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Safety of pentavalent DTaP-IPV/Hib combination vaccine in post-marketing surveillance in Guangzhou, China, from 2011 to 2017

Zhiqun Li*, Jianxiong Xu, Huifeng Tan, Chunhuan Zhang, Jian Chen, LiHong Ni, Xuexia Yun, Yong Huang, Wen Wang

Guangzhou Center For Disease Control And Prevention, Department of Immunization Planning, No.1, Qide Rd, Jiahe, Baiyun, Guangzhou, Guangdong, China

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ABSTRACT

Background: The DTaP-IPV/Hib combination vaccine can replace the acellular tetanus vaccine, polio vaccine, and the *Haemophilus influenzae* type B vaccine. Data on the safety of DTaP-IPV/Hib vaccines are required. We aimed to evaluate the safety of the vaccination program.

Methods: Using the National Adverse Events Following Immunization (AEFI) surveillance system (CNAEFIS) in Guangzhou, China, a retrospective study was performed from May 11, 2011, to December 31, 2017. There were 376 cases of adverse events after vaccination with the DTaP IPV/Hib vaccine. The primary analysis indicators were the number of vaccines used, the number of AEFI reports received, and the reporting rate (per 100,000).

Results: From May 1, 2011, to December 31, 2017, 516,000 doses of vaccine were inoculated, and 376 cases of adverse reactions were reported; the reporting rate was 72.8 per 100,000 vaccines. There were eight cases of serious AEFIs (1.5 per 100,000), with four cases of thrombocytopenic purpura (0.8 per 100,000); three cases of cyanosis of the lips, stiffness, and flexion of limbs, and convulsions (0.6 per 100,000); and one case of a high fever (0.2 per 100,000). The highest incidence of AEFIs occurred after the fourth dose (n = 207, 55.0%, 40.1 per 100,000), followed by the first dose (n = 81, 21.5%, 15.7 per 100,000), second dose (n = 48, 12.8%, 9.3 per 100,000) and third dose (n = 40, 10.6%, 7.7 per 100,000). The AEFI incidence was higher after injection of the vaccine into the deltoid muscle of the upper arm (n = 276, 73.4%, 53.5 per 100,000) than after injection of the vaccine into the thigh (n = 100, 26.6%, 19.4 per 100,000). There was a significant difference between AEFIs after injection into the deltoid of the upper arm deltoid and the thigh (x^2 = 164.8, $P < 0.05$).

Conclusions: Most of the reported AEFIs after DTaP-IPV/Hib vaccination are not serious. There were four cases of TP in this study; vaccination may be a rare cause of thrombocytopenic purpura.

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Introduction

Infectious diseases, such as diphtheria, pertussis, tetanus, *Haemophilus influenzae* type B, and poliomyelitis (polio), are seriously harmful to children's health. Vaccination is the most effective way to control these diseases. In 2010, the State Food and Drug Administration approved the DTaP-IPV/Hib combination vaccine (from now on referred to as the pentavalent vaccine) for cell-free pertussis (DTaP), inactivated poliomyelitis and *Haemophilus influenzae* type B (combination), and children started to be vaccinated with this pentavalent vaccine on May 11, 2011, in China. The immunization plan recommended by the Chinese Preventive Medicine Association is three injections of basic immunizations at the age of two, three, and four months or three, four, and five months and one booster immunization at 18–24 months of age (Chinese Preventive Medicine Association, 2011). The DTaP IPV/Hib vaccine reduces the total doses of single-antigen vaccines to prevent these five diseases from 12 to four, reducing the risk of abnormal vaccine responses caused by multiple vaccinations of the original single antigen vaccine. In 2012, the safety of the vaccine was assessed in 2167 children in the United States. The most

* Corresponding author.
E-mail addresses: 992805123@qq.com (Z. Li), gzcdc_xujianxiong@gz.gov.cn (J. Xu), gzcdc_tanhuifeng@gz.gov.cn (H. Tan), gzcdc_zhangchunhuan@gz.gov.cn (C. Zhang), gzcdc_chenjian@gz.gov.cn (J. Chen), gzcdc_nilihong@gz.gov.cn (L. Ni), gzcdc_yunxuexia@gz.gov.cn (X. Yun), gzcdc_huangyong@gz.gov.cn (Y. Huang), gzcdc_wangwen@gz.gov.cn (W. Wang).

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commonly reported local response was tenderness at the injection site. Most of the injection site reactions were grade 1 and developed and disappeared within three days after vaccination (Chatterjeea et al., 2012). In 2016, most of the systemic reactions assessed in 418 healthy infants in South Korea occurred within three days after vaccination and subsided within seven days after injection (Kang et al., 2016). Thrombocytopenic purpura (TP) is the least common systemic reaction. Taiwan reported in 2010 that the first dose of pentavalent vaccine can lead to TP within three months (Hsieh and Lin, 2010). According to LS Arya, a boy who received four doses of the DPT vaccine (the fourth dose was administered at the age of four) developed TP. DPT vaccination may be a rare cause of immune-mediated thrombocytopenia (Arya et al., 1993). Serious adverse vaccine reactions, such as TP, are rare; therefore, post-marketing surveillance of adverse events after immunization is needed to evaluate the safety of the DTaP-IPV/Hib pentavalent vaccine.

