HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 1, e2021711 (7 pages)
https://doi.org/10.1080/21645515.2021.2021711

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RESEARCH PAPER

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Surveillance on the adverse events following immunization with the pentavalent vaccine in Zhejiang, China

Xuejiao Pan, Huakun Lv, Hui Liang, Ying Wang, Linzhi Shen, Fuxing Chen, Yaping Chen, and Yu Hu

Institute of Immunization and Prevention, Zhejiang Center for Disease Control and Prevention, Hangzhou, China

ABSTRACT

Objectives: The aim of this study is to describe the reporting rate of adverse events following immunization (AEFI) with pentavalent vaccine: diphtheria-pertussis-tetanus-poliomyelitis-Haemophilus influenzae type b (DPT-IPV/Hib), and to determine whether the reporting rate of AEFI following DPT-IPV/Hib was higher than the average level of the other vaccines.

Methods: Review and describe the AEFI reported to national adverse event following immunization surveillance system (NAEFISS) in Zhejiang province from 2015 to 2020. Reporting rates of AEFI were calculated by age, city, severity of AEFI, categories of AEFI, and reaction categories. The data mining algorithm used in this study was reporting odds ratio (ROR). A value of ROR-1.96SE >1 (standard error [SE]) was considered as positive signal.

Results: NAEFISS received 5726 AEFI reports following DTP-IPV/Hib, with a reporting rate of 20.01/10000 doses. Of the reported AEFI, 202 were serious vaccine product-related reactions, including two cases of anaphylactic shock, five cases of Guillain Barre Syndrome (GBS) and two cases of acute disseminated encephalomyelitis. The reporting rate of fever/redness/induration was the highest among all the clinical diagnosis (14.97/10000 doses). The positive signals were obtained for allergic rash (ROR-1.96SE: 1.36), febrile convulsion (ROR-1.96SE: 1.32) and GBS (ROR-1.96SE: 1.16).

Conclusion: The present findings bolstered that the DTP-IPV/Hib administered as the four-dose schedule was generally well tolerated in Chinese infants as we did not identify any new/unexpected safety concern from the NAEFISS during a six-year timespan.

ARTICLE HISTORY
Received 17 September 2021
Revised 30 November 2021
Accepted 17 December 2021

KEYWORDS
AEFI (adverse events following immunization); DPT-IPV/Hib(diphtheria-pertussis-tetanus-poliomyelitis-Hib combined vaccine); surveillance; vaccination; safety

Introduction

Vaccination is considered as one of the fundamental components of public health policies for preventing or controlling the infectious diseases[1]. The incidence rates of many vaccine-preventable diseases (VPDs), such as diphtheria, tetanus, pertussis, invasive hemophilus influenza type b (Hib) and poliomyelitis, have successfully led to the regional eradication and elimination through vaccination programs, making vaccination as one of the most reliable and cost-effective public health interventions.[2] According to estimates from World Health Organization (WHO),[3] approximately two million deaths among children under 5 years of age can be prevented annually, which makes the vaccination program as one of the most reliable and cost-effective public health interventions.

The vaccination against diphtheria, pertussis, and tetanus has been mandatory for all infants under the Chinese expanded program on immunization (EPI) since 1978. In the last decade, the vaccination coverage of DPT reached and maintained at 99% and the annual incidence of reported cases of diphtheria, pertussis, and tetanus decreased to a record low (<0.5 cases per 100,000 population).[4] The current schedule of the combined diphtheria, pertussis, and tetanus vaccine (DPT) includes a three-dose primary vaccination at three, four and 5 months of age, and a booster dose at 18 months of age.

The use of oral live attenuated poliomyelitis vaccine (OPV) has led to the certified polio-free in China by the WHO in 2000.[5] However, the OPV has two defects: one is the vaccine associated paralytic poliomyelitis, which is due to the reverse mutations of the live attenuated vaccine strains and results in neurovirulence; the other is the circulation of the vaccine-derived strains, which remains a potential threat to outbreaks of poliomyelitis. The introduction of the inactivated poliomyelitis vaccine (IPV) has resolved these defects. The current schedule of the poliomyelitis vaccine comprises two doses of IPV at two, 3 months of age and two doses of OPV at 4 months and 4 years of age.

