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Safety evaluation on concomitant immunization with inactivated poliomyelitis vaccine produced from Sabin strains and other vaccines (from 2015 to 2020)

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ABSTRACT

Objective: To evaluate the safety of concomitantly administering inactivated poliomyelitis vaccine produced from Sabin strains (sIPVs) with other vaccines.

Methods: A descriptive analysis was carried out on adverse events following immunization (AEFI) based on the administration of sIPV alone or concomitant with other vaccines (from 2015 to 2020) using data from the national AEFI surveillance system of China (CNAEFIS). All adverse reactions (ADRs) of the concomitant immunization were coded using a medical dictionary for regulatory activities (MedDRA) before comparison.

Results: The CNAEFIS reported a total of 9130 sIPV-related AEFI cases, including 6842 AEFI cases collected after immunization with sIPV alone and 2288 AEFI cases collected after immunization of sIPV concomitant with other vaccines. The combination of sIPV with diphtheria, tetanus and pertussis vaccine (DTaP) was correlated with the highest frequency of AEFI, which accounted for 53.50% of all 2288 AEFI cases. After MedDRA-based coding, the most frequent ADR was fever (70.18%), followed by erythema and swelling at the injection site (6.95%), induration at the injection site (3.85%), dermatitis allergy (3.56%) and urticaria (1.55%). A statistically significant difference ($P < .001$) was found between sIPV immunization and sIPV immunization concomitant with other vaccines for general reactions (95.36% and 93.22%, respectively) and abnormal reactions (4.64% and 6.78%, respectively).

Conclusion: No new safety signal is found for sIPV administered concomitantly, although its administration with other vaccines may increase the occurrence of abnormal reactions. Vaccine manufacturers should focus on the safety of administering sIPV with DTaP and carry out relevant clinical studies when necessary.

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Inactivated poliomyelitis vaccine made from the Sabin strain; adverse events following immunization; concomitant immunization; safety; medical dictionary for regulatory activities

1. Introduction

Vaccination is recognized as the most effective medical intervention to reduce the burden of infectious diseases in the field of public health, and it has been particularly important during the coronavirus pandemic in 2020 and beyond.[1,2] The increase in available vaccines on the market has led to a potential safety risk when administering vaccines at the same, especially for children.[3] According to the WHO Expanded Program on Immunization (EPI)[4] and the National Immunization Program (NIP) Schedule for Children in China,[5] a total of 19 vaccines should be administered to children before 3 years of age. Thus, the use of a combined vaccine or a concomitant vaccination strategy for two or more vaccines is recommended to improve vaccination compliance and reduce the costs of vaccination for individuals and parents.[6–9] In 2015, an inactivated poliomyelitis vaccine produced from Sabin strains (sIPVs) independently developed by a Chinese manufacturer was approved for use in China.[10] sIPV is regarded as a powerful weapon in eliminating poliomyelitis worldwide. With increased sIPV coverage, the safety of this vaccine has been widely studied.[11–14] Previously, multiple domestic and international sIPV-related clinical studies have shown that sIPV has good safety and immunogenicity when administered separately.[15–19] However, systematic research is lacking on the immunogenicity and safety of sIPV when concomitantly vaccinated with other vaccines. According to the numerous cases of adverse events following immunization (AEFI) collected after concomitant immunization of sIPV with other vaccines from the national AEFI surveillance system in China (CNAEFIS), it is reasonable to infer that there is a considerable number of recipients who require IPV-included concomitant vaccinations; therefore, the safety of concomitant immunization strategies for sIPV and other vaccines should be investigated.

To analyze the safety of sIPV-included concomitant immunization, we performed a retrospective review and analysis on the AEFI data collected after separate sIPV immunization and sIPV-included concomitant immunization with other vaccines (from 2015 to 2020). We evaluated the safety of sIPV-included concomitant immunization and provided a reference to further guide safe sIPV immunization.

