Vital Surveillances

Post-Marketing Surveillance of Adverse Events Following Immunization with *Haemophilus Influenzae* Type b Conjugate Vaccine — China, 2010–2021

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ABSTRACT

Introduction: The *Haemophilus influenzae* type b (Hib) conjugate vaccine is widely administered in China.

Methods: We extracted data on Hib vaccine doses administered and adverse events following immunization (AEFI) reported between 2010 and 2021 from the Chinese National Immunization Information System (CNIIS). A descriptive analysis was conducted to examine the characteristics and incidence rates of AEFI with the Hib vaccine.

Results: In China, between 2010 and 2021, a total of 52,910 AEFIs with the Hib vaccine were reported, resulting in an overall AEFI reporting rate of 38.10 per 100,000 doses. Common (typically minor) and rare (potentially serious) vaccine reactions occurred at rates of 34.71 and 2.78 per 100,000 doses, respectively. Among the common vaccine reactions, the incidences of fever (axillary temperature ≥38.6 ℃), injection site redness and swelling (>2.5 cm in diameter), and injection site induration (>2.5 cm in diameter) were 11.93, 9.69, and 3.38 per 100,000 doses, respectively. Rare vaccine reactions included anaphylactic rash, angioedema, and febrile convulsion with reported incidences of 2.42, 0.10, and 0.05 per 100,000 doses, respectively. The incidence of serious rare vaccine reactions was 0.16 per 100,000 doses.

Conclusions: The reported incidence of AEFI with the Hib vaccine was low, with the occurrence of serious rare adverse reactions also being markedly low throughout the period 2010–2021 in China.

Haemophilus influenzae type b (Hib) is a major pathogen responsible for serious illnesses in young children, including pneumonia, meningitis, septicemia, suppurative arthritis, and other invasive infections. The World Health Organization (WHO) estimated that in 2008, approximately 203,000 children under the age of five succumbed to invasive Hib diseases globally (*1*). The Hib conjugate vaccine (Hib vaccine) has proven to be highly effective in preventing these diseases. In China, the Hib vaccine is one of the most broadly utilized vaccines in the non-National Immunization Program (non-NIP). This study analyzed surveillance data on adverse events following immunization (AEFI) with the Hib vaccine, as reported to the Chinese National Immunization Information System (CNIIS) from 2010 to 2021. Notably, this analysis does not include data from Hong Kong SAR, Macau SAR, and Taiwan, China. The findings offer substantial evidence supporting further post-marketing safety assessments of the Hib vaccine.

METHODS

AEFI cases with the Hib vaccine, reported between 2010 and 2021, were sourced from the CNIIS AEFI surveillance module. Data on the number of Hib vaccine doses administered during the study period were obtained from the CNIIS vaccination surveillance module.

Hib vaccines, authorized by various marketing authorization holders (MAHs), are approved for administration in children aged 2 months to 5 years. The standard immunization schedule includes three primary-series doses, administered monthly beginning at 2–3 months, followed by a booster dose at 18 months. Infants initiating Hib vaccination between 6–12 months receive two doses, while children who begin their vaccination between 1–5 years receive a single dose.

AEFI surveillance is conducted in compliance with applicable laws, regulations, and guidelines (*2*–*3*). Various entities, including medical institutions, vaccination providers, MAHs, CDCs, and medical

associations, have distinct roles in the reporting, investigation, and causality assessment of AEFIs. AEFIs are categorized into reactions related to vaccine products, reactions due to vaccine quality defects, reactions suspected to be caused by immunization errors, coincidental events, and psychogenic reactions. Among these, vaccine product-related reactions, or vaccine reactions, are adverse events that are either confirmed to be caused by the vaccine or cannot be definitively ruled out as being caused by the vaccine. These reactions are further subdivided into common reactions, which are usually minor, and rare reactions, which could be serious. Specific symptoms such as fever (axillary temperature ≥38.6 °C), redness and swelling at the injection site (diameter >2.5 cm), and induration at the injection site (diameter >2.5 cm) are mandated to be reported. Serious AEFI encompasses events that are life-threatening, may result in death, or may lead to substantial or permanent disability or significant impairment of organ function. Serious rare vaccine reactions primarily encompass those serious AEFIs that are suspected to be vaccine-related.

