

# Immunogenicity, Reactogenicity and Safety of a Diphtheria-Tetanus-Acellular Pertussis-Inactivated Polio and *Haemophilus Influenzae* Type b Combination Vaccine in a Placebo-controlled Rotavirus Vaccine Study

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## Abstract

**Introduction:** In recent years, acellular pertussis combination vaccines have facilitated compliance with and coverage of the national immunisation programme in Singapore. This phase-II study (Rota-007) evaluated the immunogenicity, reactogenicity and safety of a DTPa-IPV/Hib combined vaccine when co-administered with a rotavirus vaccine. **Materials and Methods:** A total of 2464 children aged 3 months were vaccinated with DTPa-IPV/Hib together with a randomised 1:3 ratio of either placebo (n = 653) or 1 of 3 different formulations of a rotavirus vaccine. Blood samples were collected for immunogenicity analysis 1 month after the third DTPa-IPV/Hib vaccine dose in a subset of subjects (n = 640). Local and general reactogenicity and unsolicited adverse events were recorded during the follow-up after each vaccination. **Results:** Serological analysis showed >95% response for all antigens in the co-administered DTPa-IPV/Hib vaccine, with no difference between the rotavirus vaccine and placebo groups. No differences in adverse events and reactogenicity were reported in the rotavirus vaccine and placebo groups. Only 0.2% of the subjects reported Grade 3 adverse events. Three subjects (from the vaccine groups) died during the study, which were assessed by the investigators as unrelated to vaccination. No deaths were reported in the placebo group. **Conclusion:** The combined DTPa-IPV/Hib vaccine is safe, well tolerated and highly immunogenic when given alone or co-administered with the rotavirus vaccine for infants in Singapore.

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**Key words:** Paediatric, Vaccination

## Introduction

Singapore's national immunisation programme for the 6 traditional Expanded Programme on Immunisation (EPI) vaccines (i.e. BCG, diphtheria, tetanus, pertussis, polio and measles) and hepatitis B has been in place for many years and its success has been dramatic. Despite being previously endemic to Singapore in the 1950s, diphtheria has not been reported for several years. Nevertheless, the need to be vigilant, to maintain high coverage rates for diphtheria, has long been advocated. Locally, this need was emphasised after the reappearance of diphtheria in 1982 in 4 unimmunised children.<sup>1</sup>

With tetanus and pertussis being delivered in a combined vaccination with diphtheria since 1959, Singapore has also had a long and rewarding experience with combination vaccines. Tetanus has a similar history as diphtheria, with neonatal tetanus being reported in 3% of all live births in 1914, and almost eradicated by the late 1970s.<sup>2,3</sup>

In the case of pertussis vaccination, the incidence of the disease has been reduced; however, cases persist in the very young.<sup>4</sup> The reactogenicity of the whole-cell vaccines in older subjects and the problem of ensuring adequate compliance for later vaccines has meant that boosters have until recently not been advised in pre-school children and

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beyond. Therefore, according to the Singapore National Schedule the last pertussis booster is administered at 18 months of age.<sup>1</sup>

While contributing historically to a large part of childhood mortality and morbidity up to the 1960s, the last reported cases of polio in Singapore were in 1984.<sup>5</sup> Again, this decrease has been attributed largely to the success of the universal vaccination programme, which commenced in Singapore with the polio vaccination programme in the 1950s.

*Haemophilus influenzae* type b (Hib) infection has been identified by the World Health Organisation (WHO) and other international bodies as being the next vaccine (after hepatitis B) which should be introduced into EPI. While Hib vaccination is not included in the Singapore government's public schedule, it is widely given in the private sector. Indeed, in Singapore, the practice of administering combined diphtheria-tetanus-acellular pertussis-inactivated polio (DTPa-IPV) and Hib vaccine is now very common, and a DTPa-IPV/Hib vaccine has been licensed in Singapore since 1999 for the parents who wanted Hib vaccination for their children.<sup>6</sup>

