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RESEARCH ARTICLE

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A prospective, observational, multi-center, post-marketing safety surveillance study of the GSK combined vaccine against diphtheria, tetanus, pertussis, poliomyelitis, and *Haemophilus influenzae* type b invasive infections (DTaP-IPV/Hib) in South Korean infants

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ABSTRACT

In South Korea, a combined vaccine against diphtheria, tetanus, pertussis, poliomyelitis, and *Haemophilus influenzae* type b invasive infections (DTaP-IPV/Hib) is available since 2018 for vaccination of infants from the age of 2 months. This prospective, observational, non-comparative, post-marketing study evaluated the real-world safety of DTaP-IPV/Hib primary vaccination in eligible South Korean infants from the age of 2 months between 2018 and 2022. Infants were followed up for 30 days after each vaccine dose to assess the proportion of infants experiencing any adverse event (AE), including adverse drug reactions (ADRs), unexpected AEs, and serious AEs/serious ADRs (SAEs/SADRs). Of 660 infants vaccinated during the study period, 646 were included in the total safety cohort. A total of 194 AEs were reported in 143 (22.1%) infants; 158 AEs occurred after the first dose in 130 (20.1%) infants, 21 after the second dose in 20 (13.4%) infants, and 11 after the third dose in ten (8.1%) infants. The most frequent AEs by Medical Dictionary for Regulatory Activities Preferred Terms terminology were pyrexia (13.3%), injection site swelling (5.1%), and irritability (1.7%). Most of the AEs were mild, resolved without a medical visit, and were classified as possibly related to vaccination. The incidence proportions of ADRs, unexpected AEs, and SAEs/SADRs were 19.4%, 4.3%, and 0.9%, respectively. All SAEs/SADRs resolved after hospitalization or emergency room visit, and one event was possibly related to vaccination. These results are in line with the approved label and other national/international studies, confirming the acceptable safety profile of DTaP-IPV/Hib in the South Korean pediatric population.

PLAIN LANGUAGE SUMMARY

In South Korea, a vaccine to help protect infants against five childhood diseases (diphtheria, tetanus, whooping cough, poliomyelitis, and *Haemophilus influenzae* type b invasive infections) called DTaP-IPV /Hib vaccine, has been available since 2018. As required by Korean regulation, this study aimed to confirm that DTaP-IPV/Hib was well tolerated by South Korean infants during its first 4 years of use in the country (2018–2022). This study followed 646 healthy infants aged 2–3 months who received up to three vaccine doses with 2-month intervals between doses, according to the Korean vaccination recommendations. The infants were followed for 30 days after each vaccination to evaluate how often adverse events (AEs) occurred during that period. An AE was defined as any untoward medical event after exposure to the vaccine, but not necessarily caused by that same vaccine. Overall, 194 AEs occurred during the study. On average, at least one AE was reported in 22% of infants within 30 days following vaccination. These AEs were mostly fever (body temperature >38.0°C), swelling at vaccine injection site, and irritability. A serious AE (SAE) was reported for 0.9% of infants. The infants always recovered from these SAEs after hospitalization or emergency room visit. The reported AEs are indicated in the vaccine package insert, meaning they were possibly expected to occur after vaccination. This study therefore confirms the acceptable safety profile of DTaP-IPV/Hib when given to South Korean infants in accordance with local prescribing recommendations and as part of routine childhood immunization.

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Introduction

Diphtheria, tetanus, pertussis (or whooping cough), poliomyelitis, and *Haemophilus influenzae* type b (Hib) invasive infections are life-threatening infectious diseases causing substantial morbidity and mortality among pediatric populations worldwide.[1,2] Following the World Health Organization recommendations, routine childhood vaccinations have played an instrumental role in reducing the burden and the incidence of these notorious, albeit preventable, diseases in many regions of the world.[3–7] However, extended vaccination programs against several childhood diseases can be challenging to implement due to the logistical and financial constraints associated with the

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complex schedules of split inoculations of standalone (e.g., single-component) vaccines.[1,8] Combining the vaccinations against these five diseases into one single administration (i.e., a combination vaccine) can offer a number of potential benefits, thereby improving vaccination programs. By reducing the number of injections and visits required to achieve complete vaccination, pediatric combination vaccines minimize distress and side effects for the infant,[8–10] simplify vaccination calendars,[8,10] ensure higher compliance with vaccination schedules, and improve vaccination coverage.[10–12]

