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Surveillance of adverse events following varicella vaccine immunization in Jiangsu province, China from 2017 to 2023

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Abstract To assess the safety of varicella vaccine (VarV) by conducting post-marketing surveillance on adverse events following immunization (AEFI) in Jiangsu Province, China.

Methods We utilized the AEFI Information System of mainland China to monitor and categorize adverse reactions associated with VarV.

Results The incidence rate of AEFI was significantly higher after the first dose (48.79/100,000 doses) compared to the second dose (45.18/100,000 doses) ($\chi^2 = 4.63$, $P = 0.031$). Regional variations in AEFI incidence were observed within Jiangsu Province. Common reactions comprised 90.96% of AEFIs, while rare reactions and coincidental events accounted for 6.59% and 0.51%, respectively. Notably, there were no adverse events linked to vaccine quality, program errors, psychogenic reactions, or fatalities. Over 96% of AEFIs occurred within three days of VarV administration, with redness at the injection site (2.6 cm to 5 cm in diameter) being the most frequently observed symptom.

Conclusion VarV demonstrates a commendable safety profile. Although there was a slight increase in AEFI incidence between 2022 and 2023, common vaccine reactions were predominantly observed, and the rates of rare reactions remained very low.

Keywords Varicella vaccine, Vaccination, Adverse events following immunization, Surveillance

Introduction

The varicella zoster virus causes varicella, a highly contagious disease characterized by systemic papules and pruritus, primarily affecting kindergarten and primary school students. Potential complications include pneumonia and encephalitis [1, 2]. According to the data from the China Disease Prevention and Control Information System, the reported incidence of varicella in Jiangsu Province during 2021–2022 exceeded 80/100,000, making it a major public health emergency and ranking first among infectious disease emergencies [3]. Consequently, it has become an increasingly serious public health concern. The live attenuated varicella vaccine (VarV) currently used in Jiangsu Province is produced by Changchun Bacco, China. The current VarV utilized

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is a freeze-dried product derived from the cultivation of varicella virus (OKA strain) on human diploid cells. Both children and adults receive immunization with this vaccine, which has the same composition [4].

Globally, the varicella vaccine is recognized as the most effective measure for preventing and controlling the disease. Studies have shown that while a single dose of VarV offers limited population immunity, a complete two-dose regimen effectively curtails varicella transmission [5–7]. However, as a foreign biological product, vaccines may induce adverse reactions due to individual variability. Pre-marketing clinical trials face challenges in accurately assessing safety due to limitations such as short observation periods and small sample sizes [8]. Therefore, post-marketing safety assessments are crucial.

This study aimed to evaluate the safety of VarV among children by analyzing suspected adverse reactions reported in Jiangsu Province from 2017 to 2023. Using data from the Jiangsu Provincial Comprehensive Vaccination Service Management Information System and the Adverse Events Following Immunization (AEFI) management module of the China Immunization Program Information Management System, we conducted a detailed analysis and signal mining of VarV AEFI data. This approach helps in understanding post-vaccination AEFI reports, allowing for the timely identification and assessment of potential AEFI signals, thereby providing a foundation for future safety studies.

Methods

Vaccination schedule and inclusion/exclusion criteria for VarV

The current vaccination policy in China mandates two doses of varicella vaccine for children of appropriate age in specific provinces such as Jiangsu, Tianjin, and Shanghai. In Jiangsu Province specifically, it is recommended that children under 6 years old receive two free doses of VarV. The recommended immunization schedule entails administering the first dose between 12 and 18 months of age and the second dose at 4 years old. Additionally, children aged between 4 and 6 years who have not completed the full course of two varicella vaccine doses should also receive them. Adults can select either one or two doses of the VarV depending on their individual immune status and the prevailing incidence rate in their locality.

The inclusion criteria for children were as follows: (1) Meet the vaccination age; (2) Good physical health (with axillary temperature < 38 °C and without acute or chronic diseases). The exclusion criteria were as follows: (1) Known allergic to vaccine of some components; (2) Had serious illness or other medical reasons for not participating after clinical evaluation.