This phase-IIb study of a rotavirus vaccine which included the concomitant administration of an acellular pertussis combination vaccine, assessed the immunogenicity, safety and reactogenicity of a DTPa-IPV/Hib vaccine in a large number of Singaporean infants. The results pertaining to the rotavirus vaccine, which is now commercially available in Singapore, have been previously published; this paper describes the immunogenicity and safety results of the combination DTPa-IPV/Hib vaccine.<sup>7,8</sup>

## Materials and Methods

This double-blind study (Rota-007) was undertaken in 2 large hospitals in Singapore (KK Women's and Children's Hospital and National University Hospital) and 6 polyclinics of the SingHealth and National Healthcare Groups. Full ethical clearance was granted by Singapore's Clinical Trial Coordinating Centre (CTCC; this was an Institutional Review Board at that time), Singapore and the Ministry of Health for all centres. All parents or guardians of the subjects were required to sign an Informed Consent Form. Recruitment took place over a 13-month period from January 2001 to January 2002. There was no financial compensation for the parents in this study, other than a small token travel allowance and free trial vaccines.

Healthy infants aged 3 months were randomised using a standard SAS® (Statistical Analysis System) programme to receive 2 doses of one of 3 different formulations of GlaxoSmithKline's (GSK) human rotavirus vaccine (HRV; 10<sup>4.7</sup>, 10<sup>5.2</sup> or 10<sup>6.1</sup> foci forming units [ffu]) or a placebo. Two randomisation blocking schemes (1:1:1:1 and 1:1:1

ratios) were used to ensure that balance between treatments was maintained. The parents/guardians and the study personnel remained blinded (double-blind) until the end of the study. Subjects visited the centres at 3, 4, 5, 6, 12 and 18 months of age (visits 1-6) and were given HRV/placebo on the first 2 visits. In addition, at 3, 4 and 5 months of age (visits 1-3), all subjects received routine primary vaccination with diphtheria-tetanus-acellular pertussis-inactivated polio and *Haemophilus influenzae* type b vaccine [DTPa-IPV/Hib (*Infanrix-IPV/Hib*<sup>TM</sup>); GSK Biologicals, Rixensart, Belgium]. A booster dose of DTPa-IPV/Hib was administered at 18 months. Each 0.5 mL dose of DTPa-IPV/Hib vaccine contained diphtheria toxoid  $\geq$ 30 IU, tetanus toxoid  $\geq$ 40 IU, pertussis toxin (PT) 25  $\mu$ g, filamentous haemagglutinin (FHA) 25  $\mu$ g, pertactin (PRN) 8  $\mu$ g, polio virus type-1 40 D-antigen units, polio virus type-2 8 D-antigen units, polio virus type-3 32 D-antigen units and Hib polyribosyl ribitol phosphate (PRP) 10  $\mu$ g.

In accordance with the local schedule, all subjects received 3 doses of hepatitis B vaccine at birth, 1 and 5-6 months of age. Any commercial recombinant hepatitis B vaccine was administered for the first 2 doses, but only *Engerix-B*<sup>TM</sup> (GSK Biologicals, Rixensart) was used for the last dose. Each 0.5 mL dose of HBV contained 10  $\mu$ g recombinant HbsAg.

Blood samples were collected from a subset of subjects (n = 640) from all groups for serology assessment at the first 4 visits. These subset of subjects were selected on a "first come, first serve" basis. The sera collected at visits 2 and 3 were analysed for anti-rotavirus IgA antibodies, while sera collected at visits 4 were analysed for anti-rotavirus, anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-PRP and anti-Polio 1, 2, and 3 antibodies at the laboratories of Dr Michael Pichichero, University of Rochester, New York using validated serological assays. Anti-rotavirus, anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-HBs, anti-PRP antibody levels were determined by enzyme-linked immunosorbent assay (ELISA), while anti-polio antibodies were determined by neutralisation assays (Table 1).<sup>9</sup> Seroprotection, seropositivity and antibody geometric mean titres or concentrations (GMT/GMCs) were calculated with exact 95% confidence intervals (CIs) for all antibodies. Immunogenicity endpoints included assessment of serum anti-rotavirus IgA antibody concentrations in all subjects at visit 1 and in a subset of subjects at visits 2, 3 and 4. Endpoints for assessment of safety and reactogenicity included occurrence of each type of solicited adverse event within the 15-day solicited follow-up period after each study vaccine dose, occurrence of unsolicited adverse events within 42 days after each study vaccine dose [according to the Medical Dictionary for Regulatory Activities (MedDRA) classification] and