Methods

Study design and participants

From May 11, 2011, to December 31, 2017, we conducted a retrospective study in Guangzhou, China, using the national adverse event immune information system (CNAEFIS). We collected and analyzed the data in the CNAEFIS information system and evaluated the DTaP-IPV/Hib vaccine's safety after it was placed on the market. A total of 516,000 doses of vaccine were inoculated, and all vaccinated children were monitored for AEFI. A total of 376 cases of adverse reactions were reported. The primary analysis indicators were the number of vaccines used, the number of AEFI reports received, and the reporting rate (per 100,000).

China DTaP-IPV/Hib vaccination schedule

In 2011, the Chinese Preventive Medical Association formulated the "Technical Guidelines for the Application of the Adsorbed Cell-Free Diphtheria, Inactivated Polio, and *Haemophilus Influenza* B (Combined) Vaccine (DTaP-IPV/Hib Vaccine)" (hereafter referred to as the "Guide"). The recommended immunization program is three-needle basic immunization at two, three, and four months or three, four, and five months and one booster immunization at 18–24 months of age (Chinese Preventive Medicine Association, 2011).

Vaccination and eligibility

In 2011, the Chinese Preventive Medicine Association (CPMA) introduced a new vaccination guideline, "DTaP-IPV/Hib vaccine application technology guide" (Chinese Preventive Medicine Association, 2011), to guide doctors in the proper use of the combination vaccine. The DTaP-IPV/Hib combination vaccine (Pentaxim®; Sanofi Pasteur Limited, MARCY L, ETOILE, France) contains ≥30 IU diphtheria toxoid, tetanus toxoid ≥40 IU, adsorbed pertussis toxoid (PT) 25 μg, filamentous hemagglutinin (FHA) 25 μg, inactivated poliovirus type 1 D antigen 40 units, inactivated poliovirus type 2 D antigen 8 unit, inactivated poliovirus type 3 D antigen 32 units, and *Haemophilus influenzae* b capsular polysaccharide in lyophilized powder form 10 μg, combined with tetanus protein 18–30 μg. All vaccines are given at vaccination clinics. The DTaP-IPV/Hib vaccine is injected intramuscularly, and the best injection site is the anterolateral side of the baby's thigh (the middle third). Contraindications to vaccination include allergy or previous allergy to the vaccine's active substance and any inactive substance or substances used in the production process, such as neomycin, streptomycin, polymyxin B; vaccination should be postponed in patients with fever and acute disease. The children's parents or guardians need to provide written informed consent after receiving information about the vaccination procedures, possible adverse reactions, and contraindications.

National AEFI Information Surveillance System (CNAEFIS)

The China Center for Disease Control and Prevention (CCDC) established the National AEFI Information Surveillance System (CNAEFIS) in 2005 following the World Health Organization (WHO) guidelines; the CNAEFIS is a nationwide passive surveillance system for post-marketing vaccine safety (Wu and Liu, 2016). An online national AEFI monitoring system was established in 2008.

Reports and investigations

AEFI cases (adverse event following immunization, AEFI) are defined as reactions or events that occur after vaccination and are suspected of being vaccination-related. A serious adverse event following immunization is defined as one of the following conditions suspected of occurring in response to immunization: death, life-threatening illness, and permanent or significant disability or impaired organ function. These include anaphylactic shock, anaphylactic laryngeal edema, allergic purpura, thrombocytopenic purpura, local allergic necrosis (Arthus reaction), febrile seizures, epilepsy, brachial plexus neuritis, polyneuritis, Guillain-Barre syndrome, encephalopathy, encephalitis and meningitis, vaccine-associated paralytic polio, BCG osteomyelitis, systemic disseminated BCG infection, syncope, toxic shock syndrome, systemic suppurative infection, etc.

According to the requirements of the national AEFI supervision plan, medical institutions, vaccination units, disease prevention and control institutions, ADR monitoring institutions, vaccine manufacturers, commercial vaccine enterprises, and the personnel performing the associated duties are the reporting units and reporters of suspected AEFI reactions. These entities and their personnel are required to complete the suspected AEFI case report card within 48 h after identifying a suspected AEFI and to report the event to the local district-level disease prevention and control institution; serious AEFIs, including death, serious disability, and group events, must be reported to the local district-level disease prevention and control center and the Health Committee by telephone within two hours. After the investigation of all cases is completed by the regional Center For Disease Control, the abnormal response information is monitored in real-time through the national vaccination information management system. For serious AEFI reports, an AEFI expert diagnosis team is organized immediately to discuss the case (General Office of the Ministry of Health and Office of the State Food and Drug Administration, 2010).

Statistical analysis

We analyzed the DTaP-IPV/Hib vaccine AEFI reports submitted from 2011 to 2017, described the number of vaccination doses, sex distribution, clinical symptoms, and vaccination sites, and calculated the incidence of AEFIs per 100,000 doses. The reported adverse event rate was calculated by dividing the number of vaccinated children with adverse reactions by the total number of vaccinations.

