Original Article

Immunogenicity, Reactogenicity and Safety of a Combined DTPa-IPV Vaccine Compared with Separate DTPa and IPV Vaccines in Healthy Korean Infants

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Purpose : To compare immunogenicity and reactogenicity of a combined diphtheria–tetanus–acellular pertussis–inactivated poliovirus vaccine (DTPa–IPV, *Infanrix*™ IPV, GlaxoSmithKline Biologicals) with co–administration of commercially available DTPa and IPV vaccines at separate injection sites (DTPa+IPV).

Methods : A total of 458 infants aged 8–12 weeks were randomized to receive three–dose primary vaccination at 2, 4 and 6 months with DTPa–IPV or DTPa+IPV. Blood samples were collected pre and post vaccination for measurement of immune responses. Reactogenicity was assessed following each dose using diary cards.

Results : One month post–dose 3, seroprotection rates for anti–diphtheria, anti–tetanus and anti–poliovirus types 1, 2 and 3 were ≥99.5% and vaccine response rates to pertussis antigens were at least 98.6% in both DTPa–IPV and DTPa + IPV groups. Non–inferiority between the groups was demonstrated based on pre–defined statistical criteria. Incidences of both local and systemic symptoms were within the same range across both groups with grade 3 symptoms reported following no more than 4.3% of DTPa–IPV doses and 4.5% of DTPa + IPV doses. Two serious adverse events (both pyrexia) after DTPa–IPV administration were considered vaccine–related. Both infants recovered fully.

Conclusion : Combined DTPa–IPV vaccine was immunogenic and well tolerated when used as a three–dose primary vaccination course in Korean infants. DTPa–IPV could be incorporated into the Korean vaccination schedule, reducing the number of injections required to complete primary immunization. **(Korean J Pediatr Infect Dis 2010;17:156–168)**

Key Words : Acellular pertussis, DTPa–IPV, DTPa, IPV, Primary vaccination

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Introduction

Vaccination of infants against diphtheria, tetanus, pertussis and polio is well established in Korea, with coverage rates of the third DTPa (combined diphtheria-tetanus-acellular pertussis vaccine) dose at 94%[1]. Acellular pertussis vaccines were introduced in Korea in 1982[2, 3]. The vaccines have been widely used from 1984[4] and are considered effective in preventing pertussis disease in the country. Acellular pertussis vaccines have an improved tolerability profile compared to whole cell pertussis (DTPw) vaccines[5, 6]. In Korea, after the transition from DTPw to DTPa, the five-dose coverage rates for DTPa (three primary doses and two booster doses) rose from 65% to 81% between 2004 and 2007[7], correlating with improved diphtheria, tetanus and pertussis disease control[8].

Reported cases of pertussis currently remain low in Korea. In 2006 there were only 17 pertussis cases reported to the World Health Organization[1]. However, a report suggests that as in other countries with longstanding and widespread pertussis vaccination, pertussis disease may be more common than expected in unvaccinated infants, and may frequently go unrecognized[9]. These data highlight the importance of continued high vaccination coverage against pertussis using effective and safe vaccines in Korea.

No polio cases due to wild poliovirus have been recorded in Korea since 1983[10] and Korea was declared free of wild poliovirus in 2000[11]. The Korean Advisory Committee on Immunization Practice moved to an all-IPV (inactivated poliovirus vaccine) schedule in 2005[10]. However, the introduction of IPV into the Korean vaccination schedule increased the number of injections given to children at those vaccination visits when poliomyelitis vaccine was required. Data from the United States and Germany suggest that both the timeliness of vaccination and coverage rates until 24 months of age are improved when children receive combination vaccines compared to separate vaccines that require additional injections[12, 13]. Thus, administration of the DTPa and IPV vaccines in a single injection has the potential to promote compliance with vaccination schedules by reducing the number of injections required for immunization, thereby improving subject/parents and physician acceptance.

The combined DTPa-IPV vaccine (*Infanrix*™ IPV, GlaxoSmithKline Biologicals, Belgium) provides vaccination against diphtheria, tetanus, pertussis as well as poliovirus, using IPV, in a single injection. DTPa-IPV has been licensed in Italy for primary vaccination use of infants and/or booster vaccination up until the age of 13 years. In a household contact study in Germany, the protective efficacy of the DTPa component, *Infanrix*™, against WHO-defined pertussis disease was shown to be 89%[14]. These results were confirmed in a large randomized placebo-controlled trial in Italy, where the protective efficacy was 84%[15].

The present study evaluated the immunogenicity, safety and reactogenicity of the combined DTPa-IPV vaccine compared with co-administration of DTPa and IPV vaccines at separate injection sites to healthy Korean infants at 2, 4 and 6 months of age.

Materials and Methods

1. Study design and study subjects

This was an open, randomized, phase IIIb clinical trial (E-track study no: 104871; Clinicaltrials.gov study identifier: NCT00290342) conducted between January 2006 and January 2007 in ten centers in Korea. The study protocol was approved by the Ethics Review Committee of each site. Written informed consent was obtained from the parent/guardian of each infant before study enrolment. The study was performed in accordance with Declaration of Helsinki and Good Clinical Practice guidelines.

