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Immunization Safety Monitoring and Vaccine Safety Assessment in China

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ACADEMIC DISSERTATION
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ABSTRACT

The development of vaccines is one of the most important public health achievements. The goal of immunization is to protect individuals and the population from vaccine-preventable diseases (VPD). Although modern vaccines generally are safe, there is always a risk of adverse events, as is the case with any medical technology. Vaccines licensed by the National Regulatory Authorities are considered safe, but rare adverse reactions cannot be detected in pre-licensure clinical trials because of their limited size and duration. Once vaccines are licensed and used widely in the population, the main way to evaluate their safety is by conducting post-licensure surveillance and related observational epidemiology studies. An adverse event following immunization (AEFI) is defined as a reaction or an event occurring after vaccine administration that is suspected to be related to the vaccination. All detected AEFIs do not have a causal relationship with vaccines, but the public may perceive them to be related to vaccination, which may raise concern, influence public confidence and hamper the implementation of immunization programs. As more vaccines are being introduced worldwide, high quality safety surveillance is becoming even more important to maintain public confidence in vaccines and vaccine programs.

Many developed countries have established well-functioning AEFI surveillance systems, such as the Vaccine Adverse Event Reporting System (VAERS) in the U.S. However, it may be difficult to compare the safety profiles of vaccines used in developed countries to those in low and middle-income countries because the vaccines used and the types of serious AEFIs may be different due to local programmatic, health care system, environmental and genetic differences. China has a total population of over 1.3 billion people and an annual birth cohort of 16 million. With the increasing demand for vaccines and the development of vaccine manufacturing, China now ranks among the world's largest vaccine manufacturers producing more than one billion vaccine doses annually. In 2010, the Chinese Food and Drug Administration's (CFDA) website listed 46 registered Chinese vaccine manufacturers of public or private status, collectively manufacturing 24 licensed vaccines.

In mainland China, vaccine safety surveillance began first in provinces with enough economic resources, such as Shanghai and Jiangsu, in the 1980s. However, varying guidelines and definitions made comparing the collected data between provinces difficult. Based on National AEFI guideline issued by CFDA and the Ministry of Health (MoH) in 2010, the National Immunization Program (NIP) of the Chinese Center for Disease Control and Prevention (CDC) implemented the National AEFI Surveillance System (CNAEFIS) to establish a uniform nation-wide monitoring system which covers all NIP vaccines as well as those administered in private practices. The CNAEFIS is currently the only data source available for post-licensure safety monitoring for vaccines manufactured and used in mainland China.

The studies in this dissertation focus on evaluating the performance of the CNAEFIS and on using the collected data to assess vaccine safety issues. The four studies (I to IV) describe and evaluate the national AEFI surveillance system and assess the safety of selected vaccines used in mainland China. Study I described the CNAEFIS and its performance attributes to understand its overall functioning and to identify areas needing strengthening. Studies II to IV are case studies that evaluate vaccine safety in the following topics: recipient vaccine-associated paralytic poliomyelitis (VAPP), AEFI-associated deaths and, the AEFIs associated with the Japanese Encephalitis (JE) vaccines manufactured and used in China. The findings from these studies helped to identify vaccine-related safety concerns, assess whether these concerns were associated with vaccines and find ways to strengthen surveillance and investigation capacity for the immunization services in China.

The CNAEFIS is a passive surveillance system that can collect timely national AEFI data and detect rare and severe events. With cumulating experience and data since its implementation in 2005, the CNAEFIS provides baseline data on AEFIs in the world's largest population. By using different sources of denominator data, the CNAEFIS may also have the unique ability and statistical power to detect changes in reporting rates of known adverse events to help determine whether potential changes in observed rates may reflect uneven reporting.

With the end game in progress for global eradication of polio, the schedule of polio vaccine administration in China was changed in 2016: one dose of inactivated polio vaccine (IPV) was introduced as the first polio vaccine dose and the subsequent three doses of trivalent Oral Poliovirus Vaccine (OPV) were replaced with bivalent OPV. The evaluation of VAPP cases reported in CNAEFIS provided information on the safety of trivalent OPV and will serve as reference data for VAPP occurrence after bivalent OPV in future evaluations. In Study II, the epidemiological characteristics of recipient VAPP cases, such as age distribution, were comparable

to those in previous studies from other countries. The risk of recipient VAPP, using either estimated births or vaccination doses as the denominator, was comparable to that observed in the U.S. and Japan. To further decrease the number of recipients VAPP cases in China, use of IPV was recommended.

Study III was initiated because of media reports of deaths following administration of hepatitis B vaccine in Hunan province in December 2013. These reports had raised concerns about safety of vaccines among parents and the public and had resulted in marked decline in parental and public confidence in vaccines in the province. Childhood deaths are very rare and concerning events, but vaccinations in childhood are common. Therefore, a temporal association of reported fatalities with hepatitis B vaccination may have occurred by chance, without a causal link to vaccination. Our analysis provided reassuring information about the small risk of death following immunization. The reporting peak of AEFI-associated deaths in late 2013 to early 2014 illustrated the sensitivity of passive reporting systems to public information. It also highlighted the caution that should be exercised in interpreting peaks in reports of serious AEFIs. Although the analysis was limited by small number of cases, our review of the characteristics of AEFIs and causes of death identified no vaccine safety concerns. This finding addressed the public's concerns and should bolster confidence in the vaccine program.

JE vaccines were introduced in the national immunization schedule in the mainland of China at the end of 2007. In 2013, the Japanese Encephalitis Vaccine Live (JEV-L) was the first Chinese-produced vaccine to be prequalified by the World Health Organization (WHO). Limited data were available on the safety of JE vaccines after their inclusion in the national immunization schedule and, consequently, on its large-scale use in China. In Study IV, the majority of AEFIs following JE vaccines were minor and comprised common adverse reactions. There were no significant differences between the estimated reported rates of serious AEFIs following JE Inactivated (JEV-I) and JEV-L. Most patients with serious AEFIs recovered fully. We recommended further studies to differentiate the effects of concurrent vaccination of other vaccines from those of JE vaccines and adoption of more sensitive methods to detect safety signals.

This dissertation illustrates the progress made with vaccine safety monitoring during recent years in China. In these studies, we found that national AEFI surveillance was functional and able to provide useful data to evaluate safety of vaccines in the world's largest population. The assessment of recipient VAPP, AEFI-associated deaths, and the safety of JE vaccines suggested acceptable vaccine safety profiles. However, we also identified several challenges, such as lack of standard

international diseases and symptoms coding system and case definitions, which should be introduced to reduce misclassification and strengthen the system. In addition, the causality assessment procedures should be standardized and made more rigorous. Finally, new statistical methods should be introduced for safety signal detection and hypothesis generation in future studies. These scientific improvements in the world' largest vaccine safety data source would continue building public confidence in vaccine programs in China, and perhaps serve as a model to surveillance system development in other countries.

TIIVISTELMÄ

Rokotukset ovat yksi tärkeimmistä kansanterveyden saavutuksista. Rokotusohjelmien tavoitteena on suojata yksilöä ja väestöä vakavilta, rokotuksilla estettävissä olevilta taudeilta. Vaikka nykyiset rokotteet ovat yleisesti ottaen turvallisia, niihin voi liittyä haittavaikutuksia, kuten mihin tahansa lääketieteen teknologian käyttöön. Kansallisten viranomaisten hyväksymät rokotteet on todettu turvallisiksi ja tehokkaiksi ennen myyntiluvan myöntämistä tehdyissä kliinisissä tutkimuksissa. Harvinaisia haittavaikutuksia ei näissä tutkimuksissa kuitenkaan voida havaita niiden rajoitetun koon ja keston vuoksi. Rokotusten väestövaikutusten arviointi sekä harvinaisten haittavaikutusten havaitseminen on mahdollista vain, kun rokotteita on käytetty väestössä laajasti ja tarpeeksi pitkän aikaa. Kehittyneet seurantajärjestelmät ja niihin perustuvat epidemiologiset tutkimukset ovat tärkein tapa arvioida ja varmistaa rokotteiden turvallisuus. Rokotusten haittavaikutus määritellään reaktioksi tai tapahtumaksi, jonka epäillään liittyvän rokotukseen. Kaikilla rokotteilla voi olla haittavaikutuksia, mutta niitä esiintyy vain pienellä osalla rokotetuista. Kaikilla havaituilla haittavaikutuksilla ei myöskään ole syy-yhteyttä rokotteisiin. Koska rokotukset ovat yleisiä, niiden saatetaan kuitenkin olettaa liittyvän rokotuksiin ajallisen yhteyden perusteella. Tämä voi aiheuttaa huolta, vaikuttaa yleiseen luottamukseen rokotusohjelmaa kohtaan sekä haitata sen toteuttamista. Maailmanlaajuisesti otetaan jatkuvasti käyttöön uusia rokotteita. Tällöin korkealaatuisen turvallisuus seurannan rooli tulee entistä tärkeämmäksi, jotta väestön luottamus rokotteisiin ja rokoteohjelmiin säilyy.

Useimmissa kehittyneissä maissa on hyvin toimivat, pitkäaikaiset rokotusten haittavaikutusten seurantajärjestelmät. Kehittyneissä maissa käytettyjen rokotteiden turvallisuuden seurannan tietoja on kuitenkin vaikea verrata ja soveltaa pieni- ja keskituloisiin maihin: Käytetyt rokotteet ja vakavat haittavaikutukset voivat poiketa toisistaan muun muassa rokotusohjelman, terveydenhuoltojärjestelmän, ympäristön ja väestön geneettisten erojen takia. Kiinassa on yli 1,3 miljardia ihmistä ja sen vuotuinen syntymäkohortti on 16 miljoonaa lasta. Rokotteiden kasvavan kysynnän ja rokotevalmistuksen menetelmien kehittymisen myötä Kiina on nykyään yksi maailman suurimmista rokotevalmistajista, joka valmistaa yli miljardi rokoteannosta vuodessa. Vuonna 2010 Kiinan elintarvike- ja lääkehallinnon verkkosivusto listasi 46

rekisteröityä kiinalaista rokotevalmistajaa, jotka valmistivat yhteensä 24:ttä eri rokotetta.

