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ORIGINAL RESEARCH

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Analysis of the coverage of inactivated enterovirus 71 (EV71) vaccine and adverse events following immunization with the EV71 vaccine among children from 2016 to 2019 in Guangzhou

Zhi-qun Li [a], Zi-qi Qin[b], Hui-feng Tan[a], Chun-huan Zhang[a], Jian-xiong Xu[a], Jian Chen[a], Li-Hong Ni[a], Xue-xia Yun[a], Min Cui[a], Yong Huang[a], Wen Wang[a] and Zhou-bin Zhang[a]

[a]Ministry of immunization, Guangzhou Center For Disease Control And Prevention; [b]Department of Film, Theatre & Television, University of Reading, Reading, UK

ABSTRACT

Background: Since 2016, China has approved the use of inactivated enterovirus 71 (EV71) vaccines produced by three manufacturers. The coverage and safety of different EV71 vaccines need to be evaluated.

Research design and methods: The EV71 vaccination and AEFI data were collected from the Guangzhou Children's Vaccination Information Report Management System and the China AEFI Monitoring Information Management System, and the EV71 vaccine coverage rate and the AEFI incidence rate were analyzed.

Results: From 2016 to 2019, the number of people who should have been vaccinated in Guangzhou was 2,781,618, and the coverage rates for doses 1 and 2 were 24.71% and 19.44%, respectively. The inoculation rates of vaccines from manufacturers A and B were between 3.03 and 10.46%. The reported incidence of AEFIs was 11.97 per 100,000 (147 cases), with fever (106 cases, 8.63 per 100,000) and allergic rash (59 cases, 4.80 per 100,000) being the most common reactions. There were no differences in the AEFI responses to the EV71 vaccines from the three manufacturers.

Conclusion: The EV71 vaccines from the three manufacturers have good safety, but the EV71 vaccine coverage rate is low. It is recommended that vaccine publicity be strengthened and that the vaccine coverage rate in children be increased.

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KEYWORDS
Enterovirus 71 inactivated vaccine; vaccination; inoculation rate; abnormal reaction; safety

1. Introduction

Enterovirus 71 (EV71) is the main pathogen of hand, foot, and mouth disease (HFMD), which mainly infects infants and young children under 5 years old [1]. HFMD was included in the China Disease Prevention and Control Information System in May 2008. The top 5 diseases reported in 2019 for category C infectious diseases were influenza, hand, foot and mouth disease, other infectious diarrhea, mumps and acute hemorrhagic conjunctivitis, and these accounted for 99.5% of the total number of category C infectious diseases reported. The diseases in category C with deaths reported were influenza, hand, foot and mouth disease, other infectious diarrheal diseases and hydatid disease, accounting for 100% of the total number of deaths reported by these infections [2]. During 2009–2018, China reported more than 20 million cases of hand, foot and mouth disease and 838,000 laboratory confirmed cases. The most severe (68%) and fatal (91%) cases of hand, foot and mouth disease are caused by EV71 [3]. A small number of severe HFMD cases caused by EV71 can be complicated with severe complications, and a very small number can cause death, which has become a serious public health problem [4]. There is no effective treatment for the disease, and vaccination has become an effective means of preventing and controlling HFMD. In 2015, China was the first country to successfully develop an EV71 inactivated whole-virus vaccine. At present, vaccines developed by the Institute of Medical Biology of the Chinese Academy of Medical Sciences (manufacturer A), the Sinovac Biotech Co., Ltd. (manufacturer B), and the Wuhan Institute of Biological Products Co., Ltd., of the China Biotechnology Group (manufacturer C) have been approved for marketing [5,6]. All three vaccines were developed using the C4 subtype as the seed virus [7]. After August 2016, the three products were successively used in Guangzhou inoculation units. This study analyzed the coverage rate of different enterovirus 71 (EV71) vaccines and the incidence of suspected immunization (adverse event following immunization, AEFI) in Guangzhou from 2016 to 2019. The purpose of the study was to evaluate the production by the three manufacturers and the coverage rate and safety of the EV71 vaccines to provide a reference for the formulation and adjustment of EV71 vaccination strategies.

CONTACT Zhi-qun Li 992805123@qq.com Guangzhou Center For Disease Control And Prevention No.1,Qide Rd,Jiahe,Baiyun,Guangzhou,Guangdong,China (510440).
*Zhi-qun Li, Ziqi Qin, Hui-feng Tan and Chun-huan Zhang contributed equally to this work

Article highlights

- In August 2016, the EV71 vaccine was put on the market in China.
- From 2016 to 2019, the EV71 coverage rate increased annually, but the coverage rate (19.44%) throughout this period was still low. The target number of vaccinated 1-year-olds is the largest, but the coverage rate is the lowest (16.67%). Men (20.29%) have a higher coverage rate than women (18.37%).
- The incidence of AEFI is the highest in the 1-year-old group and within 0~1 d after vaccination; males have a higher incidence than females, and the incidence in those with 1 dose is higher than in those with 2 doses.
- AEFI is mainly characterized by fever (106 cases, 8.63/per 100,000) and allergic rash (59 cases, 4.80/per 100,000).
- A total of 79.66% of allergic rashes occurred within 1 day after vaccination, 1 case of angioedema and 1 case of febrile seizures occurred within 30 minutes after vaccination, ≤ 1 day.
- There was no difference in the AEFI response to the EV71 vaccines from the three manufacturers.
- The promotion of the EV71 vaccine has an effect on the prevention and control of the occurrence of severe deaths from hand, foot and mouth disease. Strengthening the promotion of the vaccine is of great benefit to increasing the coverage rate of children.

