Methods and Applications

Safety of PCV13 with Different Carrier Proteins (CRM197, TT, and TT/DT) — Jiangsu Province, China, 2022–2024

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ABSTRACT

Introduction: This study aimed to evaluate the safety of three kinds of 13-valent pneumococcal conjugate vaccines (PCV13) with different carrier proteins — cross-reactive material 197 (CRM197), tetanus toxoid (TT), and a novel tetanus toxoid/diphtheria toxoid (TT/DT) dual-carrier — by monitoring adverse events following immunization (AEFI) in Jiangsu Province, China.

Methods: The Chinese National Adverse Events Following Immunization Information System and Jiangsu Province Vaccination Integrated Service Management Information System were used. Reporting rates (RR) per 100,000 doses were calculated and stratified. Chi-square tests with Bonferroni correction and disproportionality analyses were performed.

Results: A total of 1,734,810 PCV13 doses were administered, with 5,195 AEFI reports (RR=299.46 per 100,000 doses). RR was highest for TT/DT-carrier (399.84 per 100,000 doses) versus CRM197-carrier (286.69 per 100,000 doses) and TT-carrier (286.01 per 100,000 doses). Common adverse reactions accounted for 98.23% (5,103/5,195) of all AEFIs, with fever, local redness, and induration being the most common. Disproportionality analysis revealed positive signals for general reactions.

Conclusion: All three PCV13 carrier protein types demonstrated acceptable safety profiles in Jiangsu Province from 2022 to 2024. Despite a higher RR for TT/DT-carrier PCV13 than for the other two PCV13 carrier protein types, most AEFIs were mild and common reactions.

Streptococcus pneumoniae is the most common pathogen responsible for community-acquired pneumonia, bacterial meningitis, bacteremia, and acute otitis media, posing a serious threat to the health of infants and young children (*1*).

The pneumococcal conjugate vaccine (PCV) has been recommended by the World Health Organization (WHO) for inclusion in routine childhood immunization programs worldwide, demonstrating favorable efficacy and safety in preventing invasive pneumococcal disease and pneumonia (*1*). The currently available 13-valent PCV (PCV13) can be classified by the carrier protein type: single-carrier PCV13 using cross-reactive material 197 (CRM197, a nontoxic mutant of diphtheria toxin) or tetanus toxoid (TT), and the recently developed dual-carrier PCV13 using tetanus toxoid/diphtheria toxoid (TT/DT). The introduction of PCV13 in China has followed a phased pathway: imported PCV13 in 2016, domestic TT-carrier PCV13 in early 2020, and TT/DT dual-carrier PCV13 in 2021 (*2*). However, PCV13 has not yet been integrated into China's National Immunization Program; as a self-paid vaccine, its coverage has remained low and unevenly distributed across regions (*3*).

Post-marketing safety surveillance, as recommended by the WHO, is essential for evaluating vaccine safety in real-world settings. Since 2019, multiple PCV13s with different carrier protein types have been introduced in Jiangsu Province, China. Previous studies have evaluated the safety of CRM197- and TT-carrier PCV13s during 2019–2022, confirming that both have favorable safety profiles (*4*). However, a parallel comparison of the three carrier protein types (CRM197, TT, and TT/DT) of PCV13, particularly the real-world safety data for the TT/DT dual-carrier PCV13 after its market introduction, has not yet been reported.

This study analyzed adverse events following immunization (AEFI) reports for three PCV13 types in Jiangsu from 2022 to 2024 using the Jiangsu Province Vaccination Integrated Service Management Information System (JSEIRS) and the Chinese National Adverse Events Following Immunization Information System (CNAEFIS) to characterize the AEFI incidence and distribution for post-marketing

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safety evaluation.

METHODS

Data Source

Data were obtained from two information systems. Vaccination data were extracted from the JSEIRS, and AEFI data were sourced from the CNAEFIS (Supplementary Materials, available at https://weekly.chinacdc.cn/).

All PCV13 vaccination records and associated AEFI reports in Jiangsu Province from January 1, 2022, to December 31, 2024, were extracted. Cases with missing essential variables (e.g., age, vaccine type, and outcome) or duplicate records were excluded.

Vaccination Schedule for PCV13

The immunization schedule for all three PCV13s comprises three primary doses, followed by one reinforced dose (5). Immunization can be initiated as early as six weeks of age, with an interval of at least one month between doses. The reinforced dose is administered at 12–15 months of age. The TT-carrier PCV13 has a wider age indication, being applicable to children aged 6 weeks to 5 years.

AEFI Categorization

According to *the National Guideline for the Surveillance of Adverse Events Following Immunization* (6), AEFIs are classified into five types: adverse reactions (including common and rare adverse reactions), vaccine quality defect-related events, immunization error-related adverse events, immunization anxiety-related reactions, and coincidental events. AEFI symptoms and diagnoses were coded according to the International Classification of Diseases, Tenth Revision (ICD-10).

Data Analysis

Data analysis was performed using R (version 4.5.2; R Foundation, Vienna, Austria). The AEFI reporting rate (RR) per 100,000 doses of PCV13 administered was calculated. Bonferroni correction was applied to account for multiple comparisons, with a two-tailed significance level of α =0.05.

The Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), Medicines and Healthcare Products Regulatory Agency (MHRA) comprehensive standard method, and Bayesian Confidence Propagation Neural Network (BCPNN) method were used for disproportionality analysis (DPA) of AEFI reports. DPA was computed using the *PhViD* package (version 1.0.8) in R (Supplementary Materials, available at https://weekly.chinacdc.cn/).

RESULTS

From January 2022 to December 2024, 1,734,810 PCV13 doses were administered in Jiangsu Province: 898,533 CRM197-carrier (51.79%, 898,533/1,734,810), 636,698 TT-carrier (36.70%, 636,698/1,734,810), and 199,579 TT/DT-carrier (11.50%, 199,579/1,734,810). A total of 5,195 AEFI reports were recorded, yielding an overall RR of 299.46 per 100,000 doses (Table 1).

The AEFI RR varied significantly by age group, sex, region, vaccine type, and dose number (all P<0.001), except between children aged 1–2 and 2–3 years, CRM197-carrier and TT-carrier vaccines, and first *vs*. second, first *vs*. fourth, and second *vs*. fourth doses. (Table 2). Common adverse reaction RR was generally higher in children >3 years, males, and Southern Jiangsu, though common adverse reactions were highest with TT/DT-carrier vaccines and after the second dose, while rare adverse reactions and coincidental events were highest with CRM197-carrier vaccines, and after the first and fourth doses, respectively (Table 3).

For CRM197-carrier PCV13, 2,519 cases (49.36%) had common adverse reactions (fever, local redness, induration); fever peaked at 37.6–38.5 °C, with redness and induration most common at 2.6–5.0 cm (Figure 1A, 1B). TT-carrier and TT/DT-carrier PCV13 saw 1,792 (35.12%) and 792 (15.52%) common reactions, respectively; fever was most frequent at ≥38.6 °C, with redness and induration most common at 2.6–5.0 cm (Figure 1C–1F). The top five non-common AEFI symptoms were sweating, nausea, fatigue, abdominal pain, and diarrhea (Supplementary Table S1, available at https://weekly.chinacdc.cn/).

The DPA of the final clinical diagnoses for 5,195 AEFI cases was performed using PRR, ROR, MHRA, and BCPNN. The diagnosis of general reactions (fever/redness/induration) showed positive signals across all four methods (PRR-1.96SE=6.61; ROR-1.96SE=165.38; MHRA: AEFI cases=5,042, PRR=6.79, χ^2=24,912.69; BCPNN: IC-2SD=2.72) (SE=standard error; IC-2SD=lower limit of IC 95% confidence intervals)(Table 4).

Furthermore, the DPA of the AEFI reports

TABLE 1. PCV13 vaccination and AEFI reports in Jiangsu Province from 2022 to 2024.

Group	Total			CRM197-carrier protein			TT-carrier protein			TT/DT-carrier protein		
	Vaccine doses (%)	AEFI cases	RR (per 100,000 doses)	Vaccine doses (%)	AEFI cases	RR (per 100,000 doses)	Vaccine doses (%)	AEFI cases	RR (per 100,000 doses)	Vaccine doses (%)	AEFI cases	RR (per 100,000 doses)
Total	1,734,810 (100)	5,195	299.46	898,533 (51.79)	2,576	286.69	636,698 (36.70)	1,821	286.01	199,579 (11.50)	798	399.84
Year												
2022	603,739 (34.80)	1,253	207.54	308,304 (34.31)	605	196.23	270,107 (42.42)	578	213.99	25,328 (12.69)	70	276.37
2023	623,271 (35.93)	1,821	292.17	310,054 (34.51)	853	275.11	229,723 (36.08)	623	271.20	83,494 (41.84)	345	413.20
2024	507,800 (29.27)	2,121	417.68	280,175 (31.18)	1,118	399.04	136,868 (21.50)	620	452.99	90,757 (45.47)	383	422.01
Dose												
1st dose	493,129 (28.43)	1,532	310.67	237,926 (26.48)	793	333.30	178,917 (28.10)	461	257.66	76,286 (38.22)	278	364.42
2nd dose	460,590 (26.55)	1,476	320.46	229,448 (25.54)	606	264.11	173,940 (27.32)	624	358.74	57,202 (28.66)	246	430.05
3rd dose	413,984 (23.86)	1,060	256.05	219,587 (24.44)	525	239.09	153,304 (24.08)	380	247.87	41,093 (20.59)	155	377.19
4th dose	367,088 (21.16)	1,127	307.01	211,564 (23.55)	652	308.18	130,528 (20.50)	356	272.74	24,996 (12.52)	119	476.08
Reaction type												
Common adverse reactions	–	5,103	294.15	–	2,519	280.35	–	1,792	281.45	–	792	396.84
Rare adverse reactions	–	50	2.88	–	30	3.34	–	16	2.51	–	4	2.00
Coincidental event	–	42	2.42	–	27	3.00	–	13	2.04	–	2	1.00
Severity												
Serious	–	11	0.63	–	8	0.89	–	3	0.47	–	0	0.00
Non-serious	–	5,184	298.82	–	2,568	285.80	–	1,818	285.54	–	798	399.84
Time interval												
≤30 min	–	53	3.06	–	19	2.11	–	20	3.14	–	14	7.01
30 min<Time≤1 day	–	3,571	205.84	–	1,825	203.11	–	1,234	193.81	–	512	256.54
1 day<Time≤3 days	–	1,287	74.19	–	584	64.99	–	465	73.03	–	238	119.25
>3 days	–	284	16.37	–	148	16.47	–	102	16.02	–	34	17.04