Table 1. Assay Methods Used in This Study with Their Cut-offs

Assays method	Antibody	Assay cut-offs	Serostatus
ELISA	Anti-rotavirus	20 U/mL	Seroprotected
	Anti-diphtheria	0.1 IU/mL	Seroprotected
	Anti-tetanus	0.1 IU/mL	Seroprotected
	Anti-PT, anti-FHA, anti-PRN	5 EL.U/mL	Seropositive
	Anti-HBs	10 mIU/mL	Seroprotected
	Anti-PRP	0.15 µg/mL	Seroprotected
Neutralisation	Anti-poliovirus type-1	1:8 dilution	Seroprotected
	Anti-poliovirus type-2	1:8 dilution	Seroprotected
	Anti-poliovirus type-3	1:8 dilution	Seroprotected

ELISA: enzyme-linked immunosorbent assay; FHA: filamentous haemagglutinin; HBs: hepatitis B surface antigen; PRN: pertactin; PRP: polyribosyl ribitol phosphate; PT: pertussis toxin  
All test kits were manufactured in-house

occurrence of serious adverse events (SAEs) throughout the entire study period.

Local and general symptoms were solicited for 15 days after vaccinations at 3 and 4 months of age using diary cards. Other unsolicited symptoms were recorded for 43 days (Day 0 to Day 42) after vaccination and SAEs for the duration of the study. Adverse events were graded on a 3-point scale (0-3), where grade “3” was considered severe for vaccine adverse experience and related to vaccination.

### Statistics

In order to calculate the power of the study based on the number of subjects required for serological analysis, assessment of immunogenicity was based on seroprotection rates observed in a reference study (DTPa-IPV-029). Using an estimation of the seroprotection rates between 97.6% and 100% and assuming that the rates would be the same in the vaccine and placebo groups, a subset of 180 evaluable subjects per group was expected to provide at least 90% power that the 95% CIs on difference of seroprotection rates between each vaccine group and the placebo group would be within [-10%; +10%]. A total of 640 subjects were bled to assess immunogenicity, allowing for up to 10% of subjects who may not be evaluable for the immunogenicity analysis.

All subjects were assessed for safety. The percentages of doses and of subjects with any adverse experience during the solicited follow-up period were computed, along with exact 95% CI.

For each dose analysis, the denominator

$N$  = number of subjects having received the considered dose, and the numerator

$n$  = number of subjects reporting at least 1 symptom for the considered dose.

For overall/dose analysis, the denominator

$N$  = number of administered doses (i.e. the total number of doses given for subjects), and the numerator

$n$  = number of doses followed by at least 1 symptom (i.e. number of times a particular symptom is reported following doses).

Asymptotic standardised 2-sided 95% CIs were calculated for the difference in seroprotection/seropositivity rates. The inclusion of 0% in the interval was indicative of no difference between the 2 groups. A 2-way ANOVA model on logarithm 10 transformation of concentrations or titres was used to calculate the 2-sided 95% CI for the ratio of GMC/T between the HRV vaccine group and the placebo group. The inclusion of 1 in the interval was indicative of no difference between the 2 groups. To convert the non-symmetric distributions into symmetric-distributions, we use log transformations. These log transformed values were used for GMC calculations also by taking the anti-log {Mean of the [Log (Concentrations)]}.

Seroconversion was defined as the appearance of anti-rotavirus IgA antibody concentration  $\geq 20$  U/mL in subjects who were initially (i.e. prior to the first dose) negative for rotavirus.