Data were analyzed utilizing Microsoft Office Excel (version 2016, Microsoft, Washington, USA) and R (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were employed to elucidate the distributions, characteristics, and reported incidences of AEFI with the Hib vaccine. The incidence of AEFI was calculated by taking the number of reported AEFI cases, multiplying it by 100,000, and then dividing it by the total number of administered doses of the Hib vaccine.

RESULTS

Characteristics of AEFI

From 2010 to 2021, a total of 52,910 AEFIs with the Hib vaccine were reported in China. Of these, 58.01% involved male recipients and 41.99% female recipients, yielding a male-to-female ratio of 1.38∶1. The distribution of AEFI reports by age group showed that 51.01% were in children under 1 year, 36.65% in 1-year-olds, and 12.35% in children aged 2 years or older. Geographically, 60.66% of the reports originated from the eastern regions, 27.53% from the central regions, and 11.81% from the western regions of China. Seasonally, AEFI reports varied across the quarters of the year, comprising 17.38% in the first quarter, 34.33% in the second, 32.70% in the third, and 15.59% in the fourth quarter. The analysis of AEFI reports by dose number revealed that 53.91% occurred after the first dose, 18.15% after the second, 14.97% after the third, and 12.97% after the fourth dose. Additionally, 25.76% of AEFI cases involved children who were concurrently vaccinated with other vaccines. The most commonly co-administered vaccines were the acellular DPT vaccine (7,392 cases, 13.97%), the polio vaccine (2,509 cases, 4.74%), and the meningococcal vaccine (1,407 cases, 2.66%). The timing of AEFI onset post-vaccination was predominantly within the first day (58.42%), followed by 2 to 3 days (39.98%), 4 to 14 days (1.14%), and 15 days or more (0.46%), as summarized in Table 1.

Incidence of AEFI by Year and Cause

Between 2010 and 2021, approximately 138.88 million doses of the Hib vaccine were administered in China. The reported overall rate of AEFIs was 38.10 per 100,000 doses. This rate fluctuated annually, with a low of 18.60 and a high of 50.25 per 100,000 doses. The breakdown of AEFI rates included: common vaccine reactions at 34.71 per 100,000 doses, rare vaccine reactions at 2.78 per 100,000, coincidental events at 0.57 per 100,000, psychogenic reactions at 0.005 per 100,000, suspected immunization error-related reactions at 0.004 per 100,000, and non-classifiable events at 0.02 per 100,000 doses. No event of vaccine quality defect-related reactions was reported. Incidence rates for serious AEFIs were 0.31 per 100,000 doses, for non-serious AEFIs were 37.79 per 100,000 doses, and for serious rare vaccine reactions were 0.16 per 100,000 doses, as detailed in Table 2.

Clinical Diagnoses of Common Vaccine Reactions

The study identified 48,203 cases of common vaccine reactions. Fever (axillary temperature ≥38.6 ℃), injection site redness and swelling (diameter >2.5 cm), and injection site induration (diameter >2.5 cm) represented 34.38%, 27.91%, and 9.74% of these reactions respectively, with incidence rates per 100,000 doses of 11.93, 9.69, and 3.38. Additional reported reactions accounted for 4.67% of the total. The five most commonly observed symptoms among these additional reactions were rash (16.80%), crying (11.38%), vomiting (6.71%), pruritus (4.31%), and diarrhea (3.91%), as detailed in Table 3. The majority of the common vaccine reactions occurred within three days post-vaccination, with proportions of 99.08% for fever, 98.75% for injection site redness and swelling, and 97.93% for injection site induration.