Results

AEFIs reported after the administration of the DTaP-IPV/Hib vaccine

From May 11, 2011, to December 31, 2017, a total of 516,158 doses of the DTaP IPV/Hib vaccine were administered, and 376 cases of adverse events were reported, with a total adverse event rate of 72.8 per 100,000. Two hundred twenty-eight males

accounted for 60.6% of the total population with AEFIs, with an adverse event rate of 44.2 per 100,000; one hundred forty-eight females accounted for 39.4% of the total population with AEFIs, with an adverse event rate of 28.7 per 100,000. Also, eight cases of severe AEFIs were reported. Five cases were in males, accounting for 62.5% of the total number of severe AEFIs with a severe adverse event rate of 1.0 per 100,000, and three cases were in females, accounting for 37.5% of the total number of severe AEFIs with a severe adverse event rate of 0.6 per 100,000 (Table 1). The main symptoms of severe AEFIs were convulsions, cyanosis of the lips, rigidity, and bending of the limbs, thrombocytopenic purpura, and high fever. Among the affected children in 2012, convulsions, cyanosis of the lips, and stiffness and bending of the limbs were reported in one male, and the vaccine injection site was the thigh. In 2013, two females developed thrombocytopenic purpura after vaccination in the thigh and upper arm; one female had a fever >40.5 °C after injection in the thigh and needed hospitalization. In 2016, two males developed thrombocytopenic purpura after injection in the thigh. In 2017, two males developed convulsions after injection in the upper arm, with cyanosis of the lips and stiffness and bending of the limbs.

Incidence of AEFIs stratified by inoculation dose and symptoms

The results showed that the total incidence of adverse events with different symptoms at different vaccination times was 100% (376/376) (72.8 per 100,000). The incidence of adverse events after the first injection was 100% (81/81) (15.7 per 100,000); the incidence of adverse events after the second injection was 100% (48/48) (9.3 per 100,000); the incidence of adverse events after the third injection was 100% (40/40) (7.7 per 100,000); and the incidence of adverse events after the fourth injection was 100% (207/207) (40.1 per 100,000). With regard to the different symptoms, the incidence of different grades of AEFI was as follows: fever from 37.1 to 37.5 °C, 15.2% (57/376) (11.0 per 100,000); fever from 37.6 to 38.5 °C, 18.6% (70/376) (13.6 per 100,000); and fever ≥38.6 °C, 0.5% (2/376) (0.4 per 100,000). The incidence of redness and swelling at the inoculation site ≤2.5 cm was 6.6% (25/376) (4.8 per 100,000); the incidence of 2.6–5 cm redness and swelling at the inoculation site was 25.8% (22/376) (18.8 per 100,000), and the incidence of redness and swelling at the inoculation site >5.0 cm was 7.2% (27/376) (5.2 per 100,000). The incidence of induration ≤2.5 cm was 5.3% (20/376) (3.9 per 100,000); the incidence of induration from 2.6 to 5 cm was 5.9% (22/376) (4.3 per 100,000); and the incidence of induration >5.0 cm was 3.2% (12/376) (2.3 per 100,000). The incidence of redness and swelling was 22.2–25.0% after the first to third doses and was the most serious after the fourth dose, with a reporting rate of 53.1%. The third dose resulted in the most induration; the reporting rate was 27.5%. After the first, second, and fourth doses, the incidence of induration was between 7.4% and 14.6%. The incidence of punctuate rash was 9.6% (36/376) (7.0 per 100,000) (Table 2).

Local reactions mostly manifested as fever, and febrile reactions decreased gradually from the first dose to the fourth dose, with incidences of 48.1%, 41.7%, 30.0%, and 28.0%, respectively; the fever levels were mostly grades I and II; only two children who received the DTaP-IPV Hib vaccine reported a severe fever ≥38.6 °C (Figure 1). The most common local reaction was redness and swelling at the site of inoculation. The overall incidence rate was 39.6% (28.9 per 100,000). After the first, second, and third doses, the incidences were 22.2%, 22.9%, and 25.0%, respectively, and the highest incidence was 53.1% after the fourth dose (36.7% were between 2.6–5 cm) (Figure 2). Similarly, the incidence of induration at the inoculation site also increased with increasing numbers of inoculations, and the highest incidence was 27.5% after the third dose (Figure 3).

Incidence of AEFIs associated with different inoculation doses and sites

The DTaP-IPV/Hib vaccine can be injected into the thigh muscle or the deltoid muscle of the upper arm. The best injection site for infants is the anterolateral thigh (middle third). The total incidences of AEFIs were 73.4% (276/376) after injection in the deltoid muscle (53.5 per 100,000) and 26.6% (100/376) after injection in the thigh (19.4 per 100,000). The difference was statistically significant ($x^2 = 164.8$, $P < 0.05$). After the first dose, the incidence of AEFIs after injection in the upper arm was 8.0% (30/376) (5.8 per 100,000), while the incidence after injection in the thigh was 13.6% (51/376) (9.9 per 100,000); the difference was statistically significant ($x^2 = 10.9$, $P < 0.05$). After the fourth dose, the incidence of AEFIs after injection in the upper arm was 6.4% (24/376) (4.6/100,000), while the incidence after injection in the thigh was 48.7% (183/376) (35.5/100,000); the difference was statistically significant ($x^2 = 244.3$, $P < 0.05$) (Table 3).

