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Post-marketing safety surveillance for inactivated and live-attenuated Japanese encephalitis vaccines in China, 2008–2013

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ABSTRACT

Introduction: Two types of Japanese encephalitis (JE) vaccines, inactivated JE vaccine (JE-I) and live-attenuated JE vaccine (JE-L), are available and used in China. In particular, one JE-L, produced by a domestic manufacturer in China, was prequalified by WHO in 2013. We assessed the safety of JE vaccines in China during 2008–2013 using the Chinese National Adverse Events Following Immunization Information System (CNAEFIS) data.

Methods: We retrieved AEFI reporting data about JE vaccines from CNAEFIS, 2008–2013, examined demographic characteristics of AEFI cases, and used administrative data on vaccine doses as denominator to calculate and compare crude reporting rates. We also used disproportionality reporting analysis between JE-I and JE-L to assess potential safety signals.

Results: A total of 34,879 AEFIs related with JE-I and JE-L were reported, with a ratio of male to female as 1.3:1; 361 (1.0%) cases were classified as serious. JE vaccines were administered concurrently with one or more other vaccines in 13,592 (39.0%) of cases. The overall AEFI reporting rates were 214.4 per million vaccination doses for JE-L and 176.9 for JE-I (rate ratio [RR]: 1.2, 95% confidence interval [CI]: 1.1–1.3) in 2010–2013. Febrile convulsions (FC) following JE-I was found as a signal of disproportionate reporting (SDR). However, there was no significant difference between the reporting rates of FC of JE-I and JE-L (0.3 per million vaccination doses for JE-L, 0.4 for JE-I, p = 0.05).

Conclusions: While our analysis did not find apparent safety concern of JE vaccines in China, further study should consider JE-I vaccines and febrile convulsion, and taking more sensitive methods to detect signals.

1. Introduction

Japanese encephalitis (JE) is a mosquito-borne acute viral infection of the central nervous system caused by a flavivirus [1]. JE is the most important cause of vaccine-preventable viral encephalitis in nearly all Asian countries, whether temperate, subtropical, or tropical, and has expanded into new areas through the importation of infected-mosquito vectors. Currently, an estimated 3 billion people living in 24 countries, mainly in the South-East Asia and Western Pacific Regions are considered at risk of JE [2]. The inactivated JE vaccine (JE-I) was developed in China and has been used since the 1970 s and live-attenuated vaccine (JE-L) was in the beginning of the 1990s [1]. Since 2007, JE vaccines were included into the Expanded Program on Immunization (EPI) in the mainland of China [1]. With the decline of number of JE disease in China, the public became more concern about the adverse events following JE vaccination currently. The safety of JE vaccines manufactured in China and abroad was evaluated in previous clinical and post-marketing studies [3–7]. The vaccine safety review of JE vaccines by World Health organization (WHO) were found to have acceptable safety profiles, and data from multiple studies (including multicenter randomized controlled trail and randomized trials) had shown the same conclusion [2,8,9]. However, The JE vaccine used in China were mainly produced by domestic manufacturers, and a JE-L product was prequalified by WHO in 2013, which was the first Chinese-produced vaccine to be prequalified by WHO. Limited data are available on the safety of JE after its inclusion into the Chinese EPI and consequently its large-scale use. Concurrently with the inclusion of JE vaccines into EPI, the Chinese national adverse event following immunization (AEFI) information system

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(CNAEFIS), a passive post-marketing vaccine safety surveillance system, was also expanded to cover the entire country after a 3-year pilot study [10,11]. With 6 years of information collection, there were valuable AEFI data in the CNAEFIS which could provide some evidence for evaluation of vaccine safety in China. Also, using the passive surveillance data, the disproportionality analysis, which was first used in signal detection of drug safety, could also be necessary to generate signals, especially when the causality of the specific events and vaccination has not been well known. We conducted a study to analyze AEFI data for both JE-I and JE-L vaccines in CNAEFIS from 2008 to 2013 to understand and compare the vaccine safety profiles of these 2 vaccines.

2. Methods

2.1. Vaccination schedules of JE vaccines in China [10]

In the mainland of China, both JE-I and JE-L have been included in National Immunization Program (NIP) vaccinations since 2007. For JE-L, a 2-dose schedule is used: at 8 and 24 months of age, with at least 3 months' interval. For JE-I, a 4-dose schedule is used (2 doses at 8 months with at least 7–10 day intervals, and subsequent doses at 2 and 6 years of age).

2.2. Vaccination doses of JE vaccines

All the vaccines should be used in Vaccination clinics, which was approved by local government and supervised by local Center for diseases control and prevention (CDC). Vaccination doctors or nurses collected information of vaccination doses and reported to the county CDCs monthly. The county CDCs report the data to municipal CDCs who report to provincial CDCs. China CDC collects administered vaccination data from all provincial CDCs [3,13].