Surveillance of AEFI

Mainland China established the passive Adverse Event Following Immunization Information System (CNAEFIS) for AEFI monitoring in 2008, and it underwent updates in 2015 and 2018, respectively. Through this system, doctors of vaccination clinics with authority report and preliminary classify AEFI. This system has been described in our previous research [9]. We obtained the unique identification code, gender, age, inoculation time, reaction time, preliminary AEFI classification, final clinical diagnosis, final AEFI classification and other information of the recipients with AEFI after VarV inoculation in the selected time period from CNAEFIS. The definition of AEFI in Mainland China aligns with the World Health Organization (WHO) National Regulatory Authority assessment requirements [10]. An AEFI is defined as a reaction potentially causing organ or functional damage during or after prophylactic vaccination, suspected to be related to the vaccination. The criteria encompass the following: (1) The event must occur within a reasonable time frame after vaccination or during the course of vaccination; (2) The affected individual must exhibit specific organ or tissue damage, as well as functional impairment; (3) There should be clinical suspicion that links the observed cases to the act of vaccination. Common adverse reactions are caused by the inherent characteristics of the vaccine after vaccination, which impair the body function in a transient manner. These adverse effects mainly included fever and local redness and swelling, accompanied by malaise, fatigue, and loss of appetite. Rare adverse reactions refer to adverse reactions that damage the tissues, organs and normal functions of recipients during vaccination or after vaccination with standard vaccines.

Information on AEFIs of VarV

The adverse events following immunization (AEFIs) that occurred in Jiangsu Province after the administration of VarV between January 1st, 2017 and June 30, 2023 were systematically reviewed. This study analyzed AEFI data extracted from the China National Adverse Events Following Immunization Information System (CNAEFIS) during this period for cases involving any type or dose of VarV. The data included unique identification codes, gender, age, inoculation and reaction times, preliminary AEFI classifications, final clinical diagnoses, final AEFI classifications, and other relevant recipient details associated with AEFI occurrences following VarV inoculation.

Number of VarV doses

Our previous research introduced an individual-level Electronic Immunization Registry (EIRS) in China. Building upon this foundation, the province of Jiangsu has developed the Vaccination Services Management

Information System (SMIS). SMIS allows for detailed queries of recipient information, including name, age, gender, vaccination record, residence, and facilitates statistical summarization. Utilizing this system, the incidence rate (IR) of Adverse Events Following Immunization (AEFI) was calculated by employing the number of Varicella Vaccine doses as the denominator.

Statistical analysis

The SPSS 24.0 software was used for the establishment and compilation of a database. The incidence rate of Adverse Events Following Immunization (AEFI) caused by VarV from 2017 to 2023 was calculated, and the epidemiological characteristics were analyzed descriptively. The AEFI reported incidence rate (per 100,000 doses) was determined as the number of reported AEFI cases divided by the number of vaccine doses multiplied by 100,000. The chi-square test from R package was employed to analyze differences in AEFI occurrence based on gender, dose, and reporting year. P value of less than 0.05 was considered as an indicator of statistical significance.

Results

Baseline data

From January 1, 2017 to June 30, 2023, a total of 7,436,560 doses of VarV were administered in Jiangsu Province. This included 4,853,463 first doses and 2,583,097 s doses. In total, 3535 AEFIs cases following VarV administration were reported during 2017–2023, yielding IRs of 47.54 per 100,000 doses. The probability of AEFI after the first dose (IR=48.79/100,000 doses) was significantly higher compared to the second dose (IR=45.18/100,000 doses) (χ^2=4.628, P=0.031).The male to female ratio of AEFI IR for VarV was 1:0.91. The incidence of VarV AEFI reached its peak in 2023, exhibiting a significantly higher rate compared to other years (χ^2=104.602, P<0.001). Conversely, the lowest incidence was recorded during 2019–2020, presenting an incidence rate of 40.64. Significant variations in the incidence of AEFI were observed across different regions within Jiangsu Province. Specifically, the central region exhibited a significantly higher AEFI incidence compared to both the northern and southern areas (χ^2=2900.235, P<0.001). (See Table 1 for details). The proportion of common reactions in different age groups was above 90%, as shown in Table 2.

Classifcation and time intervals of AEFIs

Common reactions accounted for 90.96% of the AEFIs, while rare reactions and coincidental events only represented 6.59% and 0.51% of all reported cases, respectively. There were no adverse events related to vaccine quality, program errors, psychogenic reactions, or fatalities. The proportion of common reactions following the second dose was significantly higher compared to the first dose, while the proportion of rare reactions was lower than that seen with the initial dose; these differences were found to be statistically significant(χ^2=19.372, P<0.001).