Outcomes and causes of AEFIs after inoculation with the DTaP-IPV/Hib vaccine

The 376 AEFIs were grouped by the number of inoculations, patient sex, and inoculation site. The outcomes of the AEFIs were as followed: 335 AEFIs (89.1%) resulted in recovery, 35 AEFIs (9.3.%)

Table 1
Overall and serious adverse event rates of DTaP IPV/Hib vaccinators reported in Guangzhou from May 11, 2011 to December 31, 2017.

Reporting year and sex	Number of DTaP-IPV/ Hib doses distributed	All AEFI reports						AEFI reports with serious AEFI					
		Sex		Total	Rate per 100,000 DTaP-IPV/ Hib doses distributed			Sex		Total	Rate per 100,000 DTaP-IPV/ Hib doses distributed		
		Male	Female		Male	Female	Total	Male	Female		Male	Female	Total
2011	19598	4	1	5	20.4	5.1	25.5	0	0	0	0.0	0.0	0.0
2012	48070	12	5	17	25.0	10.4	35.4	1	0	1	2.1	0.0	2.1
2013	69650	23	14	37	33.0	20.1	53.1	0	3	3	0.0	4.3	4.3
2014	94120	39	25	64	41.4	26.6	68.0	0	0	0	0.0	0.0	0.0
2015	84280	35	31	66	41.5	36.8	78.3	0	0	0	0.0	0.0	0.0
2016	100112	76	54	130	75.9	53.9	129.9	2	0	2	2.0	0.0	2.0
2017	100328	39	18	57	38.9	17.9	56.8	2	0	2	2.0	0.0	2.0
Total	516158	228	148	376	44.2	28.7	72.8	5	3	8	1.0	0.6	1.5

AEFI: adverse events following immunisation;

DTaP-IPV/Hib:diphtheria-tetanus-acellular pertussis-inactivated polio and Haemophilus influenzae type B vaccine.

Table 2
Overall and adverse event rate of different symptoms of adverse event (AEFI) after dtap-ipv/Hib vaccination in Guangzhou, China from May 2011 to 2017 (n = 376).

AEFIs Symptoms and/or signs		1			2			3			4			Total		
		n	% of all AEFIs reported (n=81)	Rate per 100,000 DTaP-IPV/ Hib doses distributed (n=516158)	n	% of all AEFIs reported (n=48)	Rate per 100,000 DTaP-IPV/ Hib doses distributed (n=516158)	n	% of all AEFIs reported (n=40)	Rate per 100,000 DTaP-IPV/ Hib doses distributed (n=516158)	n	% of all AEFIs reported (n=207)	Rate per 100,000 DTaP-IPV/ Hib doses distributed (n=516158)	n	% of all AEFIs reported (n=376)	Rate per 100,000 DTaP-IPV/ Hib doses distributed (n=516158)
Fever	37.1-37.5℃	19	23.5	3.7	5	10.4	1.0	9	22.5	1.7	24	11.6	4.6	57	15.2	11.0
	37.6-38.5℃	20	24.7	3.9	14	29.2	2.7	3	7.5	0.6	33	15.9	6.4	70	18.6	13.6
	≥38.6℃	0	0.0	0.0	1	2.1	0.2	0	0.0	0.0	1	0.5	0.2	2	0.5	0.4
Subtotal		39	48.1	7.6	20	41.7	3.9	12	30.0	2.3	58	28.0	11.2	129	34.3	25.0
Injection site swelling	≤2.5cm	4	4.9	0.8	5	10.4	1.0	3	7.5	0.6	13	6.3	2.5	25	6.6	4.8
	2.6-5cm	12	14.8	2.3	4	8.3	0.8	5	12.5	1.0	76	36.7	14.7	97	25.8	18.8
	>5.0cm	2	2.5	0.4	2	4.2	0.4	2	5.0	0.4	21	10.1	4.1	27	7.2	5.2
Subtotal		18	22.2	3.5	11	22.9	2.1	10	25.0	1.9	110	53.1	21.3	149	39.6	28.9
Injection site induration	≤2.5cm	1	1.2	0.2	4	8.3	0.8	4	10.0	0.8	11	5.3	2.1	20	5.3	3.9
	2.6-5cm	3	3.7	0.6	2	4.2	0.4	5	12.5	1.0	12	5.8	2.3	22	5.9	4.3
	>5.0cm	2	2.5	0.4	1	2.1	0.2	2	5.0	0.4	7	3.4	1.4	12	3.2	2.3
Subtotal		6	7.4	1.2	7	14.6	1.4	11	27.5	2.1	30	14.5	5.8	54	14.4	10.5
Point rash		13	16.0	2.5	10	20.8	1.9	6	15.0	1.2	7	3.4	1.4	36	9.6	7.0
Thrombocytopenia		4	4.9	0.8	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	4	1.1	0.8
High fever, Cyanosis of lips, stiffness and flexion of limbs,Convulsion		1	1.2	0.2	0	0.0	0.0	1	2.5	0.2	2	1.0	0.4	4	1.1	0.8
Total		81	100.0	15.7	48	100.0	9.3	40	100.0	7.7	207	100.0	40.1	376	100.0	72.8