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2. Materials and methods

2.1. AEFI data collection

In this study, all sIPV-related AEFI data were obtained from the CNAEFIS, which is a nationwide passive surveillance system for AEFI.[20,21] Safety monitoring about sIPV was carried out and all monitoring data was registered in CNAEFIS since 2015 when sIPV was approved for use in China. AEFI cases that occurred at different times were reported and uploaded into the system by a responsible reporting unit according to the National AEFI guidelines.[22,23] The data evaluated in this article covered nationwide AEFI cases after administrating sIPV alone and simultaneous with other vaccines that were reported from January 2015 to December 2020.

2.2. AEFI classification

According to the National AEFI guidelines, AEFI can be classified into five categories according to cause, i.e., adverse reactions (ADRs), vaccine quality events, inoculation accidents, coincidental illnesses and psychogenic reactions. Among these, ADRs include general reactions and abnormal reactions, AEFI cases that cannot be classified into the abovementioned types are defined as "to be classified".

2.3. statistical analysis

Limited by the inherent system setting of CNAEFIS, as the enterprise user, we cannot obtain the total number of recipients who received sIPV alone and for whom sIPV was administered simultaneously with other vaccines during the data collection period. The data recorded in the CNAEFIS are the actual data reported from a real-world vaccination program, and uncertainties were observed in the sensitivity, normalization, integrity and other aspects of the reported data. The comparison of AEFI cases between sIPV immunization alone and concomitant with other vaccines was based on the ratio of AEFI cases to the total number of AEFI cases rather than the incidence of AEFI.

(1) All AEFI cases related to sIPV vaccination were exported from the CNAEFIS, and the screened cases were divided into two large groups, i.e., sIPV alone and concomitant with other vaccines after reviewing the clinical diagnosis. Then, the filtered AEFI cases of the two groups were subdivided into various categories based on their characteristics according to the standard AEFI classification criteria.
(2) The indicators of immunization with sIPV alone versus sIPV combined with other vaccines were retrospectively analyzed, including categories and the constituent ratio of AEFI cases, the time interval between the AEFI incidence and inoculation and outcome of the AEFI cases.
(3) Statistical analysis was performed on the distribution of AEFI cases in the various vaccine combinations modes for sIPV and other vaccines. All ADRs (general reactions and abnormal reactions) of the sIPV-included concomitant immunization were coded by using a medical dictionary for regulatory activities (MedDRA). The coded ADRs were subjected to collection and statistical analysis according to the system organ class (SOC) and a preferred term (PT) in MedDRA. The data were then compared with the coded ADRs collected from separate sIPV immunizations.
(4) The distributions of different categories of ADRs in the sIPV separate immunization group and various combination modes of sIPV with other vaccines were analyzed and compared to identify significant differences.

3. Results

In the results of this study, there are many different numbers with different meanings, including AEFI vs ADRs, as well as the number of cases vs the number of events. In order to avoid confusion, we distinguish them by a table, see Table 1. In addition, Tables 2 to 3 show the number of cases of AEFI (Corresponding to the result 3.1 to 3.3, and Tables 4 to 5 show the number of events of ADRs (Corresponding to the result 3.5 to 3.6).

3.1. AEFI classification and constituent ratio

From 2015 to 2020, a total of 9130 sIPV-related AEFI cases were reported in the CNAEFIS, of which 6842 AEFI cases were related to administrating sIPV alone, including 6408 general reactions (93.66%) and 337 abnormal reactions (4.93%), and 2288 AEFI cases were related to sIPV-included concomitant vaccination, including 2086 general reactions (91.17%) and 156 abnormal reactions (6.82%) (see Table 2).

3.2. Time interval between AEFI incidence and inoculation

The 9130 sIPV-related AEFI cases were mainly reported on Day 0 after inoculation (52.15%), followed by Day 1 after inoculation (37.21%). Similarly, the AEFI cases with sIPV alone were mainly reported on Day 0 after inoculation (55.71%), followed by Day 1 after inoculation (33.76%). The AEFI cases of sIPV-included concomitant administration were mainly reported on Day 1 after inoculation (47.51%), followed by Day 0 after inoculation (41.48%) (see Table 6).