Manner-Kiinan rokoteturvallisuuden seuranta aloitettiin 1980-luvulla provinsseissa, joilla oli riittävästi taloudellisia resursseja, kuten Shanghaissa ja Jiangsussa. Ohjeistuksen, tapausmääritelmien ja protokollien eroavaisuudet kuitenkin hankaloittivat tietojen vertailua maakuntien välillä. Kansallinen rokotusten haittavaikutusten seurantajärjestelmä (CNAEFIS) perustettiin vuonna 2010 Kiinan tautikeskuksen (Chinese Center for Disease Control and Prevention, CDC), kansallisen rokotusohjelman (National Immunization Program, NIP) ja terveysministeriön yhteistyössä kehittämän kansallisen ohjeistuksen perusteella. Yhdenmukainen, valtakunnallinen seurantajärjestelmä kattaa kansallisen rokotusohjelman rokotteiden lisäksi myös yksityisellä puolella annetut rokotteet. Tämä maailman suurimman väestön rokotteiden turvallisuustietokanta on ainoa kattava tietolähde, jonka avulla Manner-Kiinassa valmistettujen ja käytettyjen rokotteiden turvallisuutta voidaan seurata.

Tämän väitöskirjan tutkimukset keskittyvät Kansallisen rokotusten turvallisuuden seurantajärjestelmän toiminnan arviointiin sekä kerätyn tiedon hyödyntämiseen tieteellisessä tutkimuksessa vastaamaan rokotusten turvallisuuteen liittyviin tieteellisiin kysymyksiin. Neljä tutkimusta (I – IV) kuvaavat ja arvioivat kansallisen seurantajärjestelmän toimintaa ja sekä kahta tautia vastaan kehitettyjen rokotteiden turvallisuutta. Nämä taudit ovat Japanin aivotulehdus, joka on vakava hyttysten levittämä virusinfektio sekä poliovirus infektio, joka aiheuttaa poliomyeliittiä eli lapsihalvausta. Ensimmäisessä tutkimuksessa kuvataan seurantajärjestelmän toiminta ja tunnistetaan vahvistettavia alueita. Tutkimukset II – IV ovat tapaustutkimuksia, joissa arvioidaan a) elävään poliorokotteeseen liittyvän halvausoireen yleisyyttä (Recipient Vaccine Associated Paralytic Polio); b) haittavaikutusilmoituksia, joihin oli liittynyt kuolema sekä Kiinassa valmistettuihin, Japanin aivotulehdusta vastaan kehitettyihin rokotteisiin liittyviä haittavaikutuksia. Nämä tutkimukset tunnistivat rokotteisiin liittyviä turvallisuuskysymyksiä, arvioivat tieteellistä näyttöä siitä oliko haittavaikutuksilla yhteys rokotteisiin sekä tunnistivat kohtia joissa Kiinan kansallisen rokotusohjelman seurannan- ja tutkimuksen kapasiteettia voidaan vahvistaa.

Kiinan kansallinen rokotusten haittavaikutusten seurantajärjestelmä on passiivinen järjestelmä, joka on ollut toiminnassa vuodesta 2005 lähtien. Se kerää ajantasaisia tietoja ja kykenee havaitsemaan harvinaisia tai vakavia tapahtumia maailman suurimmassa väestössä. Hyödyntämällä useita nimittäjätietojen lähteitä, järjestelmällä on riittävästi tilastollista voimaa verrata ilmoitettujen haittavaikutusten havaittua määrää niiden odotettuun määrään. Tämän perusteella voidaan muun

muassa arvioida heijastelevatko havaitut muutokset haittavaikutusilmoitusten määrässä muutoksia raportointiaktiivisuudessa todellisten haittavaikutusten sijaan.

Polion maailmanlaajuiset hävittämistalkoot alkoivat Maailman terveysjärjestön (WHO) johdolla vuonna 1988. Laajamittaisten, elävää virusta sisältävien poliorokotusten ansiosta villi poliovirus ja sen aiheuttama halvausoireinen tauti on hävinnyt melkein kaikista maista ja maanosista, myös Kiinasta. Vuonna 2016 poliorokotteiden aikataulua muutettiin Kiinassa siten, että ensimmäiseksi annokseksi otettiin käyttöön inaktivoitu, pistettävä poliorokote. Seuraavat kolme annosta kolmevalenttista suun kautta otettavaa elävää poliovirusrokotetta korvattiin kaksivalenttisiella rokotteella. Seurantajärjestelmä on kerännyt tietoa kolmivalenttisen rokotteen turvallisuudesta jo vuodesta 2010 lähtien. Tutkimuksessa II suun kautta otettavaan poliorokotteeseen liittyneiden halvausoire-tapausten epidemiologiset ominaisuudet, esim. ikäjakauma, eivät poikenneet muiden maiden tuloksista. Halvausoireen riski, käytettäessä nimittäjänä joko arvioitua syntymien määrää tai annettuja rokotusannoksia, oli samaa luokkaa kuin aiemmin Yhdysvalloissa ja Japanissa tehdyissä tutkimuksissa. Harvinaisen halvausoireen (n. 4 tapausta per miljoona) ilmaantuvuutta uuden, kaksivalenttisen rokotteen käyttöönoton jälkeen verrattaan jatkossa aiempaan rokotteeseen. Tulokset tukevat pistettävän poliorokotteen käyttöä Kiinassa haittavaikutusten riskin edelleen vähentämiseksi.

Tutkimus III aloitettiin koska joulukuussa 2013 tiedotusvälineissä raportoitiin kuolemantapauksista, joiden oletettiin liittyvän hepatiitti B -rokotuksiin Hunanin maakunnassa. Nämä uutisjutut herättivät runsaasti huolta rokotteiden turvallisuudesta vanhempien ja kansalaisten keskuudessa ja väestön luottamus rokotteisiin heikkeni selvästi. Lapsen kuolema on erittäin harvinainen ja traaginen tapahtuma – rokotukset taas ovat lapsuudessa hyvin yleisiä. Tämän takia ilmoitettujen kuolemantapausten ajallinen yhteys hepatiitti B -rokotuksiin on voinut olla sattuma, jolla ei ollut syy-yhteyttä rokotukseen. Tutkimus tuotti rauhoittavaa tietoa rokotusten jälkeisestä kuoleman riskistä, joka oli äärimmäisen pieni. Haittavaikutusten ilmoitushuippu vuosien 2013-2014 vaihteessa havainnollisti kuinka herkkä passiivinen seurantajärjestelmä saattaa olla median raportoimille tiedoille, jotka eivät perustuneet tieteelliseen tutkimukseen. Tulokset myös korostivat, että on noudatettava erityistä varovaisuutta tulkittaessa nopeita muutoksia vakavien haittailmoitusten määrässä. Vaikka pieni tapausmäärä rajoitti mahdollisuuksia tehdä tuloksista varmoja johtopäätöksiä, rokoteturvallisuuteen liittyviä ongelmia ei havaittu. Näiden tulosten arvioitiin lievittäneen yleisön huolenaiheita ja palauttaneen luottamusta rokoteohjelmaan.

Rokotukset Japanin aivotulehdusta vastaan aloitettiin Kiinan kansallisessa rokotusohjelmassa vuoden 2007 lopulla. Elävä Japanin aivotulehdusrokote oli ensimmäinen Maailman terveysjärjestön (WHO) hyväksymä Kiinassa valmistettu rokote (2013). Tietoa Japanin aivotulehdusrokotteiden turvallisuudesta laajamittaisessa käytössä Kiinassa oli ennen tutkimustamme rajoitetusti. Tutkimuksessa IV suurin osa havaituista haittavaikutuksista oli vähäisiä, tiedossa olevia yleisiä haittavaikutuksia (esim. kuume, pistoskohdan kipu). Ilmoitettujen vakavien haittavaikutusten ilmaantuvuudessa ei ollut merkittäviä eroja elävän ja inaktivoidun rokotteen välillä. Useimmat potilaat toipuivat täysin myös vakavista haittavaikutuksista. Lisätutkimuksia tarvitaan erottelemaan muiden, samanaikaisesti annettujen rokotteiden vaikutukset Japanin aivotulehdusrokotteen vaikutuksista. On myös kehitettävä herkempiä menetelmiä turvallisuussignaalien havaitsemiseksi.

Tämä väitöskirja tarjoaa kokonaiskuvan rokoteturvallisuuden seurannan ja tieteellisen arvioinnin viimeaikaisesta kehityksestä Kiinassa. Tutkimuksissa osoitettiin, että kansallinen haittavaikutusten seurantajärjestelmä on toimiva ja tuottaa tärkeää tietoa rokotteiden turvallisuudesta maailman suurimmassa väestössä. Tutkimukset vahvistivat, että rokotusten jälkeiset tapahtumat tai havaitut oireet eivät välttämättä johtuneet rokotuksesta. Tutkimukset tunnistivat kuitenkin myös useita haasteita, kuten yhdenmukaisen, kansainvälisen sairauksien ja oireiden luokittelujärjestelmän sekä tapausmäärittelyjen puuttuminen. Nämä tulisi ottaa käyttöön virheellisten luokittelujen vähentämiseksi ja järjestelmän vahvistamiseksi. Lisäksi syy-yhteyden arviointimenettely olisi yhtenäistettävä ja ohjeistusta tarkennettava. Tulevissa tutkimuksissa tulisi ottaa käyttöön uusia tilastollisia menetelmiä signaalien havaitsemiseksi sekä niiden erottamiseksi datan taustakohinasta uusien tutkimuskysymysten ja -hypoteesien luomiseksi. Nämä kokemukset maailman suurimmasta rokoteturvallisuuden tietolähteestä voivat edesauttaa luottamuksen säilymistä rokotusohjelmiin. Ne voivat myös toimia mallina seurantajärjestelmien kehittämiselle muissa pieni- ja keskituloisissa maissa.

