per protocol analysis

Seroprotection rates, seroconversion rates, and non-inferiority comparison 1 month post-dose 3 (primary objective)

Antibody	Threshold	Group 1 (N=132)	Group 2 (N=131)	Difference	δ (%)	Conclusion[a]
Anti-HBs	≥10 mIU/mL	97.7 (93.5; 99.5)	96.9 (92.4; 99.2)	0.8 (–3.81; 5.56)	10	Non-inferior
Anti-PRP	≥0.15 µg/mL	100.0 (97.2; 100.0)	100.0 (97.2; 100.0)	0.0 (–2.83; 2.85)	10	Non-inferior
Anti-D	>0.01 IU/mL	100.0 (97.2; 100.0)	100.0 (97.1; 100.0)	0.0 (–2.87; 2.98)	10	Non-inferior
Anti-T	>0.1 IU/mL	99.2 (95.7; 100.0)	100.0 (97.1; 100.0)	–0.8 (–4.29; 2.29)	10	Non-inferior
Anti-polio type 1	≥8 (1/dil)	100.0 (97.2; 100.0)	100.0 (97.2; 100.0)	0.0 (–2.87; 2.85)	10	Non-inferior
Anti-polio type 2	≥8 (1/dil)	100.0 (97.2; 100.0)	100.0 (97.2; 100.0)	0.0 (–2.87; 2.91)	10	Non-inferior
Anti-polio type 3	≥8 (1/dil)	100.0 (97.2; 100.0)	100.0 (97.2; 100.0)	0.0 (–2.87; 2.89)	10	Non-inferior
Anti-PT	4-fold increase	94.6 (89.1; 97.8)	93.0 (87.1; 96.7)	1.6 (–4.68; 8.03)	10	Non-inferior
Anti-FHA	4-fold increase	91.7 (85.6; 95.8)	89.3 (82.7; 94.0)	2.4 (–4.96; 9.75)	10	Non-inferior

Data are % (95% CI) participants with titer or concentration above threshold.
PP = per protocol; D = diphtheria; T = tetanus; PT = pertussis toxin; FHA = filamentous hemagglutinin; HBs = hepatitis B surface antigen; PRP = polyribosylribitol phosphate
[a] If 95% CI for the difference (DTaP-IPV-HB-PRP~T minus DTaP-IPV//PRP~T + HB) was greater than –δ then the null hypothesis H0 was rejected (conclusion of non-inferiority)

Per protocol analysis

Summary of immunogenicity results (secondary objective)

Hepatitis B

		Group 1 DTaP-IPV-HB-PRP~T (N = 132)		Group 2 DTaP-IPV//PRP~T + HB (N = 131)	
Antibody	**Criteria**	**Pre-dose 1[a]**	**Post-dose 3**	**Pre-dose 1[b]**	**Post-dose 3**
Anti-HBs	≥10 mIU/mL	74.0 (65.7; 81.3)	97.7 (93.5; 99.5)	68.7 (60.0; 76.5)	96.9 (92.4; 99.2
	GMC (mIU/mL)	37.3 (26.0; 53.4)	1068 (805; 1416)	41.8 (29.0; 60.2)	827 (601; 1138)

Data are % (95% CI) participants fulfilling the given criteria or geometric mean concentration (GMC [95% CI]) or titer (GMT [95% CI]).
[a]Approximately 1 month pre-dose 1 (1 month of age).
[b]Immediately prior to first HB dose (1 month of age).

Per protocol analysis

Summary of immunogenicity results (secondary objective)