3.3. Outcome of AEFI cases

Among the 9130 AEFI cases reported in the CNAEFIS, 8829 cases (96.70%) recovered or improved, 221 cases (2.42%) were under treatment at the time of reporting, 3 cases (.03%) were aggravated (1 case of general reaction without recorded

Table 1. The number of sIPV AEFI and ADRs during 2015–2020.

	sIPV alone		sIPV concomitant with other vaccines		Total	
Classification	cases	events	cases	events	cases	events
AEFI[1]	6842	/	2288	/	9130	/
ADR[2]	6745	7481	2242	2388	/	9869

1. AEFI include adverse reactions (ADRs), vaccine quality events, inoculation accidents, coincidental illnesses and psychogenic reactions.
2. ADRs include general reactions and abnormal reactions.

Table 2. Classification of sIPV AEFI during 2015–2020.

Classification	sIPV alone (cases, the ratio %)	sIPV concomitant with other vaccines (cases, the ratio %)			Total (cases, the ratio %)
		Concomitant with one vaccines	Concomitant with two vaccines	Concomitant subtotal	
General reactions	6408 (93.66)	2061 (91.19)	25 (89.29)	2086 (91.17)	8494 (93.03)
Abnormal reactions	337 (4.93)	153 (6.77)	3 (10.71)	156 (6.82)	493 (5.40)
Coincidental illnesses	81 (1.18)	32 (1.42)	0 (0)	32 (1.40)	113 (1.24)
Psychogenic reactions	1 (.01)	2 (.09)	0 (0)	2 (.09)	3 (.03)
To be classified	15 (.22)	12 (.53)	0 (0)	12 (.52)	27 (.30)
Total	6842 (100)	2260 (100)	28 (100)	2288 (100)	9130 (100.00)

Table 3. Time interval between AEFI occurrence and vaccination.

Inoculation mode	Time interval (day)					Total (cases, the ratio%)
	0 (cases, the ratio%)	1 (cases, the ratio%)	2 (cases, the ratio%)	3 (cases, the ratio%)	≥4 (cases, the ratio%)	
Alone	3812 (55.71)	2310 (33.76)	371 (5.42)	117 (1.71)	232 (3.39)	6824 (100)
Concomitant	949 (41.48)	1087 (47.51)	127 (5.55)	52 (2.27)	73 (3.19)	2288 (100)
Total	4761 (52.15)	3397 (37.21)	498 (5.45)	169 (1.85)	305 (3.34)	9130 (100)

Table 4. Outcome of AEFI.

Inoculation mode	Outcome (cases, the ratio %)					Total (cases, the ratio %)
	Recovered or had improved	Under treatment	Aggravated	Deaths	Unknown	
Alone	6628 (96.87)	157 (2.29)	2 (.03)	7 (.10)	48 (.70)	6842 (100)
Combined	2201 (96.20)	64 (2.80)	1 (.04)	3 (.13)	19 (.83)	2288 (100)
Total	8829 (96.70)	221 (2.42)	3 (.03)	10 (.11)	67 (.73)	9130 (100)

Table 5. Adverse reactions of sIPV when concomitantly immunized with other vaccines during 2015–2020.

SOC (MedDRA)	PT (MedDRA)	Concomitantly		Alone	
		Events	The ratio	Events	The ratio
General Disorders and Administration Site Conditions	Fever	1676	70.18%	3418	45.69%
	Injection site erythema* Injection site swelling*	166	6.95%	1701	22.74%
	Injection site induration	92	3.85%	504	6.74%
	Febrile seizure	1	0.04%	3	0.04%
	Death	1	0.04%	0	0.00%
Injury, Poisoning and Procedural Complications	Vaccination complication	278	11.64%	1455	19.45%
Skin and Subcutaneous Tissue Disorders	Dermatitis allergic	85	3.56%	167	2.23%
	Urticaria	37	1.55%	74	0.99%
	Rash maculo-papular	18	0.75%	36	0.48%
	Henoch-Schonlein purpura	2	0.08%	3	0.04%
	Rash	8	0.34%	8	0.11%
	Rash scarlatiniform	1	0.04%	4	0.05%
Immune System Disorders	Hypersensitivity	7	0.29%	12	0.16%
	Anaphylactic shock	3	0.13%	3	0.04%
	Angioedema	1	0.04%	6	0.08%
Blood and Lymphatic Disorders	Thrombocytopenic purpura	5	0.21%	21	0.28%
Nervous System Disorders	Ataxia	1	0.04%	0	0.00%
	Secondary tic	2	0.08%	0	0.00%
	Neurological symptom	1	0.04%	0	0.00%
Gastrointestinal Disorders	Diarrhea	1	0.04%	5	0.07%
Infections and Infestations	Bronchitis	1	0.04%	0	0.00%
	Viral rash	1	0.04%	1	0.01%
Other		0	0	60	0.80%
Total		2388	100.00%	7481	100.00%