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ABBREVIATIONS

ADEM	acute disseminated encephalomyelitis
ADR	Adverse Drug Reactions
AEFI	Adverse Events Following Immunization
AESI	Adverse events of special interest
AFP	Acute Flaccid Paralysis
BCG	Bacillus Calmette-Guerin Vaccine
BCPNN	Bayesian Confidence Propagation Neural Network
CDCs	Centers for Disease Control and Prevention
CFDA	Chinese Food and Drug Administration
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CISA	the Clinical Immunization Safety Assessment network
CNAEFIS	Chinese online National AEFI Information System
DG SANCO	EU Directorate General for Health and Consumers
DMA	Data Mining Algorithms
DoV	Decade of Vaccines
DPA	Disproportionality Analysis
DT	Diphtheria and Tetanus combined vaccine
DTaP-IPV-Hib	Acellular-DTP IPV and Hib combined vaccine
DTP	Diphtheria Tetanus and Pertussis combined vaccine
DTaP	Acellular-DTP
DTwP	Whole cell-DTP
EBS	Empirical Bayes Screening
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EPI	Expanded Programme on Immunization
EV 71	Enterovirus type 71
EVPM	EudraVigilance post-authorization module
FDA	Food and Drug Administration
GACVS	Global Advisory Committee on Vaccine Safety

GBS	Guillain-Barré Syndrome
GISV	Global Immunization Vision and Strategy
GPS	Gamma-Poisson Shrinker algorithm
GVAP	Global Vaccine Action Plan
GVSB	Global Vaccine Safety Blueprint
HepA	Hepatitis A vaccine
HepB	Hepatitis B vaccine
Hib	Haemophilus Influenza type B polysaccharide conjugate vaccine
IC	Information Components
InfV	Seasonal Influenza inactive Vaccine
IPV	Inactivated Polio Vaccine
JE vaccines	Japanese Encephalitis Vaccine (live: JEV-L; inactivated: JEV-I)
LMICs	Low & middle-income countries
MCV	Measles Containing Vaccines
MedDRA	Medical Dictionary for Regulatory Activities
MenV	Meningococcal Vaccines
MenV A	Group A, MenV
MenV AC	Group A +C, MenV
MMR	Measles-Mumps-Rubella combined vaccine
MoH	Ministry of Health
MR	Measles-Rubella combined vaccine
MV	Measles Vaccine
NIP	National Immunization Programme
NRA	National Regulatory Authority
OPV	Oral poliomyelitis Vaccine (trivalent: tOPV; bivalent: bOPV)
PenV23	23-valent Pneumococcal Polysaccharide conjugate vaccine
PenV7	7-valent Pneumococcal conjugate vaccine
PMS network	a global network for the post-marketing surveillance, WHO
PRISM	Post-licensure Rapid Immunization Safety Monitoring program
PRR	Proportional Reporting Ratios
PV	Polio Vaccines
PVP	Predictive Value Positive
RabV	Rabies Vaccine for human use

ROR	Reporting Odds Ratios
RotV	Rotavirus Vaccine
SDR	Signal of Disproportionate Reporting
SEAR	South-East Asia Region
SIDS	Sudden Infant Death Syndrome
SRS	Spontaneous Reporting Systems
TIV	trivalent inactivated influenza vaccine
UMC	Uppsala Monitoring Center, WHO
VAERS	Vaccine Adverse Events Reporting Systems
VAPP	Vaccine-associated Paralytic Poliomyelitis
VarV	Varicella live attenuated Vaccine
VENICE	Vaccine European New Integrated Collaboration Effort project
VPD	Vaccine Preventable Disease
WHA	World Health Assembly
WHO	World Health Organization
WHO-ART	WHO-Adverse Reaction Terminology
WPR	Western Pacific Region
YCS	Yellow Card Scheme, UK

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I Dawei Liu, **Wendi Wu**, Keli Li, Disha Xu, Jiakai Ye, Li Li, Huaqing Wang. Surveillance of adverse events following immunization in China: Past, present, and future. Vaccine 33(2015):4041–4046.

II **Wendi Wu**, Huaqing Wang, Keli Li, J.Pekka Nuorti, Dawei Liu, Disha Xu, Jiakai Ye, Jingshan Zheng, Chunxiang Fan, Ning Wen, Zhijie An. Recipient Vaccine-associated paralytic poliomyelitis in China, 2010–2015. Vaccine 36(2018):1209–1213.

III **Wendi Wu**, Dawei Liu, Keli Li, J.Pekka Nuorti, Disha Xu, Jiakai Ye, Jingshan Zheng, Lei Cao, Huaqing Wang. Deaths reported to national surveillance for adverse events following immunization in China, 2010-2015. Vaccine 37(2019): 1182-1187.

IV **Wu Wendi**, Liu Dawei, Li Keli, J.Pekka Nuorti, Hanna M. Nohynek, Xu Disha, Ye Jiakai, Zheng Jingshan, Wang Huaqing. Post-marketing safety surveillance for inactivated and live-attenuated Japanese encephalitis vaccines in China, 2008–2013. Vaccine 35(2017): 3666–3671.

This thesis also includes data from the following supplemental reports published in Chinese:

1st **Wu WD**, Liu DW, Wu BB, Bao HH, Yue CY, Lin P, Li L, Liang XF. Analysis on the surveillance of adverse events following immunization in China, 2007–2008. Zhongguo Yi Miao He Mian Yi 2009 Dec 15(6):481–90, 538. PMID: 20518320. [Article in Chinese].

2nd **Wu Wen-di**, Liu Da-wei, Li Ke-li, Xu Di-sha, Wang Hua-qing, Liang Xiao-feng. Analysis on Adverse Events Following Immunization Surveillance in China, 2009. Chinese Journal of Vaccines and Immunization 2011 Apr; 17(2):99–108. [Article in Chinese].

3rd **Wu Wen-di**, Liu Da-wei, Li Ke-li, Xu Di-sha, Zheng Jing-shan, Cao Ling-sheng, Cao Lei, Yuan Ping, Wang Hua-qing. Analysis on Adverse Events Following Immunization Surveillance in China, 2010 Chinese Journal of Vaccines and Immunization. 2012 Oct; 18(5):385–397. [Article in Chinese].

4th **Wu Wen-di**, Li Ke-li, Zheng Jing-shan, Liu Da-wei, Xu Di-sha, Yang Hong, Cao Lei, Cao Ling-sheng, Yuan Ping, Wang Hua-qing, Li Li. Analysis on Surveillance Data of Adverse Events Following Immunization in China, 2011. Chinese Journal of Vaccines and Immunization 2013 Apr; 19(2):97–109. [Article in Chinese].

5th **Wu Wen-di**，Liu Da-wei，Li Keli, Zheng Jing-shan, Xu Di-sha, Wang Ya-min, Cao Lei, Cao Ling-sheng, Yuan Ping, Wang Hua-qing, Li Li. Analysis on Surveillance Data of Adverse Events Following Immunization in China，2012. Chinese Journal of Vaccines and Immunization 2014 Feb; 20(1):1–12, 66. [Article in Chinese].

6th Ye Jia-kai, Li Ke-li, Xu Di-sha, **Wu Wen-di**，Liu Da-wei, Zheng Jing-shan, Cao Lei, Cao Ling-sheng, Yuan Ping, Wang Hua-qing, Li Li. Evaluation of the Adverse Events Following Immunization Information Management System in China, 2013. Chinese Journal of Vaccines and Immunization 2015 Apr; 21(2):121–131, 200. [Article in Chinese].

1 INTRODUCTION

Immunization is one of the most powerful and cost-effective health interventions. It prevents related illnesses and disabilities and saves millions of lives every year(Plotkin, S. A., Orenstein, W. A. & Offit P. A., 2013). With the exception of safe water, no other modality—not even antibiotics—has had such a major effect on mortality reduction and population growth(Plotkin et al., 2013; WHO, UNICEF, & World Bank, 2009). Typically, the administration of a vaccine makes a person immune or resistant to an infectious disease. Since the first vaccine that was used to prevent smallpox, there has been over 200 years of development of vaccines(Plotkin & Plotkin, 2011).

With the help of vaccines, smallpox, which was a naturally occurring disease, was eradicated from the world; cases of poliomyelitis have been reduced by 99%, and it promises to be the next disease to be completely eradicated. At the same time, endemic measles, rubella, and congenital rubella syndrome are target diseases of the World Health Organization's (WHO) elimination program in the near future; these diseases have been virtually eliminated from the Americas since 2010(Plotkin et al., 2013).

In 1974, the 27th World Health Assembly (WHA) established the Expanded Program on Immunization (EPI) to ensure that all children in all countries can benefit from lifesaving vaccines(WHO, 2014b). Nowadays, almost all the countries in the world have their own immunization programs, and the vaccines used in the National Immunization Program (NIP) are no longer limited to the 6 vaccines recommend at that time: diphtheria, pertussis, tetanus, measles, poliomyelitis, and tuberculosis. Vaccines for rubella, mumps, Hepatitis A, Hepatitis B, Haemophilus influenza type B, rotavirus, Japanese encephalitis, influenza, meningococcal diseases, pneumococcal diseases, rabies, typhoid fever, human papillomavirus, varicella, and herpes zoster are also used in some countries or can be easily purchased(Plotkin et al., 2013; WHO, 2014b; WHO et al., 2009).

