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Safety of Japanese encephalitis live attenuated vaccination in post-marketing surveillance in Guangdong, China, 2005–2012

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ABSTRACT

We reviewed the adverse events following immunization of live attenuated Japanese encephalitis vaccine in Guangdong Province, China. During the period of 2005–2012, 23 million doses of live attenuated Japanese encephalitis vaccine were used and 1426 adverse events were reported (61.24 per million doses); of which, 570 (40%) were classified as allergic reactions (24.48 per million doses), 31 (2%) were neurologic events (1.33 per million doses), and 36 (2.5%) were diagnosed as serious adverse events (1.55 per million doses). This study suggests that the JEV-L has a reasonable safety profile, most adverse events are relatively mild, with relatively rare neurologic events being observed.

1. Introduction

Japanese encephalitis (JE) is a disease caused by a flavivirus that affects the membranes around the brain and brain parenchyma. It is estimated that three billion persons are living in countries where the JE virus is endemic worldwide [1]. Japanese encephalitis virus is the leading cause of viral encephalitis in Asia and occurs in almost all Asian countries, such as Japan, Korea, China, Malaysia, Indonesia, India, and Bangladesh, etc. [2,3], and it has recently spread to new territories, which might be partly due to the global climate change and increasing international traveling [1,4,5].

There are approximately 67,900 JE cases annually with an overall incidence of 1.8 per 100,000 population in the JE-endemic countries in Asia [6]. It is estimated that China has about half of the JE cases reported in the world, and JE occurs in most provinces of China [3,6,7]. Guangdong Province, located in Southern China, had a high prevalence of JE, with an incidence over 5 per 100,000 during 1971–1980, which decreased to 0.2 per 100,000 during 2000–2010 [8].

JE is the most common vaccine – preventable cause of encephalitis in Asia and also the most prevalent cause of neurologic infection and physical disabilities [9,10]. The live attenuated JE vaccine (JEV-L) was developed in China and was licensed in 1989 [11].

Though JEV-L was included in Guangdong's Expanded Program on Immunization (EPI) in 2004 [12], Guangdong Province has begun to use JEV-L since 1990. The target population for JEV-L vaccination included children older than 8 months in endemic areas, adolescent and adults from non-endemic areas. In Guangdong, JEV-L was given in a three-dose series to children aged 8 months, 18–24 months, and 6 years in EPI before 2009, afterwards children were immunized with two-dose series when they were 8 months and 18–24 months of age.

Adverse effects of other types of JE vaccine have been evaluated in previous studies [13–17]. And inconsistent adverse effect rate has been observed in previous studies, ranging from 10 to 260 per 100,000 doses [18,19], which might be due to different case definitions, and surveillance methods [15]. And the adverse effects of JEV-L, widely used in China, have not been systematically examined so far. The surveillance of The Adverse Effects Following Immunization (AEFI) of JEV-L has began to be conducted since May 2005 [20], in which adverse events information and dose information were collected in order to calculate the occurrence of allergic reaction and neurologic events, which provided a unique information to describe the pattern of adverse effects of the JEV-L.

2. Materials and methods

2.1. Vaccine

The vaccine is derived from JE virus strain SA 14-14-2 and produced in primary hamster-kidney cell cultures, which were infected with working seed virus. The excipients of JEV-L contained

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gelatin (1%), saccharose (5%), human serum albumin (HSA) and sodium glutamate. Sterilized water for injection was used as diluents [11].

2.2. Surveillance system

Guangdong was one of the first 10 pilot provinces of passive AEFI surveillance in China in the year 2005. Guangdong Center for Disease Control and Prevention (GDCDC), the administrative organization of this program, developed its own online surveillance system for AEFI in Guangdong according to the World Health Organization (WHO) guidelines [21]. After the National Online AEFI Reported System was established in 2008, AEFI of Guangdong Province began to follow this new national system since 2009 (http://219.141.175.204). In 2010, the "National Guideline for Surveillance of Adverse Events Following Immunization" was promulgated by China Ministry of Health (MOH) and State Food And Drug Administration (SFDA) in 2010, in which detailed requirements for data reporting, data quality and timeliness were stipulated [22]. According to the National Guideline for the Surveillance of Adverse Events Following Immunization, which was based on WHO guidelines (2005), an AEFI referred to a reaction or an event after a vaccination that was suspected to be related to the vaccination. Serious adverse events involved hospitalization, death, life-threatening illness, or permanent disability [22].