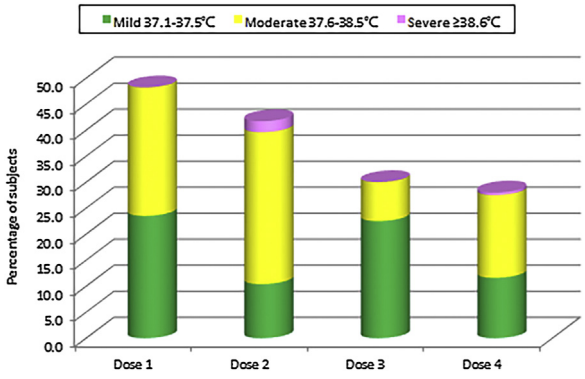

Figure 1. AEFI fever level of DTaP IPV/Hib vaccine in different doses.

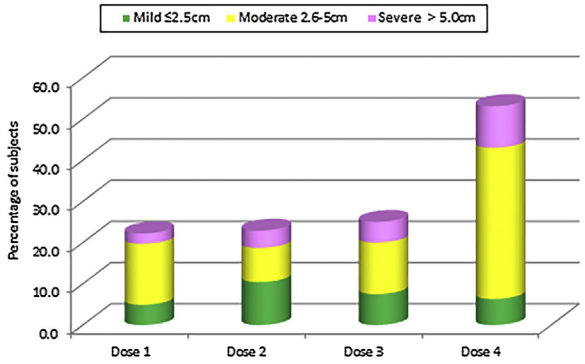

Figure 2. AEFI injection site swelling level of DTaP IPV/Hib vaccine in different doses.

resulted in improvement, five AEFIs (1.3%) resulted in sequelae, and one AEFI (0.3%) resulted in an unknown outcome. When stratified by sex, the results were as follows: in males, 203 AEFIs (89.0%) resulted in recovery, 22 AEFIs (9.6%) resulted in improvement, two AEFIs (0.9%) resulted in sequelae, and one AEFI (0.4%) resulted in an unknown outcome; in females, 132 AEFIs (89.2%) resulted in recovery, 13 AEFIs (8.8%) resulted in improvement, and three AEFIs (2.0%) resulted in sequelae. When stratified by the inoculation site, the results were as follows: after injection in the thigh, 89 AEFIs (89.0%) resulted in recovery, seven AEFIs (7.0%) resulted in improvement, and four AEFIs (4.0%) resulted in sequelae, while after injection in the upper arm, 246 AEFIs (89.1%) resulted in recovery, 28 AEFIs (10.1%) resulted in improvement, one AEFI (0.4%) resulted in sequelae, and one AEFI (0.4%) resulted in an unknown outcome.

In the AEFI causality assessment, 258 (68.6%) were evaluated as being consistent with having been caused by the immunization, and 40 (10.6%) were considered inconsistent. For 53 AEFIs (14.1%), causality was considered uncertain, and 25 AEFIs (6.6%) were deemed unclassifiable. When stratified by sex, in males, 150 AEFIs (65.8%) were evaluated as consistent, 28 (12.3%) were considered inconsistent, 33 (14.5%) were considered uncertain, and 17 (7.5%) were unclassifiable. In females, 108 AEFIs (73.0%) were evaluated as "consistent", 12 (8.1%) were considered "inconsistent", 20 (13.5%) were considered "uncertain", and eight (5.4%) were unclassifiable. When stratified by vaccination site, after inoculation in the thigh, 70 AEFIs (70.0%) were evaluated as consistent, nine (9.0%) were considered inconsistent, 12 (12.0%) were uncertain, and nine (9.0%) were considered unclassified. After inoculation in the upper arm, 188 AEFIs (68.1%) were evaluated as consistent, 31 (11.2%) were considered to be inconsistent, 41 (14.9%) were "uncertain", and 16 (5.8%) were unclassifiable (Table 4).

AEFI onset time after DTaP IPV/Hib vaccination

The onset of symptoms ranged from the vaccination day (minutes) to 16 days (384 h) after vaccination. The median interval between vaccination and the onset of symptoms was 22.7 h. Stratified by the inoculation dose, the median interval after the first inoculation was one day and 3.9 h (27.9 h); the median interval after the second inoculation was one day and one hour (25 h); the median interval after the third inoculation was one day and 2.2 h (26.2 h), and the median interval after the fourth inoculation was

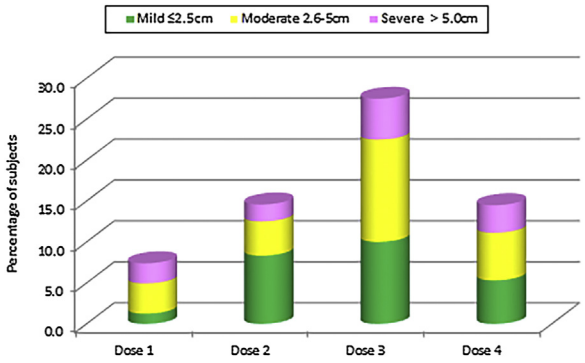

Figure 3. AEFI injection site induration level of DTaP IPV/Hib vaccine in different doses.