A vaccine is a biological product that improves and enhances immunity against a given disease. It contains a disease-causing microorganism—or a portion of it—and is often made from either live-attenuated or inactivated forms of the microbe, its

toxin, or one of its surface proteins(CIOMS & WHO, 2012; WHO/WPRO, 2013). Apart from the microorganism, vaccines usually also have other components, such as an adjuvant to enhance the immune response, antibiotics to prevent bacterial contamination, preservatives used to kill or subunit vaccines in order to inactivate the virus, detoxifying bacterial toxins to prevent serious secondary infections, and stabilizers to confirm vaccine quality or stability(WHO/WPRO, 2013). Through prequalification and other regulatory systems, the quality of the vaccines currently used is relatively assured(WHO, 2014b). However, just like drugs, vaccines are also medical products that are "foreign substances" to the human body, which means they might have adverse effects, especially given that vaccines are usually administered to healthy people, including infants(CIOMS & WHO, 2012; WHO/WPRO, 2013). Especially with the development of the NIP and EPI, certain vaccines have been mandated in some countries to prevent vaccine preventable diseases (VPDs), and the target population is typically a whole birth cohort(CIOMS & WHO, 2012). The first few years of a child's life constitutes the period of the greatest vulnerability to diseases and of the early manifestations of other problems (congenital diseases, developmental disorders, hearing impairments, and others)(WHO/PAHO, 2002). Therefore, a very high level of safety is required from vaccines.

With the growing success of vaccines and the development of other immunization programs, VPDs have become less frequent and even rare, due to which the public attention has shifted from VPDs to the safety of vaccines and adverse events following vaccines(S. Black & Zuber, 2009). Widespread concern about vaccine safety may lead to a loss of confidence in immunization and vaccines, which would lead to low vaccination coverage, and even a resurgence of VPDs (Figure 1)(Chen et al., 2015). This was seen in the case of the pertussis vaccine in Japan, the hepatitis B vaccine (HepB) in France, and the measles-mumps-rubella combined vaccine (MMR) in the UK and elsewhere. This has not only happened in developed countries but also in low- and middle-income countries (LMICs). A safety scare regarding the oral polio vaccine significantly impacted the progress of the eradication program for this disease, particularly in western Africa(S. Black & Zuber, 2009; Wilson & Marcuse, 2001). The "Hepatitis B vaccine event" that took place in 2013–2014 in Mainland China also caused a vaccine confidence crisis among the public. In fact, a telephone survey on publics showed that the percentage of vaccine confidence reduced from 85% to 26.7% during the event(W. Yu et al., 2016).

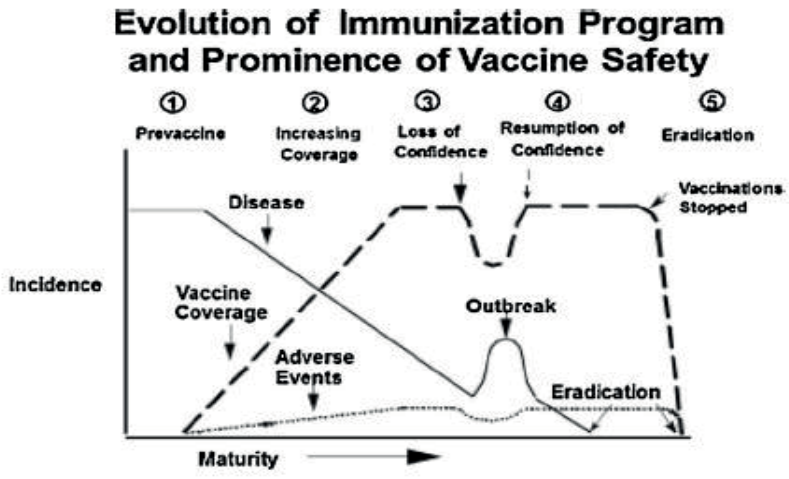

Figure 1 The evolution of immunization programs and the prominence of vaccine safety (Chen et al., 2015)

According to the Council for International Organizations of Medical Sciences (CIOMS)/WHO working group on vaccine pharmacovigilance(CIOMS & WHO, 2012), vaccine pharmacovigilance is defined as "the science and activities relating to the detection, assessment, understanding and communication of adverse event following immunization (AEFI) and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization." This not only includes pre-licensure clinical studies but also post-licensure surveillance systems. Pre-licensure clinical trials may demonstrate that common adverse events associated with licensed vaccines are minor and that serious adverse events are not common. However, rare, serious events are much less likely to be detected before licensure, even in relatively large clinical trials(Griffin, Braun, & Kenneth, 2009; Lopalco et al., 2010) .

China is the most populous country in the world. The annual birth cohort is over 16 million(Guo et al., 2013) and this number is set to go up following the change in the family planning policy in 2016 (from a one-child policy to a two-children policy). Currently, China administers an average of more than 500 million vaccine doses annually. Its NIP started in 1978 and provides government-purchased vaccines at no cost to all children under age of 7 years, regardless of socioeconomic status(Guo et al., 2013). From 2008, the NIP has included 14 types of vaccines targeting 15 VPDs(Zheng et al., 2010). China's high demand for vaccines is fulfilled by more than 60 vaccine formulations that are licensed for the Chinese market; more than 80% of these vaccines are made domestically and are administered through NIP(Hendriks,

Liang, & Zeng, 2010). Adequate pharmacovigilance for this large number of vaccines and the hundreds of millions of vaccine doses administered requires a credible system of monitoring adverse reactions, detecting and responding to emerging vaccine safety signals, and addressing the concerns of the public and the media(Guo et al., 2013). Therefore, post-licensure monitoring of AEFI is critically important in China.

Although Chinese Ministry of Health (MoH) issued guidelines for handling adverse reactions to vaccines in 1980, nationwide AEFI surveillance was not implemented until 2005(D. Liu et al., 2015). Since its establishment in 2005, and its expansion to all Chinese provinces in 2008, as a public health surveillance system, the AEFI cases collected by the Chinese online National AEFI Information System (CNAEFIS) has increased by approximately 30% each year. The CNAEFIS—responsible for monitoring AEFIs in China—has become an important public health surveillance system since its establishment. According to the Guidelines for Evaluating Public Health Surveillance Systems(US CDC, 2001), public health surveillance systems should be evaluated periodically. With more than 6 years having passed since its establishment, it is necessary to review the CNAEFIS and determine how this public health surveillance system is operating and how it can be improved in the future.

Moreover, the CNAEFIS is a spontaneous reporting system (SRS). The primary purpose of an SRS is to identify safety signals after a product has been marketed(CIOMS & WHO, 2012). In the past decade, various data mining methods have been used to evaluate vaccine safety signals from adverse event reporting systems(J. R. Curtis et al., 2009). In developed countries, data mining statistics have already been used in the analysis of the safety of vaccines(R. Harpaz et al., 2012), such as in case of human papillomavirus vaccine(Slade et al., 2009), rotavirus vaccination(M T Niu, Erwin, & Braun, 2001), and influenza vaccine.(Leroy et al., 2012a) Since the CNAEFIS has already collected several years' data on AEFIs, it is time to apply novel data mining methods to assess the safety signals of some of the vaccines used in China.

In summary, the CNAEFIS, which has served as a national passive AEFI surveillance system in China since 2008, has operated for more than 6 years, over which time it has gathered unique database on AEFI cases. It is time to review the entire system to better understand its limitations and strengths, which could provide information on how to improve vaccine safety surveillance in China. Meanwhile, in order to enhance the utility of the AEFI data collected by the CNAEFIS, we have applied commonly used data mining algorithms to signal detection in

pharmacovigilance using AEFI data on the Japanese Encephalitis(JE) Vaccine, and epidemiology analysis on recipient VAPP and fatalities captured by AEFI surveillance, to identify vaccine safety concerns which could lead to hypotheses on vaccine safety and provide evidence on vaccine safety in China.

2 REVIEW OF LITERATURE

2.1 Post-licensure vaccine safety

2.1.1 Vaccine safety monitoring

In May 2012, on its 65th anniversary, the WHA endorsed the Global Vaccine Action Plan (GVAP)—the final framework to achieve its vision of the Decade of Vaccines (DoV; 2011–2020). The GVAP (2011–2020)(WHO, 2013) builds on the success of the Global Immunization Vision and Strategy (GISV) (2006–2015) and aimed to improve health by extending the full benefits of immunization to all people, regardless of where they are born, who they are, or where they live—achieve by extending the program until 2020 and beyond. Among all six strategic objectives, the fourth one is, "Strong immunization systems are an integral part of a well-functioning health system." As part of this objective, in order to "ensure that everyone everywhere receives the safest vaccines possible and that safety concerns are not a cause of hesitancy in using vaccines," the Global Vaccine Safety Blueprint (GVSB) strategies were developed to build capacity for vaccine safety surveillance during 2011–2020(WHO, 2013).

The GVSB has eight objectives that aim to build and support effective vaccine pharmacovigilance in all LMICs. The first and second objectives were to strengthen vaccine safety monitoring in all countries and to strengthen the ability of countries to investigate vaccine safety signals. According to the GVSB, all countries should regularly assess the performance of their vaccine safety systems and development plans to close any identified gaps(WHO, 2012c).