Note: "–": Dash indicates data not available.
Abbreviation: PCV13=13-valent pneumococcal conjugate vaccine; AEFI=adverse events following immunization; CRM197=cross-reactive material 197; TT=tetanus toxoid; TT/DT=tetanus toxoid/diphtheria toxoid; RR=reporting rate (per 100,000 doses).

associated with each of the three PCV13 types is presented in Supplementary Tables S2–S4 (available at https://weekly.chinacdc.cn/). For CRM197-carrier PCV13, positive signals for allergic rash were detected using the PRR and ROR methods (PRR-1.96SE=1.11; ROR-1.96SE=1.11). For TT-carrier PCV13, positive signals for general reactions (fever/redness/induration) were detected using the PRR and ROR methods (PRR-1.96SE=1.00; ROR-1.96SE=1.03). For TT/DT-carrier PCV13, no positive signals were detected using any of the four methods.

DISCUSSION

Based on large-scale passive surveillance data from Jiangsu Province, this study investigated the post-marketing safety of three PCV13s with different carrier protein types between 2022 and 2024. The overall reported AEFI RR for PCV13 was 299.46 per 100,000 doses, which was slightly higher than the PCV13 surveillance results from Jiangsu Province in 2019–2022 (186.80 per 100,000 doses) (*4*) and Zhejiang Province in 2022 (175.8 per 100,000 doses) (*7*). This discrepancy may be attributed to improved AEFI surveillance sensitivity, the new introduction of TT/DT-carrier PCV13, and increased public awareness of vaccine safety.

This study is the first post-marketing safety evaluation of the TT/DT dual-carrier PCV13 in Jiangsu Province, China. The results showed that the AEFI reporting rate for the TT/DT-carrier PCV13

TABLE 2. Characteristics of AEFI after PCV13 in Jiangsu Province from 2022 to 2024.

Group	Total				2022		2023		2024	
	AEFI cases (%)	RR (per 100,000 doses)	χ^2	*P*	AEFI cases (%)	RR (per 100,000 doses)	AEFI cases (%)	RR (per 100,000 doses)	AEFI cases (%)	RR (per 100,000 doses)
Age										
<1 year	3,508 (67.53)	284.53	241.03	<0.001[&]	821 (65.62)	187.15	1,261 (69.25)	288.90	1,426 (67.23)	398.59
1 year≤Age<2 years	1,491 (28.70)	320.79*			381 (30.41)	252.12	472 (25.92)	275.31	638 (30.08)	448.60
2 years≤Age<3 years	48 (0.92)	259.40*			12 (0.96)	161.99	21 (1.15)	293.62	15 (0.71)	373.51
≥3 years	148 (2.85)	957.37			39 (3.11)	748.42	67 (3.68)	942.07	42 (1.98)	1339.29
Sex										
Male	2,882 (55.48)	321.07	28.97	<0.001[&]	705 (56.26)	224.74	1,021 (56.07)	317.33	1,156 (54.50)	440.93
Female	2,313 (44.52)	276.28			548 (43.74)	188.93	800 (43.93)	265.32	965 (45.50)	392.87
Region										
Southern Jiangsu	3,339 (64.27)	307.66[†]	9.82	<0.001[&]	820 (65.44)	220.21	1,213 (66.61)	311.29	1,306 (61.57)	404.01
Central Jiangsu	745 (14.34)	271.38[§]			200 (15.96)	203.30	228 (12.52)	238.34	317 (14.95)	393.87
Northern Jiangsu	1,111 (21.39)	296.28[†, §]			233 (18.60)	175.19	380 (20.87)	275.49	498 (23.48)	478.59
Vaccine Type										
CRM197	2,576 (49.59)	286.69[¶]	76.13	<0.001[&]	605 (48.28)	196.23	853 (46.84)	275.11	1,118 (52.71)	399.04
TT	1,821 (35.05)	286.01[¶]			578 (46.13)	213.99	623 (34.21)	271.20	620 (29.23)	452.99
TT/DT	798 (15.36)	399.84			70 (5.59)	276.37	345 (18.95)	413.20	383 (18.06)	422.01
Dose										
1st dose	1,532 (29.49)	310.67[**, ††]	35.71	<0.001[&]	387 (30.89)	211.96	569 (31.25)	326.58	576 (27.16)	422.53
2nd dose	1,476 (28.41)	320.46[**, §§]			359 (28.65)	217.93	527 (28.94)	318.75	590 (27.82)	452.01
3rd dose	1,060 (20.40)	256.05			241 (19.23)	168.80	381 (20.92)	256.53	438 (20.65)	356.99
4th dose	1,127 (21.69)	307.01[††, §§]			266 (21.23)	234.05	344 (18.89)	254.48	517 (24.38)	437.19

Note: Southern Jiangsu: including Nanjing, Zhenjiang, Suzhou, Wuxi, Changzhou; Central Jiangsu: including Yangzhou, Taizhou, Nantong; Northern Jiangsu: including Xuzhou, Lianyungang, Huai'an, Yancheng, Suqian;
Total number of AEFI cases=5,195; The number of AEFI cases in 2022=1,253; The number of AEFI cases in 2023=1,821; The number of AEFI cases in 2024=2,121.
Abbreviation: AEFI=adverse events following immunization; PCV13=13-valent pneumococcal conjugate vaccine; RR=reporting rate (per 100,000 doses); CRM197=cross-reactive material 197; TT=tetanus toxoid; TT/DT=tetanus toxoid/diphtheria toxoid.
*, †, §, ¶, **, ††, §§ same superscript letters indicate no significant difference between the corresponding subgroups (P>0.05, Bonferroni correction);
[&] P<0.05.