2. Methods

2.1. Research design and participants

The study was a retrospective study and was conducted from 1 August 2016, to 31 December 2019. The EV71 vaccination data came from the Guangzhou Children's Vaccination Information Report Management System and were selected from 11 districts in Guangzhou, including Conghua, Panyu, Liwan, Nansha, Yuexiu, Huadu, Baiyun, Haizhu, Huangpu, Tianhe, and Zengcheng. Vaccination cases were collected in various districts of Guangzhou; AEFI data were obtained from China's AEFI monitoring information management system. The data on the incidence of hand, foot and mouth disease came from the annual analysis report of legal infectious diseases in Guangzhou. To ensure the quality of the data, the data were exported and examined for duplication, and the inoculation rate and safety of the EV71 vaccines produced by the three manufacturers were evaluated. A total of 1,228,125 doses of the vaccines were administered, and a total of 147 cases of adverse reactions were reported. The main analytical indicators were the number of vaccinations used, the coverage rate, the number of AEFI reports, and the report rate (per 100,000). The flowchart of the research is shown in Figure 1.

2.2. Vaccines

2.2.1. Ingredients and procedures

In this study, two licensed vaccines from three manufacturers were examined. Manufacturer A's EV71 vaccine is prepared from a C4 subtype of EV71 KMB17 cell substrate containing 100 U of alum adjuvant EV71 antigen, cultured and

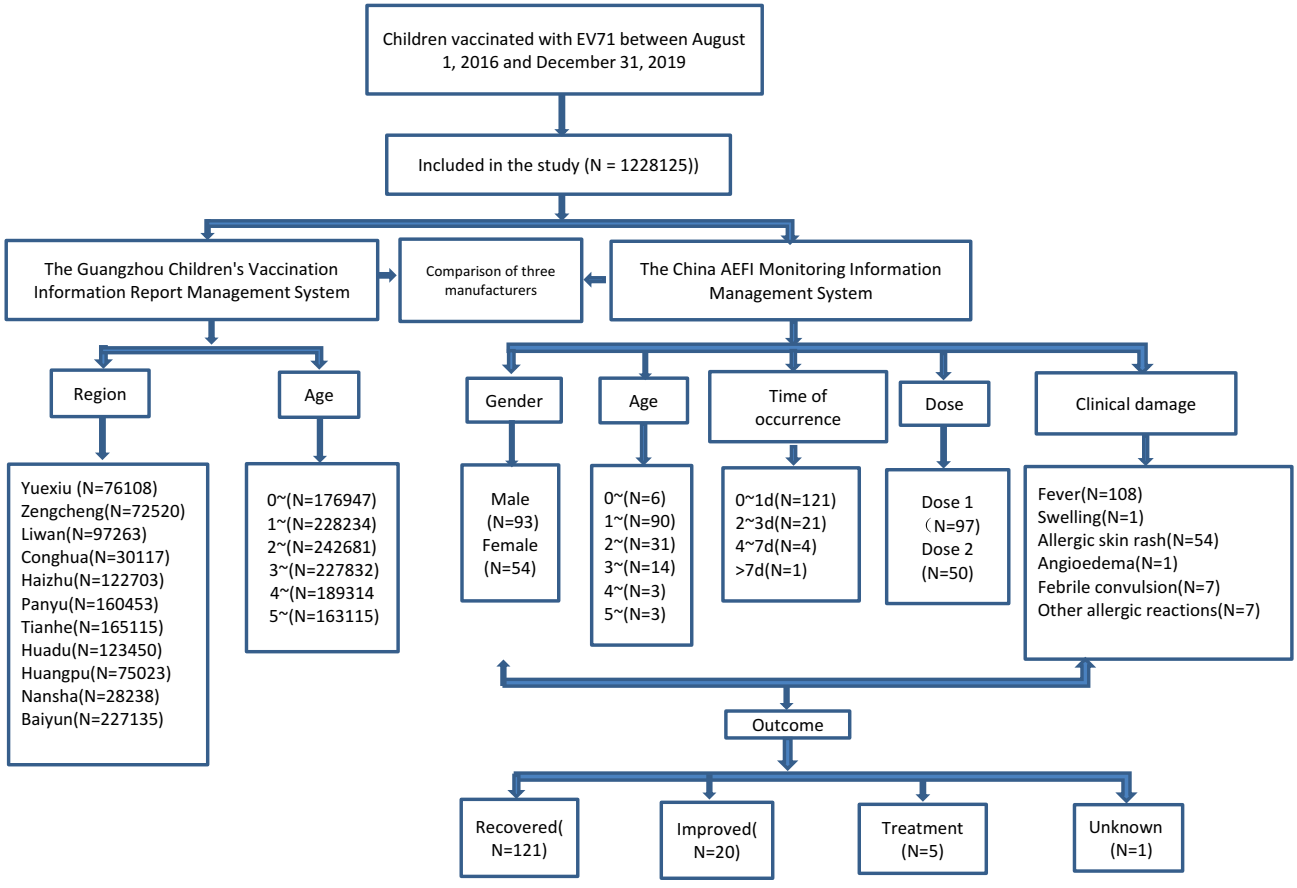

Figure 1. Flowchart of the samples in this study.

proliferated in a human diploid cell line (human diploid cell, HD) (KMB17), and then purified inactivated [7]; the vaccination targets are children aged 6 months to 5 years old. The manufacturer B and manufacturer C EV71 vaccines were prepared from the C4 subtype EV71 Vero cell substrate. Manufacturer B and manufacturer C vaccines contain 400 U and 320 U of alum adjuvant EV71 antigen, respectively [7,8], and the vaccination targets are children from 6 months to 3 years old. The three vaccines are packaged in syringes (0.5 ml per bottle), and the two doses are injected intramuscularly one month apart.

2.2.2. The distribution of vaccines and the vaccination rates

The EV71 vaccines were purchased by the district CDC through the Guangdong Drug Trading Center according to the demand plan of the community health service center and then transported to the cold storage of the community health service center by a qualified third-party pharmaceutical logistics company. The community health service center published the information on the EV71 vaccine on the mobile app of the Guangzhou vaccination service and then issued vaccination notices on the mobile app to the guardians of school-aged children that should be vaccinated with the EV71 vaccine according to the background database. The children who were willing to be vaccinated took the initiative to be vaccinated. For children who did not respond or were still hesitating, the vaccination doctor would introduce the relevant information on the EV71 vaccine when they received other vaccines and encourage or invite the children to receive immunization for EV71 after excluding the relevant contraindications.