Healthy infants aged 8-12 weeks at the time of the first vaccination were randomized (1:1 ratio) to receive primary vaccination at 2, 4 and 6 months of age with either combined DTPa-IPV (*Infanrix*™ IPV, GlaxoSmithKline Biologicals), or DTPa (*Infanrix*™, GlaxoSmithKline Biologicals) and IPV (IMOVAX Polio™, Sanofi Pasteur) co-administered at different injection sites.

Infants were excluded if they had received any new or unregistered product other than the study vaccine 30 days prior to the first vaccine dose; if they had a history of disease caused by any of the targeted pathogens or had received any other vaccine within 30 days of the study vaccines. Infants were also ineligible to participate if they had a history of allergy or had a confirmed or suspected immunosuppressive condition. Vaccination with Bacille Calmette-Guerin vaccine, hepatitis B vaccine, pneumococcal vaccine, influenza vaccine and *Haemophilus influenzae* type b vaccine was allowed during the study if administered more than 30 days before or at least one week after the study vaccines.

2. Vaccines

Each 0.5 mL dose of DTPa-IPV contained ≥30 International Units (IU) diphtheria toxoid (DT), ≥ 40 IU tetanus toxoid (TT), 25 μg pertussis toxoid (PT), 25 μg filamentous agglutinin (FHA), 8μg of pertactin (PRN), 40 Dalton (D)-antigen units of type 1 poliovirus (Mahoney strain), 8 D-antigen units of type 2 poliovirus (MEF-1 strain) and 32 D-antigen units of type 3 poliovirus (Saukett strain). The antigen composition of the DTPa vaccine was the same, without the IPV component. The standalone IPV vaccine (IMOVAX® Polio) was of the same antigen composition as the IPV component in DTPa-IPV, but was produced by another manufacturer (Sanofi Pasteur MSD).

All vaccines were administered as intramuscular injections into the anterolateral region of the thigh.

3. Analysis of immunogenicity

Blood samples were collected from all infants prior to vaccination and one month post-dose 3 (range: 21-48 days) for measurement of antibody concentrations against all vaccine antigens using standard methods. Antibodies against diphtheria, tetanus and pertussis antigens were measured using an enzyme-linked immunosorbent assay (ELISA). Infants with anti-diphtheria and anti-tetanus antibody concentrations ≥0.1 IU/mL were considered protected[16, 17]. The assay cut-off for pertussis antibodies was 5 ELISA Units (EL.U)/mL. As there is no established serological correlate of protection against pertussis, a vaccine response to pertussis was defined as the appearance of antibodies in initially seronegative infants or maintenance of pre-

vaccination antibody concentration in infants who were seropositive prior to vaccination taking into account the natural decrease of maternal antibodies [18]. Neutralizing antibodies to poliovirus types 1, 2 and 3 were determined using a modification of the WHO micro-neutralization test method[19] with a titer of 8 considered protective.

4. Analysis of safety

Parents/guardians were provided with diary cards to record solicited local (pain, redness and swelling at the injection site) and systemic drowsiness, fever axilliary temperature ≥37.5℃, irritability/fussiness and loss of appetite) symptoms for four days (Day 0-3) after each dose. Symptom intensity was graded from 0 to 3 by the investigator. The criteria for pain was defined for intensity grade 0: absent; grade 1: minor reaction to touch; grade 2: cried/protested on touch and grade 3: cried when limb was moved/spontaneously painful; for redness or swelling grade 0: absent; grade 1: diameter ≤5 mm; grade 2: diameter > 5 mm and ≤ 20 mm and grade 3: diameter >20 mm; for grade 3 temperature: >39.0℃; for irritability/fussiness grade 0: usual behavior; grade 1: crying more than usual/ no effect on normal activity; grade 2: crying more than usual/ interfered with normal activity and grade 3: crying that could not be comforted/ prevented normal activity; for drowsiness grade 0: usual behavior; grade 1: easily tolerated; grade 2: interfering with normal activity and grade 3: preventing normal activity; for loss of appetite grade 0: usual appetite; grade 1: ate less than usual/no effect on normal activity; grade 2: ate less than usual/interfered with normal activity and grade 3: did not eat at all.

All other (unsolicited) symptoms occurring for 31 days after each dose were recorded. Serious adverse events (SAEs) were defined as any untoward medical occurrence that was life-threatening, resulted in death, required hospitalization, resulted in disability/incapacity or was a congenital anomaly. The SAEs were recorded throughout the study period.