Note *Erythema and swelling at injection site were classified as the same event (red and swollen) in the CNAEFIS which was not broken down for coding.

symptoms, 1 case of thrombocytopenic purpura and 1 case of bleeding), 10 deaths (.11%) occurred (including 9 cases of coincidental illnesses and 1 case of abnormal reaction after concomitant administration) and 67 cases (.73%) had unknown outcomes (see Table 3).

3.4. Distribution of AEFI cases by vaccine type administered concomitantly with sIPV

In this study, the vaccines administered simultaneously with sIPV include Adsorbed Acellular DTP Combined Vaccine (DTaP), Diphtheria, Tetanus and Acellular Pertussis-Hemophilus

Table 6. Events and ratio of ADRs for sIPV concomitant immunization during 2015–2020.

	General reaction (events, the ratio %)					Abnormal reaction (events, the ratio %)				
Vaccine combinations	Fever	Injection site erythema and swelling	Injection site induration	Other	Subtotal	Dermatitis allergic	Urticaria	Other	Subtotal	Total (events, the ratio %)
sIPV alone	**3418(45.69)**	**1701(22.74)**	**504(6.74)**	**1511(20.20)**	**7134 (95.36)**	**167(2.23)**	**74(.99)**	**106(1.42)**	**347(4.64)**	**7481(100)**
Concomitant (sIPV included)	**1676(70.18)**	**166(6.95)**	**92(3.85)**	**292(12.23)**	**2226(93.22)**	**85(3.56)**	**37(1.55)**	**40(1.68)**	**162(6.78)**	**2388(100)**
DTaP	876(67.38)	104(8.00)	64(4.92)	145(11.15)	1189(91.46)	55(4.23)	28(2.15)	28(2.15)	111(8.54)	1300(100)
DTap-Hib	361(76.16)	14(2.95)	8(1.69)	79(16.67)	462(97.47)	8(1.69)	2(.42)	2(.42)	12(2.53)	474(100)
MMR	86(86.87)	1(1.01)	1(1.01)	11(11.11)	99(100)	0(0)	0(0)	0(0)	0(0)	99(100)
Hib	41(53.95)	13(17.11)	5(6.58)	11(14.47)	70(92.11)	4(5.26)	1(1.32)	1(1.32)	6(7.89)	76(100)
HepB	73(65.77)	10(9.01)	2(1.80)	17(15.32)	102(91.89)	5(4.50)	1(.90)	3(2.70)	9(8.11)	111(100)
AC-Hib	32(76.19)	3(7.14)	2(4.76)	3(7.14)	40(95.24)	2(4.76)	0(0)	0(0)	2(4.76)	42(100)
ORV	21(47.73)	7(15.91)	2(4.55)	11(25.00)	41(93.18)	2(4.55)	0(0)	1(2.27)	3(6.82)	44(100)
MPSV	56(78.87)	3(4.23)	3(4.23)	4(5.63)	66(92.96)	1(1.41)	2(2.82)	2(2.82)	5(7.04)	71(100)
MR	18(81.82)	1(4.55)	1(4.55)	1(4.55)	21(95.45)	1(4.55)	0(0)	0(0)	1(4.55)	22(100)
VarV	26(81.25)	1(3.13)	0(0)	2(6.25)	29(90.63)	2(6.25)	1(3.13)	0(0)	3(9.38)	32(100)
JE	25(80.65)	2(6.45)	0(0)	3(9.68)	30(96.77)	0(0)	0(0)	1(3.23)	1(3.23)	31(100)
PPV	13(61.90)	4(19.05)	3(14.29)	0(0)	20(95.24)	0(0)	0(0)	1(4.76)	1(4.76)	21(100)
EV71	3(100)	0(0)	0(0)	0(0)	3(100)	0(0)	0(0)	0(0)	0(0)	3(100)
HepA	8(57.14)	1(7.14)	1(7.14)	2(14.29)	12(85.71)	1(7.14)	1(7.14)	0(0)	2(14.29)	14(100)
InfV	10(76.92)	1(7.69)	0(0)	0(0)	11(84.62)	1(7.69)	1(7.69)	0(0)	2(15.38)	13(100)
BCG	4(66.67)	0(0)	0(0)	1(16.67)	5(83.33)	0(0)	0(0)	1(16.67)	1(16.67)	6(100)
DTaP+MPSV	1(100)	0(0)	0(0)	0(0)	1(100)	0(0)	0(0)	0(0)	0(0)	1(100)
DTaP+Hib	1(100)	0(0)	0(0)	0(0)	1(100)	0(0)	0(0)	0(0)	0(0)	1(100)
ORV+DTaP	10(76.92)	0(0)	0(0)	1(7.69)	11(84.61)	2(15.38)	0(0)	0(0)	2(15.38)	13(100)
ORV+AC-Hib	5(83.33)	1(16.67)	0(0)	0(0)	6(100)	0(0)	0(0)	0(0)	0(0)	6(100)
ORV+MMR	3(75.00)	0(0)	0(0)	0(0)	3(75.00)	1(25.00)	0(0)	0(0)	1(25.00)	4(100)
ORV+DTap-Hib	2(66.67)	0(0)	0(0)	1(33.33)	3(100)	0(0)	0(0)	0(0)	0(0)	3(100)
ORV+DT	1(100)	0(0)	0(0)	0(0)	1(100)	0(0)	0(0)	0(0)	0(0)	1(100)
Total	**5094 (51.62)**	**1867 (18.92)**	**596 (6.04)**	**1803(18.27)**	**9360 (94.84)**	**252 (2.55)**	**111 (1.12)**	**146 (1.48)**	**509 (5.16)**	**9869(100)**