TABLE 1. Characteristics of Hib vaccine AEFI in China, 2010–2021.

Characteristics	AEFI		Serious AEFI		Common vaccine reaction		Rare vaccine reaction	
	Number	Proportion (%)	Number	Proportion (%)	Number	Proportion (%)	Number	Proportion (%)
Sex								
Male	30,693	58.01	252	59.29	27,953	57.99	2,253	58.29
Female	22,217	41.99	173	40.71	20,250	42.01	1,612	41.71
Age group								
<1 years	26,987	51.01	263	61.88	24,346	50.51	2,166	56.04
1–2 years	19,390	36.65	128	30.12	17,697	36.71	1,399	36.20
≥2 years	6,533	12.35	34	8.00	6,160	12.78	300	7.76
Region								
Eastern	32,094	60.66	198	46.59	29,208	60.59	2,415	62.48
Central	14,566	27.53	147	34.59	13,543	28.10	848	21.94
Western	6,250	11.81	80	18.82	5,452	11.31	602	15.58
Quarter								
1	9,195	17.38	112	26.35	8,240	17.09	769	19.90
2	18,166	34.33	105	24.71	16,679	34.60	1,237	32.01
3	17,301	32.70	120	28.24	15,861	32.90	1,200	31.05
4	8,248	15.59	88	20.71	7,423	15.40	659	17.05
Dose number								
1	28,525	53.91	256	60.24	25,831	53.59	2,187	56.58
2	9,601	18.15	80	18.82	8,631	17.91	818	21.16
3	7,919	14.97	49	11.53	7,323	15.19	500	12.94
4	6,865	12.97	40	9.41	6,418	13.31	360	9.31
Vaccinated with other vaccines								
No	39,279	74.24	238	56.00	35,899	74.47	2,803	72.52
Yes	13,631	25.76	187	44.00	12,304	25.53	1,062	27.48
Onset time after vaccination								
0–1 day	30,912	58.42	218	51.29	27,914	57.91	2,504	64.79
2–3 day	21,151	39.98	143	33.65	19,631	40.73	1,235	31.95
4–14 day	604	1.14	47	11.06	478	0.99	81	2.10
≥15 day	243	0.46	17	4.00	180	0.37	45	1.16
Total	52,910	100.00	425	100.00	48,203	100.00	3,865	100.00

Abbreviation: AEFI=adverse events following immunization.

Causality Assessment of Rare Vaccine Reactions

Among the rare reactions to vaccination, the incidence of allergic reactions was reported as 2.60 per 100,000 doses; specifically, the rates of allergic rash, angioedema, anaphylactic shock, and laryngeal edema were 2.42, 0.10, 0.01, and 0.004 per 100,000 doses, respectively. Reports of nervous system reactions were 0.07 per 100,000 doses, with specific incidences of febrile convulsion, convulsion, Guillain-Barre syndrome (GBS), and acute disseminated encephalomyelitis (ADEM) at 0.05, 0.01, 0.002, and 0.002 per 100,000 doses, respectively. Local reaction rates, which included sterile abscess, Arthus reaction, lymphangitis and lymphadenitis, were recorded as 0.02, 0.01, and 0.003 per 100,000 doses, respectively. Incidences of thrombocytopenic purpura (TP) and Henoch-Schonlein purpura (HSP) were documented at 0.05 and 0.01 per 100,000 doses, respectively (Table 3). Additionally, there were two reported cases of TP in two distinct vaccine batches.

TABLE 2. Number and incidence per 100,000 doses of Hib vaccine AEFI by year, causality, and severity in China, 2010–2021.