The occurrence of more than 96% of AEFIs was observed within three days following the administration of VarV. The average duration between the first dose and the occurrence of AEFI was shorter compared to that after the second dose, with 62.84% of cases observed within a 30-minute timeframe for the former, while only 47.04% were recorded within the same time period following administration of the second dose. The predominant symptoms occurring within a time interval of less than 30 min were indicative of allergic reactions, primarily characterized by allergic dermatitis. The longest interval observed between vaccination and AEFI onset

Table 1 Basic distribution characteristics of varicella vaccine AEFI in Jiangsu Province from 2017 to 2023

Variables		Vaccine doses	AEFI cases	IR (per 100,000 Vaccine doses)	χ^2 value	*P* value
Sex	Male	3,938,486	1857	47.15	0.26	0.609
	Female	3,498,074	1678	47.97		
Age (years)	1–2	3,508,590	1828	52.1	82.52	<0.001
	3–4	2,152,312	1018	47.3		
	5–6	1,480,258	592	39.99		
	≥6	295,400	97	32.84		
Year	2017–2018	1,035,518	492	47.51	104.60	<0.001
	2019–2020	2,175,090	884	40.64		
	2021–2022	2,193,160	931	42.45		
	2023	2,032,792	1228	60.41		
Dose	First Dose	4,853,463	2368	48.79	4.63	0.031
	Second Dose	2,583,097	1167	45.18		
place of residence	Northern Jiangsu	2,248,181	1300	57.82	2900.24	<0.001
	Central Jiangsu	1,087,331	1547	142.27		
	Southern Jiangsu	4,101,048	688	16.78		
Total		7,436,560	3535	47.54		

Table 2 Varicella vaccine classification and AEFIs time intervals of AEFIs

		Total									
		First Dose			Second Dose			χ^2 value	*P* value	Total		
		AEFI cases	Proportion(%)	IR (per 100,000 doses)	AEFI cases	Proportion(%)	IR (per 100,000 doses)			AEFI cases	Proportion(%)	IR (per 100,000 doses)
Classification of AEFIs	Common reaction	2194	92.65	45.2	1120	95.97	43.36	19.37	<0.001	3314	93.75	44.56
	Rare reaction	156	6.59	3.21	37	3.17	1.43			193	5.46	2.6
	Coincidental event	12	0.51	0.25	5	0.43	0.19			17	0.48	0.23
	Not classified	6	0.25	0.12	5	0.43	0.19			11	0.31	0.15
AEFIs time intervals	≤ 30 min	1488	62.84	30.66	549	47.04	21.25	85.99	<0.001	2037	57.62	27.39
	30 min-3 days	787	33.23	16.22	584	50.04	22.61			1371	38.78	18.44
	>3 days	93	3.93	1.92	34	2.91	1.32			127	3.59	1.71
	Total	2368	-	48.79	1167	100.00	45.18			3535	-	47.54

was 34 days, with thrombocytopenic purpura emerging as a clinical symptom. Although the recipient's guardian attributed this condition to the vaccine, an investigation by the AEFI expert panel classified it as a coincidental event. (See Table 3 for details).

Symptoms of AEFIs

A total of 3535 AEFIs associated with the VarV vaccine were reported, among which 1303 were localized injection site reactions. The most prevalent systemic symptoms included fever, irritability, and allergic skin eruptions.The incidence rates (IRs) of different symptoms varied from 0.09 to 13.98 (per 100,000 doses). The most frequently observed symptom at the injection site for VarV is redness, ranging from 2.6 cm to 5 cm in diameter. The current status indicates all AEFI have been successfully treated.(See Table 4 for details).