Since its initial marketing approval in Europe in 1997, a combined pentavalent vaccine against diphtheria, tetanus, pertussis, poliomyelitis, and Hib invasive infections (DTaP-IPV/Hib; *Infanrix-IPV/Hib*, GSK)[13] has been widely used for the active immunization of infants from the age of 2 months in many countries of the European Economic Area, as well as in other countries worldwide. The immunogenicity and safety of DTaP-IPV/Hib as primary and/or booster administration have been assessed in several clinical trials conducted in pediatric populations worldwide.[14–19]

In South Korea, DTaP-IPV/Hib has been registered since 2018 for vaccination of infants from the age of 2 months. According to the local prescribing information (PI) and the Korean Disease Control and Prevention Agency (KDCA) guidelines, the vaccine should be administered as a three-dose primary series in infants aged 2, 4, and 6 months.[20] Moreover, additional safety information in real-world settings (according to local PI and routine clinical practice) is needed 4–6 years following vaccine registration in the country as per Korean Ministry of Food and Drug Safety (MFDS) regulation requirement.[21] Post-marketing surveillance (PMS) studies are relevant to further characterize the safety profile of a medicine as they can help reveal safety issues that were not identified during clinical development. These PMS studies complement spontaneous reporting, which is the mainstay of passive surveillance.[22] Similar studies were previously conducted for other DTaP-IPV vaccines (with or without Hib antigens) in South Korea.[23–25]

In accordance with the Korean MFDS regulation,[21] this PMS study was conducted as a post-licensure commitment to evaluate the safety of DTaP-IPV/Hib when prescribed for pediatric primary vaccination in real-world settings in South Korea over a 4-year period (2018–2022). The objective of the study was to assess the proportion of participants experiencing at least one AE throughout the study period (up to 30 days after the administration of the last vaccine dose) as well as after each primary vaccine dose. Additionally, AEs were classified by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) terminology,[26] maximum intensity, outcome (including medical attention required for resolution), and causal relationship to study vaccination. Another study objective was to assess the proportion of participants experiencing adverse drug reactions (ADRs), unexpected AEs (including unexpected ADRs), and serious AEs/serious ADRs (SAEs/SADRs), and to classify these AEs by MedDRA PT terminology,[26] outcome (for SAEs/SADRs), and causal relationship to study vaccination (for unexpected ADRs and SAEs/SADRs).

Material and methods

Study design and study population

This prospective, observational, non-comparative, active safety surveillance study was conducted in 12 general hospitals and clinics across South Korea from October 26, 2018 to October 25, 2022. The participating sites are located in the Seoul, Icheon, and Gyeonggi regions. The study participants were healthy male or female infants aged at least 2 months at the time of study vaccination, who were assessed as eligible to receive the DTaP-IPV/Hib primary vaccination based on local PI and the medical judgment of the investigator, and for whom parent(s)/legally acceptable representative(s) (LAR[s]) provided a signed informed consent form (ICF). Eligible infants were identified by the local investigator at each participating site.

Infants were followed up for the occurrence of AEs for a period of 30 days after receiving any DTaP-IPV/Hib dose and for the occurrence of SAEs from the first DTaP-IPV/Hib dose up to 30 days following the last administered dose.

Ethics statement

Infants' parent(s)/LAR(s) provided written consent via ICF prior to any study procedure and were allowed to withdraw consent to study participation on their own free will at any time. The main reason for study discontinuation was documented in the electronic case report form (eCRF). The ICF, along with the protocol and any other necessary documentation, was approved by the institutional review board at each participating site.