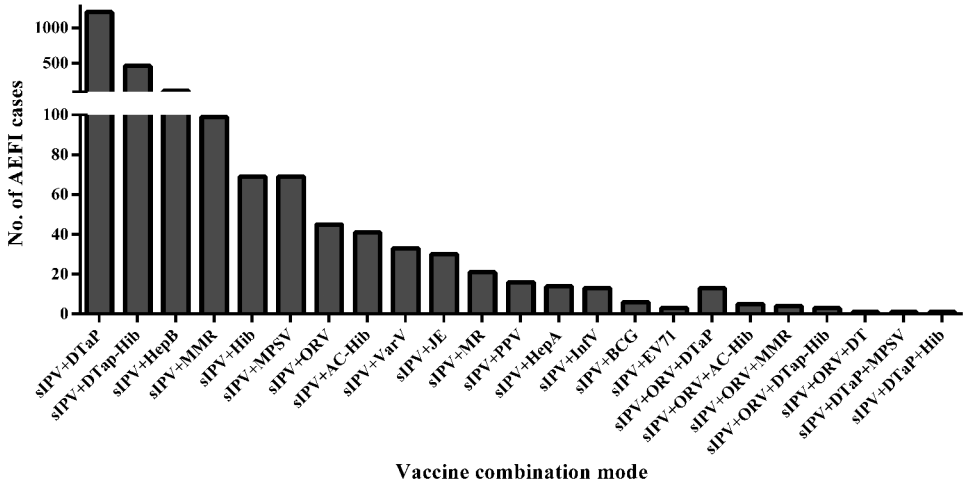

Figure 1. Number of AEFI cases when sIPV was administered concomitantly with other vaccines from 2015–2020.