2.3. AEFI investigation, diagnosis and classification

The safety of EV71 vaccines was monitored in accordance with the report scope of the 'National Suspected Vaccination Abnormal Response Monitoring Program' (Health Affairs Control Fa [2010] No. 94) [9]. Suspected causes of abnormal vaccination reactions are divided into the following five types: adverse reactions, vaccine quality accidents, vaccination accidents, coincidences, and psychogenic reactions. Among these, adverse reactions are divided into common adverse reactions and abnormal reactions. Common adverse reaction refers to a reaction that causes only transient physiological dysfunction in the body, mainly fever, redness and swelling and induration at the inoculation site; abnormal reaction refers to a reaction that causes damage to the body's tissues, organs, and functions. Coincidental reactions were defined as a recipient that was in the incubation period or prodromal period of a certain disease at the time of vaccination, and the reaction happened by coincidence after vaccination. The district-level disease prevention and control agency organized an investigation within 48 hours after receiving a report of a suspected abnormal vaccination reaction. It is necessary to verify the basic information, time and number of occurrences, main clinical manifestations, preliminary clinical diagnosis, vaccination, etc. of the suspected abnormal vaccination reaction. The preliminary completion of the questionnaire for suspected cases of abnormal vaccination reaction occurred within 3 days after the determination of vaccine-related AEFI in addition to direct network reporting through China's AEFI monitoring information management system. In this study, all infants and children vaccinated with the EV71 vaccine in 11 districts of Guangzhou were included as observation objects. The passive monitoring mode reported by the parents of the children was adopted; that is, the parents of the children observed whether AEFI occurred in the children without corresponding reminders and voluntarily reported such instances to the vaccination clinic. Then, the community service center summarized these instances in the AEFI database. CDCs at all levels in Guangzhou managed AEFI case information through the system.

2.4. Statistical analyses

The AEFI case data were exported to Microsoft Excel files, SPSS 19.0 software was applied for statistical analyses, and the EV71 coverage rate of each district and age group was calculated. EV71 coverage rate (%) = EV71 vaccination number/target number×100. Incidence rate of AEFI reports (100,000 doses) = number of AEFI reported cases/EV71 vaccination number × per 100,000. The denominator (target number) refers to the total population of children aged 6 m-5 years old in Guangzhou, derived from the annual report of basic information of Guangzhou's immunization plan; the numerator (number of people vaccinated) refers to the number of children aged 6 m-5 years old in Guangzhou who received the EV71 vaccine, according to the Guangzhou Vaccination Information Platform.

3. Results

3.1. EV71 vaccination

3.1.1. Overview of vaccinations

From August 2016 to 31 December 2019, Guangzhou received a total of 1,228,125 doses of the EV71 vaccine; the annual numbers of doses from August 2016 to 2019 were 50,338, 168,350, 235,703 and 233,021, respectively. The inoculation rate was 8.20%~32.94%; the annual numbers of two-dose vaccinations were 36,613 doses, 126,062 doses, 188,348 doses and 189,691 doses, and the inoculation rate was between 5.96%~26.32% (Table 1).

From August 2016 to 31 December 2019, the inoculation rates of doses 1 and 2 were 24.71% and 19.44%, respectively, among which the inoculation rates of doses 1 and 2 of the manufacturer A vaccine were 10.45% and 8.21%, respectively; the inoculation rate of dose 1 of the manufacturer B vaccine was 10.46 and that of dose 2 was 8.19%; The EV71 vaccine of manufacturer C was introduced in 2018, and the coverage rate of manufacturer C in 2018–2019 were 3.80% and 3.03%, respectively (Table 1).

3.1.2. Sex and age distribution

The coverage rates for males and females receiving EV71 vaccines were 23.08% and 26.76%, respectively, for one dose,

Table 1. EV71 coverage rate of different manufacturers in Guangzhou from August 2016 to 2019.

		Manufacturer A				Manufacturer B				Manufacturer C				Total			
		Dose 1		Dose 2		Dose 1		Dose 2		Dose 1		Dose 2		Dose 1		Dose 2	
Year	Total number of people	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)
2016	614,033	33,770	5.50	24,402	3.97	16,567	2.70	12,211	1.99	0	0.00	0	0.00	50,338	8.20	36,613	5.96
2017	695,151	65,544	9.43	48,608	6.99	102,806	14.79	77,454	11.14	0	0.00	0	0.00	168,350	24.22	126,062	18.13
2018	715,551	85,609	11.96	68,848	9.62	103,756	14.50	83,069	11.61	46,338	6.48	36,430	5.09	235,703	32.94	188,348	26.32
2019	756,883	105,833	13.98	86,612	11.44	67,845	8.96	55,151	7.29	59,343	7.84	47,927	6.33	233,021	30.79	189,691	25.06
Total	2,781,618	290,756	10.45	228,471	8.21	290,974	10.46	227,885	8.19	105,681	3.80	84,357	3.03265	687,412	24.7127	540,713	19.44

20.29% and 18.37%, respectively, for the full course of two doses and 24.71% and 19.44%, respectively, in children under 5 years of age. At the age of 5 years, the coverage rate of 1 dose was between 21.19% and 20.30%, and the coverage rate of 2 doses was between 16.67% and 23.84%. Manufacturer A's 0 ~ 5 years old vaccine coverage rate for dose 1 was between 8.97% and 12.82% and for dose 2 was 7.05%~10.06%; for the same age range, the coverage rate for the manufacturer B vaccine was between 8.97% and 12.72% for dose 1 and between 7.02% and 9.99% for dose 2; for manufacturer C's vaccine, the coverage rate was between 3.25% and 4.76% for dose 1 and between 2.60% and 3.79% for dose 2 (Table 2).