		Group 1 DTaP-IPV-HB-PRP~T (N = 132)		Group 2 DTaP-IPV//PRP~T + HB (N = 131)	
Antibody	**Criteria**	**Pre-dose 1[a]**	**Post-dose 3**	**Pre-dose 1[b]**	**Post-dose 3**
Anti-PRP	≥0.15 µg/mL	NC	100.0 (97.2; 100)	NC	100.0 (97.2; 100)
	≥1 µg/mL	NC	87.1 (80.2; 92.3)	NC	96.9 (92.4; 99.2)
	GMC (µg/mL)	NC	5.44 (4.37; 6.77)	NC	9.35 (7.67; 11.4)
Anti-D	>0.01 IU/mL	54.7 (45.7; 63.5)	100.0 (97.2; 100)	48.1 (39.3; 57.0)	100.0 (97.1; 100)
	>0.1 IU/mL	5.5 (2.23; 10.9)	98.5 (94.6; 99.8)	4.6 (1.70; 9.70)	97.6 (93.1; 99.5)
	GMC (IU/mL)	0.01 (0.008; 0.013)	1.01 (0.874; 1.16)	0.009 (0.007; 0.012)	0.676 (0.582; 0.786)
Anti-T	>0.01 IU/mL	NC	100.0 (97.2; 100)	NC	100.0 (97.1; 100)
	>0.1 IU/mL	NC	99.2 (95.7; 100)	NC	100.0 (97.1; 100)
	GMC (IU/mL)	NC	3.05 (2.67; 3.48)	NC	2.53 (2.30; 2.78)

Data are % (95% CI) participants fulfilling the given criteria or geometric mean concentration (GMC [95% CI]) or titer (GMT [95% CI]).
[a]Approximately 1 month pre-dose 1 (1 month of age). [b]Immediately prior to first HB dose (1 month of age).
NC, not calculated

Per protocol analysis

Summary of immunogenicity results (secondary objective)

		Group 1 (N = 132)		Group 2 (N = 131)	
Antibody	**Criteria**	**Pre-dose 1[a]**	**Post-dose 3**	**Pre-dose 1[b]**	**Post-dose 3**
Anti-polio 1	≥8 (1/dil)	NC	100.0 (97.2; 100)	NC	100.0 (97.2; 100)
	GMT ([1/dil))	NC	823 (695; 975)	NC	1210 (1003; 1459)
Anti-polio 2	≥8 (1/dil)	NC	100.0 (97.2; 100)	NC	100.0 (97.2; 100)
	GMT ([1/dil))	NC	1380 (1126; 1692)	NC	1588 (1255; 2009)
Anti-polio 3	≥8 (1/dil)	NC	100.0 (97.2; 100)	NC	100.0 (97.2; 100)
	GMT ([1/dil))	NC	899 (721; 1120)	NC	1280 (1000; 1639)
Anti-PT	GMC (EU/mL)	2.84 (2.35; 3.43)	99.0 (90.6; 108)	2.98 (2.40; 3.69)	143 (129; 157)
	≥LLOQ	59.1 (50.2; 67.2)	NC	57.3 (48.3; 65.9)	NC
	VR[c]	NA	98.4 (94.5; 99.8)	NA	98.4 (94.5; 99.8)
Anti-FHA	GMC (EU/mL)	6.30 (5.20; 7.64)	153 (141; 166)	6.84 (5.50; 8.51)	163 (148; 180)
	≥LLOQ	91.7 (85.6; 95.8)	NC	90.1 (83.6; 94.6)	NC
	VR[c]	NA	97.7 (93.5; 99.5)	NA	96.2 (91.3; 98.7)

Data are % (95% CI) participants fulfilling the given criteria or geometric mean concentration (GMC [95% CI]) or titer (GMT [95% CI]). LLOQ, lower limit of quantitation; NC, not calculated; NA, not applicable

[a]Approximately 1 month pre-dose 1 (1 month of age). [b]Immediately prior to first HB dose (1 month of age).

[c]Vaccine response

Participants experiencing solicited injection site adverse reactions occurring in the 7 days after any dose of study vaccine

		Group 1 DTaP-IPV-HB-PRP~T (N = 149)		Group 2 DTaP-IPV//PRP~T + HB (N = 155)	
	Grade[a]	**%**	**(95% CI)**	**%**	**(95% CI)**
Any injection site reaction	Any	77.2	(69.6; 83.7)	73.5[b]	(69.3; 83.2)
Pain	Any	61.7	(53.4; 69.6)	58.1[b]	(53.8; 69.6)
	Grade 3	2.0	(0.4; 5.8)	1.3[b]	(0.2; 4.6)
Erythema	Any	53.7	(45.3; 61.9)	44.5[b]	(39.0; 55.3)
	Grade 3	2.7	(0.7; 6.7)	2.6[b]	(0.7; 6.5)
Swelling	Any	47.7	(39.4; 56.0)	43.2[b]	(39.7; 55.9)
	Grade 3	1.3	(0.2; 4.8)	0.6[b]	(0.0; 3.5)