5. Statistical analysis

The primary objective of the study was to demonstrate non-inferiority of the combined DTPa-IPV vaccine to DTPa and IPV vaccines administered separately, in terms of the immune response to each vaccine antigen. A reduction in the immune response in the DTPa-IPV group was excluded if the lower limit of the standardized asymptotic 95% confidence interval (CI) for difference between groups (DTPa-IPV group minus DTPa+IPV group) in terms of seroprotection rates against diphtheria, tetanus, poliovirus types 1, 2 and 3 and vaccine response rates to the three pertussis antigens, one month post-dose 3, was above -10%. A reduction in the pertussis immune response was also excluded if the lower limit of the standardized 95% CIs for the GMC ratios (DTPa-IPV group divided by DTPa+IPV group) for anti-PT, anti-FHA and anti-PRN antibodies was above 0.67 one month post-dose 3.

With 191 subjects per group, the study had an overall power of 89% to meet the primary objectives. After adjusting for dropouts and eliminations, 225 subjects per group were to be enrolled.

The primary analysis for immunogenicity was performed on the according-to-protocol (ATP) cohort for immunogenicity. The percentage of subjects with antibody concentrations above the specified cut-offs or with a vaccine response was cal-

culated with exact 95% CIs. Geometric mean antibody concentrations/titers (GMC/GMT) were calculated from the anti-log of the mean of the log10 concentration/titer transformations. Antibody levels below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMT/GMC calculation.

The analysis of safety was performed on the Total Vaccinated Cohort. All safety analyses were descriptive.

Statistical analyses were performed using Statistical Analysis System (SAS®) version 8.2 and StatXact-5 on SAS®.

Results

A total of 458 infants were enrolled and 452 infants were vaccinated (Fig. 1). The mean age of infants at the time of the first dose was 8.8 weeks (standard deviation=0.90 weeks, range: 6-14 weeks). The male to female ratio was 51:49. Majority of the infants were of East Asian heritage. Other demographic characteristics are shown in Table 1.

1. Immunogenicity

One month post-dose 3, all infants were seropro-

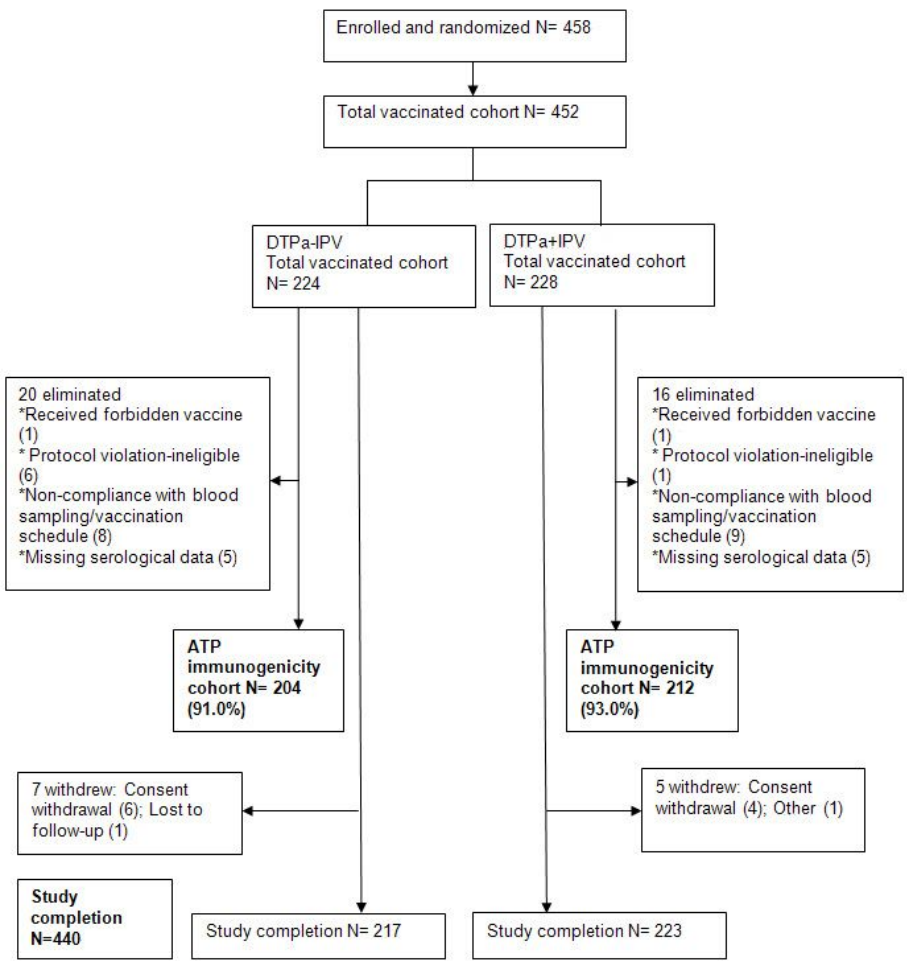

Fig. 1. Participant flow.

tected with respect to anti-diphtheria, anti-tetanus and anti-polio type 1 antibodies. At least 99.5% of subjects in both groups were seroprotected against poliovirus type 2 and type 3 antigens (Table 2). The vaccine response to PT, FHA and PRN was observed in at least 98.6% of subjects in both groups (Table 2).