2.3. The scope of reporting

According to the guideline by China MOH and SFDA, the scope of reporting AEFI is divided into the following categories based on the timing of the incidence [22]: (1) within 24 h: anaphylactic shock, allergic reactions without shock (urticarial, generalized rash, laryngeal edema, etc.), toxic shock syndrome, syncope, hysteria psychosis; (2) within 5 days: fever (axillary temperature $\geq 38.6\,^{\circ}C$), angioedema, systemic purulent infection (toxemia, septicemia, sepsis), redness and swelling in the injection site (diameter > 2.5 cm), scleroma (diameter > 2.5 cm), localized purulent infection (localized abscess, lymphangitis and lymphadenitis, cellulitis), etc.; (3) within 15 days: measles-like or scarlet fever rash, Henoch-Schonlein Purpura (HSP), localized allergic necrosis reaction (Arthus reaction), febrile convulsion, epilepsy, polyneuritis, encephalopathy, encephalitis and meningitis; (4) within 6 weeks: thrombocytopenic purpura, Guillain-Barré syndrome, vaccine-related paralytic polio; (5) within 3 months: brachial plexus neuritis, sterile abscess in the injection site; (6) others: other serious AEFI related to the vaccination and any medical events considered related to the vaccination. However, if one event was beyond the above time periods, the clinic physicians would report to the surveillance system if it was suspected to be related to the vaccination based on the clinical diagnosis. And the classification of the events was based on the physician's diagnosis.

We classified some scope as allergic reaction: anaphylactic shock, allergic reactions without shock (urticarial, generalized rash, laryngeal edema, etc.), angioedema, HSP, localized allergic necrosis reaction (Arthus reaction), etc. We also classified some scope as neurologic reaction: syncope, hysteria psychosis, febrile convulsion, epilepsy, polyneuritis, encephalopathy, encephalitis and meningitis, brachial plexus neuritis, etc.

This scope of reporting AEFI applies to the surveillance system, and considers adverse events that might be related to the vaccination, but may not necessarily mean causal relationship between the adverse events and the vaccinations [22].

2.4. Reporting and investigation

Healthcare facilities, vaccinating units, CDCs, vaccine manufacturers and vaccine wholesale businesses are the responsible reporting units and reporters for AEFIs. When receiving a report of an adverse event, the reporting unit is required to fill out a case-report form and submits it to the county CDC. After verification, the county CDC should report it through the online National AEFI Surveillance System. The county CDC should field investigate adverse event and completes detailed case-investigation forms for all adverse events except for those with clear diagnosis (e.g., fever, redness and swelling on the injection site).

According to the guideline for the Identification of Adverse Reaction after Immunization issued by the Chinese MOH [23], each county, prefectural, and provincial CDC must set up an expert panel to investigate the adverse events using the criteria by the Chinese Standard Procedures for Vaccination. Each panel should consist of physicians, epidemiologists, pharmacists, and other relevant experts. In general, prefectural or provincial expert panels investigate deaths, life-threatening illnesses, and permanent disabilities; county-level expert panels investigate other adverse events, and immunization program managers or vaccination providers investigate common, minor adverse events.

Information from case-report form and detailed case-investigation form is reported to the GDCDC through the online National AEFI Surveillance System. All serious adverse events are investigated by expert panels of the county, prefectural, or GDCDC immediately after receipt of reports. Prefectural and GDCDC check the accuracy and completeness of the data within 1 week after adverse events are reported.

2.5. Data on vaccine consumption

Vaccinating unit reported the data of vaccine consumption to the county CDC every month, after that county CDC reported the data to municipal CDC and municipal CDC reported to Guangdong Provincial CDC. As this reporting system only included the dose number of vaccine, without the information of age, sex, we cannot calculate the rate of AEFI for specific population group in terms of age or gender.

2.6. Data analysis

We examined the age and sex distribution of the adverse events, concurrent vaccine use, time interval from vaccination to onset of symptoms, reported symptoms, case diagnosis. When more than one symptom was reported by one person, only the main symptom or the most serious diagnosis was recorded in AEFI reporting system. The outcome measures in this study included the rate of reported adverse events and the proportion of each event category. Crude reporting rates of AEFI, serious AFEI, allergic reaction, neurologic events following JEV-L vaccination were calculated as per million doses.

3. Results

3.1. Adverse events following JEV-L vaccination

From May 2005 to December 2012, a total of 23.29 million doses of the JEV-L vaccine were used and 1426 adverse cases of AEFI were reported in Guangdong Province. The overall rate of reported adverse events was 61.2 per million doses, with the annual incidence rate ranging from 10.4 per million doses in 2005 to 146.5 per million doses in 2012. There were 36 cases with serious AEFI, the overall rate was 1.55 per million vaccine doses, with the annual