19.4 h. The median time to the onset of symptoms was 20.5 h for males and one day and 2.1 h (26.1 h) for females. The median interval after thigh vaccination was one day and 4.4 h (28.4 h). The median interval after inoculation in the deltoid muscle was 20.6 h.

Thrombocytopenic purpura (TP)

In this study, four of the 376 cases of AEFIs after vaccination were TP, all of which occurred within three months after the first dose (0.8 per 100,000 doses). In 2012, one female patient developed TP after inoculation in the thigh; in 2013, one female developed TP after inoculation in the upper arm; and in 2016, two males developed TP after inoculation in the thigh. The median interval between inoculation and the onset of thrombocytopenic purpura was 4.5 days (range three to eight days). Four patients had no possible cause of TP other than vaccination, therefore, these cases were classified as vaccine responses. The case of thrombocytopenic purpura in 2012 occurred eight days after vaccination; the cases in 2013 and 2016 all occurred within 3–4 days after vaccination. Four cases were considered to be consistent with having been caused by the immunization.

Discussion

We summarized the results of adverse event monitoring after 516,158 doses of DTaP-IPV/Hib vaccine were administered in Guangzhou, China, from 2011 to 2017. The reported incidence of adverse events was 72.8 per 100,000. Most of the events were not serious; the reported incidence of serious adverse events was 1.5 per 100,000. The reported incidence of adverse events was 44.2 per 100,000 in males and 28.7 per 100,000 in females. Adverse events are more prevalent in males than in females, with those in males accounting for 60.7% of the total. The median interval between vaccination and the onset of AEFIs was 22.7 h. After the fourth dose, the median interval was 19.4 h; the median interval after other doses was 25.0–27.9 h. The onset time was 5.6 h earlier in males than in females, and the onset time was 7.8 h earlier after inoculation in the arm injection than after inoculation in the thigh. The incidences of injection site and systemic reactions and serious adverse events were similar to those in children in the United States and Canada (Guerra et al., 2009; Halperin, 2006; Hansen et al., 2016).

In this study, four patients developed thrombocytopenic purpura (TP) after the first dose (2–3 months), while the inoculation with the second, third, and fourth doses did not induce TP. This is similar to the report from Taiwan (Hsieh and Lin, 2010). Arya et al. reported that a boy who received four doses of the DPT vaccine (the fourth dose was administered at the age of four) developed TP (Arya et al., 1993). Thrombocytopenia caused by vaccination is very rare. Thrombocytopenia after vaccination is caused by autoantibodies that cross-react with antigen targets naturally present on platelets, which can be detected in approximately 80% of cases (Cecinati et al., 2013). These autoantibodies are mainly directed against platelet surface antigens, primarily IgM, and can be detected instantaneously in most children with acute TP (Perricone et al., 2014). In 2013, Jin et al. reported the development of purpura after the administration of the oral polio vaccine (Jin et al., 2013). TP after vaccination with the polio vaccine or Hib vaccine has not been reported. From 1992 to 2007, Canada and the United States reported the occurrence of TP after vaccination with tetanus and acellular pertussis (DTaP) vaccines (Sauvé and Scheifele, 2009; Woo et al., 2011). We suspect that the DTaP component of the DTaP IPV/Hib vaccine was the cause of TP, but it is difficult to determine which component of the DPT vaccine causes TP (Arya et al., 1993b).

After the first immunization, the local reactions at the vaccination site were relatively mild. After the first, second, and third doses, the incidence of redness or swelling was 22.2–25.0%, and most (8.3–14.8%) were in the range of 2.6–5 cm, while the incidence of reactions >5.0 cm was 2.5–5.0%. The incidence of swelling at the site of vaccination is usually higher after intensive immunization. A total of 53.1% of the patients had redness or swelling after the fourth dose of vaccination. Approximately 36.7% of the patients had redness or swelling between 2.6 and 5 cm in size, while 10.1% of the children had redness or swelling measuring >5.0 cm, and 6.3% of the children had redness or swelling measuring ≤2.5 cm. The needle length affects the speed of the development of a local reaction, and the use of a 1-inch needle can minimize the possibility of developing a reaction to the vaccine (Scheifele et al., 2005a). Also, Halperin et al. reported that using a local anesthetic lidocaine procaine (EMLA) patch did not interfere with the antibody response in infants aged two to six months and could safely and effectively relieve local pain. Pain relief increases the parents' satisfaction, which leads to improved compliance with the immunization schedule (Halperin et al., 2002). The immunological basis of the local reaction to the fourth dose is still uncertain, but the immune response rate in children with the highest incidence of local adverse reactions to pertussis toxin was significantly higher than that in children without local reactions. The

Table 3
Incidence of adverse events (AEFI) at different injection sites after DTaP IPV/Hib vaccination in Guangzhou, China from May 2011 to 2017 (n = 376).

times and site	1		2		3		4		Total	
	thigh	arm	thigh	arm	thigh	arm	thigh	arm	thigh	arm
n	30	51	26	22	20	20	24	183	100	276
% of all AEFIs reported (n=376)	8.0	13.6	6.9	5.9	5.3	5.3	6.4	48.7	26.6	73.4
Rate per 100,000 DTaP-IPV/ Hib doses distributed (n=516158)	5.8	9.9	5.0	4.3	3.9	3.9	4.6	35.5	19.4	53.5

Table 4
Evaluation of the results and causality of the individual case safety report (AEFI) of DTaP-IPV/Hib vaccination in Guangzhou in 2011–2017 (n = 376) according to vaccination times, gender and vaccination site.