The observed antibody GMC (geometric mean concentration)/GMTs (geometric mean titers) against each vaccine antigen were higher in DTPa-IPV group than in the DTPa+IPV group.

Non-inferiority of the combined DTPa-IPV vaccine with separately administered DTPa+IPV was established according to all pre-specified criteria (Table 3).

2. Reactogenicity and safety

Redness at the injection site and irritability were the most commonly reported local and systemic solicited symptoms in both vaccine groups (Table 4). Grade 3 symptoms were reported after 4.3% of doses in the DTPa-IPV group and 4.5% of doses in the DTPa+IPV group. Fever >39.0℃ was not reported in either group during the vaccination course. Incidence of solicited local and systemic symptoms are reported per grade (Table 4).

Unsolicited symptoms during the 31-day follow-up period were reported after 31.9% of DTPa-IPV doses and 30.5% of DTPa+IPV doses. Infections and infestations (upper respiratory tract infection reported after 13.2% of doses in the DTPa-IPV group and 12.1% of doses in the DTPa+IPV group; bronchiolitis reported after 2.6% of doses in the DTPa-IPV group and 1.6% of doses in the DTPa+IPV group), gastrointestinal disorders (diarrhea reported after 2.4% of doses in the DTPa-IPV group and 1.2% of doses in the DTPa+IPV group) and skin and subcutaneous tissue disorder (atopic dermatitis reported after 2.7% of doses in the DTPa-IPV group and 3.0% of doses in the DTPa+IPV group) were the most commonly reported unsolicited symptoms (Table 5). At least one grade 3 unsolicited symptom was reported following 1.2% of doses in the DTPa-IPV group and 0.4% of doses in the DTPa+IPV

Table 1. Demographic Characteristics (Total vaccinated cohort)

Characteristics	Categories	DTPa-IPV group‡ (N*=224) Value/n (%)†	DTPa+IPV group∫ (N*=228) Value/n (%)†	Total (N*=452) n (%)†
Age (weeks)	Mean	8.8 (-)	8.8 (-)	8.8 (-)
	SD‖	0.90 (-)	0.91 (-)	0.90 (-)
	Median	9.0 (-)	9.0 (-)	9.0 (-)
	Range	6-13 (-)	8-14 (-)	6-14 (-)
Weight (Kg)	Mean	5.9 (-)	5.9 (-)	5.9 (-)
	SD‖	0.74 (-)	0.71 (-)	0.72 (-)
	Median	5.9 (-)	6.0 (-)	6.0 (-)
Gender	Female	112 (50)	110 (48.2)	222 (49.1)
	Male	112 (50)	118 (51.8)	230 (50.9)
Race	Asian-east asian heritage	224 (100)	224 (98.2)	448 (99.1)
	Asian-south east asian heritage	0 (0)	4 (1.8)	4 (0.9)

*N=total number of subjects; †n (%)=number/percentage of subjects in a given category †Value=value of the considered parameter; ‡DTPa-IPV=GSK Biologicals' combined *Infanrix*-IPV vaccine; ∫DTPa+IPV=Concomitant administration of GSK Biologicals' *Infanrix* and Sanofi Pasteur MSD's *Imovax Polio*; ‖SD=standard deviation

Table 2. Immunogenicity Pre-Vaccination and one Month Post-Dose 3 (According-to-Protocol Immunogenicity Cohort)