3.1.3. Regional distribution

The inoculation rate of the EV71 vaccine for children in various districts of Guangzhou was between 11.59% (Nansha) and 28.75% (Tianhe), and the coverage rate of 2 doses was between 8.57% (Nansha) and 26.01% (Baiyun). Among them, the inoculation rate of the doses in each district of manufacturer A's vaccine was between 3.30% (Conghua)and 16.09% (Huadu) for dose 1 and between 2.60% (Conghua) and 12.28% (Tianhe) for dose 2; for the vaccine from manufacturer B the inoculation rate was between 5.21% (Yuexiu)and 15.68% (Liwan) for dose 1 and between 3.26% (Nansha) and 13.16% (Liwan) for dose 2; the inoculation rate of the vaccine from manufacturer C was between 0.70% (Panyu) and 8.95% (Huadu) for dose 1 and between 0.50% (Panyu) and 6.69% (Huadu) for dose 2 (Table 3).

3.2. AEFI report

3.2.1. AEFI classification

A total of 147 cases of AEFI were reported after EV71 vaccination in Guangzhou from August 2016 to 31 December 2019, with a reported incidence of 11.97 per 100,000 vaccinations; 62 cases of common adverse reactions (5.05 per 100,000), 54 cases of abnormal reactions (4.40 per 100,000), 31 cases of coincidental events (2.52 per 100,000), and no vaccine quality accidents, vaccination accidents or psychogenic reactions were reported (Table 4).

From August 2016 to 31 December 2019, Guangzhou received a total of 519,227 doses of manufacturer A's EV71 vaccine, and 62 cases of AEFIs were reported (11.94/per 100,000), including 24 cases (38.71%) of common adverse reactions, 24 cases of abnormal reactions (38.71%) and 14 cases of coincidental events (22.58%); 518,859 doses of manufacturer B's vaccine were received and 64 cases of AEFIs were reported (12.33/per 100,000), of which 28 cases (43.75%) were common adverse reactions (43.75%), 20 cases (31.25%) were abnormal reactions, and 16 cases (25%) were of concomitant disease; from 2018 to 31 December 2019, manufacturer of C provided 19,039 doses to Guangzhou and 21 cases of AEFIs were reported (11.05/per 100,000), of which 10 cases (47.62%) were common adverse reactions (47.62%), 10 cases were abnormal reactions (47.62%) and 1 case (4.76%) occurred with incidental disease (Table 4). The EV71 vaccines from the three manufacturers did not report severe AEFIs, and there were no differences in the AEFI responses of the three manufacturers (X^2 = 0.2170, P > 0.05); there were no differences in AEFI responses between manufacturer A (diploid cells) and manufacturers B and C (Vero cells) (X^2 = 0.0278, P > 0.05) (Table 4).

3.2.2. Sex, age, time of occurrence, and doses distributed

Among all AEFIs, the ratio of males to females was 1.72:1; for the 93 males that had AEFIs (13.85/per 100,000), the incidences of AEFIs from the vaccines of manufacturers A ~ C were between 10.25 and 14.98/per 100,000; for the 54 females (9.70/per 100,000) that experienced AEFIs, the incidences of AEFIs from the vaccines of manufacturers A ~ C were between 9.06 and 12.10/per 100,000. The maximum number of AEFIs at 1 year of age was 90 (39.43/per 100,000), and the incidences of AEFIs from the vaccines of manufacturers A-C were between 34.08 ~ 53.86/per 100,000; only manufacturer A's vaccine produced AEFIs in the 4- and 5-year-old groups. A total of 82.31% (121,9.85/per 100,000) of the AEFIs occurred in 0 ~ 1 day after vaccination, vaccines from manufacturers A ~ C produced AEFI incidences between 7.89 and 10.21/per 100,000; 14.29% (21,1.71/per 100,000) of the AEFIs occurred in 2 ~ 3 days after vaccination, between vaccines from manufacturers A and C AEFI incidences were from 1.16 to 2.12 per 100,000. The incidence rate of AEFIs resulting from one dose of the vaccine was 14.11/per 100,000, between the vaccines from manufacturers A ~ C AEFI incidence rates were between 12.30 and 15.13/per 100,000; the incidence rate of AEFIs resulting from two doses of the vaccine was 9.25/per 100,000, between the vaccines from manufacturers A ~ C AEFI incidence rates were between 7.88 and 10.53/10 per 10,000 doses (Table 5).

3.2.3. Clinical damage

Fever was the most common adverse reaction, among which 88 cases (7.17/per 100,000) had a high fever of ≥ 38.5°C, followed by 16 cases (1.30/per 100,000) with a fever of 37.6–-38.5°C and 2 cases (0.16/per 100,000) with a fever of 37.1–-37.5°C. There was only one case of swelling (0.08/per 100,000), and there were no induration reactions. Among the abnormal reactions (5.86/per 100,000), the reported incidences of anaphylactic rash, angioedema, febrile convulsion and other allergic convulsions were 4.80, 0.08, 0.41 and 0.57, respectively (Table 6). A total of 79.66% of anaphylactic rashes occurred within 1 day after vaccination, 1 case of angioedema and 1 case of febrile convulsion occurred within 30 minutes after vaccination, ≤ 1 day.

3.2.4. Outcome

Among all AEFIs, 141 cases were cured or improved (95.92%), 5 cases were treated (3.40%), and the outcome of 1 case (0.68%) was unknown.

3.3. Hand, foot, and mouth disease case report

A total of 277,305 cases of hand, foot, and mouth disease were reported in Guangzhou from 2016 to 2019, with an incidence rate of 486.95 cases/100,000 inhabitants. The incidence of hand, foot and mouth disease in 2018 was the lowest in recent years, with an incidence rate of 337.49/100,000; the incidence increased in 2019 (615.56/100,000), but among the laboratory-diagnosed cases, EV71 infections have been declining annually. Viral infection was the main type of infection (889

Table 2. Gender and age distribution of EV71 vaccination coverage rate of different manufacturers in Guangzhou from August 2016 to 2019.