Hib is a leading cause of the childhood bacterial meningitis, pneumonia, and other serious invasive infections.[6] Approximately 3 million serious cases and 400,000 to 700,000 deaths among children are caused by Hib infection in each year over the world.[2] WHO has recommended that Hib conjugate vaccine should been integrated into the routine vaccination program.[7] Hib conjugate vaccine has been licensed since 2000 in China as a self-paid vaccine. However, the vaccination coverage is still low as the lack of a formal national recommendation for its use and the exclusion of EPI, resulting an estimated 19,000 childhood deaths from Hib infection each year in China.[6]

Multivalent vaccines or combination vaccines allow the administration of multiple antigens in a single injection, offering significant advantages over the single or monovalent

CONTACT Yu Hu husix@163.com Institute of Immunization and Prevention, Zhejiang Center for Disease Control and Prevention, No. 3399 Binsheng Road, Binjiang District, Hangzhou, P.R. China

vaccines.[8–10] For example, increasing the receipt' s compliance and acceptance and higher vaccination coverage, reducing the visits of vaccination clinic and the related costs, as well as increasing the parental consent. Moreover, using the combination vaccine can also benefit the vaccination providers, such as minimizing the risk of administration errors and missed doses and decreasing the logistical challenges and operational costs. The diphtheria-pertussis-tetanus-poliomyelitis-Hib combined vaccine (DPT-IPV/Hib) has been licensed in China since 2011, and its vaccination schedule includes four doses at 2, 3, 4 and 18 months of age. DTP-IPV/Hib has been demonstrated to be well tolerated and immunogenic in previous studies conducted in infants in other countries outside China.[11,12]

Continuous assessment of the safety analysis of the post-licensure vaccines can evaluate the benefit-risk profiles of a specific vaccine that cannot be evaluated in pre-licensure clinical trials due to sample size limitations.[13] Public trust in vaccines can also be strengthened by monitoring the vaccine safety. Surveillance of adverse events following immunization (AEFI) enables us to monitor the safety of vaccination programs and thereby contribute to validating the vaccination program. In this way, the undesirable adverse events of the immunization program can be effectively managed, and any inappropriate measures based on reports of AEFI that may cause concern in society can be prevented. China Ministry of Health (MOH) has established a nation-wide AEFI surveillance since 2005, with the technical support of WHO and the experience from other countries.[14] The national AEFI surveillance system (NAEFISS) was a passively collected spontaneous database, which was established in 2008 and was upgraded in 2012 by adding variables of the case reporting form and improving the logic control of data entry and statistical functions.

The aim of this study was to examine the reporting rate of AEFI following DPT-IPV/Hib by causal categories and severity according to the guidance for AEFI surveillance of China. We also used the disproportionality analysis to determine whether the reporting rate of AEFI following DPT-IPV/Hib was higher than the average level of the other vaccines. Our findings might help policy-makers in their decisions to continue adjusting its vaccination schedule or introducing it into vaccination programs.

Methods

Study design

This study was a retrospective descriptive study for the AEFI following DPT-IPV/Hib, based on the NAEFISS from 2015 to 2020.

Setting

Zhejiang is a developed province with a large population of 70 million people in eastern areas of China. Of the total population, 7.23% children were under 7 years of age, 7.43% were 7–15 years old and 84.34% were above 15 years of age. Zhejiang province launched the EPI since 1978 with four vaccines and it continued to increase the number of vaccines up to 11 to date and with the administration of 20 million doses of vaccines every year.

NAEFISS was established by China center for disease control and prevention (CDC) as a national spontaneous reporting system for AEFI following all of the vaccines marketed in mainland China and Zhejiang province joined in the NAEFISS in 2009[13]. The NAEFISS aimed to detect the new, unusual, or rare AEFIs, evaluate the safety of newly licensed vaccines, identify potential risk factors for AEFIs, monitor increases in known AEFIs, determine the possible reporting clusters, and provide a reliable safety monitoring system that extends to the entire population.

AEFI reporting and investigation procedures

In June 2010, MOH and China Food and Drug Administration (CFDA) jointly issued national AEFI guidance.[14] According to this guidance, any AEFI should be reported mandatorily when it was detected by these authorized reporters, including health-care facilities, CDC at any administrative levels, adverse drug reaction (ADR) monitoring agencies, and vaccine manufacturers executive staff. In addition, the public or the caregivers could notify any of the above authorized reporters to report an AEFI. AEFI reports were gathered by local, county-level CDCs, which were responsible for completing AEFI case reporting cards and submitting data to the NAEFISS. Once AEFI information was entered, it could be viewed by all administrative levels of CDCs and ADRs.