Study vaccination

Each 0.5 mL dose of DTaP-IPV/Hib contains antigens against the target pathogens: ≥30 International Units (IU) diphtheria toxoid, ≥40 IU tetanus toxoid, three purified antigens of *Bordetella pertussis* (25 µg pertussis toxoid, 25 µg filamentous hemagglutinin, and 8 µg pertactin, all adsorbed onto aluminum salt), three distinct poliovirus antigens (40 D-antigen units [DU] inactivated poliovirus type 1, 8 DU inactivated poliovirus type 2, and 32 DU inactivated poliovirus type 3), 10 µg purified Hib polyribosyl-ribitol phosphate capsular polysaccharide conjugated to tetanus toxoid (~25 µg), and 500 µg aluminum hydroxide as an adjuvant.[13]

The vaccine was administered via a deep intramuscular injection of a 0.5 mL dose in the anterolateral thigh as a three-dose primary schedule (at 2, 4, and 6 months after birth), according to routine clinical guidelines in South Korea (approved PI and KDCA guidelines). The three vaccine doses were to be administered during three separate visits.

Data collection

Demographic data and baseline medical characteristics

For each infant, the following information was collected during the first study visit and updated during subsequent visits if needed: age, gender, ethnicity, height, weight, clinically significant conditions (including allergies and renal/

hepatic disorders) diagnosed within 30 days prior to receipt of the first dose of DTaP-IPV/Hib or illnesses experienced throughout the study period, any other vaccine administered within 30 days prior to receipt of the first dose of DTaP-IPV /Hib, any vaccine administered within 30 days prior to receipt of the first dose of DTaP-IPV/Hib and 30 days after receipt of the last dose of DTaP-IPV/Hib, any medication given within 30 days before or after receipt of each dose of DTaP-IPV/Hib (excluding vitamins and/or dietary supplements but including medications given to treat or prevent any vaccine-related AE or reaction).

Safety outcomes

An AE was defined as any untoward medical occurrence temporally associated with the use of a medicinal product, regardless of any causal relationship. An unexpected AE was defined as any event not documented in the approved PI. An ADR was defined as any adverse, unintended reaction for which the causal relationship with the medicinal product cannot be excluded after normal administration/use. An SAE (and SADR) was defined as any untoward medical occurrence (any adverse, unintended reaction) that is life-threatening, results in death, disability/incapacity, requires hospitalization or prolongs existing hospitalization.

Infants' parent(s)/LAR(s) were instructed to provide records of AEs occurring within 30 days post-vaccination after each study visit via completion of diary cards, telephone contact/mail, or during a follow-up contact, up to the date of study completion (30 days after last dose). The period for collecting all AEs started immediately following receipt of the first dose of DTaP-IPV/Hib. Upon reporting, all AEs were proactively followed up by the investigators during subsequent visits/contacts until resolution, until the condition stabilized, or until the infant was lost to follow-up.

Causality and intensity assessment of AEs was performed by the investigator. All AEs were matched to MedDRA PT terminology using a verbatim term,[26] and were graded as mild (causing minimal discomfort without interference with everyday activities, for fever: an axillary/oral/tympanic temperature ≥ 37.5°C to ≤ 38.0°C), moderate (sufficiently discomforting to interfere with everyday activities, for fever: an axillary/oral/tympanic temperature > 38.0°C to ≤ 39.0°C), or severe (interfering with everyday activities and causing the parent[s]/LAR[s] to seek medical advice, for fever: an axillary/oral/tympanic temperature > 39.0°C).

AEs were classified as resolved, not resolved, resolving, resolved with sequelae, fatal SAE, or unknown. For any resolved AE, the medical attention required for resolution was also considered: no visit needed, attention from medical personnel, hospitalization, or emergency room visit. The causal relationship to vaccination, as assessed by the investigators and applying the classification from the MFDS guidelines on re-examination of new drugs was reported as certain, probable/likely, possible, unlikely/not related, conditional/unclassified, or not assessable/unclassified.[21]

Statistical methods

In accordance with the Korean MFDS regulation requirements[21] and assuming a drop-out rate of 10%, the study initially planned to enroll approximately 660 infants throughout the study period to reach a final target sample size of 600 infants in the total safety cohort (i.e., all infants who had been vaccinated per product information and underwent safety follow-up after at least one dose of DTaP-IPV/Hib, regardless of the number of doses received and the length of follow-up period). A sample size of 600 infants provides a probability of approximately 95% of observing any AE (at least one occurrence) with an incidence of 0.5% or more.[21]

Demographic data and baseline medical characteristics in the total safety cohort were tabulated along with descriptive statistics including mean and standard deviation for continuous variables, or percentages for categorical data. Safety analyses were performed on the total safety cohort. The number and percentage of infants experiencing any AE within 30 days post-vaccination were tabulated across all vaccine doses and per dose, according to the outcome, maximum intensity, and causality assessment. Percentages were calculated with their corresponding 95% confidence intervals (CIs). All statistical analyses were carried out with SAS Software version 9.4 or a more recent version.

