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Post-marketing surveillance of live-attenuated Japanese encephalitis vaccine safety in China

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ABSTRACT

Japanese encephalitis (JE) is the most severe form of viral encephalitis in Asia and no specific treatment is available. Vaccination provides an effective intervention to prevent JE. In this paper, surveillance data for adverse events following immunization (AEFI) related to SA-14-14-2 live-attenuated Japanese encephalitis vaccine (Chengdu Institute of Biological Products) was presented. This information has been routinely generated by the Chinese national surveillance system for the period 2009–2012. There were 6024 AEFI cases (estimated reported rate 96.55 per million doses). Most common symptoms of adverse events were fever, redness, induration and skin rash. There were 70 serious AEFI cases (1.12 per million doses), including 9 cases of meningoencephalitis and 4 cases of death. The post-marketing surveillance data add the evidence that the Chengdu institute live attenutated vaccine has a reasonable safety profile. The relationship between encephalitis and SA-14-14-2 vaccination should be further studied.

1. Introduction

Japanese encephalitis (JE) is the most severe form of viral encephalitis in Asia. There are approximately 67,900 typical cases occurred per year in the JE-endemic countries. Approximately 20–30% of JE cases are fatal and 30–50% of survivors have significant neurologic sequelae [1]. Since there is no special treatment for JE virus infection, vaccination has been the most effective way to prevent the disease [2].

JE outbroke in China in 1957 with more than 30,000 cases. JE vaccine has been used in China since 1960 and being included in national childhood immunization programs since 2007 [3]. The coverage of first dose of JE vaccine to the children at the age of 1–2 years old was 97.18% and the second dose was 89.49% in 2011 [4]. Due to JE vaccine usage, JE incidence rates decreased from 11.9/100,000 in the 1960s to 2.63/100,000 in the 1990s, and remained stable in about 1/100,000 since 1998 [3]. However JE still outbreaks occasionally in some of the provinces.

There are 7 JE vaccine manufacturers and both inactivated and live attenuated JE vaccines are used in China. Chengdu Institute of Biological Products (Chengdu Institute) is one of the largest biological manufacturers in China, who can manufacture live-attenuated JE (LA-JE) vaccine based on the SA 14-14-2 strain. LA-JE vaccine production was licensed to Chengdu Institute in 1988 and with more than 300 million doses released since then [5]. Just to count the number of lots released in 2009 alone, vaccines from Chengdu Institute occupied 30% of the domestic market. LA-JE vaccine is currently used not only in China, but also in Korea, Sri Lanka, Nepal, India, Thailand, Laos, Cambodia and Burma.

The active component of LA-JE vaccine is SA 14-14-2 strain. The others are lactose, sucrose, human blood albumin, urea and gelatin. LA-JE vaccine is typically administered at 8 months and 2 years of age with 0.5 ml per person per time. This vaccine also can be used in adults.

In the paper, Adverse Events Following Immunization (AEFI) of LA-JE vaccine produced by Chengdu Institute from 2009 to 2012 will be presented and analyzed, based on records of Chinese post marketing surveillance system.

2. Methods

2.1. AEFI information

The current Chinese AEFI surveillance system was established in 2005 and became an online system since 2008 [6]. The system covers all levels of Centers of Disease Control and Prevention (CDC) that includes 1 national CDC, 31 provincial CDCs, hundreds of

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Table 1
Gender, age and geographic distribution of reported AEFI cases.

Characteristic	Non serious AEFI (n = 5954)		Serious AEFI (n = 70)		Total (n = 6024)	
	No.	(%)	No.	(%)	No.	(%)
Gender						
Male	3327	55.88	43	61.43	3370	55.94
Female	2627	44.12	27	38.57	2654	44.06
Age (yrs)						
<1	2715	45.60	23	32.86	2738	45.45
1–2	2871	48.22	39	55.71	2910	48.31
3–6	337	5.66	6	8.57	343	5.69
≥7	31	0.52	2	2.86	33	0.55
Region[a]						
Eastern	3346	56.20	32	45.71	3378	56.08
Central	2179	36.60	25	35.71	2204	36.59
Western	429	7.20	13	18.57	442	7.34
Total	5954	100.00	70	100.00	6024	100.00

[a] Eastern region includes Beijing, Tianjin, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong and Hainan. Central region includes Shanxi, Hebei, Jilin, Helongjiang, Anhui, Jiangxi, Henan, Hubei, Hunan, Liaoning and Guangxi. Western region includes Sichuan, Chongqing, Guizhou, Yunnan, Inner Mongolia, Tibet, Shaanxi, Gansu, Qinghai, Ningxia and Xinjiang.

prefectural CDCs and thousands of county CDCs. Up to 2012, more than 300,000 AEFI cases have been reported.