Antibody	Timing	DTPa-IPV group†			DTPa+IPV group‡		
		N¶	Value/%**	[95% CI]††	N¶	Value/%**	[95% CI]††
Diphtheria	Pre∫ % ≥ 0.1 IU/mL	202	4.0	[1.7; 7.7]	212	2.8	[1.0; 6.1]
	Pre∫ GMC††	202	0.052	[0.051; 0.054]	212	0.053	[0.050; 0.055]
	Post‖ % ≥ 0.1 IU/mL	204	100	[98.2; 100]	211	100	[98.3; 100]
	Post‖ GMC††	204	4.3	[3.9; 4.8]	211	2.6	[2.4; 2.9]
Tetanus	Pre∫ % ≥ 0.1 IU/mL	202	9.9	[6.2; 14.9]	212	13.7	[9.4; 19.1]
	Pre∫ GMC††	202	0.059	[0.055; 0.064]	212	0.060	[0.056; 0.065]
	Post‖ % ≥ 0.1 IU/mL	204	100	[98.2; 100]	211	100	[98.3; 100]
	Post‖ GMC††	204	10.3	[9.5; 11.2]	211	7.1	[6.5; 7.8]
PT	Pre∫ % ≥ 5 EL.U/mL	200	15.0	[10.4; 20.7]	210	20.5	[15.2; 26.6]
	Pre∫ GMC††	200	3.0	[2.8; 3.2]	210	3.2	[3.0; 3.5]
	Post‖ % ≥ 5 EL.U/mL	204	100	[98.2; 100]	211	100	[98.3; 100]
	Pos‖t % vaccine response*	200	100	[98.2; 100]	209	98.6	[95.9; 99.7]
	Post‖ GMC††	204	63.3	[58.7; 68.2]	211	55.6	[50.9; 60.7]
FHA	Pre∫ % ≥ 5 EL.U/mL	202	67.3	[60.4; 73.7]	212	71.7	[65.1; 77.7]
	Pre∫ GMC††	202	7.4	[6.5; 8.4]	212	8.5	[7.4; 9.7]
	Post‖ % ≥ 5 EL.U/mL	204	100	[98.2; 100]	211	100	[98.3; 100]
	Post‖ % vaccine response*	202	99.5	[97.3; 100]	211	99.1	[96.6; 99.9]
	Post‖ GMC††	204	294.3	[269.5; 321.4]	211	259.6	[235.1; 286.6]
PRN	Pre∫ % ≥ 5 EL.U/mL	202	4.5	[2.1; 8.3]	212	7.5	[4.4; 77.7]
	Pre∫ GMC††	202	2.7	[2.5; 2.8]	212	2.7	[2.6; 2.9]
	Post‖ % ≥ 5 EL.U/mL	204	100	[98.2; 100]	211	99.5	[97.4; 100]
	Post‖ % vaccine response*	202	100	[98.2; 100]	211	99.5	[97.4; 100]
	Post‖ GMC††	204	205.0	[187.7; 223.9]	211	155.6	[140.7; 172.1]
Polio type 1	Pre∫ % ≥ 8	199	26.6	[20.6; 33.3]	212	26.4	[20.6; 32.9]
	Pre∫ GMT††	199	6.3	[5.5; 7.1]	212	6.1	[5.4; 6.9]
	Post‖ % ≥ 8	204	100	[98.2; 100]	207	100	[98.2; 100]
	Post‖ GMT††	204	755.7	[643.5; 887.4]	207	263.0	[232.1; 298.0]
Polio type 2	Pre∫ % ≥ 8	202	25.2	[19.4; 31.8]	211	30.8	[24.6; 37.5]
	Pre∫ GMT††	202	5.8	[5.2; 6.5]	211	6.5	[5.8; 7.3]
	Post‖ % ≥ 8	204	100	[98.2; 100]	205	99.5	[97.3; 100]
	Post‖ GMT††	204	704.7	[599.5; 828.4]	205	267.6	[233.4; 306.8]
Polio type 3	Pre∫ % ≥ 8	202	13.4	[9.0; 18.8]	212	11.3	[7.4; 16.4]
	Pre∫ GMT††	202	5.0	[4.5; 5.4]	212	4.9	[4.5; 5.3]
	Post‖ % ≥ 8	204	99.5	[97.3; 100]	207	99.5	[97.3; 100]
	Post‖ GMT††	204	1209.5	[1040.1; 1406.5]	207	438.3	[383.1; 501.3]

*subjects either seropositive or seronegative at pre-vaccination; †DTPa-IPV = GSK Biologicals' combined *Infanrix*-IPV vaccine; ‡DTPa+IPV=Concomitant administration of GSK Biologicals' *Infanrix* and Sanofi-Pasteur's *Imovax Polio*; ∫Pre=blood sample taken before the first dose at the first study visit; ‖Post=blood sample taken one month after the third dose; ¶N=number of subjects with results; ¶N for vaccine response: number of subjects with pre and post vaccination results available; **value: number of the considered parameter; **%= percentage of subjects with antibody concentrations ≥specified cut-off/vaccine response; ††95% CI=95% confidence interval; GMT/GMC=The Geometric Mean titres (GMTs)/Geometric Mean concentration (GMCs) calculations were performed by taking the anti-log of the mean of the log10 titre/concentration transformations. Titres/antibody concentrations below the cut-off of the assay was given an arbitrary value of half the cut-off for the purpose of GMT/GMC calculation

group. The grade 3 unsolicited symptoms for the two groups are shown in Table 5. Causally related symptoms were reported after 2.6% of DTPa-IPV doses and 3.0% of DTPa+IPV doses. In both groups,

Table 3. Criteria to Conclude Non-Inferiority between the DTPa-IPV and DTPa+IPV Groups in Terms of the Immune Response to the Administered Vaccine Antigens (According-to-Protocol Immunogenicity Cohort)