Results

Disposition of study participants

During the study period, eCRFs of 661 infants were collected (i.e., total enrolled cohort). Of these, 660 infants were included in the total vaccinated cohort (i.e., all infants who received at least one dose of DTaP-IPV/Hib), and 646 infants in the total safety cohort. Among the infants in the total safety cohort, 493 (76.3%) received a single dose of DTaP-IPV/Hib, 33 (5.1%) received two doses, and 120 (18.6%) received three doses (Figure 1).

Demographic data and baseline medical characteristics

Demographic data and baseline medical characteristics of infants in the total safety cohort are presented in Table 1. Of the 646 infants in this cohort, 52 (8.1%) had pre-existing medical conditions and 53 (8.2%) had ongoing medical conditions. Thirty-nine (6.0%) infants had a history of allergic diseases (all of unknown origins), and eight (1.3%) infants had renal or hepatic disorders (Table 1). A total of 203 (31.4%) infants had a history of vaccination within 30 days before the administration of the first dose of DTaP-IPV/Hib and 634 (98.1%), 136 (91.3%), and 113 (91.1%) infants received other vaccines within 30 days after the first, second, and third dose of DTaP-IPV/Hib, respectively (Table 1).

In addition, 22 (3.4%) infants received any medication within 30 days before DTaP-IPV/Hib vaccination, and 51 (7.9%), 11 (7.4%), and two (1.6%) infants received concomitant medication after the first, second, and third dose of DTaP-IPV/Hib, respectively (Table 1).

Safety outcomes

Incidence proportion and description of AEs

The incidence proportion and description of all AEs (including ADRs, unexpected AEs, unexpected ADRs, and SAEs/SADRs)

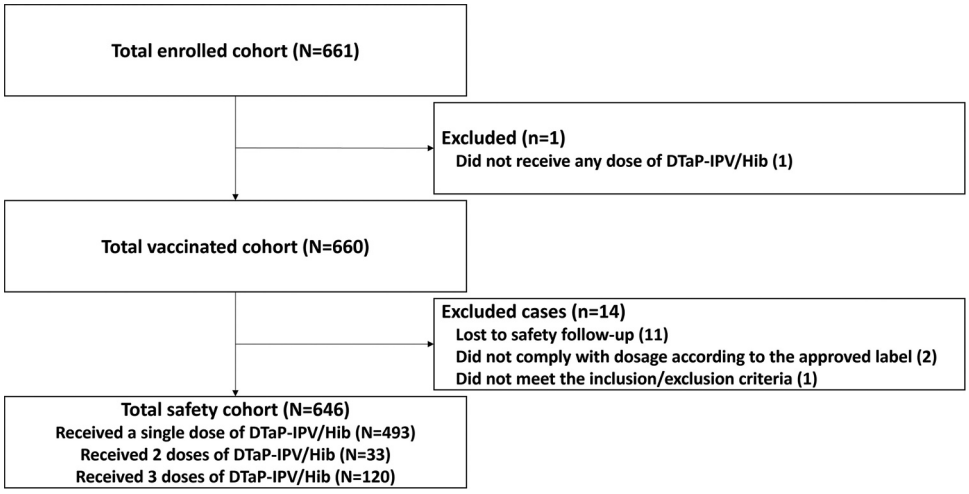

Figure 1. Flow diagram of study participants. DTaP-IPV/Hib, combined diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and *Haemophilus influenzae* type b vaccine; n, number of infants in each category.

in the total safety cohort are presented in Table 2. During the study period, a total of 194 AEs were reported in 143 infants (22.1% [95% CI: 19.0, 25.5]). When stratified by vaccine dose, 158 AEs in 130 (20.1%) infants occurred after the first dose, 21 AEs in 20 (13.4%) infants occurred after the second dose, and 11 AEs in ten (8.1%) infants occurred after the third dose (Table 2).