Influenza Type B Combined Vaccine (DTap-Hib), Measles, Mumps, And Rubella Vaccine (MMR), Hemophilus Influenza Type B Conjugate Vaccine (Hib), Hepatitis B Vaccine (Hepb), Meningococcal Groups A and C and Hemophilus Influenza Type B Conjugate Vaccine (AC-Hib), Live Oral Rotavirus Vaccine (ORV), Meningococcal Polysaccharide Vaccine (MPSV), Measles And Rubella Vaccine (MR), Varicella Attenuated Live Vaccine (Varv), Japanese Encephalitis Vaccine (JE), Pneumococcal Polysaccharide Vaccine (PPV), Inactivated Enterovirus 71 Vaccine (EV71), Hepatitis A Vaccine (Hepa), Influenza Vaccine (Infv), Bacillus Calmette Guerin Vaccine (BCG) and Diphtheria and Tetanus Vaccine (DT). Figure 1 shows the combination mode of sIPV-included concomitant vaccination and the number of reported AEFI cases of each combination mode. Among the concomitant vaccines, the administration of sIPV with DTaP presented the highest number of AEFI cases, i.e., 1224 AEFI cases, which accounted for 53.50% of all 2288 cases after concomitant immunization. When administrating sIPV with two other vaccines simultaneously, the concomitant administration of sIPV, DTaP and ORV had the greatest number of AEFI at 13, which accounted for .57% of all 2288 AEFI cases after concomitant immunization.

3.5. Meddra-Based coding results of ADR (general reaction and abnormal reaction)

From 2015 to 2020, a total of 7481 ADR events were reported among 6745 cases (general reactions and abnormal reactions) after immunization with sIPV alone. After concomitantly administering sIPV with other vaccines, 2388 ADR events were reported among 2242 cases. Because multiple ADR events might occur in individual cases, the term "ADR events" rather than "ADR cases" was used for the statistics on MedDRA-coded results (see Table 4).

According to the MedDRA-based medical coding results, the ADRs with the SOC term "General Disorders and Administration Site Conditions" accounted for the highest proportion, with 5626 (75.20%) out of 7481 ADR events and 1936 (81.07%) out of 2388 ADR events occurring after administering sIPV alone and with other vaccines, respectively (see Table 4). Some of the reactions in the CNAEFIS were generally coded as "vaccination complications" as the PT term because the vaccine name and inoculation time of the case were recorded but lacked any specific symptoms or definite diagnosis (see Table 4).

The MedDRA-based coding results showed that relative to the separate administration of sIPV, the ADRs that were frequently reported after concomitant immunization of sIPV with other vaccines were fever, erythema and swelling at the injection site, induration at the injection site, dermatitis allergy and urticaria. The ratios of these five types of ADRs after administering sIPV alone and with other vaccines were 78.39% (5864 events) and 86.10% (2056 events), respectively (see Table 4).

3.6. ADR (general reaction and abnormal reaction) distribution

Referring to the five most frequently reported types of ADRs after concomitant immunization of sIPV with other vaccines, i.e., fever, erythema and swelling at injection site, induration at injection site, dermatitis allergic and urticaria, the statistical analysis revealed that the number of each ADR differently when sIPV was administered alone and concomitant with other vaccines (see Table 5).

Taking the general reactions as an example, the event frequency of general reactions after immunization with sIPV alone or together with other vaccines varied from 1 to 7134, although the proportions of total general reactions among the ADRs were almost all higher than 90%. According to the results, the proportion of general reactions observed after administering sIPV alone accounted for 95.36% while abnormal reactions account for 4.64% and the proportion of general reactions after administering sIPV with other vaccines accounted for 93.22% while abnormal reactions accounted for 6.78%. Statistically significant differences were observed in the number of general reaction and abnormal reaction events between sIPV administered alone and in combination with other vaccines ($P < .001$). The proportion of general reactions after administering sIPV alone was higher than that after concomitant vaccine administration (95.36% and

93.22%, respectively), although the proportion of abnormal reactions after administering sIPV alone was lower than that after concomitant vaccine administration (4.64% and 6.78%, respectively) (see Table 5).

4. Discussion

In 2016, IPV was included in the Chinese NIP.[24] According to the provisions of *NIP Immunization Procedures and Instructions for Children* (2021 Edition),[5] NIP vaccines can be applied concomitantly according to immunization schedules or supplementary immunization principles, which provide a policy basis for simultaneous immunization with NIP vaccines. However, restrictive national policies have not been issued for the simultaneous immunization of NIP vaccines with non-NIP vaccines. Therefore, constant updates on the safety of concomitant immunization are required to provide better guidance for immunization and ensure the safety of subjects upon improved data analysis.