### Results

A total of 2464 subjects were enrolled in the study of which 99 failed to complete the study (Fig. 1). All subjects ( $N = 1811$ ) received the combined DTPa-IPV/Hib vaccine, co-administered with either the rotavirus vaccine (Group HRV  $10^{4.7}$  ffu:  $n = 510$ ; Group HRV  $10^{5.2}$  ffu:  $n = 648$ ; Group HRV  $10^{6.1}$  ffu:  $n = 653$ ) or placebo ( $n = 653$ ). The cohort analysed for immunogenicity (per-protocol cohort) comprised a subset of 155, 158, 167 and 160 subjects across the 3 vaccine groups and the placebo group,

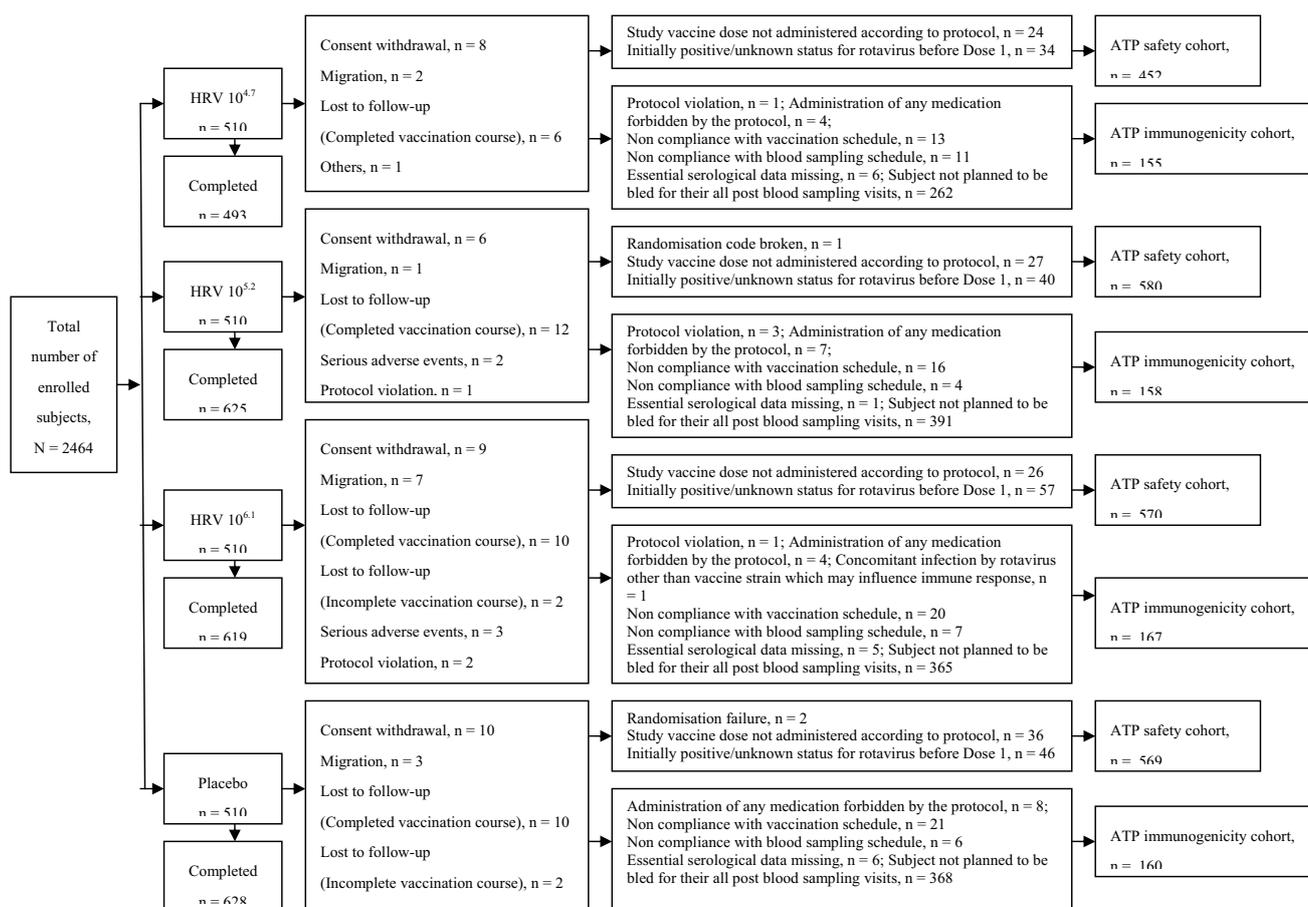


Fig. 1. CONSORT diagram for subjects lost to follow-up.

respectively. The sample size of the HRV 10<sup>4.7</sup> ffu group was lower than the other groups, due to an unavailability of sufficient number of 10<sup>4.7</sup> ffu HRV vaccine doses.

The mean age at enrolment was 13.3 weeks, with a standard deviation of 0.9. There were almost equal numbers of males and females (49.8% vs. 50.2% respectively) and, almost reflecting Singapore’s population, the babies comprised 93% Asian race, and 6.9% classified as “Others”. Two babies were Caucasian.