2.1.2 Definition of Adverse Events Following Immunization

According to CIOMS(CIOMS & WHO, 2012), Adverse Events Following Immunization (AEFI) are defined as any untoward medical occurrences following immunization. Although AEFIs do not necessarily have a causal relationship with

the vaccine, they may be considered to be related to vaccination and may influence public confidence and make the implementation of an immunization program difficult(CIOMS & WHO, 2012; WHO/WPRO, 2013). This definition is similar to WHO's definition of AEFIs in their Immunization Safety Surveillance Guidelines(WHO/WPRO, 1999, 2013).

In the US, an "adverse event" is any health problem that occurs after a shot or other vaccine has been administered. An adverse event might be truly caused by a vaccine or it might be pure coincidence (https://www.cdc.gov/vaccinesafety/ensuringsafety/sideeffects/index.html). In China, an AEFI refers to a reaction or an event after a vaccination that is suspected to be related to the vaccination(China MoH & China FDA, 2010).

Although there are only minute differences in these two definitions, they share two key factors: i) it includes any event following immunization; ii) it does not necessarily have a causal relationship with the usage of the vaccine.

2.1.3 Methods of post-licensure vaccine safety surveillance

There are several methods of conducting post-licensure vaccine safety surveillance: passive reporting, active surveillance, global vaccine safety networks, and different epidemiological methods(S. Black & Zuber, 2009; Verma & Lahon, 2013). Passive surveillance systems rely on health care professionals (or vaccine recipients) to voluntarily submit reports of illness after vaccination. In active surveillance, the health department, such as national authorities, maintains regular contact with health care providers or related stakeholders to identify cases of adverse events following immunization. For LMICs with limited resources, the passive reporting system would be the most cost-effective method to evaluate vaccine safety(Breugelmans & Gessner, 2011).

Many developed countries have established well-functioning AEFI surveillance systems, such as the Vaccine Adverse Event Reporting System (VAERS) in the US(Zhou et al., 2003; Shimabukuro et al., 2015), the EudraVigilance system in the European Union (EU) and European Economic Area (EEA) countries(Lopalco et al., 2010), and the UK's Yellow Card Scheme (YCS),a national spontaneous reporting system(Hawcutt et al., 2012). However, it might be difficult to apply developed countries' vaccine safety profiles to developing countries where the vaccines used and the types of serious AEFIs may differ greatly due to local environmental and genetic differences(Breugelmans & Gessner, 2011). In many

LMICs, no regular surveillance for vaccine safety exists, as the primary immunization program focus continues to be on increasing coverage in the target population(WHO, 2012b).

2.2 Global post-licensure vaccine safety surveillance systems

2.2.1 WHO and the European Union (EU)

2.2.1.1 WHO

The WHO's Program for International Drug Monitoring (PIDM) is an international adverse event monitoring system, which was set up at the WHO Headquarters in Geneva in 1971. It was then moved to Uppsala, Sweden, in 1978. Countries participating in the PIDM submit not only adverse drug reaction (ADR) reports but also AEFI reports. In 2007, in over 3.7 million reports, around 8% of AEFIs were found to be vaccine related(Letourneau et al., 2008).

In order to enhance the monitoring, reporting, and sharing of vaccine safety data among countries introducing new prequalified vaccines, the Global Advisory Committee on Vaccine Safety (GACVS), an expert clinical and scientific advisory body established by WHO, started a WHO-led pilot project in 2007—a global network for the post-marketing surveillance (PMS network) of AEFIs(WHO, 2012a). According to the terms of the project, all surveillance data should be reported into a central database (i.e., Vigibase) located at the WHO Collaborating Center for international drug monitoring—the Uppsala Monitoring Center (UMC) in Sweden. For this, the UMC provided a software platform called Vigiflow to report and upload AEFI cases and methods of causality assessment for vaccine AEFI classification(WHO, 2012a). In this pilot study, since some of the participating countries already had their own AEFI surveillance systems, the different reporting variables and definitions made it difficult to harmonize the database. Furthermore, due to the heterogeneous nature of the surveillance data, it was hard to generate global safety signals and the study therefore only provided limited information on vaccine safety.

To improve the efficiency and quality of AEFI surveillance activities at national and regional levels, under the guidance of the GACVS, WHO developed a global manual on the surveillance of AEFIs in 2014(WHO, 2014a). Parts of WHO's

regional office, such as those in the South-East Asia Region (SEAR) and the Western Pacific Region (WPR), also had their own guidelines for AEFI surveillance(WHO/SEARO, 2014; WHO/WPRO, 2013). These global and regional manuals provide guidance on every aspect of AEFI surveillance systems, including reporting, investigation, causality assessment, and the classification of AEFIs.

2.2.1.2 The European Union (EU)

Over the past few decades, immunization programs have achieved great success in EU countries, which has brought about a remarkable reduction there in child mortality(WHO/EURO, 2015). However, with the development of vaccination and immunization, today the most important threat in Europe is the perceived risk of immunization adverse events among the public. There have been several such examples in European countries, such as in the UK regarding the suspected association of MMR and autism, and in France regarding multiple sclerosis and the HepB vaccine. In both countries, the related vaccination coverage dropped significantly following public outcry, and even after the casual association was rejected, rumors about it still appear now and then among the general public(Lopalco et al., 2010).

The AEFI cases from Finland's passive vaccine safety reporting system was reported by health care providers, mainly by nurses or physicians working in baby clinics. Health centers and referral hospitals sent in 500–600 reports per year. At the National Institute for Health and Welfare of Finland (THL), there is a full-time vaccine safety physician working with a part-time nurse on assessing the reports(Postila & Kilpi, 2004). Other countries in the EU either have their own surveillance systems for vaccines or use their ADR surveillance systems. In 2007, the Vaccine European New Integrated Collaboration Effort (VENICE) project, which was funded by the EU Directorate General for Health and Consumers (DG SANCO) and later by the European Centre for Disease Prevention and Control (ECDC), conducted a survey on vaccine adverse event monitoring systems across EU countries. According to the survey, 18 of 26 responding countries have a specific safety monitoring system for AEFIs in place, and only 9 countries (i.e., Finland, Germany, Hungary, Iceland, Latvia, Lithuania, Netherlands, Romania, and Slovakia) have such a system in addition to pharmacovigilance(Zanoni et al., 2009). It is advised that since immunization is different from drug treatment for many issues, monitoring of AEFIs should be done with the involvement of health authorities dealing with vaccine administration(Zanoni et al., 2009). Also, the AEFI case

definitions, reporting forms, and investigation procedures were found to be different among the many EU countries(Lankinen et al., 2004), which made it nearly impossible to achieve data integration and sharing.

At the EU level, there is a unified pharmacovigilance surveillance system called EudraVigilance, which was established by the European Medicines Agency (EMA). The EudraVigilance post-authorization module (EVPM) served as the surveillance system for all reports of suspected serious adverse reactions related to medicines subject to marketing authorization in the EU, including vaccines(Kurz et al., 2011). European pharmacovigilance researchers not only used the term of "AEFI," they also defined lists of "adverse events of special interest (AESI)" for surveillance purposes: these are syndromes, diseases, or special conditions that could theoretically or potentially be linked to specific vaccines(Kurz et al., 2011; Lopalco et al., 2010). For example, during the pandemic A/H1N1 influenza vaccination program, they used the EVPM to monitor AESIs using standard case definitions (such as anaphylaxis, convulsions, demyelination, and facial palsy). This spontaneous reporting system was shown to be effective for monitoring the safety of A/H1N1 vaccines during the 2009–2010 influenza pandemic(Kurz et al., 2011).

Besides the passive surveillance of AEFIs or AESIs, the ECDC and its related stakeholders launched the Vaccine Adverse Events, Surveillance and Communication (VAESCO) I and II projects in the EU countries. During the two phases of the VAESCO project, data linkage of large computerized clinical databases and immunization registries was developed to complement the routine passive surveillance system, EVPM. The establishment of this European vaccine safety data linkage system known as E-VSD was prompted by the US Vaccine Safety Data Linkage system (VSD) to conduct a risk assessment and safety signal verifications(Chen et al., 2015; Lopalco et al., 2010).

2.2.2 US, Canada, and Australia

In the US, there were a series of vaccine crises during the 1970s and 1980s, which resulted in lawsuits, a rise in vaccine prices, and a threat to the NIP. As a result, Congress issued the National Childhood Vaccine Injury Act (NCVIA) in 1986(Smith, 1988). This act mandated post-marketing surveillance for vaccine safety. Initially, there were two surveillance systems: a monitoring system for AEFIs maintained by the US CDC for public providers, and a spontaneous reporting system maintained by the US Food and Drug Administration (FDA) for private providers

and vaccine manufacturers. These two systems finally merged into one—the VAERS—and began to act as the national passive vaccine surveillance system in 1990(Singleton et al., 1999). The VAERS, jointly sponsored by the FDA and CDC, covered all adverse events following the receipt of vaccines licensed in the US.

As part of its post-marketing vaccine safety surveillance efforts, VAERS accepts voluntary reports from health care providers, parents, patients, or just about anyone else, as well as a smaller number of mandated reports of specific events(Varricchio et al., 2004). The flow chart of information of VAERS is shown in Figure 2.