Each AEFI case should be investigated and the relevant information should be entered into the NAEFISS online, including the information on the vaccinated individual, storage and transportation of vaccines, vaccine administrations and the AEFI itself. Signs and symptoms of AEFI were coded using the international classification of diseases (version 10.0, ICD-10), a clinically validated, internationally standardized terminology.[15] A single AEFI report might be assigned more than one term and be referred to more than one suspected vaccine. In cases of co-administration of two or more vaccines in an individual, we attributed the reported AEFI to the reporter suspected vaccine according to the following principle: (1) the injection site reaction could be determined by the record of vaccination; (2) the systematic reactions could not be determined which vaccine was to be suspected when the co-administration occurred. In that case, we attributed the reported AEFI to all vaccines co-administrated.

Variables

An AEFI was defined as a reaction or an event following vaccination that was suspected to be related to the vaccination according to the guidance for AEFI surveillance, supported by the Law on the Prevention and Treatment of Infectious Diseases of the People's Republic of China, the Pharmaceutical Administration Law of the People's Republic of China, and other laws and regulations.

Expert panel, which was composed of independent experts from clinical medicine, epidemiology, laboratory practices, pharmacy, vaccinology, vaccine regulation, and other relevant fields, was organized to review the reported AEFIs and to make the classification.[16]

All AEFI records were divided into five categories: (1) vaccine product-related reaction (non-serious reaction and serious reaction); (2) vaccination error; (3) vaccine quality defect-related reaction; (4) coincidental event; (5) anxiety reaction. Similarly, all AEFI records were assessed as non-serious or serious: (1) non-serious, with no intervention necessary or with physician visit or event interfering with daily activities or loss of working hours; (2) serious, with any untoward medical occurrence that results in death, hospitalization, prolongation of hospitalization, persistent or significant disability/incapacity, life threatening or birth defect.

Data sources

In this study, AEFI records following the DTP-IPV/Hib were reported from January 01, 2015 to December 31, 2020. The AEFI were extracted from the national AEFI surveillance system on March 1, 2021, when all the revision or modification of each case report had been done. The number of various vaccines doses in Zhejiang province from 2015 to 2020 was obtained from the online individual immunization information system of Zhejiang province (ZJIIS),[17] which was established in 2005.

Statistical Methods

A database was organized as an Excel file (Microsoft Office Excel 2020). The AEFI reporting rates of DPT-IPV/Hib were calculated dividing the doses administered in Zhejiang province during the study period, by the variables including gender, dose number, the AEFI onset interval (from vaccination date [day 0] to onset of first symptoms), AEFI categories, severity, type of reporter and the clinical diagnosis. These reporting rates between these variables were compared through chi-square tests at a two-tail significance of 0.05. We graphically depicted monthly reporting rates in the study period to display the reporting trends.

Disproportionality analysis was applied by using the algorithm of reporting odds ratio (ROR).[18] The ROR was the ratio of the odds of reporting of one specific AEFI versus all other AEFIs for a given vaccine compared to the reporting odds for all other vaccines present in the database. Generally, a value of ROR-1.96SE >1 (standard error [SE]) was considered as a cutoff value and it was considered as a positive signal if the ROR above the threshold value. The higher the value, the stronger the disproportion appears to be. The positive signal meant that the reporting rate of DTP-IPV/Hib was higher than the average level of the other vaccines.

Results

From 2015 to 2020, NAEFISS received 5726 AEFI reports following DTP-IPV/Hib without any duplicated reports and death reports. During the study period, 2860884 doses of DTP-IPV/Hib were administered and the crude reporting rate of AEFI following DTP-IPV/Hib was 20.01/10000 doses, while the reporting rate of serious AEFI was 0.79/10000 doses (Figure 1).