(399.84 per 100,000 doses) was significantly higher than that for the CRM197-carrier (286.69 per 100,000 doses) and the TT-carrier (286.01 per 100,000 doses). Although a dual-carrier design may enhance immunogenicity, it may also increase reactogenicity. Animal studies have suggested that different carrier proteins elicit distinct T helper cell responses, potentially leading to carrier-induced epitopic suppression or synergistic enhancement (*8*). However, given that the TT/DT-carrier PCV13 was licensed only recently, its higher AEFI reporting rate may also be related to the Weber effect — a phenomenon in which new vaccines often experience elevated adverse event reporting rates shortly after market introduction, which then stabilize over time (*9*). Furthermore, the relatively small number of TT/DT-carrier vaccine doses administered in the present study (199,579 doses) suggests that the statistical stability of this finding needs to be confirmed with additional accumulated data. Of note, a

TABLE 3. Characteristics of AEFI RR after PCV13 in Jiangsu Province from 2022 to 2024.

Group	Common adverse reactions		Rare adverse reactions		Coincidental event	
	AEFI cases	RR (per 100,000 doses)	AEFI cases	RR (per 100,000 doses)	AEFI cases	RR (per 100,000 doses)
Age						
<1 year	3,450	279.82	32	2.60	26	2.11
1 year≤Age<2 years	1,460	314.12	16	3.44	15	3.23
2 years≤Age<3 years	47	253.01	1	5.38	0	0.00
≥3 years	146	944.43	1	6.47	1	6.47
Sex						
Male	2,826	314.84	33	3.68	23	2.56
Female	2,277	271.98	17	2.03	19	2.27
Region						
Southern Jiangsu	3,266	300.93	34	3.13	39	3.59
Central Jiangsu	741	269.92	3	1.09	1	0.36
Northern Jiangsu	1,096	292.28	13	3.47	2	0.53
Vaccine Type						
CRM197	2,519	280.35	30	3.34	27	3.00
TT	1,792	281.45	16	2.51	13	2.04
TT/DT	792	396.84	4	2.00	2	1.00
Dose						
1st dose	1,507	305.60	17	3.45	8	1.62
2nd dose	1,453	315.46	13	2.82	10	2.17
3rd dose	1,040	251.22	8	1.93	12	2.90
4th dose	1,103	300.47	12	3.27	12	3.27

Note: Southern Jiangsu: including Nanjing, Zhenjiang, Suzhou, Wuxi, Changzhou; Central Jiangsu: including Yangzhou, Taizhou, Nantong; Northern Jiangsu: including Xuzhou, Lianyungang, Huai'an, Yancheng, Suqian.
Abbreviation: AEFI=adverse events following immunization; PCV13=13-valent pneumococcal conjugate vaccine; RR=reporting rate (per 100,000 doses); CRM197=cross-reactive material 197; TT=tetanus toxoid; TT/DT=tetanus toxoid/diphtheria toxoid.

significant difference in AEFI reporting rates was observed between the CRM197-carrier and TT-carrier PCV13s, consistent with previous findings from Jiangsu Province (*4*) and multi-center findings (*10*). This further confirms the established safety profiles of these two conventional carrier-protein vaccines.

Age-stratified analysis revealed that the AEFI RR in children older than 3 years (3,829.48 per 100,000 doses) was significantly higher than that in other age groups, which differs from previous study results. A PCV13 surveillance study in Zhejiang Province reported the highest AEFI reporting rate in infants aged 6–11 months (*7*), and the Australian AusVax Safety system identified children aged 6 months to 4 years as a high-risk population for AEFIs (*11*). Although children older than 3 years had the highest AEFI RR in the present study, the majority of these events were mild common reactions, and the absolute reporting rate remained low and clinically acceptable. The higher relative rate in this age group is likely attributable to enhanced self-expression and greater guardian attention rather than a true increase in biological risk (*12*–*13*).

Fever, local redness, and local induration were the most frequently reported common adverse reactions, which is consistent with PCV13 safety studies conducted both domestically and internationally (*7*,*14*). Notably, the proportion of high-grade fever (≥ 38.6 °C) following vaccination with the TT-carrier and TT/DT-carrier PCV13s was higher than that with the CRM197-carrier PCV13, whereas the CRM197-carrier vaccine was predominantly associated with moderate-grade fever (37.6–38.5 °C). This difference may be related to variations in the cytokine profiles induced by different carrier proteins (*10*).