The most frequently reported AEs were pyrexia (13.3% [95% CI: 10.8, 16.2]), injection site swelling (5.1% [3.5, 7.1]), and irritability (1.7% [0.9, 3.0]). Of the 194 AEs reported in this study, 182 were classified as mild, 188 were ultimately resolved, and 161 did not require medical attention (Table 2). No sequelae nor fatal events were reported. The causal relationship to vaccination by MedDRA PT is presented in Table 3. Most AEs (135/194) were considered as possibly related to vaccination. The investigators evaluated the causal relationship between an administration site swelling and DTaP-IPV/Hib as certain (Table 3).

Incidence proportion and description of ADRs, unexpected AEs/ADRs, and SAEs/SADRs

A total of 160 ADRs were reported in 125 infants (19.4% [95% CI: 16.4, 22.6]). The most frequently observed ADRs were pyrexia (12.9% [10.4, 15.7]), injection site swelling (5.1% [3.5, 7.1]), and administration site induration (1.6% [0.7, 2.8]) (Table 2).

Thirty-three unexpected AEs were reported in 28 infants (4.3% [95% CI: 2.9, 6.2]). The most frequently observed unexpected AEs were abnormal sleep-related event (0.6% [0.2, 1.6]), gastroenteritis (0.5% [0.1, 1.4]), oral candidiasis (0.5% [0.1, 1.4]), conjunctivitis (0.3% [0.0, 1.1]), nasopharyngitis (0.3% [0.0, 1.1]), dermatitis atopic (0.3% [0.0, 1.1]), seborrheic dermatitis (0.3% [0.0, 1.1]), and rhinorrhea (0.3% [0.0, 1.1]) (Table 2).

Among the unexpected AEs, six unexpected ADRs were reported in six infants (0.9% [95% CI: 0.3, 2.0]). Four unexpected ADRs were abnormal sleep-related events; the two remaining events were injection site mass and cough (Table 2). All unexpected ADRs were assessed as possibly related to vaccination, except for cough, which had a conditional/unclassified relationship with vaccination.

Six SAEs (including one SADR) were reported in six infants (0.9% [95% CI: 0.3, 2.0]). The reported SAEs were irritability (0.3% [0.0, 1.1]) (two events in two infants), pyrexia (0.2% [0.0, 0.9]) (one event in one infant), gastroenteritis viral (0.2% [0.0, 0.9]) (one event in one infant), pyelonephritis acute (0.2% [0.0, 0.9]) (one event in one infant), and urinary tract infection (0.2% [0.0, 0.9]) (one event in one infant) (Table 2). Of the six SAEs, three required hospitalization, three required an emergency room visit, and all cases were ultimately resolved. Only pyrexia (which was considered an SADR) was assessed as possibly related to vaccination.

Discussion

The objective of this PMS study was to collect real-world safety data on DTaP-IPV/Hib in South Korea, when administered according to national routine pediatric vaccination guidelines. During the study period, 194 AEs were reported in 22.1% of infants. Most AEs were mild, resolved without medical attention, and were considered as possibly related to vaccination. The most common solicited symptoms were pyrexia, injection site swelling, and irritability. Among the AEs, 19.4% were reported as ADRs, for which unintended reaction to normal administration of the vaccine cannot be excluded. Six SAEs (including one SADR) were reported (0.9%). All SAEs resolved after hospitalization or emergency room visit and one SAE was assessed as possibly related to DTaP-IPV/Hib vaccination.

The safety results obtained in real-world settings of this study are consistent with the information included in the approved label of the licensed vaccine, reporting fever, swelling at the injection site, and irritability as very common solicited symptoms, with an incidence proportion per dose ≥10%.[13] The results are also in line with a phase 3 study evaluating the safety of DTaP-IPV/Hib when administered to South Korean infants.[27] In this previous study, injection site swelling and irritability were among the most common solicited local and

Table 1. Summary of demographic and baseline medical characteristics of infants at first study visit (total safety cohort, N = 646).