The reporting rate of AEFI following DTP-IPV/Hib was significantly higher among the vaccine for receiving the 4th dose (25.92/10000 doses). The reporting rate of the minor vaccine product-related reaction (19.09/10000) was significantly higher than other categories of AEFI. Most of the AEFI was non-serious, with a reporting rate of 19.22/10000

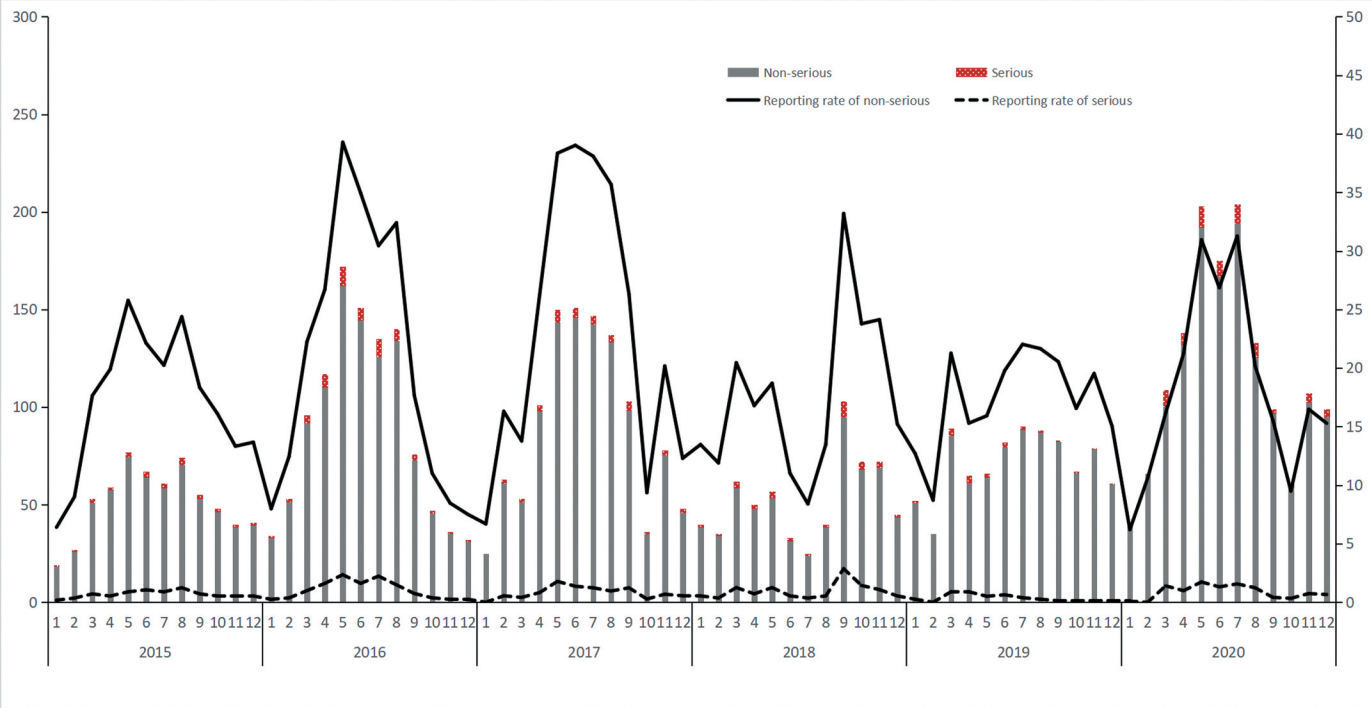

Figure 1. The reporting rate of AEFI following DPT-IPV/Hib from 2015 to 2020, by month of onset.

doses. The reporting rate of AEFI was higher among those reported by caregivers, with a rate of 17.27/10000 doses. The majority of AEFI occurred in 48 hours after vaccination, with a reporting rate of 12.57/10000 doses (Table 1).

The reporting rate of the total AEFI was the highest in Wenzhou city (24.17/10000 doses), and the reporting rate of serious AEFI was the highest in Quzhou city (1.75/10000 doses). The reporting rate of the total AEFI was the lowest in Zhoushan city (15.28/10000 doses), and the reporting rate of serious AEFI was the lowest in Lishui city (0.97/10000 doses) (Table 2).