The immunogenicity results for the DTPa-IPV/Hib vaccination in the pooled HRV groups vs. the placebo group showed 95% CI including 0% for both seroprotection/seroconversion rates and including 1 for GMC/T ratios, indicating similarity between the 2 groups (Figs. 2 and 3). One month after the third dose of DTPa-IPV/Hib, all subjects (95% CI, 99.1 to 100) were seroprotected for all 3 types of poliovirus. Only 1 subject was not seroprotected for tetanus, giving a seroprotection level of 100% (95% CI, 99.1 to 100) for the pooled HRV groups and 99.3% (95% CI, 96.2 to 100) for the placebo group. For diphtheria,

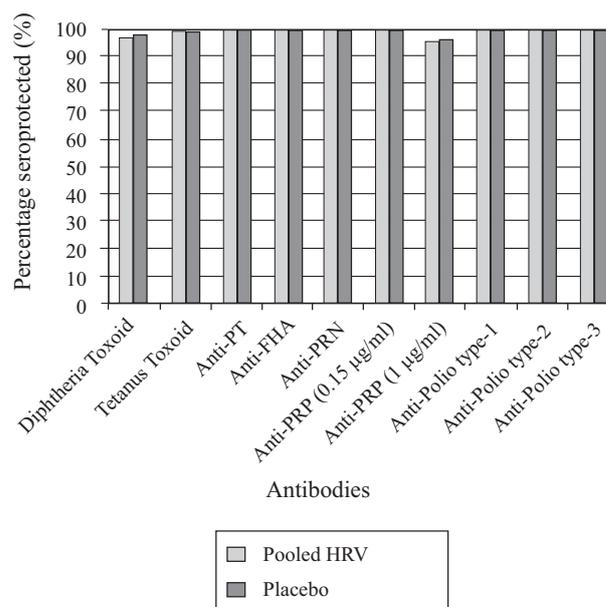


Fig. 2. Percentage seroprotection/seropositivity for DTPa-IPV/Hib and HBV vaccines in the pooled HRV and placebo groups.

Table 2. Percentage of Subjects for Whom Fever, Vomiting, or Diarrhoea was Reported During the 15-day Follow-up Period After Administration of DTPa-IPV/Hib Vaccine with HRV and Placebo Groups