In the present study, DPA results showed that general reactions (fever, redness, and induration) exhibited strong positive signals across all four

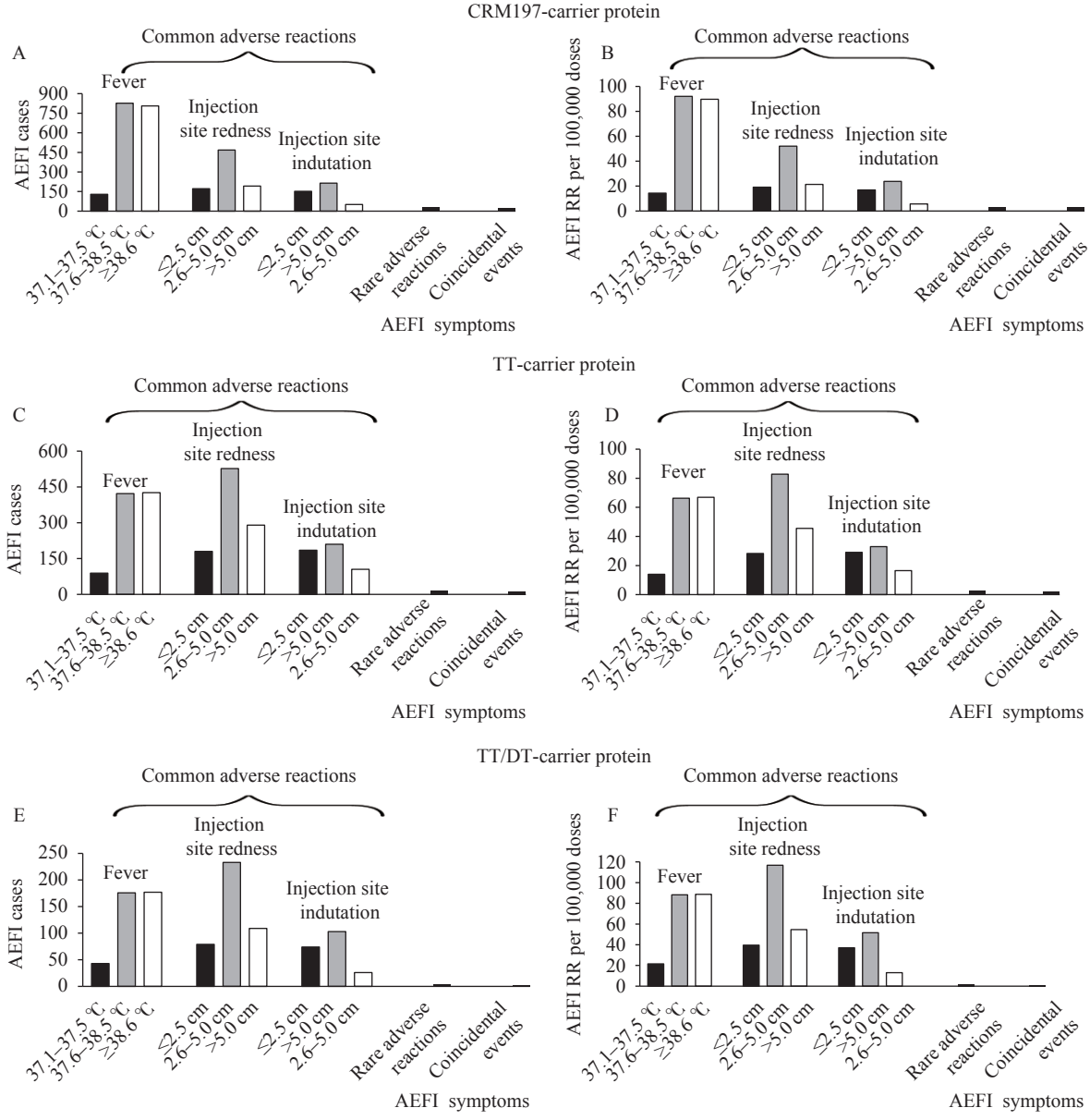


FIGURE 1. Distribution of AEFI cases (left panel) and RR per 100,000 doses (right panel) associated with PCV13 in Jiangsu Province from 2022 to 2024. (A) AEFI cases of CRM197 carrier protein. (B) AEFI RR per 100,000 doses of CRM197-carrier protein. (C) AEFI cases of TT-carrier protein. (D) AEFI RR per 100,000 doses of TT-carrier protein. (E) AEFI cases ofTT/DT-carrier protein. (F) AEFI RR per 100,000 doses of TT/DT-carrier protein.
Abbreviation: AEFI=adverse events following immunization; PCV13=13-valent pneumococcal conjugate vaccine; RR=reporting rate (per 100,000 doses); CRM197=cross-reactive material 197; TT=tetanus toxoid; TT/DT=tetanus toxoid/diphtheria toxoid.

methods, consistent with the known safety profile of PCV13 (*7*). Collectively, these results indicated that general reactions are AEFIs of particular concern following PCV13 vaccination. Subgroup analysis revealed a weak signal for allergic rash associated with the CRM197-carrier PCV13 under PRR/ROR, but this was not corroborated by BCPNN; the evidence remains inconclusive and hypothesis-generating, warranting continued attention. A previous study reported that CRM197, a non-toxic diphtheria toxin mutant, may induce IgE-mediated allergic reactions through cross-reactivity with human proteins (*15*). Vaccine Adverse Event Reporting System data show rash-reporting rates after PCV13 vaccination ranging from 0.6 to 2.3 per 100,000 doses, predominantly with CRM197-carrier products (*16*). However, the signal value in this study was close to the threshold, necessitating a comprehensive assessment in

TABLE 4. Disproportionality analysis of AEFI reports (clinical diagnosis) associated with PCV13 in Jiangsu Province from 2022 to 2024.