Antibody	Endpoint	DTPa-IPV group*		DTPa+IPV group†		Criteria		
		N‡	%	N‡	%**	Difference††	[95% CI]‖	LL∫ of 95% CI‖
Diphtheria	% ≥0.1 IU/mL	204	100	211	100	0.00	[-1.85; 1.79]	> -10%
Tetanus	% ≥0.1 IU/mL	204	100	211	100	0.00	[-1.85; 1.79]	> -10%
PT	% VR	200	100	209	98.6	1.44	[-0.46; 4.13]	> -10%
FHA	% VR	202	99.5	211	99.1	0.45	[-1.88; 2.95]	> -10%
PRN	% VR	202	100	211	99.5	0.47	[-1.40; 2.64]	> -10%
Polio type 1	% ≥8	204	100	207	100	0.00	[-1.85; 1.82]	> -10%
Polio type 2	% ≥8	204	100	205	99.5	0.49	[-1.36; 2.71]	> -10%
Polio type 3	% ≥8	204	99.5	207	99.5	-0.01	[-2.28; 2.24]	> -10%
		N‡	GMC¶	N‡	GMC¶	GMC ratio	[95% CI]‖	LL∫ of 95% CI‖
PT	GMC¶	204	63.3	211	55.6	1.14	[1.01; 1.28]	>0.67
FHA	GMC¶	204	294.3	211	259.6	1.13	[0.99; 1.29]	>0.67
PRN	GMC¶	204	205.0	211	155.6	1.32	[1.15; 1.51]	>0.67

*DTPa-IPV=GSK Biologicals' combined *Infanrix*-IPV vaccine; †DTPa+IPV=Concomitant administration of GSK Biologicals' *Infanrix* and Sanofi Pasteur MSD's Imovax Polio; ‡N=number of subjects with available results; ∫N for vaccine response (VR): number of subjects with pre and post vaccination results available; ∫LL=Lower Limit; ‖95% CI=95 percent confidence interval; ¶GMC=geometric mean antibody concentration; calculations were performed by taking the anti-log of the mean of the concentration transformations. Antibody concentrations below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMC calculation; **%=percentage of subjects with the specified endpoint. ††Difference=DTPa-IPV group minus DTPa+IPV treatment group. GMC ratio DTPa-IPV group divided by DTPa+IPV group

injection site induration comprised the majority of causally related unsolicited events (following 1.8% of DTPa-IPV doses and 2.2% of DTPa+IPV doses). No causally related events of grade 3 severity were reported during the study.

In total, 32 subjects (15 subjects in the DTPa-IPV group and 17 subjects in the DTPa+IPV group) reported at least one SAE during the study period. No events were fatal. Two SAEs (both in the DTPa-IPV group) were determined by the investigator to be causally related to the vaccination: two infants developed pyrexia on the day of receipt of the first DTPa-IPV dose (temperature of 38.2℃ approximately) and were hospitalized for the condition. Both events resolved after three days.

Discussion

This randomized controlled study confirmed that the DTPa-IPV combination vaccine was highly immunogenic, with more than 99.5% of subjects achieving post-primary vaccination series antibody concentrations/titers associated with seroprotection and a vaccine response to pertussis antigen. Non-inferiority of the combined DTPa-IPV vaccine to the separately administered, commercially available DTPa and IPV component vaccines was demonstrated. DTPa-IPV had a good reactogenicity profile that did not differ in any clinically relevant way from separately administered DTPa+IPV vaccines.

The results of this study are consistent with other trials of DTPa-IPV conducted in European, Australian, American and Taiwanese populations

Table 4. Incidence of Solicited Local and Systemic Symptoms (Per Grade) Recorded Overall Per dose during the 4-Day Post-Vaccination Period (Total Vaccinated Cohort)

		DTPa-IPV group*				DTPa+IPV group†			
		Local Symptoms							
Symptoms	Type	N‡	n∫	%‖	95% CI¶	N‡	n∫	%‖	95% CI¶
Pain	Any	654	164	25.1	[21.8; 28.6]	673	161	23.9	[20.7; 27.3]
	Grade 1	654	123	18.8	[15.9; 22.0]	673	119	17.7	[14.9; 20.8]
	Grade 2	654	36	5.5	[3.9; 7.5]	673	34	5.1	[3.5; 7.0]
	Grade 3	654	5	0.8	[0.2; 1.8]	673	8	1.2	[0.5; 2.3]
Redness (mm)	Any	654	212	32.4	[28.8; 36.2]	673	209	31.1	[27.6; 34.7]
	≤5 mm	654	113	17.3	[14.5; 20.4]	673	110	16.3	[13.6; 19.4]
	>5 mm and ≤20 mm	654	71	10.9	[8.6; 13.5]	673	71	10.5	[8.3; 13.1]
	>20 mm	654	28	4.3	[2.9; 6.1]	673	28	4.2	[2.8; 6.0]
Swelling (mm)	Any	654	114	17.4	[14.6; 20.6]	673	128	19.0	[16.1; 22.2]
	≤5 mm	654	64	9.8	[7.6; 12.3]	673	60	8.9	[6.9; 11.3]
	>5 mm and ≤20 mm	654	26	4.0	[2.6; 5.8]	673	38	5.6	[4.0; 7.7]
	>20 mm	654	24	3.7	[2.4; 5.4]	673	30	4.5	[3.0; 6.3]
		Systemic symptoms							
Drowsiness	Any	656	152	23.2	[20.0; 26.6]	673	161	23.9	[20.7; 27.3]
	Grade 1	656	122	18.6	[15.7; 21.8]	673	132	19.6	[16.7; 22.8]
	Grade 2	656	26	4.0	[2.6; 5.8]	673	27	4.0	[2.7; 5.8]
	Grade 3	656	4	0.6	[0.2; 1.6]	673	2	0.3	[0.0; 1.1]
Fever/(Axillary) (℃)	Any (>= 37.5℃)	656	76	11.6	[9.2; 14.3]	673	44	6.5	[4.8; 8.7]
	>38.0℃	656	12	1.8	[0.9; 3.2]	673	8	1.2	[0.5; 2.3]
	>38.5℃	656	4	0.6	[0.2; 1.6]	673	1	0.1	[0.0; 0.8]
	>39.0℃	656	0	0.0	[0.0; 0.6]	673	0	0.0	[0.0; 0.5]
	>39.5℃	656	0	0.0	[0.0; 0.6]	673	0	0.0	[0.0; 0.5]
Irritability	Any	656	238	36.3	[32.6; 40.1]	673	241	35.8	[32.2; 39.6]
	Grade 1	656	162	24.7	[21.4; 28.2]	673	181	26.9	[23.6; 30.4]
	Grade 2	656	61	9.3	[7.2; 11.8]	673	50	7.4	[5.6; 9.7]
	Grade 3	656	15	2.3	[1.3; 3.7]	673	10	1.5	[0.7; 2.7]
Loss of appetite	Any	656	130	19.8	[16.8; 23.1]	673	115	17.1	[14.3; 20.1]
	Grade 1	656	112	17.1	[14.3; 20.2]	673	99	14.7	[12.1; 17.6]
	Grade 2	656	17	2.6	[1.5; 4.1]	673	16	2.4	[1.4; 3.8]
	Grade 3	656	1	0.2	[0.0; 0.8]	673	0	0.0	[0.0; 0.5]