After a thorough review of the clinical diagnoses of the 5276 reports, 202 were serious vaccine product-related reactions. Of them, the majority were urticarial (107 reports), followed by aseptic abscess (25 reports), angioedema (21 reports), allergic purpura (15 reports), thrombocytopenic purpura (12 reports), febrile convulsion (12 reports), Guillain Barre Syndrome (GBS) (5 reports), anaphylactic shock (2 reports), acute disseminated encephalomyelitis (2 reports), epilepsy (1 report). Among the 5460 minor vaccine product-related reactions, fever/redness/induration was the most common AEFI (4255 reports), followed by allergic rash (1202 reports). The reporting rate of fever/redness/induration was the highest among all the clinical diagnosis (14.97/10000 doses), followed by allergic rash (4.02/10000 doses) and urticarial (0.38/10000 doses). The positive signals were obtained for allergic rash (ROR-1.96SE: 1.36), febrile convulsion (ROR-1.96SE: 1.32) and GBS (ROR-1.96SE: 1.16) (Table 3).

Discussion

Vaccination is among the most significant public health success stories of all time. However, like any pharmaceutical product, no vaccine is completely safe or completely effective. For example, the antigen components and other ingredients in the vaccine may cause allergic reactions. For the combined vaccine, the complex components would have the physical and chemical interactions, which can trigger the undesirable variation in the immune response to vaccines.[19] In this study, we attempted to evaluate the reporting rate of AEFI associated with the DTP-IPV/Hib to evaluate the safety of this combined vaccine. As we known, it was the first report that aimed to provide evidence regarding the safety profile of the DTP-IPV/Hib in Zhejiang province.

Table 1. Characteristics and reporting rate of AEFI reports following DPT-IPV/Hib from 2015 to 2020.

Variable	Level	Administered doses	AEFI reports	Reporting rate*	χ^2	*p*
		2860884	5726			
Gender	Male	1430420	2858	19.98	6.22	>.05
	Female	1430464	2868	20.05		
Dose number	1	730223	1066	14.60	201.62	<.01
	2	721654	1304	18.07		
	3	711423	1548	21.76		
	4	697584	1808	25.92		
Category	Vaccine product-related reaction (minor)	2860884	5460	19.09	338.29	<.01
	Vaccine product-related reaction (severe)	2860884	202	0.71		
	Vaccination error	2860884	17	0.06		
	Coincidental event	2860884	42	0.15		
	Anxiety reaction	2860884	5	0.02		
Severity	Serious	2860884	227	0.79	280.45	<.01
	Non-serious	2860884	5499	19.22		
Type of reporter	Health care provider	2860884	778	2.72	163.82	<.01
	Caregivers	2860884	4941	17.27		
	Manufacturer	2860884	7	0.02		
Onset from vaccination	0–1d	2860884	3597	12.57	118.5	<.01
	2–3d	2860884	1507	5.27		
	4–7d	2860884	367	1.28		
	8–14d	2860884	177	0.62		
	≥15d	2860884	78	0.27		
Administrated alone		2577129	5211	20.22		

*: /10000 doses.

Table 2. Serious AEFI and non-serious AEFI reports following DPT-IPV/Hib from 2015–2020, by city.

		AEFI reports		Serious AEFI reports		Non-serious AEFI reports	
City	Administered doses	No.	Reporting rate*	No.	Reporting rate*	No.	Reporting rate*
Hangzhou	789244	1609	20.39	125	1.58	1484	18.80
Ningbo	710320	1335	18.79	111	1.56	1224	17.23
Wenzhou	288818	698	24.17	44	1.52	654	22.64
Jiaxing	271362	547	20.16	41	1.51	506	18.65
Huzhou	101275	200	19.75	17	1.68	183	18.07
Shaoxing	208334	380	18.24	32	1.54	348	16.70
Jinhua	182077	399	21.91	28	1.54	371	20.38
Quzhou	45776	87	19.01	8	1.75	79	17.26
Zhoushan	29456	45	15.28	4	1.36	41	13.92
Taizhou	172477	309	17.92	28	1.62	281	16.29
Lishui	61744	117	18.95	6	0.97	111	17.98
Total	2860884	5726	20.01	444	1.55	5282	18.46

*: /10000 doses.

Table 3. Clinical diagnosis of AEFI reports following DPT-IPV/Hib from 2015–2020.