		Manufacturer A				Manufacturer B				Manufacturer C				Total			
		Dose 1		Dose 2		Dose 1		Dose 2		Dose 1		Dose 2		Dose 1		Dose 2	
	Total number of people	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)
Sex																	
Male	1,548,527	165,731	10.70	125,659	8.11	157,126	10.15	129,895	8.39	58,442	3.77	48,927	3.16	357,454	23.08	314,154	20.29
Female	1,233,091	125,025	10.14	102,812	8.34	133,848	10.85	97,991	7.95	47,239	3.83	35,430	2.87	329,958	26.76	226,559	18.37
Age																	
0~	448,914	41,871	9.33	32,903	7.33	41,860	9.32	32,881	7.32	15,267	3.40	12,166	2.71	98,998	22.05	77,949	17.36
1~	602,808	54,045	8.97	42,493	7.05	54,101	8.97	42,319	7.02	19,602	3.25	15,674	2.60	127,748	21.19	100,486	16.67
2~	540,682	57,468	10.63	45,211	8.36	57,203	10.58	44,772	8.28	21,128	3.91	16,900	3.13	135,799	25.12	106,882	19.77
3~	463,643	53,732	11.59	42,163	9.09	54,989	11.86	42,937	9.26	18,909	4.08	15,101	3.26	127,630	27.53	100,202	21.61
4~	424,234	45,001	10.61	35,384	8.34	44,503	10.49	34,874	8.22	16,442	3.88	13,110	3.09	105,945	24.97	83,369	19.65
5~	301,337	38,639	12.82	30,317	10.06	38,318	12.72	30,102	9.99	14,333	4.76	11,406	3.79	91,290	30.30	71,825	23.84
Total	2,781,618	290,756	10.45	228,471	8.21	290,974	10.46	227,885	8.19	105,681	3.80	84,357	3.03	687,412	24.71	540,713	19.44

Table 3. Regional distribution of EV71 vaccination coverage rate of different manufacturers in Guangzhou from August 2016 to 2019.

Region	Total	number of people	Manufacturer A				Manufacturer B				Manufacturer C				Total	
		Dose 1		Dose 2		Dose 1		Dose 2		Dose 1		Dose 2		Dose 1		Dose 2	
		Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)	Vaccinated	Coverage rate (%)
Conghua	140,024	4620	3.30	3643	2.60	8337	5.95	6368	4.55	3839	2.74	3310	2.36	16,796	12.00	13,321	9.51
Panyu	371,412	45,140	12.15	34,457	9.28	44,796	12.06	31,595	8.51	2599	0.70	1866	0.50	92,534	24.91	67,919	18.29
Liwan	188,190	22,089	11.74	18,036	9.58	29,510	15.68	24,759	13.16	1557	0.83	1312	0.70	53,156	28.25	44,108	23.44
Nansha	140,078	6933	4.95	5540	3.96	6799	4.85	4562	3.26	2503	1.79	1900	1.36	16,236	11.59	12,002	8.57
Yuexiu	246,128	23,888	9.71	20,149	8.19	12,824	5.21	11,045	4.49	4445	1.81	3757	1.53	41,157	16.72	34,950	14.20
Huadu	207,788	33,424	16.09	24,054	11.58	18,380	8.85	15,093	7.26	18,605	8.95	13,894	6.69	70,409	33.89	53,041	25.53
Baiyun	474,708	66,656	14.04	53,265	11.22	54,096	11.40	43,635	9.19	32,894	6.93	26,589	5.60	153,646	32.37	123,489	26.01
Haizhu	326,569	13,998	4.29	11,540	3.53	42,164	12.91	35,019	10.72	11,033	3.38	8949	2.74	67,195	20.58	55,508	17.00
Huangpu	179,764	10,454	5.82	7550	4.20	24,923	13.86	20,053	11.16	6295	3.50	5749	3.20	41,671	23.18	33,352	18.55
Tianhe	326,074	51,085	15.67	40,035	12.28	32,851	10.07	24,308	7.45	9815	3.01	7021	2.15	93,751	28.75	71,364	21.89
Zengcheng	180,883	12,469	6.89	10,203	5.64	16,296	9.01	11,447	6.33	12,095	6.69	10,011	5.53	40,860	22.59	31,660	17.50
Total	2,781,618	290,756	10.45	228,471	8.21	290,974	10.46	227,885	8.19	105,681	3.80	84,357	3.03	687,412	24.71	540,713	19.44

Table 4. Incidence rates (100,000 doses) of AEFI cases for EV71 vaccine by manufacturer and classification in Guangzhou from August 2016 to 2019.

	Manufacturer A		Manufacturer B		Manufacturer C		Manufacturer B + C		Total	
Classification	n	Incidence rates (%)	n	Incidence rates (%)	n	Incidence rates (%)	n	Incidence rates (%)	n	Incidence rates (%)
Common adverse reaction	24	4.62	28	5.40	10	5.26	38	5.36	62	5.05
Abnormal reaction	24	4.62	20	3.85	10	5.26	30	4.23	54	4.40
Coincidental event	14	2.70	16	3.08	1	0.53	17	2.40	31	2.52
Total	62	11.94	64	12.33	21	11.05	85	11.99	147	11.97

Table 5. Incidence rates (100,000 doses) of AEFI cases for EV71 vaccine by manufacturer and sex、age、time of occurrence and dose distribution in Guangzhou from August 2016 to 2019.