Outcome and causality assessment			Outcomea				Causality assessmentb				Total
			Recovered	Improved	Sequelae	Unknown	Consistent	Inconsisten	Indeterminate	Unclassifiable	
First dose	Male	n(thigh)	11	2	2	0	9	2	2	2	15
		%	16.2	20.0	66.7	0.0	18.8	12.5	18.2	33.3	100
		n(arm)	31	6	0	0	22	8	4	3	37
		%	45.6	60.0	0.0	0.0	45.8	50.0	36.4	50.0	100
	Female	n(thigh)	14	0	1	0	8	2	4	1	15
		%	20.6	0.0	33.3	0.0	16.7	12.5	36.4	16.7	100
		n(arm)	12	2	0	0	9	4	1	0	14
		%	17.6	20.0	0.0	0.0	18.8	25.0	9.1	0.0	100
	Subtotal	n(thigh)	25	2	3	0	17	4	6	3	30
		%	36.8	20.0	100	0.0	35.4	25.0	54.5	50.0	100
		n(arm)	43	8	0	0	31	12	5	3	51
		%	63.2	80.0	0.0	0.0	64.6	75.0	45.5	50.0	100
		n(Male)	42	8	2	0	31	10	6	5	52
		%	61.8	80.0	66.7	0.0	64.6	62.5	54.5	83.3	100
		n(Female)	26	2	1	0	17	6	5	1	29
		%	38.2	20.0	33.3	0.0	35.4	37.5	45.5	16.7	100
		n	68	10	3	0	48	16	11	6	81
		%	84.0	12.3	3.7	0.0	59.3	19.8	13.6	7.4	100.0
Second doses	Male	n(thigh)	14	1	0	0	11	3	0	1	15
		%	33.3	20.0	0.0	0.0	40.7	33.3	0.0	33.3	100
		n(arm)	14	2	0	1	6	5	5	1	17
		%	33.3	40.0	0.0	100.0	22.2	55.6	55.6	33.3	100
	Female	n(thigh)	10	1	0	0	8	0	2	1	11
		%	23.8	20.0	0.0	0.0	29.6	0.0	22.2	33.3	100
		n(arm)	4	1	0	0	2	1	2	0	5
		%	9.5	20.0	0.0	0.0	7.4	11.1	22.2	0.0	100
	Subtotal	n(thigh)	24	2	0	0	19	3	2	2	26
		%	57.1	40.0	0.0	0.0	70.4	33.3	22.2	66.7	100
		n(arm)	18	3	0	1	8	6	7	1	22
		%	42.9	60.0	0.0	0.0	29.6	66.7	77.8	33.3	100
		n(Male)	28	3	0	1	17	8	5	2	32
		%	66.7	60.0	0.0	0.0	63.0	88.9	55.6	66.7	100
		n(Female)	14	2	0	0	10	1	4	1	16
		%	33.3	40.0	0.0	0.0	37.0	11.1	44.4	33.3	100
		n	42	5	0	1	27	9	9	3	48
		%	100	100	0	0	100	100	100	100	100
Third doses	Male	n(thigh)	11	1	0	0	5	2	4	1	12
		%	31.4	25.0	0.0	0.0	23.8	33.3	40.0	33.3	100
		n(arm)	10	1	0	0	4	3	4	0	11
		%	28.6	25.0	0.0	0.0	19.0	50.0	40.0	0.0	100
	Female	n(thigh)	7		1	0	6		1	1	8
		%	20.0	0.0	100.0	0.0	28.6	0.0	10.0	33.3	100
		n(arm)	7	2	0	0	6	1	1	1	9
		%	20.0	50.0	0.0	0.0	28.6	16.7	10.0	33.3	100
	Subtotal	n(thigh)	18	1	1	0	11	2	5	2	20
		%	51.4	25.0	0.0	0.0	52.4	33.3	50.0	66.7	100
		n(arm)	17	3	0	0	10	4	5	1	20
		%	48.6	75.0	0.0	0.0	47.6	66.7	50.0	33.3	100
		n(Male)	21	2	0	0	9	5	8	1	23
		%	60.0	50.0	0.0	0.0	42.9	83.3	80.0	33.3	100
		n(Female)	14	2	1	0	12	1	2	2	17
		%	40.0	50.0	0.0	0.0	57.1	16.7	20.0	66.7	100
		n	35	4	1	1	21	6	10	3	40
		%	100	100	0	0	100	100	100	100	100
Fourth doses	Male	n(thigh)	14	2	0	0	11	1	2	2	16
		%	7.4	12.5	0.0	0.0	7.0	10.0	7.7	15.4	100
		n(arm)	98	7	0	0	80	5	13	7	105
		%	51.6	43.8	0.0	0.0	50.6	50.0	50.0	53.8	100
	Female	n(thigh)	8	0	0	0	8	0	0	0	8
		%	4.2	0.0	0.0	0.0	5.1	0.0	0.0	0.0	100
		n(arm)	70	7	1	0	59	4	11	4	78
		%	36.8	43.8	100	0.0	37.3	40.0	42.3	30.8	100
	Subtotal	n(thigh)	22	2	0	0	19	1	2	2	24
		%	11.6	12.5	0.0	0.0	12.0	10.0	7.7	15.4	100
		n(arm)	168	14	1	0	139	9	24	11	183
		%	88.4	87.5	0.0	0.0	88.0	90.0	92.3	84.6	100
		n(Male)	112	9	0	0	91	6	15	9	121
		%	58.9	56.3	0.0	0.0	57.6	60.0	57.7	69.2	100
		n(Female)	78	7	1	0	67	4	11	4	86
		%	41.1	43.8	0.0	0.0	42.4	40.0	42.3	30.8	100
		n	190	16	1	1	158	10	26	13	207
		%	100	100	0	0	100	100	100	100	100
Total	Male	n(thigh)	50	6	2	0	36	8	8	6	58
		%	14.9	17.1	40.0	0.0	14.2	19.5	14.3	24.0	100
		n(arm)	153	16	0	1	112	21	26	11	170
		%	45.7	45.7	0.0	100	44.1	51.2	46.4	44.0	100
	Female	n(thigh)	39	1	2	0	30	2	7	3	42
		%	11.6	2.9	40.0	0.0	11.8	4.9	12.5	12.0	100
		n(arm)	93	12	1	0	76	10	15	5	106
		%	27.8	34.3	20.0	0.0	29.9	24.4	26.8	20.0	100
	Subtotal	n(thigh)	89	7	4	0	66	10	15	9	100
		%	26.6	20.0	0.0	0.0	26.0	24.4	26.8	36.0	100
		n(arm)	246	28	1	1	188	31	41	16	276
		%	73.4	80.0	0.0	0.0	74.0	75.6	73.2	64.0	100
		n(Male)	203	22	2	1	148	29	34	17	228
		%	60.6	62.9	0.0	0.0	58.3	70.7	60.7	68.0	100
		n(Female)	132	13	3	0	106	12	22	8	148
		%	39.4	37.1	0.0	0.0	41.7	29.3	39.3	32.0	100
		n	335	35	5	1	254	41	56	25	376
		%	100	100	0.0	0.0	100	100	100	100	100