Discussion

Immunocompromised children who contract varicella are at risk of severe illness and serious complications, particularly affecting children in nurseries, kindergartens, and schools [11, 12]. Since 2017, the reported incidence of varicella and the number of public health emergencies in Jiangsu Province have remained persistently high, indicating that varicella has emerged as a significant public health concern [13]. Despite the implementation of a one-dose VarV vaccination strategy, breakthrough varicella cases continue to occur frequently, indicating that this approach has not effectively curbed transmission [14]. In Jiangsu Province, VarV has been included in the Expanded Program on Immunization (EPI) since January 1st, 2023. The two-dose vaccination strategy for VarV is provided free of charge to school-age children: the first dose at 12 months old and the second at 4 years old. This study aims to analyze the reported incidence of AEFI related to VarV from June 2017 to June 2023, providing valuable insights for enhancing VarV vaccination services and assessing its safety.

The total reported incidence of rare reaction following VarV vaccination in Jiangsu Province from 2017 to 2023 was 2.60 per 100,000 doses, which is higher than the reported incidence of 1.35/100,000 doses during 2001–2016 in Henan Province butlower than the reported incidence of 3.12/100,000 doses during 2014–2020 in China [15, 16]. AEFI reports for VarV in Jiangsu Province were more frequent in 2022–2023, likely due to increased surveillance sensitivity and enhanced AEFI reporting training during this period [17].

Among children aged 12–23 months, the incidence of adverse events following varicella vaccine was highest, which may be attributed to their developing immune systems or heightened parental vigilance, leading to increased reporting. Similar trends have been observed

Table 3 Varicella vaccine systemic reaction and injection site reactions

AEFIs symptoms		First Dose		Second Dose		Total		
		Number	Proportion(%)	Number	Proportion(%)	Number	Proportion(%)	IR (per 100,000 doses)
Systemic reaction	Body temperature (> 39.0 ℃)	751	31.74	289	24.76	1040	29.42	13.98
	Body temperature (38.6℃ -39.0℃)	512	21.62	354	30.33	866	24.50	11.65
	Body temperature (38.0 ℃-38.5℃)	89	3.76	112	9.60	201	5.69	2.7
	Irritability	232	9.80	286	24.49	518	14.65	6.97
	Allergic eruption	154	6.50	102	8.73	256	7.24	3.44
	Fatigue	114	4.81	75	6.41	189	5.35	2.54
	Loss of appetite	101	4.27	138	11.78	239	6.76	3.21
	Drowsiness	78	3.29	46	3.92	124	3.51	1.67
	Vomiting	49	2.07	48	4.09	97	2.74	1.3
	Diarrhea	29	1.22	19	1.62	48	1.36	0.65
	Pruritus	56	2.36	85	7.23	141	3.99	1.9
	Cough	5	0.21	15	1.28	20	0.57	0.27
	Sweat	12	0.51	12	1.02	24	0.68	0.32
	Rhinorrhea	6	0.25	4	0.34	10	0.28	0.13
	pallor	7	0.30	8	0.68	15	0.42	0.2
	Abdominal pain	1	0.04	6	0.51	7	0.20	0.09
Injection site reactions	Redness(> 5 cm)	96	4.05	74	6.27	170	4.81	2.29
	Redness(2.6–5 cm)	315	13.30	120	10.15	435	12.31	5.85
	Redness(≤ 2.5 cm)	188	7.94	82	6.93	270	7.64	3.63
	Induration(> 5 cm)	35	1.48	17	1.44	52	1.47	0.7
	Induration(2.6–5 cm)	122	5.15	75	6.33	197	5.57	2.65
	Induration(≤ 2.5 cm)	114	4.81	65	5.48	179	5.06	2.41
Total		2368	-	1167	98.32	3535	-	47.54

Table 4 AEFIs of varicella vaccine in different age groups

		Total			
		Common reaction(%)	Rare reaction(%)	Coincidental event(%)	Not classified(%)
Age (years)	1–2	1692 (92.6)	126 (6.9)	9 (0.5)	1 (0.0)
	3–4	964 (94.7)	47 (4.6)	5 (0.5)	2 (0.2)
	5–6	566 (95.6)	18 (3.1)	5 (0.8)	3 (0.5)
	≥ 6	92 (94.8)	2 (2.1)	3 (3.1)	0 (0.0)