	Manufacturer A		Manufacturer B		Manufacturer C		Total	
	n	Incidence rates (%)	n	Incidence rates (%)	n	Incidence rates (%)	n	Incidence rates (%)
Sex								
Male	39(62.90)	13.38	43(67.19)	14.98	11(52.38)	10.25	93(63.27)	13.85
Female	23(37.10)	10.09	21(32.81)	9.06	10(47.62)	12.10	54(36.73)	9.70
Age								
0~	3(5.00)	4.01	2(3.03))	2.68	1(4.76)	3.65	6(4.08)	3.39
1~	33(55.00)	34.18	38(57.58)	39.41	19(90.48)	53.86	90(61.22)	39.43
2~	12(20.00)	11.69	19(28.79)	18.63	0(0.00)	0.00	31(21.09)	12.77
3~	6(10.00)	6.26	7(10.61)	7.15	1(4.76)	2.94	14(9.52)	6.14
4~	3(5.00)	3.73	0(0.00)	0.00	0(0.00)	0.00	3(2.04)	1.58
5~	3(5.00)	4.35	0(0.00)	0.00	0(0.00)	0.00	3(2.04)	1.84
Time of occurrence								
0 ~ 1d	53(85.48)	10.21	53(82.81)	10.21	15(71.43)	7.89	121(82.31)	9.85
2 ~ 3d	6(9.68)	1.16	11(17.19)	2.12	4(19.05)	2.10	21(14.29)	1.71
4 ~ 7d	2(3.23)	0.39	0(0.00)	0.00	2(9.52)	1.05	4(2.72)	0.33
>7d	1(1.61)	0.19	0(0.00)	0.00	0(0.00)	0.00	1(0.68)	0.08
Dose								
Dose 1	44(70.97)	15.13	40(62.50)	13.75	13(61.90)	12.30	97(65.99)	14.11
Dose 2	18(29.03)	7.88	24(37.50)	10.53	8(38.10)	9.48	50(34.01)	9.25

Table 6. Incidence rates (100,000 doses) of AEFI cases for EV71 vaccine by manufacturer and clinical damag in Guangzhou from August 2016 to 2019.

		Manufacturer A		Manufacturer B		Manufacturer C		Manufacturer B + C		Total	
Classification		n	Incidence rates (%)	n	Incidence rates (%)	n	Incidence rates (%)	n	Incidence rates (%)	n	Incidence rates (%)
Common adverse reaction											
Fever	37.1℃-37.5℃	1	0.19	0	0.00	2	1.05	2	0.28	3	0.24
	37.6℃-38.5℃	10	1.93	5	0.96	2	1.05	7	0.99	17	1.38
	≥38.5℃	41	7.90	39	7.52	8	4.21	47	6.63	88	7.17
Swelling	≤2.5 cm	0	0.00	1	0.19	0	0.00	1	0.14	1	0.08
	2.5 ~ 5.0 cm	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	≥5.0 cm	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Abnormal reaction											
Anaphylactic rash		22	4.24	22	4.24	10	5.26	32	4.51	54	4.40
Angioedema		0	0.00	1	0.19	0	0.00	1	0.14	1	0.08
Febrile convulsion		5	0.96	2	0.39	0	0.00	2	0.14	7	0.57
Other allergic convulsion		5	0.96	2	0.39	0	0.00	2	0.28	7	0.57

cases, accounting for 51.96%), followed by CoxA16 infection (524 cases, accounting for 30.63%) and EV71 infection (298 cases, accounting for 17.41%) (Table 7).

4. Discussion

There are many pathogens that cause hand, foot and mouth disease, and the routes of transmission are complicated. A total of 277,305 cases were reported in Guangzhou from 2016 to 2019, with an incidence rate of 486.95 cases/100,000 inhabitants. The number of EV71 infection cases has been declining annually, and the proportions of annual EV71 infections in laboratory diagnosed cases from 2017 to 2019 were 29.45%, 20.18%, and 17.42%. These results show that the EV71 vaccine launched in August 2016 has an effect on the prevention and control of severe deaths from hand, foot, and mouth disease. There is currently no specific antiviral drug for hand, foot and mouth disease, and vaccination is considered to be

Table 7. Ncidence statistics of hand foot mouth disease case report in Guangzhou from 2016 to 2019.

Year	Total number of people	Number of cases	Incidence (/100,000)	Laboratory diagnosed cases			
				EV71	CoxA16	Other enterovirus infections	Total
2016	13,501,170	60,600	448.85	369	451	1038	1858
2017	14,043,481	76,030	541.39	607	155	1299	2061
2018	14,498,207	48,930	337.49	225	363	527	1115
2019	14,904,315	91,745	615.56	298	524	889	1711
Total	56,947,172	277,305	486.95	1499	1493	3753	6745

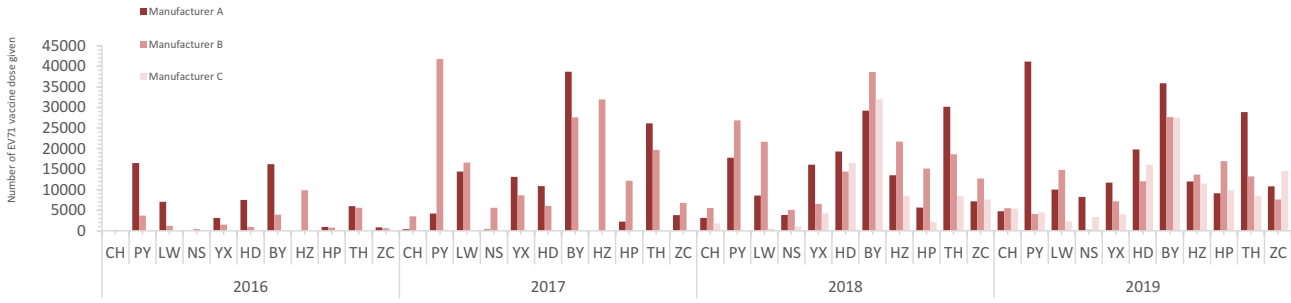

Figure 2. Comparison of 11 districts vaccinated with 1 dose and 2 doses of EV71 vaccine in Guangzhou from August 2016 to December 2019.