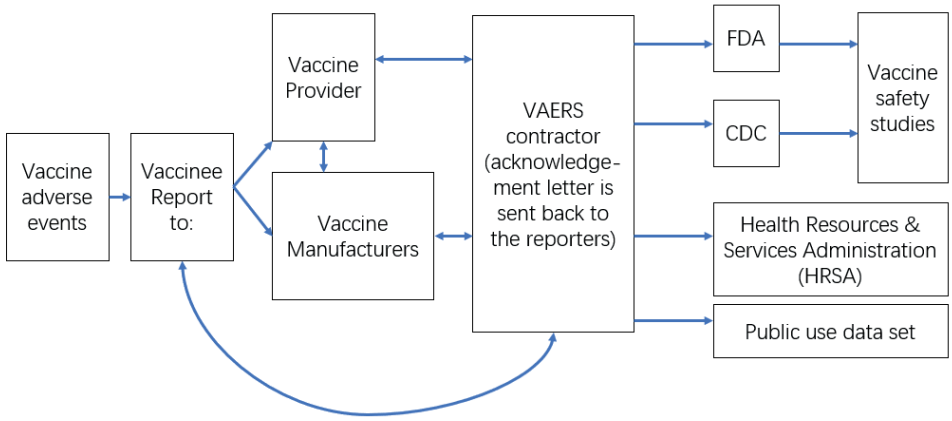

Figure 2 Flow of information within VAERS from reporters to VAERS contractors and then to the FDA, CDC, and other interested parties (Singleton et al., 1999)

The primary function of VAERS is to detect early safety signals and generate hypotheses on possible new vaccine adverse events or changes in the frequency of known events(Varricchio et al., 2004). An analysis of VAERS data from 1991–2001 showed that 128,717 cases were reported and more than 1.9 billion net doses of human vaccines were distributed, with overall reporting rates for 27 vaccine types with 11.4 reports per 100,000 net doses distributed(Zhou, Weigong Pool, Vitali Iskander, 2003). VAERS played an important role in vaccine safety evaluation, detecting rare adverse events that were either not found or not completely understood during clinical trials. One famous example is the withdrawal of the first generation rotavirus vaccine (RotV) due to VAERS' detection of intussusception reports associated with this vaccine(Zanardi et al., 2001). In this case, the manufacturer voluntarily withdrew the vaccine from the market. Also, the surveillance data records the increase and decrease in known adverse events, thereby acting as the baseline of interest events nationally and in a timely manner. After the

oral poliomyelitis vaccine (OPV) in the NIP was replaced with the Inactivated Polio Vaccine (IPV) in the 1990s, VAERS has documented the disappearance of vaccine-associated paralytic poliomyelitis (VAPP) in the US(Varricchio et al., 2004).

The post-marketing vaccine safety surveillance infrastructure in the US not only includes the passive surveillance system VAERS but also VSD, an active surveillance system(Baggs et al., 2011; Chen et al., 1997). VSD started in 1990, with eight managed care organizations (MCOs) participating in the research, covering a large population of 8.8 million members annually (about 3% of the US population). From 2000 onward, the number of MCOs increased along with improvements in data collection procedures, and it evolved into a near real-time surveillance system. VSD data can now be used to generate the background rate of interested events, and it collaborates with VAERS to evaluate vaccine safety, especially for newly licensed vaccines. After symptoms of intussusception following the administration of the RotV were detected by VAERS, in order to determine the expected number of intussusception cases that would occur by chance alone, the background rates of intussusception without vaccination could be determined using VSD data(Penina et al., 2008). A more recent example is the occurrence of febrile seizures following the influenza vaccine. After Australia reported an increased risk of febrile seizures in young children following the administration of the 2010 Southern Hemisphere trivalent inactivated influenza vaccine (TIV) from one manufacturer, VAERS data was used to detect similar signs of a possible increased risk of febrile seizures following TIV in the US (Leroy et al., 2012a). A further epidemiologic assessment of a possible association between TIV and febrile seizures was thereafter undertaken in the VSD system(Tse et al., 2012). Thus, along with individual vaccine safety studies, VSD data can also be used to study the safety of the childhood immunization schedule(CDC, 2018), such as vaccine schedules and the risk of asthma.

Apart from VAERS and VSD, the department of Health and Human Services also has developed other new research systems for vaccine safety, such as the Post-licensure Rapid Immunization Safety Monitoring (PRISM) program of the US FDA(Baker et al., 2013) and the Clinical Immunization Safety Assessment (CISA) network of the US CDC(LaRussa et al., 2011).

In Canada, located close to the US, the situation is a bit different. In the late 1980s, in the face of growing societal concern about the relationship between the whole-cell pertussis vaccine (wP) and fever among children(Scheifele et al., 2003), the health ministry of the federal government of Canada (Health Canada) launched Canadian Adverse Event Following Immunization Surveillance System (CAEFISS). This collaborative post-marketing federal/provincial/territorial (F/P/T)

surveillance system includes spontaneous, enhanced, and active AEFI reporting processes(Health Canada, 2014). Passive reports can come from health care professionals, market authorization holders, and the public for routine surveillance, and enhanced surveillance is conducted by immunization program authorities when needed. The Immunization Monitoring Program-ACT-ive (IMPACT) is a pediatric hospital-based network funded by the Public Health Agency of Canada (PHAC) and administered by the Canadian Paediatric Society, which conducts active surveillance on behalf of the CAEFISS(Health Canada, 2014). After years of surveillance and study, IMPACT has resulted in the publication of over 60 articles and abstracts along with important output on vaccine safety, such as a substantial decrease in the risk of the development of febrile seizures and hypotonic-hyporesponsive episodes since the country switched from wP to acellular pertussis-containing vaccines, and no evidence has been found for encephalopathy resulting from these vaccines(Scheifele et al., 2003).

In Australia, local reporting mechanisms of AEFI have been in place for many years. A national passive surveillance system was also established in 2000, and AEFIs were reported to the Adverse Drug Reactions Unit (ADRU) of the Therapeutic Goods Administration (TGA) of Australia by health care professionals or by the public. The AEFI data were further analyzed and evaluated by the National Centre for Immunization Research and Surveillance of vaccine-preventable diseases (NCIRS)(Isaacs et al., 2005; Wood & Isaacs, 2006). The flow of information in AEFI surveillance in Australia is shown in Figure 3. The annual data analysis shows that serious adverse events are rare in Australia.

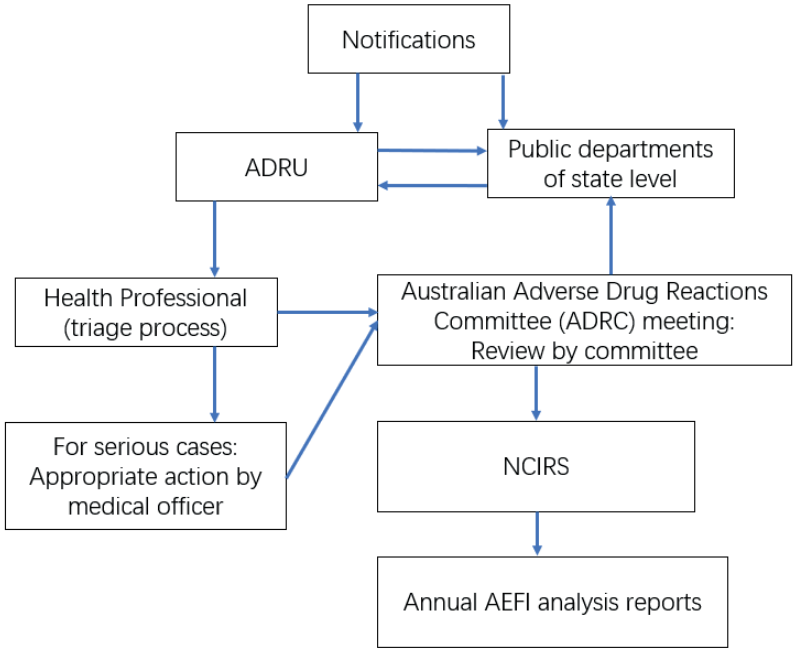

Figure 3 The flow of the surveillance of AEFI in Australia

Like VSD in the US, Australia also tried conducting data linkage as a sophisticated form of active surveillance for vaccine safety. A pilot study using data linkage as a means of vaccine safety surveillance by linking immunization records from the Australian Childhood Immunization Register (ACIR) to hospital outcome data was conducted in South Australia (SA). It examined the risk of convulsions following the administration of the MMR and Diphtheria-Tetanus-Pertussis combined vaccines (DTP). This pilot study showed that the ability and feasibility of safety signal evaluation was the same as in the case of VSD(M. Gold et al., 2010).

2.2.3 Japan, Korea, and India

In Japan, information on adverse reactions to vaccination were collected in three ways: i) sentinel reporting of all health problems after vaccinations (regardless of causative relationship with vaccinations); ii) formal reports of vaccine-related injuries from local authorities (highly probable causative relationship); and iii) appeals to the vaccine injury compensation committee (seeking judgment regarding the causative relationship)(Bakatani, Sano, & Iuchi, 2002). The primary method used was the national passive AEFI surveillance system known as the National Adverse Reaction

Reporting System (NARRS) that has been maintained by the Japanese Ministry of Health and Welfare (JMHW) since 1994. All immunization providers, school nurses, and parents are required to notify the NARRS in case of any vaccine adverse reactions that meet the reporting criteria. There were two reporting channels at the time: the legitimate channel and the private manufacturers' channel. In the legitimate channel, physicians were responsible for reporting serious vaccine-associated events to the regional government through their regional Public Health Center. Then the case should be registered by the JMHW. Also, the cases is reported to the respective vaccine manufacturers and should be registered through the private manufacturers' channel (Nakayama & Onoda, 2007).