Clinical diagnosis	No. of AEFI reports					Reporting rate*	ROR-1.96SE
	Vaccine product-related reaction(minor)	Vaccine product-related reaction(severe)	Coincidental event	Anxiety reaction	Vaccination error		
Aseptic abscess	0	25	0	0	0	0.09	0.83
Urticaria	2	107	0	0	0	0.38	0.92
Allergic purpura	0	15	3	0	0	0.06	0.78
Thrombocytopenic purpura	0	12	3	0	0	0.05	0.92
Angioedema	0	21	0	0	0	0.07	0.53
Febrile convulsion	1	12	2	0	0	0.05	1.32
Anaphylactic shock	0	2	0	0	0	0.01	0.70
Guillain Barre Syndrome	0	5	6	0	0	0.04	1.16
Epilepsy	0	1	6	0	0	0.02	0.59
Cellulitis	0	0	4	0	10	0.05	0.62
Acute disseminated encephalomyelitis	0	2	3	0	0	0.02	0.73
Allergic rash	1202	0	0	0	0	4.20	1.36
Fever/redness/induration	4255	0	15	5	7	14.97	0.59

*: /10000 doses.

The results of this study showed that the reporting rate of AEFI following DTP-IPV/Hib was 20.01/10000 doses, which was lower than an active surveillance study implemented in Chinese infants but was similar to the studies of the passive surveillance from Netherlands[20] and U.K.[21] A high reporting rate of AEFI accompanying by a lower rate of serious AEFI observed in this study indicated that the NAEFISS was sensitive and DTPa-IPV/Hib administered at 2, 3, 4 and 18 months of age was generally well tolerated in Chinese infants. Another finding in this analysis was that the reporting rates for general and serious AEFI associated with DTP-IPV/Hib were higher than those for all the vaccines used in Zhejiang province in 2019 (5.66/10000 doses for the general AEFI and 0.57/10000 doses for the serious AEFI).[13] These serious AEFI reports included urticarial, aseptic abscess, angioedema, allergic purpura, thrombocytopenic purpura, febrile convulsion, GBS, anaphylactic shock, acute disseminated encephalomyelitis, epilepsy.We also found that allergic rash, febrile convulsion and GBS as a positive signal for the higher reporting rate of AEFI associated with DTP-IPV/Hib. Although the reporting rates of these serious AEFI were still at low level, some of them were considered as the positive signals and were not found in the the pre- or post-safety studies or pharmacovigilance data (discussed below). It was assumed that the variety of antigens and followed by containing a higher amount of antigens in the combined vaccines would be the main reason for the higher reporting rate of AEFI.

We observed no significant difference in the reporting rate of AEFI between male and female, which was consistent with the previous reports.[8,22] A comparison of the reporting rate of AEFI between doses showed that the probability of AEFI for the later doses was significantly higher than that for the initial dose. It was similar to the findings from AEFI reports on other vaccines,[23,24] which could be explained as the subsequent dose was more likely to cause allergic reactions due to the body sensitization by the early dose. The most frequently reported AEFI following DTP-IPV/Hib was categorized as the minor vaccine product-related reaction or non-serious. Our findings was consistent with the results obtained from a meta-analysis,[25] in which the minor reactions such as pain and redness were more prevalent among the children received the combined vaccines. Our previous reports also revealed that the majority of the AEFI were non-serious events.[13] Of them, fever and injection site reaction were the most common forms of reactogenicity experienced after immunization.

Similar to the previous reports,[13,16] most of the AEFI cases were reported by caregivers in this study, which would provide more sufficient identifying information and help the following medical review for inducing a confirmed category. On the other hand, it would also induce the report bias that caregivers would not be sensitive enough or even ignored to some mild AEFI. In this study, majority of AEFI reports were onset on the day of vaccination, which was consistent with the previous reports on the surveillance of AEFI for all vaccines used in Zhejiang province.[13] The interval between vaccination and onset of AEFI was generally very short for the most frequent AEFI, such as fever or rash. Most of the AEFI associated with DTP-IPV/Hib was in the case of being administered alone in our analysis. The package insert recommends that the DTP-IPV/Hib better not to be co-administered with other vaccines and we assumed it would be the main reason for this finding. The reporting rates of AEFI were different between cities, which was similar to the findings from other counties' AEFI passive surveillance system.[26–28] It indicated the sensitivity of the AEFI surveillance system was not consistent across different areas. It was likely to know the disparities in the notification or investigation of AEFI might exist among different cities. Further study to evaluate and compare AEFI surveillance sensitivity across cities would help to elucidate it.

In our study, we found the highest reporting rate of AEFI was observed for fever/redness/induration, but it did not present as a positive signal. This finding was similar to the Iranian studies on the AEFI following DTP and pentavalent vaccination, in which mild fever was found to be the most commonly experienced complication that occurred after vaccination.[29,30] Furthermore, we compared our results with the a report from Indian,[31] which had monitored the AEFI following a hexavalent vaccine during one month after administration. They found that 37.9% of the infants experienced the injection site reaction and 54.6% experienced the systemic reaction, respectively.