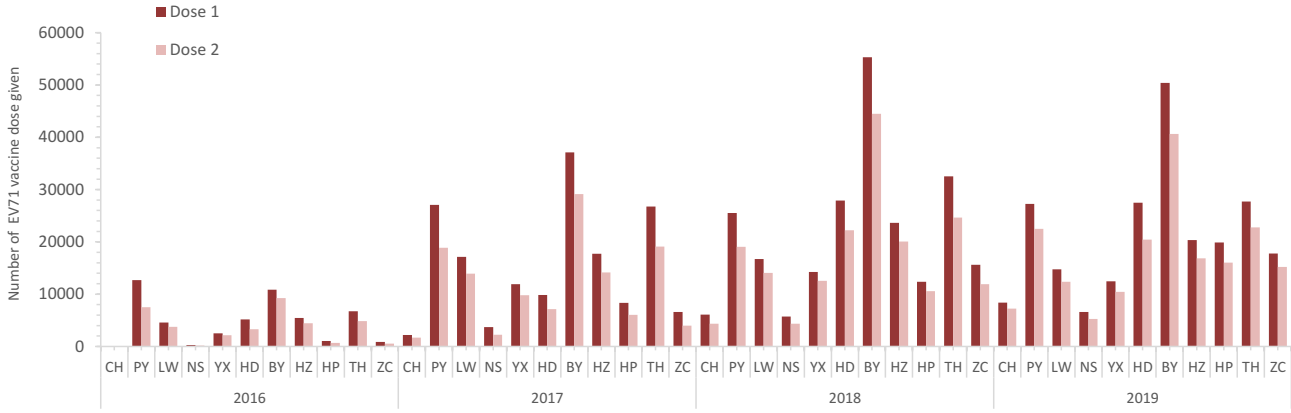

Figure 3. Comparison of 11 districts vaccinated with manufacturer A、 B and C EV71 vaccine in Guangzhou from August 2016 to December 2019.

the most effective way to prevent and control this disease [10]. From August 2016 to December 2019, a total of 1,228,125 doses of the EV71 vaccine were administered, and the annual vaccination rate in 11 districts showed an upward trend (Figures 2,3). The coverage rate for one dose from August 2016 to 2019 was between 8.20 and 32.94%, and the coverage rate for the whole course of 2 doses was between 5.96 and 26.32%. The inoculation rate of manufacturer A's vaccine was between 3.97% and 13.98%, the inoculation rate of manufacturer B's vaccine was between 1.99% and 14.79%, and the inoculation rate of manufacturer C's vaccine was between 6.33% and 7.84%. The EV71 vaccine coverage rate in Guangzhou is still low, which is lower than the rate of 38.30% for 1 dose and 35.05% for 2 doses in Shanghai in children under 5 years old [11].

As a newly marketed vaccine, the EV71 vaccine is not as acceptable to children's parents as the vaccines that have been used for many years. There are large differences in the coverage rates among districts in Guangzhou. The top five coverage rates among 11 districts are Huadu (33.89%), Baiyun (32.37%), Tianhe (28.75%), Liwan (28.25%) and Panyu (24.91%), while the coverage rate is only 16.72% in downtown Yuexiu. The high coverage rates are concentrated in the urban-rural areas. The reason for this may be that the parents in the surrounding areas have low levels of education and vaccine knowledge, and they are willing to follow the doctor's advice for vaccination. The parents in the central area have high levels of education and knowledge on the safety of new vaccines. There are concerns about the effectiveness of the vaccine and the reluctance to vaccinate. The coverage rate of older children is higher than that of younger children. The maximum number of people vaccinated in the 1-year-old group should be 602,808, while the coverage rates of 1 and 2 doses is the lowest (21.19% and 16.67%) in this group; the 5-year-old target population was 301,337, and the highest coverage rates of 1 and 2 doses were 30.30% and 23.84%, respectively. According to Tang Zhimin, the results of a questionnaire survey completed by 328 parents of children aged 6 to 18 months in Yunnan and Sichuan provinces showed that the proportion of EV71 vaccine hesitation was

33.8%, which was higher than the proportion of parents with general vaccine hesitation [12]. In addition, the population access to knowledge was a single source, publicity knowledge was not comprehensive, and the awareness rate of the EV 71 vaccine among Chinese parents was 39.82% [13]. Another study showed that a population coverage rate reaching 91% can block the spread of EV71 [14], and the EV71 coverage rate of 19.44% in Guangzhou is much lower than 91%. It is necessary to strengthen the communication about HFMD and EV71 vaccine knowledge and improve parental awareness to increase the child's willingness to be vaccinated.

A total of 147 cases of AEFIs were reported after EV71 vaccination in Guangzhou, with a reported incidence of 11.97/per 100,000, including 62 cases of common adverse reactions (5.05/per 100,000), 54 cases of abnormal reactions (4.40/per 100,000), and 31 cases of coincidental events (2.52/per 100,000). The most common adverse reaction was fever, most of which were ≥38.5°C (83.02%). The most common rare adverse reaction was anaphylactic rash (81.94%). Adverse reactions, such as angioedema and febrile convulsions, are rare, and very few cases of these reactions were reported. In addition, 95.92% of AEFIs were improved or cured, which is similar to studies in Hubei and Shanghai [11,15]. At the same time, this study shows that the incidence of AEFI reports is the highest in the 1-year-old group of children after being vaccinated with the EV71 vaccine, and as age increases, the incidence of AEFI reports continues to decrease. This may be due to the more mature immune system of children and better responses to vaccines as they age. Tolerability increases, and thus the occurrence of adverse reactions gradually decreases. The time interval distribution of AEFIs after EV71 vaccination showed that AEFIs occurred in at most 121 cases (82.31%) from 0 to 1 day with an incidence rate of 9.85 per 100,000, and only 1 case (0.68%) occurred after > 7 days. More AEFIs were reported after one dose after than two doses, and the incidences were 14.11/per 100,000 and 9.25/per 100,000, respectively. It is suggested that doctors should inform parents of children to pay special attention to the observation of children's performance on the first day of vaccination and after the first dose of EV71 vaccine.