Diagnosis	RR (per 100,000 doses)	PRR-1.96SE	ROR-1.96SE	MHRA			BCPNN
				AEFI cases	PRR	χ^2	IC-2SD
General Reaction (Fever/Redness/Induration, etc.)	290.64	6.61	165.38	5,042	6.79	24912.69	2.72
Allergic Reactions-Allergic Purpura	0.06	0.00	0.00	1	0.00	740.14	−12.42
Allergic Reactions-Allergic Rash	4.15	0.08	0.07	72	0.10	605.13	−3.71
Allergic Reactions-Urticaria	0.98	0.01	0.01	17	0.02	708.53	−6.15
Febrile Seizures	0.12	0.00	0.00	2	0.00	738.15	−10.58
Thrombocytopenic Purpura	0.35	0.00	0.00	6	0.01	730.19	−8.13
Others	3.17	0.06	0.05	55	0.07	636.22	−4.14

Note: PRR: Proportional Reporting Ratio, the lower limit of the 95% two-sided confidence interval >1; ROR: Reporting Odds Ratio, the lower limit of the 95% two-sided confidence interval >1; MHRA: the Medicines and Healthcare Products Regulatory Agency method, the number of AEFI reports a≥3, PRR≥2 and χ^2≥4; BCPNN: Bayesian Confidence Propagation Neural Network method, the lower limit of the 95% two-sided confidence interval of the Information Component (IC) is greater than 0.
Abbreviation: AEFI=adverse events following immunization; PCV13=13-valent pneumococcal conjugate vaccine; RR=reporting rate (per 100,000 doses).

conjunction with clinical evaluation and subsequent surveillance data.

This study provides the first evidence for a post-marketing safety assessment of the new TT/DT-carrier PCV13. Some limitations should be acknowledged. This study used passive surveillance data, which has inherent limitations. For example, the vaccine safety awareness of the vaccinees or their guardians, as well as the completeness of reports by healthcare professionals, can affect the quality of reports. Passive surveillance only captures information from AEFI reporters; therefore, some conclusions in this study lack control groups. Further prospective active surveillance studies are warranted to confirm these results. Although the carrier protein type was the focus of this study, AEFI is a multifactorial outcome, and other factors, such as manufacturer-specific production processes, adjuvant formulation, and host characteristics, may also influence reactogenicity and should be addressed in future studies.

The findings indicate that AEFIs reported following administration of the three PCV13s with different carrier protein types in Jiangsu Province (2022–2024) were predominantly mild and fell within the category of common adverse reactions, which is broadly consistent with safety data from pre-licensure or post-licensure trials. These results may help alleviate parental concerns regarding the safety of the TT/DT dual-carrier PCV13 and improve vaccination coverage among children in China.

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SUPPLEMENTARY MATERIALS

Introduction to the Data Sources

The data used in this study have several advantages. First, the Jiangsu Province Vaccination Integrated Service Management Information System (JSEIRS) is an advanced system in the field of disease control in China, achieving multiple pioneering and unprecedented accomplishments. Data quality can be guaranteed, with the authenticity of individual vaccination records reaching 100% through full traceability using three pathways: electronic traceability code, vaccine lot number, and vaccine code. Second, the AEFI surveillance sensitivity in Jiangsu Province has consistently ranked among the highest in the country, exceeding 1 per 1,000 doses, which is far above the national requirement of 0.5 per 1,000 doses. Third, regarding the 13-valent pneumococcal conjugate vaccines with different carrier proteins, we began investigating differences in adverse reaction rates several years ago, as documented in relevant publications. Jiangsu Province has invested considerable time and effort in researching PCV13s with different carrier proteins. Unmatched records were returned to the local CDCs for verification. After confirming the reasons for non-matching, primarily missing or incorrect basic information, the records were corrected and included in the study.

Data Analysis for DPA

For each PCV13 type, we performed a separate disproportionality analysis. In each analysis, the target vaccine was defined as the specific PCV13 type under evaluation (CRM197-carrier, TT-carrier, or TT/DT-carrier). Control vaccines were defined as all other vaccines administered in Jiangsu Province during the same study period (January 2022 to December 2024), excluding the target PCV13 itself. However, because our study period included only three PCV13s and no other vaccine types were included in the AEFI reports relevant to PCV13, the control group for each target vaccine consisted of the remaining two PCV13 types (i.e., other PCV13s).

Usually, the positive signal markers for proportionality imbalance analysis are: 1) PRR: the lower limit of the 95% two-sided confidence interval >1; 2) ROR: the lower limit of the 95% two-sided confidence interval >1; 3) MHRA: the number of AEFI reports a $\geq$3, PRR $\geq$2 and $\chi^2 \geq 4$; 4) BCPNN: the lower limit of the 95% two-sided confidence interval of the Information Component (IC) is greater than 0. We applied the Haldane–Anscombe correction (adding 0.5 to all four cells) to calculate the PRR and ROR, preventing division by zero when b, c, or d equaled zero (*1*). For the MHRA method, no correction was used; a positive signal was considered only when the raw count a $\geq$3, regardless of the corrected values.

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SUPPLEMENTARY TABLE S1. Symptoms and diagnostic characteristics of AEFI after PCV13 in Jiangsu Province, 2022–2024.