Allergic rash is a common clinical manifestation of the hypersensitivity reactions. We found the allergic rash as a positive signal of the AEFI associated with DTP-IPV/Hib in

this study. All of them were mild, which was consistent with the pre- and post- licensure studies.[16] To our knowledge, most of the antigens in vaccine are heterologous proteins, which can cause the allergic reactions to the recipients. The autoimmune disorders is considered as a kind of the adverse reaction following vaccination and GBS is a autoimmune disorder that affects the nervous system although it is rare. Previous post-licensure surveillance data on DTP-IPV/Hib did not indicate the GBS as a frequently reported AEFI.[20,21] However, our finding was inconsistent with the previous reports from other settings, in which we identified the GBS as a positive signal although the reporting rate was very low.[13] It was assumed that the complex clinical diagnosis standard and the sensitivity in determining the association between vaccination and GBS might induce the over-reporting of GBS. Febrile convulsion was a pre-identified adverse reaction of significant interest. As similar to the previous report,[32] we observed the febrile convulsion as a positive signal of AEFI following DTP-IPV /Hib. The reporting rate of febrile convulsion was 0.05/10000 doses in our analysis, which was very similar to that report of 0.43/100,000 doses.[32] Another study[33] indicated that the incidence of febrile convulsion was under 0.1% for the first and second dose, and was at 0.1% following the third- or fourth-dose booster. Other severe vaccine product-related reactions, such as aseptic abscess, angioedema, allergic purpura, thrombocytopenic purpura, anaphylactic shock, acute disseminated encephalomyelitis and epilepsy, were not found as the positive signal for the higher reporting rates of AEFI. Our results were different with the findings from the previous reports.[32,34] The possible reasons would be the guidance or standard of the causality assessment of AEFI, as well as the capacity of the expert panel for the category of AEFI were inconsistent among different areas.

Vaccination safety had become as important as the efficacy of the VPDs control. Unlike drugs, vaccines were usually administered to healthy people. Hence, the problems arising from the vaccine or vaccination were less acceptable to the general public. Widespread concern about the occurrence of AEFI might lead to a loss of confidence in the safety of vaccines, low vaccination coverage, and even a resurgence of VPDs. Vaccine safety monitoring in post-licensure surveillance had relied primarily on passive reporting systems. The NAEFISS has a horizon of scope and could provide the important signals that needed further evaluation and could address the limitation of the pre-licensure surveillance through observing more vaccinated individuals.

There were still several limitations. First, the signals detected could not be confirmed as this study was lack of the control group. We recommended to conduct the extensive studies or collect pharmacological evidence to address this limitation. Second, reporting bias and information bias could not be well controlled as this study was based on a passive surveillance system. It would affect the accuracy of the results and should be addressed in the future active surveillance studies. Considering to the above limitations, our findings of AEFI from the real-world application could complete and supplement the safety profile of DTP-IPV/Hib after its licensure.

Conclusion

DTP-IPV/Hib is a pediatric-combined vaccine that can simplify the vaccination schedules, reduce the number of injections, increase the acceptance, and finally improve the vaccination coverage. The present findings bolstered that the DTP-IPV /Hib administered as the four-dose schedule was generally well tolerated in Chinese infants as we did not identify any new/unexpected safety concern from the NAEFISS during a six-year timespan. This evaluation would serve as a reference for discussing the benefits and risks of the combined vaccines.

Acknowledgments

We are grateful to all physicians in all health centers and different administrative CDCs in Zhejiang province, for reporting, collecting and collating the AEFI records.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This study was funded by medical and health science and technology project of Zhejiang province [Grant number: 2020KY522, 2020KY516, 2020KY091].

Ethics approval and consent to participate

This study was approved by the ethical review board of Zhejiang provincial CDC. All the data were anonymous when we exported them from ZJIIS and kept confidential without individual identifiers.

Author contributions

Y.H. and XJ. P conceived and designed the experiments; H.L. and Y. C. performed the experiments; HK. L. and Y.W. analyzed the data; LZ. S. and FX. C. contributed reagents/materials/analysis tools; XJ. P and Y. H. wrote the paper.

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