In this study, AEFI cases collected from 2015 to 2020 after administering sIPV alone and with other vaccines were analyzed to evaluate the safety of concomitant immunization. No significant difference in the AEFI incidence was observed between sIPV administered alone and in combination with other vaccines. General reactions accounted for the highest proportion of AEFI cases (93.66% vs. 91.17%), followed by abnormal reactions (4.93% vs. 6.82%). The AEFI cases mainly occurred within 3 days after inoculation (>96%). More than 96% of AEFI after administering sIPV concomitantly with other vaccines recovered or improved (96.87%), which is consistent with the AEFI outcomes after administering sIPV alone (96.20%).[24,25] The AEFI cases after administering sIPV with other vaccines were consistent with those after administering sIPV alone in terms of the AEFI category, the time interval between AEFI incidence and inoculation, and disease outcomes.

We further analyzed the types of vaccines that caused AEFI after concomitant immunization. From 2015 to 2020, the vaccines administered concomitantly with sIPV included DTaP, DTap-Hib, MMR, Hib, HepB, AC-Hib, MPSV, MR, VarV, JE, PPV, EV71, HepA, InfV, BCG and DT. The combinations with the highest number of AEFI cases after immunization were sIPV+DTaP, sIPV+DTaP-Hib, sIPV+HepB and sIPV+MMR, although all of them were NIP vaccines except for DTaP-Hib. These data suggested that more attention should be focused on the safe administration of sIPV concomitantly with the above vaccines during safety monitoring, despite previous research revealing that the administration of IPV+DTaP-Hib is relatively safe.[26,27] In a study by Clake et al.[28] on the safety and immunogenicity of administering IPV along with vaccines for yellow fever and measles–rubella, there were 3 (16.67%), 3 (26.67%), and 4 (16.67%) cases of fever when administering sIPV alone, MR vaccine alone, and IPV concomitant with MR vaccine, respectively, and no safety concerns were reported. There were 3418 (45.69%) cases of fever after administering sIPV alone, whereas there were 18 (81.82%) cases of fever after concomitant immunization with the sIPV and MR vaccines, which may have been associated with different study designs that included active surveillance and passive surveillance. In addition, the study also suggested that there is a high demand (73.86%) for administering sIPV combined with DTaP- or DTaP-containing vaccines. These data correlated with the high coincidence of inoculation times. According to the immunization schedules, infants should be inoculated with sIPV at the ages of 2, 3, 4 and 18 months and with DTaP and DTap-Hib at the ages of 3, 4, 5 and 18 months.

The international sharing of regulatory information of medical products for humans (MedDRA) is a rich and highly specific set of standardized medical terminology developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[29] MedDRA is widely adopted in databases and individual case safety reports for drug regulatory authorities and pharmaceutical enterprises. In this study, a total of 6824 cases AEFI were reported after sIPV alone and 2288 cases AEFI after sIPV with other vaccines. By comparison, a total of 6745 cases ADRs were reported after sIPV alone, and 2242 cases ADRs after sIPV with other vaccines. In addition to ADRs, AEFI also includes other adverse events not related to vaccination, such as coincidental illnesses and psychogenic reactions. In this study, we focused on vaccine-related adverse events, known as ADRs (General and abnormal reactions in AEFI). To compare the differences in the number of events of specific ADRs occurring after administrating sIPV alone and concomitant with other vaccines, we coded all reported ADRs by MedDRA terms and further nominated and analyzed these ADRs at the PT level. Our results indicated among the ADRs after administering sIPV with other vaccines, fever accounted for the highest proportion (70.18%), followed by erythema and swelling at the injection site (6.95%), induration at the injection site (3.85%), allergic dermatitis (3.56%) and urticaria (1.55%). In a phase III clinical trial of sIPV sponsored by the Institute of Medical Biology Chinese Academy of Medical Sciences,[15] the local ADRs after inoculation with sIPV mainly included redness (1.3%) and pain (1.3%). The systemic ADRs mainly included fever (43.8%), diarrhea (7.5%), agitation (10.7%) and vomiting (5.3%). Compared to the results in this study, the proportions of the three most reported ADRs were higher than those in previous reports, i.e., fever (70.18%), erythema and swelling at the injection site (6.95%) and induration at the injection site (3.85%). These data were consistent with the characteristics of a relatively high incidence of local redness and induration after immunization with the DTaP vaccine alone.[30] In addition, the data from Zhiqun Li et al.[27] suggested that from 2011 to 2017 in the Guangdong area, the various symptoms after DTaP-IPV/Hib administration included fever (48.1%), swelling at injection site (22.2%), induration at injection site (7.4%), and point rash (16.0%). In this study, however, the various symptoms for stand-alone immunization and concomitant immunization were fever (45.69% and 70.18%, respectively), swelling at injection site (22.74% and 6.95%, respectively), induration at injection site (6.74% and 3.85%, respectively), and allergic dermatitis (2.23% and 3.56%, respectively). It follows that the proportions of fever, swelling at injection site, induration at injection site after DTaP-IPV/Hib immunization were much closer to the proportions after