domestically and internationally, with higher reported AEFI incidences for the first dose of VarV compared to the second [18, 19]. There were no significant monthly variations noted, suggesting that AEFI occurrence does not exhibit seasonal characteristics. Additionally, there were no significant differences in incidence rates between males and females, consistent with previous research findings. Central Jiangsu reported a higher incidence of VarV-related AEFIs compared to the southern and northern regions which may be attributed to enhanced reporting sensitivity resulting from intensified AEFI reporting training within central Jiangsu region along with a recommendation for strengthening pre-vaccination health consultations. After January 1, 2023, we conducted AEFIs reporting training in central Jiangsu Province in response to the implementation of the two-dose free varicella vaccination strategy, which may have contributed to an increase in reported AEFIs. A comparison of 2023 AEFI reports for VarV with other vaccines that had unchanged vaccination schedules revealed no significant changes in AEFI numbers, supporting the hypothesis that the increased reports in central Jiangsu were primarily due to the impact of training.The primary abnormal reaction associated with VarV was an allergic reaction, while angioedema, anaphylactic shock, anaphylactoid purpura, and other severe abnormalities were not observed.

Our findings demonstrate that the incidence of AEFI associated with VarV in this study surpassed that of other vaccines in the national AEFI monitoring system. It is notable that VarV is not included in the national immunization program, and its administration primarily targets children from families with higher socioeconomic status and educational attainment [20]. These parents tend to be more vigilant about post-vaccination outcomes, leading to increased AEFI reporting and sensitivity. As a live attenuated vaccine, VarV carries a higher risk of adverse reactions compared to inactivated vaccines [21].

The occurrence of AEFI in VarV primarily manifests within a three-day window post-vaccination and typically subsides after approximately 72 h, aligning with the findings of our study. During the period from 2017 to 2023, a total of three cases of serious adverse effects were observed: two cases of Kawasaki disease. However, after expert review, both cases were determined to be coincidental. Another serious adverse reaction identified was acute lymphoblastic leukemia, which was also diagnosed by experts as a coincidence. Currently, all three patients have a favorable prognosis. AEFI induced by VarV predominantly presents as common reactions such as fever, erythema, or induration, commonly appearing between 2 and 5 days following vaccination. Over time, guardians' vigilance towards reporting AEFI tends to diminish. Although some minor adverse reactions may occur beyond the initial five-day period, they are often disregarded by guardians due to their perceived mild nature. Similar trends have been observed in post-marketing surveillance studies of other vaccines [22, 23]. This phenomenon indeed represents one limitation of passive monitoring.

The limitations of this study include the reliance on passive surveillance for VarV AEFI reports, which may have resulted in underreporting, as well as the short observation period following VarV vaccination, leading to an underestimation of incidence. Our analysis was conducted based on the National Adverse Events Following Immunization Surveillance System. In accordance with the monitoring guidelines for suspected adverse reactions during national immunization (2022 edition), only redness and swelling as well as induration at the injection site are collected under local reactions; tenderness at the injection site is not included. In future studies, it is imperative to enhance the analysis of VarV coverage rate and AEFI incidence within birth cohorts after implementing a two-dose VarV immunization strategy, thereby providing a more robust reference for VarV vaccination among school-age children.

In conclusion, the incidence of adverse reactions following varicella vaccine (VarV) immunization in Jiangsu province remains within expected parameters. Most reported reactions are mild and general, with severe reactions being rare. Continuous monitoring of AEFI for VarV is imperative to enhance the sensitivity and quality of reporting and investigation. It is important to reassure the public that concerns regarding the safety profile of VarV vaccination are unwarranted.

Author contributions

Conceived and designed the experiments: Lei Zhang, Yuanbao Liu，Ran Hu. Contributed reagents/materials/analysis tools: YaLi Fu, Wen Wang, Zhiguo Wang . Wrote the paper: Lei Zhang, Sun Xiang. All authors read and approved the final manuscript.

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Data availability

The data used and analyzed for the current study is available upon request from the first author Lei Zhang (E-mail: 1020389031@qq.com).

Declarations

Ethics approval and consent to participate

The authors promise that only the specific monitoring results will be used in the article, and no personal privacy information such as the names of any specific participants in the monitoring will be used. There was no biological sample material in this monitoring. Because this work is a routine monitoring work according to the requirements, the ethical review committee of Jiangsu Center for Disease Control and Prevention decided that there was no need for ethical review and it was not necessary to obtain written informed consent from all participants. The publication of the article takes into account the requirement of privacy protection for the participants and complies with ethical norms.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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