Group	CRM197-carrier protein		TT-carrier protein		TT/DT-carrier protein		Total	
	AEFI cases (%)	RR (per 100,000 doses)	AEFI cases (%)	RR (per 100,000 doses)	AEFI cases (%)	RR (per 100,000 doses)	AEFI cases (%)	RR (per 100,000 doses)
Common Adverse Reactions								
Fever (℃)								
37.1–37.5	129 (5.01)	14.36	89 (4.89)	13.98	43 (5.39)	21.55	261 (5.02)	15.04
37.6–38.5	827 (32.10)	92.04	422 (23.17)	66.28	176 (22.06)	88.19	1,425 (27.43)	82.14
≥38.6	806 (31.29)	89.70	426 (23.39)	66.91	177 (22.18)	88.69	1,409 (27.12)	81.22
Total	1,762 (68.40)	196.10	937 (51.46)	147.17	396 (49.62)	198.42	3,095 (59.58)	178.41
Redness (cm)								
≤2.5	172 (6.68)	19.14	180 (9.88)	28.27	79 (9.90)	39.58	431 (8.30)	24.84
2.6-5.0	468 (18.17)	52.08	527 (28.94)	82.77	233 (29.20)	116.75	1,228 (23.64)	70.79
>5.0	192 (7.45)	21.37	290 (15.93)	45.55	109 (13.66)	54.61	591 (11.38)	34.07
Total	832 (32.30)	92.60	997 (54.75)	156.59	421 (52.76)	210.94	2,250 (43.31)	129.70
Induration (cm)								
≤2.5	152 (5.90)	16.92	185 (10.16)	29.06	74 (9.27)	37.08	411 (7.91)	23.69
2.6-5.0	214 (8.31)	23.82	210 (11.53)	32.98	103 (12.91)	51.61	527 (10.14)	30.38
>5.0	51 (1.98)	5.68	105 (5.77)	16.49	26 (3.26)	13.03	182 (3.50)	10.49
Total	417 (16.19)	46.41	500 (27.46)	78.53	203 (25.44)	101.71	1,120 (21.56)	64.56
Other Symptoms								
Sweating	24 (0.93)	2.67	16 (0.88)	2.51	3 (0.38)	1.50	43 (0.83)	2.48
Nausea	1 (0.04)	0.11	3 (0.16)	0.47	1 (0.13)	0.50	5 (0.10)	0.29
Fatigue	100 (3.88)	11.13	84 (4.61)	13.19	32 (4.01)	16.03	216 (4.16)	12.45
Abdominal Pain	0 (0.00)	0.00	1 (0.05)	0.16	0 (0.00)	0.00	1 (0.02)	0.06
Diarrhea	47 (1.82)	5.23	19 (1.04)	2.98	13 (1.63)	6.51	79 (1.52)	4.55
Arthralgia	0 (0.00)	0.00	2 (0.11)	0.31	1 (0.13)	0.50	3 (0.06)	0.17
Cough	98 (3.80)	10.91	43 (2.36)	6.75	25 (3.13)	12.53	166 (3.20)	9.57
Myalgia	8 (0.31)	0.89	17 (0.93)	2.67	13 (1.63)	6.51	38 (0.73)	2.19
Rhinorrhea	34 (1.32)	3.78	16 (0.88)	2.51	6 (0.75)	3.01	56 (1.08)	3.23
Pallor	0 (0.00)	0.00	1 (0.05)	0.16	0 (0.00)	0.00	1 (0.02)	0.06
Vomiting	33 (1.28)	3.67	36 (1.98)	5.65	8 (1.00)	4.01	77 (1.48)	4.44
Rash	122 (4.74)	13.58	36 (1.98)	5.65	15 (1.88)	7.52	173 (3.33)	9.97
Itching	52 (2.02)	5.79	45 (2.47)	7.07	18 (2.26)	9.02	115 (2.21)	6.63
Poor Appetite	114 (4.43)	12.69	76 (4.17)	11.94	29 (3.63)	14.53	219 (4.22)	12.62
Drowsiness	75 (2.91)	8.35	35 (1.92)	5.50	16 (2.01)	8.02	126 (2.43)	7.26
Headache	2 (0.08)	0.22	0 (0.00)	0.00	5 (0.63)	2.51	7 (0.13)	0.40
Dizziness	0 (0.00)	0.00	0 (0.00)	0.00	2 (0.25)	1.00	2 (0.04)	0.12
Chest Tightness	0 (0.00)	0.00	0 (0.00)	0.00	1 (0.13)	0.50	1 (0.02)	0.06
Pharynx Redness	12 (0.47)	1.34	3 (0.16)	0.47	1 (0.13)	0.50	16 (0.31)	0.92
Others	22 (0.85)	2.45	26 (1.43)	4.08	8 (1.00)	4.01	56 (1.08)	3.23
Total	744 (28.88)	82.80	459 (25.21)	72.09	197 (24.69)	98.71	1,400 (26.95)	80.70

Note: Total number of AEFI cases=5,195; The number of AEFI cases from CRM197-Carrier Protein=2,576; The number of AEFI cases from TT-Carrier Protein=1,821; The number of AEFI cases from TT/DT-Carrier Protein=798.

Abbreviation: AEFI=adverse events following immunization; PCV13=13-valent pneumococcal conjugate vaccine; CRM197=cross-reactive material 197; TT=tetanus toxoid; TT/DT=tetanus toxoid/diphtheria toxoid; RR=reporting rate (per 100,000 doses).