Before 2010, only doses of vaccines provided by the government for free were reported. Therefore, complete data on all JE vaccination doses given during 2008–2009 are not available. Since 2010, however, the vaccination information system collected all vaccination doses administered in the vaccination clinics, enabling the analysis of the reporting rates. As the denominator information only included the number of vaccine doses, without information on age or sex, the rates of AEFI for specific population groups by age or gender could not be calculated.

2.3. CNAEFIS

The online CNAEFIS is administered by the Chinese Center for Disease Control and Prevention (CCDC). After two pilot studies, it was expanded to cover all 31 provinces in the mainland of China in 2008 [10]. The pilot studies included a passive surveillance system for AEFI in 10 provinces and an enhanced AEFI surveillance system in 5 counties. CNAEFIS is operated in accordance with China's national AEFI guidelines [12]. According to this guidance, CNAEFIS became the official AEFI information system and was to be owned and maintained by China CDC [10].

An AEFI case is defined as a reaction or an event occurring after vaccine administration that is suspected to be related to the vaccination. AEFI surveillance and reporting covers all vaccines marketed in the mainland of China [10].

2.4. Reporting and investigation [10–13]

Healthcare facilities, vaccination clinics, Centers for Disease Control and Prevention (CDCs) at all 4 administrative levels, adverse drug reaction monitoring agencies (ADRs), and vaccine manufacturers are required by law to report suspected AEFIs. The public or the guardian (parents) can notify any of the above authorized reporters to report an AEFI. Cases are investigated by local, county-level CDCs, which are responsible for completing AEFI Case Reporting Cards and submitting the data to online CNAEFIS. Once the information is entered, it can be viewed by all administrative levels of CDCs and ADRs. Based on the address, name and birthday of the child, vaccines, and vaccination dates, duplicate reports are identified and potential multiple reports are combined into one case.

Investigation is required for all AEFIs, except common adverse reactions with a clear diagnosis (e.g., fever; redness, swelling, and induration on the injection site). For deaths, serious AEFIs, AEFI clusters, and AEFIs of significant public concern that are suspected to be related to vaccination, prefectural or provincial CDCs must immediately organize an AEFI expert panel for investigation upon receiving CNAEFIS reports.

2.5. Serious and non-serious AEFIs [13]

Serious AEFI is defined as an event that is causing a potential risk to the health/life of a recipient leading to prolonged hospitalization, disability/incapacity, congenital abnormalities/birth defects or death. In CNAEFIS, it include, but are not limited to, allergic shock, allergic laryngeal edema, allergic purpura, thrombocytopenic purpura, localized allergic necrotic reaction (Arthus reaction), febrile convulsion, epilepsy, brachial neuritis, polyneuritis, Guillain–Barre syndrome, encephalopathy, encephalitis and meningitis, syncope, toxic shock syndrome, and systemic purulent infection.

2.6. Data analysis

We analyzed AEFI reports submitted during 2008–2013, for subjects vaccinated with JE-L or JE-I. In CNAEFIS, a maximum 3 suspected vaccines can be reported at the same time in a single report. JE vaccines listed as the first, second, or third suspected vaccine were all included. When more than one symptom was reported for a case, only the main symptom or the most serious diagnosis was recorded in CNAEFIS.

The age and sex distribution and clinical diagnoses were described, and crude AEFI reporting rates per million doses given were calculated. Since there is no information on whether the vaccines were NIP vaccine or not in AEFI cases, the incidence of NIP vaccine or voluntary vaccination could not be estimated during the study year.

We used disproportionality analysis of data mining algorithms to compare the frequency of reports for JE-L and JE-I to detect any signal of disproportionate reporting (SDR) [14]. Disproportionality analysis identifies AEFIs that were more frequent than expected and relies on the principle that when a SDR is identified for a specific vaccine, this event (or diagnosis) is reported relatively more frequently in association with this specific vaccine than all the other vaccine in the database. Three disproportionality analysis methods were applied: the proportional reporting ratio (PRR) [15,16], Bayesian confidence propagation neural network (BCPNN) [17], and empirical Bayesian (EB) data mining [18–20]. Disproportionality analysis were based on a $2 * 2$ contingency table similar to a case-control study or cohort study [21]. Calculations were performed using R (version i386 3.2.3), and the PhViD package were used in analysis.

Since disproportionality analysis required "vaccine and diagnosis" as a pair, cases without confirmed clinical diagnosis were excluded. For the cases in which diagnosis included common minor adverse reactions, with a mix of symptoms such as fever, local redness, local swelling, and other minor local or systemic

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