Year	Classification by cause												Seriousness				Total	
	Common vaccine reaction		Rare vaccine reaction		Coincidental event		Psychogenic reaction		Immunization error-related reaction		Non-classifiable event		Serious*		Non-serious			
	Number	Incidence (/100,000)	Number	Incidence (/100,000)	Number	Incidence (/100,000)	Number	Incidence (/100,000)	Number	Incidence (/100,000)	Number	Incidence (/100,000)	Number	Incidence (/100,000)	Number	Incidence (/100,000)	Number	Incidence (/100,000)
2010	1,872	16.46	180	1.58	58	0.51	1	0.01	0	0.00	4	0.04	33	0.29	2,082	18.31	2,115	18.60
2011	3,840	26.68	278	1.93	59	0.41	1	0.01	0	0.00	0	0.00	34	0.24	4,144	28.80	4,178	29.03
2012	5,196	37.09	390	2.79	79	0.56	0	0.00	1	0.01	0	0.00	44	0.31	5,622	40.13	5,666	40.44
2013	5,871	40.13	500	3.42	83	0.57	1	0.01	0	0.00	2	0.01	46	0.31	6,411	43.82	6,457	44.14
2014	5,612	36.22	572	3.69	100	0.65	3	0.02	0	0.00	5	0.03	59	0.38	6,233	40.23	6,292	40.61
2015	5,068	32.46	483	3.09	93	0.60	0	0.00	1	0.01	1	0.01	39	0.25	5,607	35.92	5,646	36.17
2016	4,155	40.79	356	3.49	69	0.68	0	0.00	0	0.00	3	0.03	49	0.48	4,534	44.51	4,583	44.99
2017	3,627	32.51	301	2.70	61	0.55	0	0.00	0	0.00	4	0.04	30	0.27	3,963	35.53	3,993	35.79
2018	3,983	38.11	315	3.01	59	0.56	0	0.00	0	0.00	7	0.07	30	0.29	4,334	41.47	4,364	41.75
2019	3,766	46.25	244	3.00	81	0.99	0	0.00	1	0.01	0	0.00	26	0.32	4,066	49.94	4,092	50.25
2020	3,110	45.54	162	2.37	31	0.45	1	0.01	1	0.01	4	0.06	25	0.37	3,284	48.09	3,309	48.46
2021	2,103	31.78	84	1.27	25	0.38	0	0.00	1	0.02	2	0.03	10	0.15	2,205	33.32	2,215	33.47
Total	48,203	34.71	3,865	2.78	798	0.57	7	0.005	5	0.004	32	0.02	425	0.31	52,485	37.79	52,910	38.10

Abbreviation: AEFI=adverse events following immunization.

* Among serious AEFI, there were 224 cases of serious rare vaccine reactions, representing an incidence of 0.16 per 100,000 doses.

TABLE 3. Number, proportion and incidence of reported Hib vaccine reactions in China, 2010–2021.

Clinical diagnosis	Number	Proportion (%)	Incidence (/100,000)
Common vaccine reactions			
Fever (axillary temperature)			
≥38.6 ℃	16,573	34.38	11.93
Injection site redness and swelling (diameter)			
2.6–5.0 cm	10,304	21.38	7.42
> 5.0 cm	3,149	6.53	2.27
Injection site induration (diameter)			
2.6–5.0 cm	3,658	7.59	2.63
> 5.0 cm	1,038	2.15	0.75
Other common vaccine reactions	2,250	4.67	1.62
Rare vaccine reactions			
Allergic reactions			
Allergic rash	3,365	87.06	2.42
Angioedema	142	3.67	0.10
Anaphylactic shock	14	0.36	0.01
Laryngeal edema	5	0.13	0.004
Other allergic reactions	66	1.71	0.05
Nervous system diseases			
Febrile convulsion	71	1.84	0.05
Convulsion	11	0.28	0.01
GBS	3	0.08	0.002
ADEM	3	0.08	0.002
Polyneuritis	2	0.05	0.001
Local reactions			
Sterile abscess	27	0.70	0.02
Arthus reaction	7	0.18	0.01
Lymphangitis and lymphadenitis	4	0.10	0.003
Other rare vaccine reactions			
TP	67	1.73	0.05
HSP	14	0.36	0.01
Others	64	1.66	0.05
Total	52,068	100.00	37.49

Abbreviation: GBS=Guillain-Barre syndrome; ADEM=acute disseminated encephalomyelitis; TP=thrombocytopenic purpura; HSP=Henoch-Schonlein purpura.