*DTPa-IPV=GSK Biologicals' combined *Infanrix*-IPV vaccine; †DTPa+IPV=Concomitant administration of GSK Biologicals' *Infanrix* and Sanofi-Pasteur MSD's *Imovax Polio*; ‡N=number of documented doses; ∫n/‖(%)=number/percentage of doses followed by at least one type of symptom; ¶95% CI=Exact 95% confidence interval

during infancy and childhood[20-25] in which the immunogenicity of DTPa-IPV was shown to be comparable to separate administration of existing commercially available DTPa-based and IPV-containing vaccines, with similar tolerability. Notably, the immunogenicity of the DTPa component of the vaccine was within the range previously reported in a Korean population, in which the seroprotection rates against diphtheria and tetanus and the seropositivity rates against pertussis antigens (PT, FHA and PRN) were

Table 5. Percentage of doses with any and Grade 3 Unsolicited Symptoms Reported during the 31-Day Post-Vaccination Period (Total Vaccinated Cohort)

		DTPa-IPV* N∫=661		DTPa+IPV† N∫=675	
Primary System Organ Class	Preferred Term	n (%)‖	95% CI¶	n (%)‖	95% CI¶
At least one symptom‡		211 (31.9)	[28.4 35.6]	206 (30.5)	[27.1; 34.1]
Gastrointestinal disorders	Diarrhoea	16 (2.4)	[1.4 3.9]	8 (1.2)	[0.5; 2.3]
General disorders and administration site conditions	Injection site induration	12 (1.8)	[0.9; 3.1]	16 (2.4)	[1.4; 3.8]
	Pyrexia	17 (2.6)	[1.5; 4.1]	5 (0.7)	[0.2; 1.7]
Infections and infestations	Bronchiolitis	17 (2.6)	[1.5 4.1]	11 (1.6)	[0.8; 2.9]
	Bronchitis	8 (1.2)	[0.5; 2.4]	12 (1.8)	[0.9; 3.1]
	Gastroenteritis	12 (1.8)	[0.9 3.1]	15 (2.2)	[1.2; 3.6]
	Nasopharyngitis	8 (1.2)	[0.5 2.4]	9 (1.3)	[0.6; 2.5]
	Upper respiratory tract infection	87 (13.2)	[10.7 16.0]	82 (12.1)	[9.8; 14.9]
Skin and subcutaneous tissue disorders	Dermatitis atopic	18 (2.7)	[1.6 4.3]	20 (3.0)	[1.8; 4.5]
	Dermatitis diaper	10 (1.5)	[0.7; 2.8]	7 (1.0)	[0.4; 2.1]
		Grade 3 symptoms			
At least one symptom‡		8 (1.2)	[0.5; 2.4]	3 (0.4)	[0.1; 1.3]
Gastrointestinal disorders	Diarrhoea	1 (0.2)	[0.0; 0.8]	0 (0.0)	[0.0; 0.5]
	Infantile colic	1 (0.2)	[0.0; 0.8]	0 (0.0)	[0.0; 0.5]
Infections and infestations	Bronchiolitis	1 (0.2)	[0.0; 0.8]	0 (0.0)	[0.0; 0.5]
	Gastroenteritis	1 (0.2)	[0.0; 0.8]	0 (0.0)	[0.0; 0.5]
	Pneumonia	0 (0.0)	[0.0; 0.6]	1 (0.1)	[0.0; 0.8]
	Upper respiratory tract infection	3 (0.5)	[0.1; 1.3]	2 (0.3)	[0.0; 1.1]
Skin and subcutaneous tissue disorders	Dermatitis atopic	1 (0.2)	[0.0; 0.8]	0 (0.0)	[0.0; 0.5]