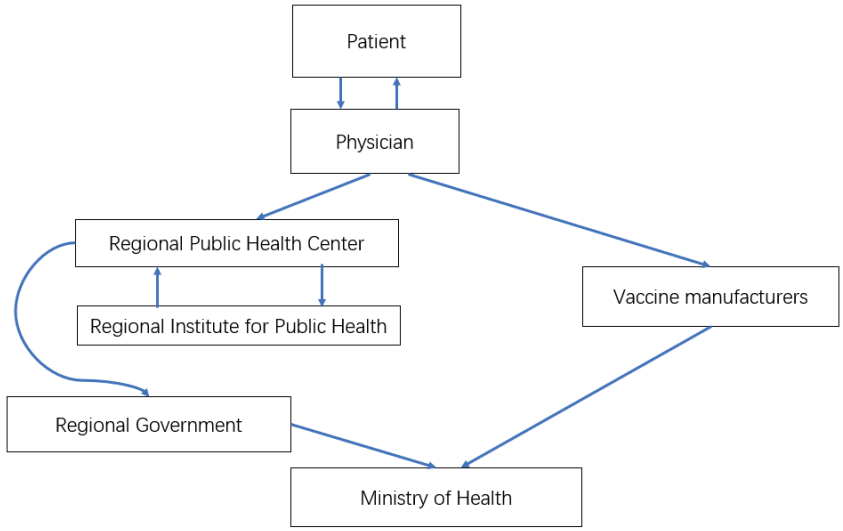

Figure 4 Japan's reporting system for serious vaccine-associated adverse events after vaccination (Nakayama & Onoda, 2007)

In Korea, the importance of AEFI surveillance was prompted by reports of adverse events associated with JE vaccine, subsequently shown to be due to the poor storage of the vaccine in 1994(Cho et al., 2010). A passive electronic reporting system was also established, which allowed patients, their guardians, and physicians to submit information. At the same time, the investigation of AEFIs by the National Regulatory Authority (NRA) and the Vaccine Injury Compensation Program were also established(Choe et al., 2011). The Infectious Diseases Prevention Act was revised to mandate that all healthcare workers must report AEFIs through passive surveillance. However, the number of reports was very low. Although the annual

distributed doses of vaccines were more than 16 million, the total number of reports in the passive surveillance system from 1994–2010 were 5,339(Choe et al., 2011; Choe & Bae, 2013). In 2009, during the 2009–2010 influenza season, the Korean CDC conducted active surveillance for the detection of AEFIs against the 2009 pandemic A(H1N1) influenza vaccine in order to supplement the collection of AEFI data from the routine passive surveillance system(Choe et al., 2011).

India is the largest developing country with many manufacturers of vaccines. The tracking of AEFIs in India started in 1985, with the launch of the Universal Immunization Program (UIP)(Lahariya, 2014). The first documented AEFI report and guidelines were published in 1988(Lahariya, 2014). However, the incidence of AEFIs in India was poor until early 2005(Vashishtha & Kumar, 2013). In 2005–2006, national AEFI surveillance and Response Operational Guidelines were issued by the Government of India, which were then further revised and updated in 2010(Chiekara et al., 2013). From 2007, AEFI events are being linked to the closure of three government-owned units (PSUs) in India, and the reporting has slightly improved since then(Patile, 2014). In the national AEFI surveillance system (Figure 5), most reports originate from the public health sectors(Bhaumik, 2013), which were covered by the UIP. Since 10–20% of the total immunization in India is provided by the private sector, which are not part of the UIP and therefore not covered by the AEFI surveillance system, in recent years, stakeholders in India have tried to find ways to include the private sector in AEFI surveillance(Bhaumik, 2013; Chiekara et al., 2013). According to the 2015 Operational Guidelines for the AEFI Surveillance Program in India, common and minor reactions can be reported monthly, but serious AEFIs such as death, hospitalization, prolonged disability, in the form of a cluster, or any single event that raises significant community/parental concern, is to be reported for investigation within 48 hours(Joshi et al., 2018), which is consistent with the WHO guidelines(WHO/WPRO, 2013).

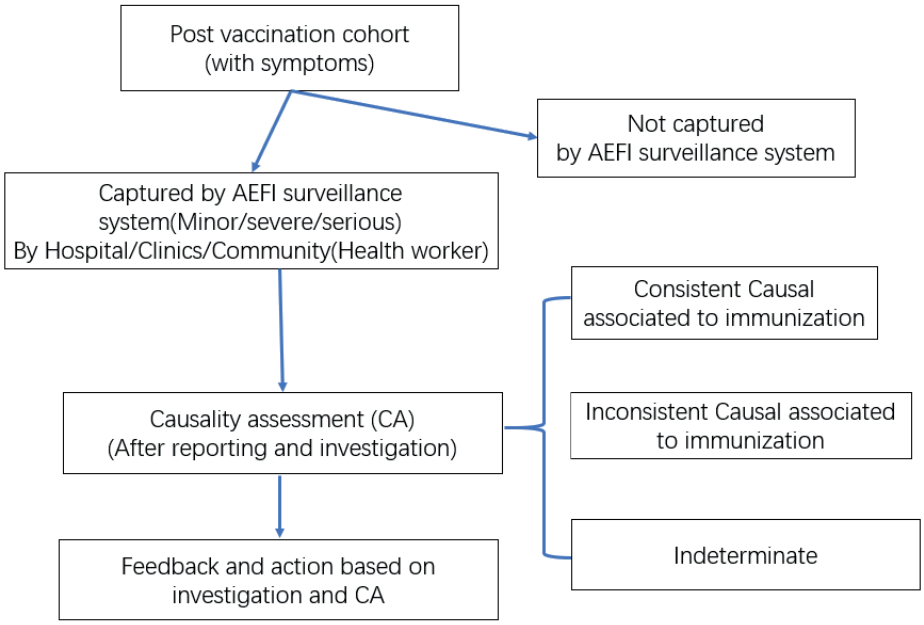

Figure 5 The AEFI surveillance system in India (Joshi et al., 2018)

2.2.4 Mainland China

2.2.4.1 Vaccines in China

China initiated its National EPI in 1978. The vaccines covered by the NIP were the Bacillus Calmette-Guérin vaccine (BCG), OPV, the measles vaccine (MV), and the DTP vaccine, following the recommendations of WHO. In 2002, HepB was added into the NIP, and in December 2007, vaccines against meningococcal meningitis, Japanese encephalitis, hepatitis A, rubella, and mumps were further included in the national immunization schedule(Zheng et al., 2010). Today there are 14 vaccines targeting 15 VPDs in the NIP (Table 1). The vaccines included in the NIP are funded by the central government and administered to target children free of charge(Guo et al., 2013). Currently, about 500 million vaccine doses administered annually in the NIP(Guo et al., 2013). There are still vaccines used outside the NIP in the private market, produced by manufacturers based on market demand, and these can be purchased by consumers on a voluntary basis.

Table 1 Vaccines in Chinese national immunization schedule (Hendriks et al., 2010)

Vaccines	Year of Introduction	Remarks
Hepatitis B vaccine (HepB)	2002	
BCG Vaccine (BCG)	1978	
Oral Poliomyelitis vaccine (OPV)	1978	
Combined Vaccine of Pertussis, Diphtheria and Tetanus (DTP)	1978	
Measles containing vaccine (MCV)		
MV	1978	Combined vaccine introduced in 2007-2008
MR	2007-2008	
MMR	2007-2008	
Combined vaccine of Diphtheria and Tetanus (DT)	2008	
Hepatitis A vaccine (HepA)	2008	
Meningococcus vaccine, A/ A+C (MenA, MenAC)	2008	
Japanese Encephalitis Vaccine (JEV)	2008	
Hemorrhagic Fever Renal Syndrome vaccine (HFV)	2008	Only for high risk population in endemic regions
Anthrax vaccine	2008	
Leptospira vaccine	2008	

With the development of vaccine manufacturing in China and the high demand for vaccine doses, China ranks as one of the world's largest vaccine manufacturing countries, with an annual output of more than one billion doses(Hendriks et al., 2010). Most of the NIP vaccines are manufactured domestically; however, some vaccines like MMR and the Hepatitis A vaccine (HepA or HAV) are also produced by international manufacturers(Guo et al., 2013). In 2010, the Chinese FDA's website listed 46 Chinese registered vaccine manufacturers of public and private status, collectively manufacturing 24 licensed vaccines(Hendriks et al., 2010) (Table 2).

Table 2 Major vaccines available in China, 2010(Hendriks et al., 2010)

Vaccines	Number of manufacturers
HepB	8
BCG	5
OPV	2
DTP	6
MV	5
DT	6
DTaP	7
HepA	6
MenA and MenAC	9
JE	9
MMR	1
HFV	6
Anthrax vaccine	2
Leptospira vaccine	3
Absorbed Tetanus vaccine	6
Combined vaccine of HepA and HepB	1
Rabies vaccine	14
Tracheitis vaccine	4
Typhoid Vi Polysaccharide vaccine	6
Tick-borne encephalitis vaccine	1
Split A(H1N1) influenza vaccine	10
Seasonal influenza vaccine	11
Pandemic (H5N1) influenza vaccine	1
Brucella vaccine	2

2.2.4.2 Development of Nationwide AEFI surveillance in China

AEFI surveillance began in China after it initiated the EPI in 1978(Zheng et al., 2010). The first formal guidelines for AEFI surveillance issued by Chinese MoH have been in place since 1980(Guo et al., 2013). Some of the local CDCs and local ADR monitoring agencies in more developed areas like Shanghai began to collect AEFI data at that time(Dong, mei Jing, & hua Sun, 2011). The pharmacovigilance system in China was initiated in 1989, and after 20 years of development, a relatively mature regulatory system has been established(L. Zhang et al., 2014). However, prior to 2003, ADR cases were reported to provincial ADR agencies in paper form. It is only after 2003 that the online spontaneous reporting system was established. A limited number of AEFI cases were reported through this pharmacovigilance system, mainly from vaccine manufacturers.