The proportions of allergic rash, HSP, TP, febrile convulsion, GBS, polyneuritis, and sterile abscess occurring within three days post-vaccination were 98.16%, 85.71%, 65.67%, 98.59%, 33.33%, 50.00%, and 11.11%, respectively. Additionally, laryngeal edema, ADEM, angioedema, anaphylactic shock, convulsion, and Arthus reactions all occurred within this timeframe following vaccination.

DISCUSSION

The CNIIS serves as the principal platform for AEFI surveillance across Chinese mainland. It compiles comprehensive data on AEFI reports and vaccine doses administered for all post-marketed vaccines, which is pivotal for the quantitative analysis of AEFI. Our study, utilizing data from CNIIS, revealed that AEFIs with the Hib vaccine were more frequently reported in males, within the eastern region, and during the second and third quarters of the year. This distribution mirrors the trend observed in AEFI reports for other vaccines that are market-authorized in China (*4*). Predominantly, AEFIs with the Hib vaccine occurred in infants, aligning with the typical age for Hib

vaccination, and was higher in proportion after the administration of the first dose. Other studies indicate that the AEFI rate was more prevalent following the second and subsequent doses — a trend potentially linked to the cellular immune memory responses (*5*). Additionally, our analysis showed that 25% of Hib vaccine doses were administered concomitantly with other vaccines. The WHO's position paper indicates Hib vaccines are safe and effective when given simultaneously with other vaccines (*1*).

From 2010 to 2021, the incidence of reported AEFI with the Hib vaccine was 38.10 per 100,000 doses. This rate was lower compared to the incidence reported in Australia in 2020, which was 69.4 per 100,000 doses (*6*). Studies conducted in China indicated higher incidences of AEFI for the combined DTP-IPV/Hib vaccine compared to our findings for the standalone Hib vaccine (*4*–*5*,*7*). Our data showed that annual reported incidences ranged from 18.60 to 50.25 per 100,000 doses, with an initially increasing trend that later stabilized. Notably, the highest incidence of AEFI was recorded in 2019, coinciding with an overall increase in AEFI reports for all post-marketed vaccines that year (*8*), possibly due to heightened societal concerns and enhanced surveillance of AEFI. The subsequent decrease in the number and incidence of AEFI reports in 2021 may be attributable to the impact on AEFI surveillance and immunization program services amidst the COVID-19 pandemic. In the same year, the incidence of rare reactions also decreased to 1.27 per 100,000. Furthermore, serious AEFIs were reported at a rate of 0.31 per 100,000 doses, and the incidence of serious rare vaccine reactions (0.16 per 100,000) aligned with the average incidences reported for other vaccines in China (*4*). It is important to note, however, that incidences of AEFI across different countries and regions are not directly comparable due to variations in AEFI reporting systems and methodologies.

The majority (91%) of the AEFI with Hib vaccination were common vaccine reactions. These included local reactions such as redness, swelling, induration, and rash at the injection site, along with systemic reactions such as fever, crying, and vomiting. These findings align with similar observations reported in the United States (*9*) and various regions of China (*5*,*7*). Our analysis indicated that 98% of these common vaccine reactions occurred within three days post-vaccination, consistent with previous national AEFI reports (*4*). Most of these reactions were either effectively managed with treatment or resolved spontaneously.