Solicited general symptom	Dose of HRV							
	10 <sup>4.7</sup> ffu		10 <sup>5.2</sup> ffu		10 <sup>6.1</sup> ffu		Placebo	
	Dose 1 (n = 510)	Dose 2 (n = 501)	Dose 1 (n = 648)	Dose 2 (n = 639)	Dose 1 (n = 653)	Dose 2 (n = 639)	Dose 1 (n = 653)	Dose 2 (n = 642)
<b>Fever</b>								
Total	30 (26–34)	32 (28–37)	28 (25–32)	32 (29–36)	25 (22–29)	27 (24–31)	28 (25–32)	29 (26–33)
Severe	0 (0–1)	0 (0–1)	1 (0–2)	1 (0–2)	1 (0–2)	0 (0–1)	0 (0–1)	1 (0–2)
<b>Vomiting</b>								
Total	5 (3–7)	4 (3–6)	5 (3–7)	5 (3–7)	7 (5–9)	4 (2–6)	6 (4–8)	4 (3–6)
Severe	1 (0–2)	1 (0–2)	2 (1–3)	2 (1–3)	1 (1–3)	0 (0–1)	1 (0–2)	1 (0–2)
<b>Diarrhoea</b>								
Total	1 (1–3)	2 (1–4)	1 (1–3)	2 (1–4)	3 (2–5)	2 (1–4)	2 (1–3)	1 (0–2)
Severe	0 (0–1)	0 (0–1)	1 (0–1)	0 (0–1)	1 (0–1)	1 (0–2)	0 (0–1)	0 (0–1)

ffu: focus-forming units; HRV: human rotavirus vaccine

Severe fever is defined as temperature >39.5°C (measured rectally) or >39.0°C (measured orally/axillary)

Severe vomiting is defined as ≥3 episodes of vomiting/day

Severe diarrhoea is defined as ≥6 looser-than-normal stools/day

Total: All reports of the specified symptom, irrespective of severity

97.3% (95% CI, 95.2 to 98.6) were seroprotected in the pooled HRV groups and 97.8% (95% CI, 93.6 to 99.5) in the placebo groups. For both diphtheria and tetanus, GMC levels were ≥1.43 and 2.87 IU/mL for the pooled HRV and placebo groups, respectively.

After completion of primary vaccination, all subjects in the study were seropositive for FHA (pooled GMC ≥74.8 EL.U/mL) and PRN (pooled GMC ≥174.7 EL.U/mL) antigens. All but 3 subjects were not seropositive for anti-PT, 99.5% (95% CI, 98.2 to 99.9) in the pooled HRV groups and 99.3% (95% CI, 96 to 100) in the placebo group, with the pooled GMC in both ≥44 EL.U/mL in both groups.

All subjects were seroprotected for anti-PRP (anti-PRP concentration ≥0.15 µg/mL) one month after primary vaccination. Using a cut-off of 1.0 µg/mL, 96.3% (95% CI, 94.1 to 97.9) of the pooled HRV groups and 96.6% (95% CI, 92.2 to 98.9) of the placebo group were seroprotected. The GMC was 4.986 µg/mL for the pooled HRV groups and 5.819 µg/mL for the placebo group.

Hepatitis B vaccination was administered separately. In the pooled HRV groups, 94.4% (95% CI, 91.7 to 96.3) of subjects were seroprotected (anti-HBs antibody concentration ≥10 mIU/mL) vs. 94.3% (95% CI, 89.1 to 97.5) in the placebo group. GMC were 603.974 mIU/mL and 688.844 mIU/mL, respectively. Again, no difference was observed between the 2 groups on 95% CI for seroprotection difference and 95% CI for GMC ratios.

In the 15 days following the first or the second vaccine

dose, the incidences of solicited or unsolicited adverse events were similar in the 4 study groups (Table 2). The incidence of general symptoms such as fever, irritability and loss of appetite after any and all doses was not different between the rotavirus vaccine groups and the placebo group. Only 0.9% (95% CI, 0.9 to 1.4) of subjects in the pooled HRV group and 1.1% (95% CI, 0.4 to 2.2) of subjects in the placebo group were assessed to have unsolicited Grade 3 SAEs (Table 3). Five subjects (0.2%), all in the vaccine groups, were assessed to have a Grade 3 symptom related to vaccination.