[a] Grade 1, 2, and 3 pain were defined as 'minor reaction when injection site is touched,' 'cries or protests when injection site is touched,' and 'cries when injected limb is moved or the movement of the injected limb is reduced.' For erythema and swelling, a diameter of <2.5 cm was assessed as Grade 1, from 2.5 to <5 cm as Grade 2 and ≥5 cm as Grade 3. Grade 1, 2, and 3 pyrexia were defined as temperature ≥38 °C–≤38.5 °C, >38.5 °C–≤39.5 °C, and >39.5 °C, respectively. Other systemic symptoms were defined as: vomiting (Grade 1, 1 episode/day; Grade 2, 2 to 5 episodes/day; Grade 3, ≥6 episodes /day or requiring parenteral hydration), crying abnormal (Grade 1, <1 h; Grade 2, 1–3 h; Grade 3, >3 h), drowsiness (Grade 1, unusually sleepy; Grade 2, not interested in surroundings or did not wake up for a meal; Grade 3, sleepy most of the time or difficult to wake up), appetite lost (Grade 1, eating less than normal; Grade 2, missed 1 to 2 meals; Grade 3, missed ≥3 meals) and irritability (Grade 1, easily consolable; Grade 2, requiring increased attention; Grade 3, inconsolable)

[b] For the DTaP-IPV//PRP~T vaccine injection site only.

Participants experiencing systemic adverse reactions occurring in the 7 days after any dose of study vaccine

		Group 1 (N = 149)		Group 2 (N = 155)	
	Grade[a]	**%**	**(95% CI)**	**%**	**(95% CI)**
Any systemic reaction	Any	74.5	(66.7; 81.3)	69.0[c]	(61.1; 76.2)
Pyrexia	Any	20.1	(14.0; 27.5)	7.7[c]	(4.1; 13.1)
	Grade 3	0.0	(0.0; 2.4)	0.0[c]	(0.0; 2.4)
Vomiting	Any	26.8	(19.9; 34.7)	24.5[c]	(18.0; 32.1)
	Grade 3	0.7	(0.0; 3.7)	1.3[c]	(0.2; 4.6)
Crying	Any	48.3	(40.1; 56.6)	33.5[c]	(26.2; 41.6)
	Grade 3	4.0	(1.5; 8.6)	2.6[c]	(0.7; 6.5)
Somnolence	Any	51.0	(42.7; 59.3)	45.2[c]	(37.2; 53.3)
	Grade 3	2.0	(0.4; 5.8)	1.9[c]	(0.4; 5.6)
Decreased appetite	Any	34.9	(27.3; 43.1)	35.5[c]	(28.0; 43.6)
	Grade 3	0.7	(0.0; 3.7)	0.6[c]	(0.0; 3.5)
Irritability	Any	53.7	(45.3; 61.9)	49.0[c]	(40.9; 57.2)
	Grade 3	3.4	1.1 (7.7)	1.9[c]	(0.4; 5.6)

[C] For DTaP-IPV//PRP~T at 2 and 4 months of age and DTaP-IPV//PRP~T and HB vaccines together at 6 months of age.

Summary

- Administration of the investigational vaccine at 2, 4, 6 months (resulting in four consecutive HB vaccine administrations) induced anti-HB seroprotective titers that were slightly higher than following monovalent HB vaccine at 0, 1, 6 month, with no difference in reactogenicity.
- Alternative HB schedule is equally valid from both immunogenicity and safety perspectives, with the advantage of having all antigens delivered in a single vaccine.
- Both groups demonstrated a good and similar overall safety profile, with few vaccine-related AEs, although the incidence of pyrexia was slightly higher for the investigational vaccine.
- This overall good safety profile for each vaccine is consistent with previous clinical experience with these vaccines

Conclusion

- This study further add to the growing literature on this fully liquid hexavalent vaccine in a wide range of countries, and demonstrate its safety and immunogenicity in Korean infants.

Thank you