Variable	N	Mean ± SD	n (%)
Age[a] (months)			
At first dose of DTaP-IPV/Hib	646	2.2 ± 0.2	
At second dose of DTaP-IPV/Hib	149	4.3 ± 0.3	
At third dose of DTaP-IPV/Hib	124	6.5 ± 0.3	
Weight (kg)	632	5.6 ± 0.8	
Gender	646		
Female			296 (45.8)
Male			350 (54.2)
Medical history	646		
Presence of preexisting medical conditions[b]			52 (8.1)
Skin and subcutaneous tissue disorders			27 (51.9)
Respiratory, thoracic and mediastinal disorders			11 (21.2)
Infections and infestations			8 (15.4)
Presence of ongoing medical conditions[b]			53 (8.2)
Skin and subcutaneous tissue disorders			15 (28.3)
Congenital, familial and genetic disorders			12 (22.6)
Infections and infestations			9 (17.0)
Renal and urinary disorders			7 (13.2)
History of allergic diseases			39 (6.0)
Presence of renal disorder			7 (1.1)
Presence of hepatic disorder			1 (0.2)
Vaccination	646		
Presence of prior vaccination within 30 days before the first dose			203 (31.4)
Presence of concomitant vaccination			635 (98.3)
Within 30 days after the first dose of DTaP-IPV/Hib	646		634 (98.1)
Within 30 days after the second dose of DTaP-IPV/Hib	149		136 (91.3)
Within 30 days after the third dose of DTaP-IPV/Hib	124		113 (91.1)
Medication	646		
Presence of prior medication within 30 days before vaccination[c]			22 (3.4)
Corticosteroids, dermatological preparations			7 (31.8)
Nasal preparations			7 (31.8)
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents			6 (27.3)
Cough and cold preparations			5 (22.7)
Antihistamines for systemic use			4 (18.2)
Drugs for obstructive airway diseases			4 (18.2)
Antibacterials for systemic use			4 (18.2)
Drugs for functional gastrointestinal disorders			3 (13.6)
Presence of concomitant medication[c]			56 (8.7)
Corticosteroids, dermatological preparations			20 (35.7)
Analgesics			11 (19.6)
Nasal preparations			10 (17.9)
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents			8 (14.3)
Ophthalmologicals			8 (14.3)
Cough and cold preparations			7 (12.5)
Drugs for functional gastrointestinal disorders			7 (12.5)
Antibacterials for systemic use			6 (10.7)
Within 30 days after the first dose of DTaP-IPV/Hib	646		51 (7.9)
Within 30 days after the second dose of DTaP-IPV/Hib	149		11 (7.4)
Within 30 days after the third dose of DTaP-IPV/Hib	124		2 (1.6)

[a]Considering that 1 month equals on average 30.25 days, infant age was calculated as follows: Age = (Date of each dose of study vaccine - Date of birth + 1)/30.25.

[b]Only the most frequent MedDRA System Organ Classes (i.e., with a prevalence > 10%) are shown. Pre-existing medical conditions were defined as clinically significant diseases diagnosed within 30 days before the first visit.

[c]Only the most frequent Anatomical Therapeutic Chemical level 2 classifications (i.e., with a prevalence > 10%) are shown.

DTaP-IPV/Hib, combined diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Haemophilus influenzae type b vaccine; N, total number of infants with available data; n (%), number (percentage) of infants in each category; SD, standard deviation.

systemic events (reported after >30% and >50% of doses, respectively), and none of the reported SAEs were assessed as related to vaccination.[27] The lower proportion of injection site swelling and irritability in the current PMS study could be explained by the different data collection strategy compared to the phase 3 clinical trial, in which solicited local (pain, injection site redness, swelling) and general symptoms (fever, drowsiness, irritability/fussiness, loss of appetite) were collected up to four days after each vaccine dose while in the current study there was no pre-defined list of solicited AEs corresponding to reactogenicity.

Apart from the clinical evidence collected in South Korea, similar safety outcomes were obtained when DTaP-IPV/Hib was administered to pediatric populations in China,[15] Singapore,[28] and Russia,[16] or co-administered with hepatitis B vaccine in Taiwanese[17] and Spanish infants.[19] However, dosing interval and schedule differed across these studies. Among these Asian studies, pain and swelling at the injection site and fever and irritability were described as the most frequently occurring local and systemic solicited events, respectively, and only a limited number of SAEs were assessed as related to vaccination.[15,17,28]

The main strength of this study is to provide DTaP-IPV /Hib safety data in a real-world setting, i.e., when administered according to the label and routine national clinical guidelines. To monitor drug safety, post-marketing studies

Table 2. Incidence proportion and description of AEs reported in the total safety cohort (N = 646).