Three subjects (2 in the HRV 10<sup>6.1</sup> ffu group and 1 in the 10<sup>5.2</sup> ffu group) died during the study. One subject died during the 43-day post-vaccination follow-up post-dose 1 while the remaining 2 subjects died after completion of the 43-day post-vaccination follow-up post-dose 2) due to viral pneumonitis, myelomonocytic leukaemia and subarachnoid haemorrhage (Table 3; the 2 subjects who died after completion of the 43-day post-vaccination follow-up period are not listed in the table). Two other subjects (1 each from the HRV10<sup>6.1</sup> ffu and 10<sup>5.2</sup> ffu group) failed to complete the study due to seizure and urinary tract infection. All of these SAEs were assessed by the investigators as unrelated to vaccination. There were no drop-outs due to non-SAEs.

## Discussion

After proof of disease burden, the implementation of a vaccine into immunisation programmes depends on adequate proof of safety, immunogenicity and efficacy. The Singapore National Immunisation Programme has

Table 3. Percentage of Subjects with Grade 3 Serious Adverse Events Reported During the 43-day Follow-up Period After Each Vaccination

WHO Body System (CODE)	WHO preferred term	Pooled HRV groups N = 1811				Placebo N = 653			
		s	%	95% CI		s	%	95% CI	
				LL	UL			LL	UL
At least one adverse event		16	0.9	0.5	1.4	7	1.1	0.4	2.2
Body as a whole general	Fever	1	0.1	0	0.3	0	0	0	0.6
Central and peripheral nervous system	Convulsions	1	0.1	0	0.3	0	0	0	0.6
Fetal	Atrial septal defect	1	0.1	0	0.3	0	0	0	0.6
Gastrointestinal system	Intestinal obstruction	1	0.1	0	0.3	0	0	0	0.6
Resistance mechanism	Infection bacterial	1	0.1	0	0.3	1	0.2	0	0.9
	Infection viral	0	0	0	0.2	3	0.5	0.1	1.3
	Pneumonitis	1	0.1	0	0.3	0	0	0	0.6
	Upper respiratory tract infection	2	0.1	0	0.4	0	0	0	0.6
Respiratory system	Bronchitis	2	0.1	0	0.4	1	0.2	0	0.9
	Coughing	0	0	0	0.2	1	0.2	0	0.9
	Pharyngitis	1	0.1	0	0.3	0	0	0	0.6
	Pneumonia	3	0.2	0	0.5	2	0.3	0	1.1
	Rhinitis	0	0	0	0.2	1	0.2	0	0.9
Urinary system	Urinary tract infection	2	0.1	0	0.4	1	0.2	0	0.9

N = number of subjects having received at least one dose

s/% = number/percentage of subjects reporting at least once a specified unsolicited adverse event

95% CI = exact 95% confidence interval; LL: lower limit; UL: upper limit

At least one adverse event = number of subjects reporting at least one unsolicited adverse event, whatever the WHO preferred terms

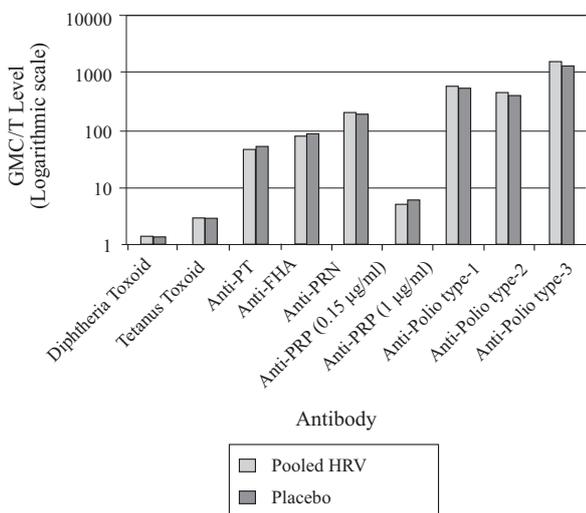


Fig. 3. GMC/T for DTPa-IPV/Hib and HBV in the pooled HRV and placebo groups.

offered free basic DTPw vaccine until 2007 when it was replaced by DTPa vaccine. However, combination vaccines such as DTPa-IPV/Hib have already been commonly given in the private market, due to the advantages of a combined

vaccine, namely protection against several diseases (4 diseases in the national immunisation schedule and in addition, Hib disease) with fewer injections.