a. Classification according to the results of the national monitoring program for suspected abnormal vaccination reactions issued by the Ministry of health and the State Food and Drug Administration

b.According to the WHO classification user manual (Second Edition) revised by the World Health Organization (who) in 2018 ISBN 978-92-4-151365-4

Evaluate the causal relationship of AEFI.

n(thigh): Number of thigh intramuscular injection

n(arm):Number of injections into deltoid muscle of upper

possible reason for the increase in local reactions is the presence of an aluminum adjuvant in the main vaccine series, which is generally considered to be required to achieve the best immune response. Aluminum is also an effective inducer of IgE. The production of IgE antibodies against pertussis toxin is induced by the acellular pertussis vaccine, especially in children with local reactions after enhanced immunization (Mark et al., 1995; Edelman et al., 1999). Although the benefits of vaccination far outweigh the hazards of local reactions, adverse reaction rates can affect people's confidence in vaccination. Therefore, vaccine companies ought to look for alternative adjuvants to replace aluminum.

From May 1, 2011, to December 31, 2017, approximately 517,000 doses of DTaP-IPV/Hib vaccine were administered in Guangzhou. Most reported AEFIs were not serious, such as fever, redness or swelling, rash, and induration. A total of 2.1% (eight cases) of the AEFIs were severe (SAE), which was lower than the 16.1% (28 cases) reported in the United States in 2018, and 4.8% (29 cases) reported in Canada in 2005 (Klein et al., 2019; Scheifele et al., 2005b). The majority of SAEs occurred after the first immunization, with five cases after the first dose, and one case each after the second, third, and fourth doses; there were five cases after inoculation in the thigh and three cases after inoculation in the upper arm. There were five cases in males and three cases in females. There were no deaths. At the time of reporting, most SAEs resulted in complete recovery, and all were considered to be the result of vaccination.

Conclusions

Most of the reported AEFIs after DTaP-IPV/Hib vaccination are not serious. There were four cases of TP in this study, and vaccination may be a rare cause of thrombocytopenic purpura.

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Conflicts of interest

None.

Author contribution

ZQL made substantial contributions to the conception and design of the study. JXX, HFT、CHZ、JC、LHN、XXY contributed to the acquisition of data and YH、WW made a substantial contribution to the analysis of data. All authors were involved in the writing, reviewing, and editing of the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work.

Ethical approval

This article is based on a retrospective study and was conducted oncases of adverse events during DTaP IPV/Hib vaccination using theChinese national surveillance system for post-immunization adverse events (CNAEFIS). The study does not contain any intervention onhuman participants or animals. No AEFI patient identifying information regarding treatment details are disclosed in this manuscript.

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