Safety outcome	Number of infants reporting the event	Incidence proportion, % (95% CI)	Number of events
Overall	143	22.1 (19.0, 25.5)	194
ADRs	125	19.4 (16.4, 22.6)	160
Unexpected AEs	28	4.3 (2.9, 6.2)	33
Unexpected ADRs	6	0.9 (0.3, 2.0)	6
SAEs	6	0.9 (0.3, 2.0)	6
SADRs	1	0.2 (0.0, 0.9)	1
Maximum intensity, overall			
Mild			182
Moderate			11
Severe			1
Outcome, overall			
Recovered/resolved			188
Not recovered/not resolved			1
Recovering/resolving			5
Requiring medical attention, overall			
None			161
Attention from medical personnel			27
Hospitalization			3
Emergency room visit			3
By vaccine dose, overall			
First	130	20.1 (17.1, 23.4)	158
Second	20	13.4 (8.4, 20.0)	21
Third	10	8.1 (3.9, 14.3)	11
By MedDRA PT, overall [a]			
Pyrexia	86	13.3 (10.8, 16.2)	104
Injection site swelling	33	5.1 (3.5, 7.1)	33
Irritability	11	1.7 (0.9, 3.0)	11
Administration site induration	10	1.6 (0.7, 2.8)	10
By MedDRA PT, ADRs[a]			
Pyrexia	83	12.9 (10.4, 15.7)	100
Injection site swelling	33	5.1 (3.5, 7.1)	33
Administration site induration	10	1.6 (0.7, 2.8)	10
By MedDRA PT, unexpected AEs[b]			
Abnormal sleep-related event	4	0.6 (0.2, 1.6)	4
Gastroenteritis	3	0.5 (0.1, 1.4)	3
Oral candidiasis	3	0.5 (0.1, 1.4)	3
Conjunctivitis	2	0.3 (0.0, 1.1)	2
Nasopharyngitis	2	0.3 (0.0, 1.1)	2
Dermatitis atopic	2	0.3 (0.0, 1.1)	2
Seborrheic dermatitis	2	0.3 (0.0, 1.1)	2
Rhinorrhea	2	0.3 (0.0, 1.1)	2
By MedDRA PT, unexpected ADRs[b]			
Abnormal sleep-related event	4	0.6 (0.2, 1.6)	4
Injection site mass	1	0.2 (0.0, 0.9)	1
Cough	1	0.2 (0.0, 0.9)	1
By MedDRA PT, SAEs			
Irritability	2	0.3 (0.0, 1.1)	2
Pyrexia	1	0.2 (0.0, 0.9)	1
Gastroenteritis viral	1	0.2 (0.0, 0.9)	1
Pyelonephritis acute	1	0.2 (0.0, 0.9)	1
Urinary tract infection	1	0.2 (0.0, 0.9)	1
By MedDRA PT, SADRs			
Pyrexia	1	0.2 (0.0, 0.9)	1

[a]Only the most frequent MedDRA PTs (i.e., with a percentage of infants experiencing the AE > 1.5%) are shown.
[b]Only the most frequent MedDRA PTs (i.e., with a percentage of infants experiencing the AE > 0.2%) are shown.
ADRs, adverse drug reactions; AEs, adverse events; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of infants; PT, preferred term; SAEs/SADRs, serious adverse events/serious adverse drug reactions; %, percentage of infants in each category (relative to the number of infants in the total safety cohort).

with active safety surveillance can complement spontaneous reporting of AEs (passive method). We believe the study population adequately represents the population of South Korean infants eligible for vaccination with DTaP-IPV/Hib. However, the study has several limitations. First, the sample size of 646 infants in the total safety cohort may limit the detection of rare events; therefore, spontaneous AE reporting remains essential to detect new or rare ADRs. Second, only 120 infants (18.6%) in the total safety cohort completed the primary series by receiving three doses of DTaP-IPV/Hib within the frame of this study. Most infants who did not complete the full vaccination schedule in study centers were most likely lost to follow-up due to care-seeking behaviors as participants may have completed the primary vaccination series at other centers, or because there was no incentive for parent(s)/LAR(s) to go to the same hospital for subsequent vaccinations. These doses could thus have been administered at other sites not participating in the study. In addition, the COVID-19 pandemic and associated control measures may have prevented some parent(s)/LAR(s) from returning to the initial vaccination center. Finally, as in other PMS studies, there was no comparator or control group to assess the significance of these safety outcomes in a broader clinical context.