*DTPa-IPV=GSK Biologicals' combined *Infanrix*-IPV vaccine; †DTPa+IPV=Concomitant administration of GSK Biologicals' *Infanrix* and Sanofi-Pasteur MSD's *Imovax Polio*; ‡At least one symptom=at least one symptom experienced; ∫N=number of administered doses; ‖n (%)=number (percentage) of doses with the symptom; ¶95% CI=exact 95% confidence interval

100% after three doses of primary vaccination with *Infanrix*™[3].

Over 28 million doses of *Infanrix*™ IPV have been distributed worldwide since it was first licensed in 1996 and the vaccine has been extensively evaluated in clinical trials[20-24, 26-29], and in 13 years of post-marketing experience when used for primary and/or booster vaccination. The present study demonstrates similar immunogenicity and tolerability in a Korean population, suggesting the vaccine will be similarly effective in preventing illness due to diphtheria, tetanus, pertussis and poliovirus.

Combination vaccines such as DTPa-IPV include antigens against multiple diseases in a single injection and have an ongoing and important role in facilitating high vaccine coverage worldwide. In Korea, use of DTPa-IPV vaccines for primary immunization of infants would reduce the number of injections needed at each immunization visit to a single injection. This study has demonstrated that the DTPa-IPV combination vaccine has a similar immunogenicity and reactogenicity profile to DTPa+IPV

vaccine co-administered at separate injection sites in Korean infants. Use of DTPa-IPV in the Korean vaccination schedule could improve vaccine acceptance and would help maintain high vaccine coverage in Korean infants.

1. Trademarks

Infanrix and *Infanrix*-IPV are trademarks of the GlaxoSmithKline group of companies.

IMOVAX Polio™ is a trademark of Sanofi Pasteur.

2. Conflict of interest:

G Ramakrishnan, O Van Der Meeren and HL Bock were employees of GlaxoSmithKline Biologicals, at the time of the study, analysis and interpretation of results, and manuscript preparation. JJ Ok was a medical consultant to GSK Biologicals on this study, and had received consulting fees for her services rendered. She is currently employed at Seoul Wooridul Hospital, Seoul, Korea. All other authors have no conflict of interest.

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요 약

한국의 건강한 영아를 대상으로 DTPa-IPV 혼합백신을 접종한 경우와 DTPa 백신과 IPV 백신을 각각 투여하였을 경우의 면역원성, 반응원성 및 안전성

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목 적: 디프테리아, 파상풍, 백일해 및 불활화 폴리오 백신인 GlaxoSmithKline Biologicals의 *Infanrix*™-IPV (DTPa-IPV)를 접종시, 시판되고 있는 DTPa 백신과 IPV 백신을 각각 다른 부위에 동시 접종 했을 때(DTPa+IPV)와의 면역원성과 반응원성을 비교하기 위하여 본 연구를 시행하였다.

방 법: 생후 8-12주의 영아 458명을 무작위 배정하여, 각각 2, 4, 6개월에 DTPa-IPV 혹은 DTPa+IPV를 3회 기초접종 하였다. 면역반응을 확인하기 위하여 백신 접종 전과 후에 채혈을 하였다. 반응원성은 각 백신 접종 후 작성된 증상기록카드를 통하여 평가하였다.

결 과: 3차 백신접종 한달 후에, 항-디프테리아, 항-파상풍 그리고 항-폴리오바이러스 type 1, 2, 3에 대한 혈청 방어율(seroprotection rate)은 ≥99.5%였고, 두 군 모두 백일해 항원에 대한 백신 반응률(vaccine response rates)은 적어도 98.6% 이상이었다. 두 군간의 비 열등성은 사전 정의된 통계적 기준에 따라 보여주었다. 국소증상과 전신증상 발생률은 두 군 모두 비슷하게 보고되었고, grade 3의 증상이 DTPa-IPV 투여군에서

4.3%, DTPa+IPV 투여군에서는 4.5%로 보고되었다. 두 건의 중대한 이상반응(모두 발열)이 DTPa-IPV 투여 후에 보고되었고, 백신과의 연관성이 있는 것으로 간주되었다. 두 명의 영아는 모두 회복되었다.

결 론 : DTPa-IPV 혼합백신은 한국의 소아들에게 기초접종으로 3회 투여시 충분한 면역반응을 보였고, 내약성이 우수했다. DTPa-IPV는 한국 예방접종 스케줄에 편입되어, 기초 접종을 완료하기 위한 접종 회수를 줄일 수 있다.

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