administering sIPV alone while the proportion of allergic dermatitis (which is regarded as point rash by Zhiqun Li et al.) was far higher than that for administering sIPV alone or in combination. However, the lower number of cases in this study could be a cause.

To verify the differences in the number of ADRs after immunization with sIPV alone and in combination with other vaccines, the number of events of the five types of the most frequently reported ADRs was compared, and a difference was found in the frequency of ADRs. Taking fever as an example, the proportion of fever in ADRs after administering sIPV alone and in combination with other vaccines was 45.69% and 70.18%, respectively. Except for the vaccine combination modes with less than 10 ADRs reported, the combination of sIPV+ORV showed the lowest proportion (47.73%) while the combination of sIPV+MMR showed the highest proportion (86.87%) of fever. However, according to the ADR types, the administration of sIPV alone and in combination with other vaccines demonstrated a high proportion of general reactions, with ratios of 95.36% and 93.22%, respectively, and there were statistically significant differences between them ($P < .001$). Fever accounted for the most frequently reported general reaction, with a proportion of >47%, which was consistent with the monitoring results obtained at the provincial level.[24] Statistically significant differences were found in the ratio of abnormal reactions in all ADRs after the administration of sIPV alone (4.64%) and with other vaccines (6.78%), suggesting that the concomitant administration of sIPV with other vaccines may increase the frequency of abnormal reactions.

This study has some limitations. As a passive surveillance method, CNAEFIS has inherent drawbacks, including potentially biased reporting and a lack of control groups.[31, 32] Compared to the national AEFI monitoring results,[25] no new safety signal was found for sIPV-included concomitant immunization. It should be noted that the death of a 2-month-old boy was recorded on the day of immunization with sIPV +ORV, and it was recorded as an "abnormal reaction" in the system. Limited records in the CNAEFIS and measures to protect the privacy of recipients meant that no additional relevant information was available; therefore, the case was not further analyzed. Additionally, 1 case of ataxia, 1 case of neurological symptoms and 1 case of bronchitis were recorded in this study. These rare ADRs were not observed following sIPV immunization only. Due to the limited information available, it was impossible for us to further confirm and assess the safety signal. However, these data suggest that concomitant immunization with sIPV and other vaccines may aggravate ADRs and result in ADRs that do not occur following the administration of sIPV alone.

In conclusion, the characteristics of AEFI reported after sIPV-included concomitant immunization are consistent with those reported after separate sIPV immunization. Our preliminary data suggest that sIPV-included concomitant immunization is feasible. However, it is undeniable that certain AEFI cases that were not observed in clinical studies and for separate sIPV immunization were reported when concomitantly administering sIPV with other vaccines; thus, concomitant vaccination potentially increases the occurrence of abnormal reactions. Because the data used in this research are from passive surveillance in a real-world setting, there are certain limitations in the results. To further clarify sIPV-included concomitant immunizations, it is particularly important for vaccine manufacturers to perform studies for sIPV-included concomitant immunization, especially for sIPV in combination with DTaP, DTaP-Hib and MMR, because these combinations showed higher AEFI proportions due to the overlap of inoculation time points.

Disclosure statement

We confirm that all of the listed authors have actively participated in the present study, and have read and approved the submitted manuscript. The authors do not have any potential conflicts of interest to declare.

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