Allergic reactions were identified as the most commonly reported rare vaccine reactions, exhibiting a reporting rate of 2.60 per 100,000. This rate was significantly lower compared to that observed in the Yinzhou District of Ningbo City, which stands at 18.4 per 100,000 (*10*). Among these, allergic rash accounted for 87% of the cases, with the majority being non-serious, of short duration, and resolving favorably. The reported incidence of angioedema, at 0.10 per 100,000, was slightly higher than the incidence of other vaccines in China (*4*). Cases of anaphylaxis, including manifestations such as anaphylactic shock and laryngeal edema, were exceedingly rare, recorded at 0.01 per 100,000. This incidence was considerably lower than the rates of anaphylaxis reported in the United States, which range from 0.2 to 1.5 per 1,000,000 (*11*–*12*). Most anaphylactic reactions occurred within thirty minutes following vaccination and could pose a life-threatening risk if not promptly managed. Consequently, a post-vaccination observation period of 30 minutes is crucial to timely identify and address any cases of immediate anaphylaxis.

AEFI involving the nervous system are a significant concern post-vaccination. The incidence of nervous system events post-Hib vaccination was reported to be relatively low at 0.07 per 100,000 doses. Febrile convulsions, which generally have a favorable prognosis, emerged as the most common nervous system reaction in our study. These were reported at a rate of 0.05 per 100,000 doses, a figure that aligns with the incidences of similar reactions to other vaccines used in China (*4*) and is notably lower than the rate of febrile convulsions following the DPT-IPV/Hib vaccine in Zhejiang province, which stands at 0.50 per 100,000. The incidence of other neurological events such as GBS and ADEM was exceedingly rare, not exceeding 0.01 per 100,000 doses. Furthermore, no causal link has been established between these neurological conditions and the Hib vaccine. Based on these findings, we advocate for the continuation of vigilant neurological event surveillance following Hib vaccination.

Other rare vaccine reactions have also been reported. In our study, the incidence of TP was 0.05 per 100,000 doses, aligning with the average incidence reported for other vaccines in China (*4*). Comparatively, a survey in France examining TP cases among individuals under 18 years from 2009 to 2011 identified an incidence of 2.9 per 100,000 person-years, with the highest incidence occurring between ages 1 and 5 (*13*). However, the diagnostic criteria for TP differ between China and other countries,

complicating direct comparisons. The incidence of HSP with Hib vaccine in our study was 0.01 per 100,000, slightly lower than the average incidence observed across other vaccines in China (*4*). Meanwhile, studies in Sweden and France indicated an annual incidence of HSP in children under 15 years of age ranging from 17.5 to 30 per 100,000 doses (*14*–*15*). The WHO position paper on the Hib vaccine has not identified any safety concerns (*1*).

This study is subject to some limitations. Passive surveillance systems, such as the one used in this research, are inherently vulnerable to underreporting. Additionally, inaccuracies in data entry and variations in the quality of causality assessments, particularly for non-NIP vaccines, may affect the reliability of our findings. Furthermore, we were unable to ascertain the incidence of AEFI among different subgroups due to the lack of available data regarding the number of Hib vaccine doses administered to these subgroups. Our analysis was also confined to the evaluation of AEFI with monovalent Hib vaccines, thereby excluding combination vaccines from our study. Despite these limitations, the extensive administration of monovalent Hib vaccine doses across China lends substantial support to the robustness of our safety evaluation for this vaccine.

In conclusion, the predominant adverse reactions with the Hib vaccine included fever, injection site reactions, and other common vaccine-related symptoms. The incidence of rare adverse reactions was exceedingly low, primarily consisting of allergic rashes. Serious reactions were extremely uncommon. It is imperative to conduct AEFI surveillance and improve the quality of reporting systems. The favorable safety profile of the Hib vaccine advocates for its broader implementation in China.

Conflicts of interest: No conflicts of interest.

Acknowledgements: The staff at the provincial, prefectural, and county CDCs, as well as all the vaccination clinics involved in conducting the adverse event surveillance. Also, Lance Rodewald, senior consultant at China CDC, for his insightful comments and recommendations on the manuscript.

Funding: Supported by the Emergency Response Mechanism Operation Programme of China CDC (102393220020010000017).

doi: 10.46234/ccdcw2024.180

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Submitted: April 03, 2024; Accepted: June 26, 2024

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