Table 3. Causal relationship to vaccination in the total safety cohort (N = 646).

	Number of adverse events						
	Certain	Probable/likely	Possible	Unlikely/ not related	Conditional/unclassified	Not assessable/unclassified	Total
General disorders and administration site conditions							
Overall	1	20	124	4	0	0	149
Pyrexia	0	7	93	4	0	0	104
Injection site swelling	0	5	28	0	0	0	33
Administration site induration	1	8	1	0	0	0	10
Injection site erythema	0	0	1	0	0	0	1
Injection site mass	0	0	1	0	0	0	1
Infections and infestations							
Overall	0	0	0	16	0	0	16
Gastroenteritis	0	0	0	3	0	0	3
Oral candidiasis	0	0	0	3	0	0	3
Conjunctivitis	0	0	0	2	0	0	2
Nasopharyngitis	0	0	0	2	0	0	2
Gastroenteritis viral	0	0	0	1	0	0	1
Impetigo	0	0	0	1	0	0	1
Otitis media acute	0	0	0	1	0	0	1
Pyelonephritis acute	0	0	0	1	0	0	1
Upper respiratory tract infection	0	0	0	1	0	0	1
Urinary tract infection	0	0	0	1	0	0	1
Psychiatric disorders							
Overall	0	3	10	2	0	0	15
Irritability	0	3	6	2	0	0	11
Abnormal sleep-related event	0	0	4	0	0	0	4
Skin and subcutaneous tissue disorder							
Overall	0	0	0	7	0	0	7
Dermatitis atopic	0	0	0	2	0	0	2
Seborrheic dermatitis	0	0	0	2	0	0	2
Dermatitis contact	0	0	0	1	0	0	1
Rash	0	0	0	1	0	0	1
Urticaria	0	0	0	1	0	0	1
Respiratory, thoracic and mediastinal disorders							
Overall	0	0	0	2	1	0	3
Rhinorrhea	0	0	0	2	0	0	2
Cough	0	0	0	0	1	0	1
Eye disorders							
Overall	0	0	0	1	0	0	1
Eye discharge	0	0	0	1	0	0	1
Gastrointestinal disorders							
Overall	0	0	0	1	0	0	1
Diarrhea	0	0	0	1	0	0	1
Injury, poisoning and procedural complications							
Overall	0	0	0	1	0	0	1
Skin abrasion	0	0	0	1	0	0	1
Metabolism and nutrition disorders							
Overall	0	0	1	0	0	0	1
Hypophagia	0	0	1	0	0	0	1
Total	1	23	135	34	1	0	194

N, total number of infants.

Conclusion

This PMS did not identify any safety concern that would impact the benefit-risk ratio of primary vaccination with DTaP-IPV/Hib in pediatric populations eligible for vaccination in South Korea. Considering the incidence proportion and the nature of AEs, ADRs, and SAEs reported here, these results are reassuring and in line with safety information gathered from the approved label/package insert and previous studies conducted in South Korea as well as in other Asian or European countries. Congruent with previous data collected during a large cumulative post-marketing exposure over 24 years, these findings further consolidate the acceptable safety profile of DTaP-IPV/Hib for active immunization of infants aged at least 2 months against diphtheria, tetanus, pertussis, poliomyelitis, and Hib invasive infections.

Disclosure statement

DME, SX, EB, GDS, and AG are employees of GSK. GDS and AG hold financial equities in GSK. JSH, SSK, Y-KK and JHL declare no conflicts of interest. The authors declare no other financial or non-financial relationships or activities.

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Authors contribution statement

All authors were involved in study design, acquisition, analysis, and/or interpretation of data. All authors reviewed the manuscript, revised it critically for intellectual content, and gave their final approval of the version to be published. All authors agree to be accountable for all aspects of their work.

Data availability statement

For requests for access to anonymized subject level data, please contact the corresponding author.

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