The events after vaccination which listed in the timeframe of National Guideline for Surveillance of AEFI issued in 2010 [7] or other events which thought to be temporally associated with vaccine could be reported. The reporter, such as healthcare facilities, vaccinating unit, vaccine manufacturers and patients, should fill out the "AEFI Reporting Card" and submit it to the county CDC. County CDCs are charged with verifying case information such as demographics, adverse event and vaccine, and enter it into the web-based system. All serious and unusual cases (especially the cases beyond fever, redness or induration) must be investigated by county CDC within 48 h after receiving the reports.

According to the Guideline for the Identification of Adverse Reaction after Immunization issued by the Chinese Ministry of Health in 2008 [8], each county, prefectural, and provincial CDC in China must assemble an expert panel to investigate adverse events and assess causality. The panels consist of physicians, epidemiologists, pharmacists, and other relevant experts. The criteria of causality assessment refer to Causality Assessment of An Adverse Event Following Immunization published by WHO [9].

Any of the followings can be defined as serious AEFI: death or life-threatening condition, hospitalization, permanent or significant disability or impaired organs and functions. This definition of serious AEFI is similar to that proposed by WHO [9].

For this study, we searched the data base from January 1st, 2009 to December 31st, 2012 and selected all events related to LA-JE vaccine manufactured by Chengdu Institute.

2.2. Estimation of reported rate

The reported rate in the paper was estimated using the dose released of LA-JE vaccine made by Chengdu Institute during 2009 to 2012 as denominator. The data of lot release could be obtained from website published by the National Institute for Food and Drug Control (http://www.nicpbp.org.cn/directory/web/WS02/CL0001/).

3. Results

3.1. AEFI reports and classification

From 2009 to 2012, 6024 AEFI cases associated with LA-JE vaccine (the events should be reported according to the National Guideline for Surveillance of AEFI) made by Chengdu Institute were collected through the national post-marketing surveillance system (Table 1). Among the 6024 cases, 3370 cases were male (56%) and 2654 were female (44%). Most of the cases (94%) were among children younger than 3 years old, reflecting the recommended vaccination schedule. Of all AEFI reported, 70 (1%) were considered serious cases, 62 of which were among children younger than 3 years old.

The 6024 cases were reported from 26 provinces of China. 3378 (56%) cases, were from the Eastern region, 2204 (37%) cases were from the Central region, and 442 (7%) cases were from the Western region. For the 70 serious cases, 32 (46%) were from the Eastern region, 25 (36%) were from the Central region, and 13 (19%) were from the Western region.

3.2. Symptoms and clinical diagnosis of AEFI

The total number of lot release of LA-JE vaccine made by Chengdu Institute from 2009 to 2012 was 62.39 million. The reported rate of AEFI with 6024 cases was 96.55 per million doses using lot release data as denominator. The events with more than 5 cases and the reported rates are listed in Table 2. Fever,

Table 2
Clinical diagnoses of AEFI.

Symptom and clinical diagnoses	Total case (n = 6024)		Reported rate (/million dose distributed)
	Case number	(%)	
Fever	4789	79.50	76.76
Redness and swelling	827	13.73	13.26
Rash	432	7.17	6.92
Induration	347	5.76	5.56
Upper respiratory tract infection	22	0.37	0.35
Febrile convulsion	20	0.33	0.32
Thrombocytopenic purpura	10	0.17	0.16
Angioedema	9	0.15	0.14
Meningoencephalitis[a]	9	0.18	0.14
Sterile abscesses	8	0.13	0.13
Allergic purpura	7	0.12	0.11
Amygdalitis	7	0.12	0.11
Exanthema subitum	5	0.08	0.08

[a] Meningoencephalitis included Encephalitis, Meningitis, Viral encephalitis, Purulent meningitis and Japanese encephalitis.