This DTPa-IPV/Hib vaccine has been licensed in Singapore since 1999. Published safety and immunogenicity data from the Asian region, extending from Turkey in the West to Taiwan in the East, for various combinations of acellular DTP vaccines produced by several vaccine manufacturers are available.<sup>10-14</sup> More studies on the DTPa combination vaccines (including the DTPa-IPV/Hib and the newer hexavalent DTPa-HBV-IPV/Hib vaccine) have been undertaken in Europe, where the results were similar to those collected in other Asian studies.<sup>15-18</sup>

This paper focuses on the immunogenicity, safety and reactogenicity of the DTPa-IPV/Hib vaccine in Singaporean infants when given alone or co-administered with the rotavirus vaccine, to add to the limited pool of available data for such combinations in Asian infants. In addition to the findings pertaining to the rotavirus vaccine, the results reported here show that the immunogenicity of the DTPa-IPV/Hib vaccine is not different when administered concomitantly with either placebo or varying doses of HRV vaccine.<sup>7,8</sup> Over 95% of all subjects reached

Table 4. Listings of Previous Study Results Used for Comparison of Safety and Reactogenicity Between Acellular and Whole Cell Pertussis Vaccines

Author's name (number)	Results
Shek LP, et al (19)	The overall incidence of local and general symptoms was significantly higher in the group receiving DTPw vaccine when compared to the group receiving GSK DTPa vaccine. Solicited local symptoms like pain (47.4% vs 15.1%), redness (95.9% vs 84.9%) and swelling (46.2% vs 18.5%) were reported more commonly in the DTPw group. Four SAEs occurred in the DTPw group compared to two in the DTPa group.
Greco D, et al (20)	Local and systemic adverse events were significantly more frequent after the administration of the DTPw vaccine. Solicited local symptoms like local swelling, local tenderness and general symptoms like fever were more frequently reported in the DTPw group.
Jefferson T, et al (review article) (21)	Separate comparative analyses of DTPw vaccines with placebo/DT vaccines indicated that DTPw vaccines were associated with significantly higher incidences of swelling and induration (odds ratio 4.72), fever >39°C (odds ratio 3.36) and crying (odds ratio 4.72). Similar analyses of DTPa vaccines with placebo/DT vaccines did not indicate such a high incidence of local and general symptoms.

seroprotection correlates or showed good response to the pertussis antigens. When considering previous immunological results from the Asian region, the combination used in Singapore in this study is comparable, especially when comparing seroprotection for those antigens where correlates are established. Even for the Hib vaccine, where 2 cut-offs were used, the results from this study in Singapore compare favourably with the past clinical trial experience in Asia of combination Hib vaccines.

The demonstrated lack of interference of HRV on the DTPa-IPV/Hib vaccine supports co-administration and in turn a more convenient immunisation schedule if rotavirus vaccine is implemented into a future national programme.

Safety and reactogenicity results for fever in this study indicate that there was no difference between vaccinated and placebo groups irrespective of the dose of HRV vaccine. In terms of all reactogenicity, no differences were observed between the pooled HRV and placebo groups. There were no vaccine-related deaths.

Previous experience from Singapore, Indonesia, Germany, and a meta-analysis, has shown acellular pertussis combination vaccines to have clear advantage over whole-cell pertussis combinations with regard to reactogenicity and safety (Table 4).<sup>19-21</sup> However, when compared to other published data on DTPa combination vaccines, it is clear that the reactogenicity and safety profile of these vaccines are similar in all settings, as confirmed here.

In conclusion, the combination diphtheria-tetanus-acellular pertussis-inactivated poliomyelitis and *Haemophilus influenzae* type b vaccine is highly immunogenic, safe and well tolerated in Singaporean infants. The co-administration of a human rotavirus vaccine does not interfere with either the immune response to the vaccine or its reactogenicity profile.

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