SUPPLEMENTARY TABLE S2. Disproportionality analysis of AEFI reports (clinical diagnosis) associated with CRM197-carrier protein PCV13 in Jiangsu Province from 2022 to 2024.

Diagnosis	RR	PRR-1.96SE	ROR-1.96SE	MHRA			BCPNN
				AEFI cases	PRR	χ^2	IC-2SD
General Reaction (Fever/Redness/Induration etc.)	143.13	0.98	0.45	2,483	0.99	7.91	−0.07
Allergic Reactions-Allergic Purpura	0.06	0.12	0.12	1	Inf	1.02	−1.87
Allergic Reactions-Allergic rash	2.65	**1.11**	**1.11**	46	1.80	5.98	−0.06
Allergic Reactions-Urticaria	0.63	0.69	0.69	11	1.86	1.56	−0.49
Febrile Seizures	0.06	0.11	0.11	1	1.02	0.00	−2.87
Thrombocytopenic Purpura	0.23	0.39	0.39	4	2.03	0.70	−1.02
Others	1.73	0.72	0.72	30	1.22	0.55	−0.39

Note: PRR: Proportional Reporting Ratio, the lower limit of the 95% two-sided confidence interval >1; ROR: Reporting Odds Ratio, the lower limit of the 95% two-sided confidence interval >1; MHRA: the Medicines and Healthcare Products Regulatory Agency method, the number of AEFI reports a≥3, PRR≥2 and χ^2≥4; BCPNN: Bayesian Confidence Propagation Neural Network method, the lower limit of the 95% two-sided confidence interval of the Information Component (IC) is greater than 0.
Abbreviation: AEFI=adverse events following immunization; PCV13=13-valent pneumococcal conjugate vaccine; RR=reporting rate (per 100,000 doses); CRM197=cross-reactive material 197.

SUPPLEMENTARY TABLE S3. Disproportionality analysis of AEFI reports (clinical diagnosis) associated with TT-carrier protein PCV13 in Jiangsu Province from 2022 to 2024.

Diagnosis	RR	PRR-1.96SE	ROR-1.96SE	MHRA			BCPNN
				AEFI cases	PRR	χ^2	IC-2SD
General Reaction (Fever/Redness/Induration etc.)	102.60	**1.00**	**1.03**	1,780	1.01	4.72	−0.06
Allergic Reactions-Allergic Purpura	0.00	0.03	0.03	0	0.00	0.54	−
Allergic Reactions-Allergic rash	0.98	0.34	0.34	17	0.57	4.20	−1.27
Allergic Reactions-Urticaria	0.17	0.14	0.14	3	0.40	2.27	−2.66
Febrile Seizures	0.06	0.19	0.19	1	1.85	0.20	−2.37
Thrombocytopenic Purpura	0.12	0.22	0.22	2	0.93	0.01	−2.11
Others	1.04	0.53	0.52	18	0.90	0.13	−0.78

Note: PRR: Proportional Reporting Ratio, the lower limit of the 95% two-sided confidence interval >1; ROR: Reporting Odds Ratio, the lower limit of the 95% two-sided confidence interval >1; MHRA: the Medicines and Healthcare Products Regulatory Agency method, the number of AEFI reports a≥3, PRR≥2 and χ^2≥4; BCPNN: Bayesian Confidence Propagation Neural Network method, the lower limit of the 95% two-sided confidence interval of the Information Component (IC) is greater than 0.
Abbreviation: AEFI=adverse events following immunization; PCV13=13-valent pneumococcal conjugate vaccine; RR=reporting rate (per 100,000 doses); TT=tetanus toxoid.

SUPPLEMENTARY TABLE S4. Disproportionality analysis of AEFI reports (clinical diagnosis) associated with TT/DT-carrier protein PCV13 in Jiangsu Province from 2022 to 2024.

Diagnosis	RR	PRR-1.96SE	ROR-1.96SE	MHRA			BCPNN
				AEFI cases	PRR	χ^2	IC-2SD
General Reaction (Fever/Redness/Induration etc.)	44.90	0.99	0.78	779	1.01	1.05	−0.10
Allergic Reactions-Allergic Purpura	0.00	0.08	0.08	0	0.00	0.18	−
Allergic Reactions-Allergic rash	0.52	0.42	0.41	9	0.79	0.46	−1.26
Allergic Reactions-Urticaria	0.17	0.41	0.41	3	1.18	0.07	−1.47
Febrile Seizures	0.00	0.05	0.05	0	0.00	0.36	−
Thrombocytopenic Purpura	0.00	0.02	0.02	0	0.00	1.09	−
Others	0.40	0.40	0.39	7	0.80	0.30	−1.36

Note: PRR: Proportional Reporting Ratio, the lower limit of the 95% two-sided confidence interval >1; ROR: Reporting Odds Ratio, the lower limit of the 95% two-sided confidence interval >1; MHRA: the Medicines and Healthcare Products Regulatory Agency method, the number of AEFI reports a≥3, PRR≥2 and χ^2≥4; BCPNN: Bayesian Confidence Propagation Neural Network method, the lower limit of the 95% two-sided confidence interval of the Information Component (IC) is greater than 0.
Abbreviation: AEFI=adverse events following immunization; PCV13=13-valent pneumococcal conjugate vaccine; RR=reporting rate (per 100,000 doses); TT/DT=tetanus toxoid/diphtheria toxoid.