The total adverse reaction rates for EV71 vaccines from the three manufacturers are all at a relatively low level. The incidence rates of vaccines from manufacturers A, B and C were 11.94/per 100,000, 12.33/per 100,000 and 11.05/per 100,000, respectively, and there was no difference in AEFI responses between the vaccines from the three manufacturers (X^2 = 0.2170, P > 0.05). There was no difference in AEFI responses between the vaccines from manufacturer A (diploid cells) and manufacturers B and C (Vero cells) (X^2 = 0.0278, P > 0.05). The main reaction was a general reaction, the most common adverse reaction was fever with an incidence rate of 7.17 per 100,000, and there were no differences in the AEFI reactions of the vaccines from the three manufacturers (X^2 = 2.7937, P > 0.05;X^2 = 0.6708, P > 0.05). The abnormal reactions to the vaccines from the three manufacturers were mainly anaphylactic rashes, with an incidence of 4.18 per 100,000, which was the same as those reported in Shanghai, Wenzhou and Chengdu [11,16,17].

In summary, the safety of the EV71 vaccine in Guangzhou is acceptable. The main adverse reactions are fever and anaphylactic rash. The EV71 vaccines of the three manufacturers have good safety. However, the EV71 coverage rate in Guangzhou is low. To establish an effective immune barrier in the population to control the HFMD epidemic, the EV71 vaccination rate needs to be increased and maintained at a relatively high level. We should continue to strengthen the publicity for HFMD and EV71 vaccination to increase parents' willingness for children's vaccination, thereby increasing the vaccination rate in children. This study has some shortcomings. Our study is based on the AEFI monitoring information management system that collects data on the adverse events reported by the children's parents. Therefore, it is not clear whether the children's parents understand the standards for adverse events, which may lead to information bias. The possibility of mutation of epidemic strains of EV71 hasn't been ruled out, and the safety and effectiveness of large-scale population vaccination should be monitored after the vaccine is introduced into the market. Antigen quantification standards are also one of the topics that need to be addressed. As price may affect the use of vaccines in some regions or populations, when the effectiveness of the EV71 vaccine reaches 70% and the single-dose vaccine price is less than US 25, USD it will have better cost-effectiveness in large-scale vaccination of infants and young children [18]. There are several constraints to this goal. If combined with government financial subsidies, medical insurance, or included in free EPI vaccines, vaccination coverage can be guaranteed, which is one of the issues that government departments need to consider when formulating immunization policies in the future. This indicates that the future of vaccine promotion has good prospects. If the EV71 vaccine is added to the Expanded Program of Immunizations (EPI), it will be more effective in the prevention of severe hand, foot and mouth disease and related diseases. The inclusion of EV71 in the pentavalent combination vaccine (polio, pertussis, tetanus, diphtheria, influenza b) in animal experiments does not affect the mutual antibody responses [19]. There are also studies that combine rotavirus (RV) and EV71 into a combined vaccine. Immunization of mice can effectively stimulate the body to produce a specific humoral immune response, and there is no mutual influence between RV and EV71 [20]. In the context of the EPI combination vaccine becoming a development trend, the incorporation of EV71 into the combination vaccine is one of the directions of future research. In addition, we found that infections caused by CoxA16 increased in HFMD surveillance,hand, foot and mouth disease is caused by a variety of pathogens, and an ideal vaccine should provide long-term protection against multiple pathogen infections,obtaining a more broad-spectrum and efficient vaccine will be the focus of future research and development.

5. Conclusions

The implementation of the EV71 vaccine has an effect on the prevention and control of severe deaths from hand, foot, and

mouth disease. The EV71 vaccines from the three manufacturers have good safety, but the EV71 vaccine coverage rate is low. It is recommended that vaccine publicity be strengthened and that the coverage rate of children be increased.

6. Expert opinion

Enterovirus 71 (EV71) is a hand, foot, mouth disease pathogen that has become a serious public health problem. There is no effective treatment for this disease. Vaccination has become an effective means of preventing and controlling HFMD. Since 2016, China has approved the use of inactivated enterovirus 71 (EV71) vaccines produced by three manufacturers. At present, there are few reports on the coverage and safety of EV71 vaccines from different manufacturers. We are formulating the EV71 vaccination strategy and adjusting to provide a reference basis for research. The results show that the number of EV71 infections in Guangzhou has been declining annually. From 2017 to 2019, the annual proportions of EV71 infections in laboratory-diagnosed cases were 29.45%, 20.18% and 17.42%, indicating that the EV71 vaccine launched in August 2016 was effective and provides a certain degree of prevention and control of severe deaths. The annual vaccination doses administered in 11 districts of Guangzhou are on the rise. However, the EV71 coverage rate in Guangzhou is relatively low, with a 1-dose coverage rate of 24.71% and a full 2-dose coverage rate of 19.44%, which is lower than that in Shanghai in children under 5 years old (single dose coverage rate of 38.30% and a full 2- full coverage rate of 35.05%). To establish an effective immune barrier in the population to control the HFMD epidemic, it is necessary to increase and maintain the EV71 vaccine coverage rate at a relatively high level. The main reason for the low coverage rate is that parents and doctors do not understand the safety of the EV71 vaccine. According to the results of this study, the EV71 vaccines from the three manufacturers have good safety, and we can help doctors to further understand the safety of the vaccine. For example, 1 dose had a higher incidence rate of AEFIs than 2 doses. The main AEFIs are fever and anaphylactic rash. AEFIs mostly occurred 0~1 day after vaccination, and less severe AEFIs occurred in >7 days. Doctors should inform parents of children to pay special attention to the performance of children on the first day of vaccination and after the first dose of the EV71 vaccine. The results of this study will greatly assist doctors in promoting EV71 vaccination and increase the willingness of parents to vaccinate their children.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Authors' contributions author contribution statement

ZQL made substantial contributions to the conception and design of the study. ZQQ, HFT, CHZ, JXX, JC, LHN, XXY, MC, ZBZ contributed to the acquisition of data and YH, WW made a substantial contribution to the analysis of data. All authors were involved in the writing, reviewing and editing of the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Guangzhou Center for Disease Control and Prevention. This paper is based on a retrospective study, was conducted on cases of adverse events during EV71 vaccination using the Chinese national surveillance system for post-immunization adverse events (CNAEFIS). The study does not contain any intervention on human participants or animals. No AEFI patient identifying information regarding treatmalest details are disclosed in this manuscript.

ORCID

Zhi-qun Li http://orcid.org/0000-0002-4058-2389

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