China CDC, affiliated with the MoH, was responsible for the implementation of the EPI, and a division of the NIP was established in 2002. With the help of the WHO/HQ and the WPR regional office (WPRO), NIP office in China CDC launched a pilot study for AEFI surveillance, initially in the Hebei and Guangdong provinces(Guo et al., 2005), and later expanding to 10 provinces in China(Guo et al., 2007). This pilot study of passive surveillance in China was based on the first edition of the WHO/WPRO's guidelines called "Immunization Safety Surveillance: Guidelines for Managers of Immunization Programme on Reporting and Investigating Adverse Events Following Immunization," which was published in 1999(WHO/WPRO, 1999). During this pilot study, the China CDC organized training workshops on AEFI surveillance not only for staff in pilot provinces but also other provinces in China. After two years of development, 16 of China's 32 provinces (including Xijiang Corps) reported AEFI cases into the national database(D. Liu et al., 2007a). In 2007, to coordinate with the development of the EPI and enhance AEFI surveillance, an intensive online surveillance study in five counties was launched by the China CDC over two years. In this study, on the basis of passive surveillance, intensive surveillance on several vaccines was also implanted, similar to a clinical trial: at least three follow-up visits after vaccination by nurses or physicians in vaccination clinics. The results of this study showed that the data quality and surveillance sensitivity were improved in the pilot counties(Yue et al., 2012). After these two pilot studies, the China CDC expanded the passive surveillance system to include all the provinces in China and utilized an online system known as the CNAEFIS. Since its establishment, CNAEFIS has covered AEFIs of all vaccines both part of the NIP or purchased on a voluntary basis.

From 2008, CNAEFIS entered a stage of rapid development. During the pandemic A(H1N1) influenza vaccination in 2009–2010, CNAEFIS played a key role in collecting data on AEFI cases(Liang et al., 2011). In 2010, China launched a nationwide measles supplementary immunization activity (SIA) to further decrease the susceptibility to measles(Ma et al., 2011), covering more than 100 million children within 10 days. CNAEFIS also served as the AEFI reporting system in this SIA(Wu et al., 2012). In the same year, national guidelines of AEFI surveillance(China MoH & China FDA, 2010) were also issued together by the MoH and the FDA. According to these guidelines, as required by the WHO NRA assessment, all AEFI cases were to be reported to the CNAEFIS. This indicated that even AEFI cases in the pharmacovigilance system reported by manufacturers should be reported to CNAEFIS, making it the only passive surveillance system for AEFIs, with data being shared by CDCs and ADRs in China.

CNAEFIS is operated in accordance with Chinese national AEFI guidelines. These guidelines are, in turn, supported by the Law on the Prevention and Treatment of Infectious Diseases of the People's Republic of China, the Pharmaceutical Administration Law of the People's Republic of China, the Administrative Regulation on the Circulation of Vaccines and Vaccination, the Regulations on Preparedness for and Responses to Public Health Emergencies, and other laws and regulations, with reference to WHO's guidelines on AEFIs, and with the intent to improve vaccine safety and immunization service quality.

2.3 Surveillance system evaluation

The plague in London in the seventeenth century is one of the earliest examples of surveillance(Declich & Carter, 1994). After decades of development, surveillance has evolved into a complete discipline(Declich & Carter, 1994), with its own objectives, data sources, methodologies, and evaluation procedures. Vaccines and their adverse reactions are one of the several health events under surveillance. Many experts on public health surveillance recommend that every surveillance system should be evaluated periodically to ensure that it is serving public health functions and is meeting its objectives(Declich & Carter, 1994; Thacker et al., 1988).

2.3.1 Guidelines for public health surveillance system evaluation

The US CDC's guidelines for evaluating surveillance systems are the benchmark for public health surveillance. The first edition was published in 1988(Klaucke et al., 1988) to promote the best use of public resources through the development of efficient and effective public surveillance systems, and it was then updated in 2001 to address new needs(US CDC, 2001). WHO also developed a "Protocol for the Evaluation of Epidemiological Surveillance System"(WHO, 1997) in 1997 that served as a tool for assessing existing systems and identifying areas of improvement. Some other guidelines and frameworks for specific surveillance systems were also studied and published, such as the WHO's Assessment Protocol for National Communicable Disease Surveillance and Response System(WHO, 2001), the draft framework for the evaluation syndromic surveillance system(Sosin, 2003), and the evaluation framework for injury surveillance systems(Mitchell, Williamson, & O'Connor, 2009). These guidelines have provided valuable information on how to

evaluate the performance of a surveillance system based on the widely used guidelines developed by US CDC.

Various surveillance systems were evaluated based on US CDC guidelines, including the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Projective (NEISS-CADES)(Jhung et al., 2007) and Non-Name-Bases HIV surveillance(Solomon et al., 1999) in the US; the HIV/AIDS surveillance system in Norway(Aavitsland, Nilsen, & Lystad, 2001); the National Notifiable Diseases Surveillance System (NNDSS) in Australia(M. Miller et al., 2004); the National Health Services (NHS) Direct, a national telephone health advice service, in England and Wales(Doroshenko et al., 2005); and syndromic surveillance in French Guyana(Jefferson et al., 2008). Apart from the US and European countries, the US CDC guidelines were also used in China and Japan to evaluate epidemiological surveillance systems. The National HIV sentinel surveillance system in China(Lin et al., 2012) and the Japanese School Health Surveillance System for Influenza(Takahashi et al., 2001) were evaluated by researchers based on these widely used guidelines. Even some researchers in animal health surveillance tried to adopt these guidelines to evaluate scrapie surveillance systems in the US(Lynn et al., 2007), which indicates the wide application and usefulness of these guidelines. In the field of AEFI surveillance, Singleton et al.(Singleton et al., 1999) evaluated VAERS according to these guidelines and found that VAERS is simple to use, flexible, and timely for AEFI surveillance. This indicates that the evaluation of a passive AEFI surveillance system could adopt these widely used guidelines.

2.3.2 Attributes of surveillance systems

According to the US CDC's updated evaluation guidelines, an evaluation involves four tasks: i) engage the stakeholders in the evaluation; ii) describe the surveillance system to be evaluated; iii) focus on the evaluation design; iv) gather credible evidence regarding the performance of the surveillance system(US CDC, 2001). Task iv was the key output of this evaluation and can be further divided into two: i) utility and cost, including the importance, objective, components, usefulness, and cost; ii) system attributes, including simplicity, flexibility, data quality, acceptability, sensitivity, predictive value positive (PVP), representativeness, timeliness, and stability(US CDC, 2001).

System attributes represent the quality of the system and can be reviewed regularly. They can also be divided into two groups: qualitative and quantitative

attributes. Sensitivity, PVP, timeliness, representativeness, and data quality can be expressed in numerical terms, while all the other attributes are more subjective measures and are thus less easily quantified(Thacker et al., 1988).

Simplicity

The simplicity of a surveillance system refers to both its structure and its ease of operation(US CDC, 2001). Simplicity should be inherent in a system as a whole as well as in each of its individual components (case definition, reporting procedures, etc.)(Declich & Carter, 1994). A flowchart of surveillance could demonstrate a system's simplicity. Also, simplicity is closely related to acceptance and timeliness(US CDC, 2001), and a more simple system might be more flexible.

Flexibility

Flexibility refers to the ability of a surveillance system to accommodate to changes in operating conditions or information needs(Declich & Carter, 1994). A flexible system can easily adapt to the addition of new diseases or situations or more population groups in a short time(Declich & Carter, 1994) and can also integrate with other systems(US CDC, 2001).

Sensitivity and PVP

The assessment of sensitivity and PVP provides different perspectives on how well a system is operating(German, 2000). Sensitivity is defined as the ability of a surveillance system to detect a true health event(Thacker et al., 1988). Quantitatively, sensitivity is the proportion or ratio of cases of health events detected by a system(US CDC, 2001). PVP is the proportion of reported cases that actually have the health event under surveillance. Both sensitivity and PVP can be calculated in the form of a 2 × 2 table (Table 3).

Table 3 Calculation of the sensitivity and PVP of a surveillance system

Detected by surveillance	Condition present		
	Y	N	
Y	True positive A	False positive B	A+B
N	False nagative C	True negative D	C+D
	A+C	B+D	

According to the table above, sensitivity and PVP can be calculated as follows:

Sensitivity = A/(A + C)

PVP = A/(A + B)

To assess sensitivity, it is necessary to collect and assess data external to the system in order to determine the true frequency of the condition in the population under surveillance. This is because A+C are confirmed cases collected by the system;

therefore, A is a required value. For PVP, since there are already cases detected by the surveillance system (i.e., A + B), the important factor needed is the same as sensitivity—confirmed cases in the surveillance system. In the evaluation of the quality of an injury surveillance system, Macarthur(Macarthur & Pless, 1999a) used an independent review to confirm false-positive cases.

The computation of sensitivity and PVP for a surveillance system can be complicated in the absence of an appropriate gold standard(German, 2000). In the review study conducted by German(German, 2000) on report sensitivity and PVP for public health surveillance systems, it was found that different gold standards have been used in different studies. In all 31 studies reviewed, 6 or 19% of the studies used the estimation of the total cases. In the AEFI surveillance system, there are two studies on sensitivity—VAERS in the US(Rosenthal & Chen, 1995) and CAEFISS in Canada(Tadrous, 2010). Although these two studies analyzed different vaccines, events, and time periods, the estimation of expected or true case frequency in the population under surveillance was calculated in both as "administered doses × event incidence rate". The event incidence rates used in both studies were from literature reviews.

Low sensitivity does not mean the surveillance system is ineffective. It is still useful in monitoring trends and providing baselines as long as the sensitivity remains constant over time. However, a low PVP does indicate a waste of resources(US CDC, 2001).

Timeliness

Timeliness reflects the duration between the steps of a public health surveillance system(US CDC, 2001). The time interval usually considered is the amount of time between the onset of the surveillance event and the reporting of that event to the public health agency responsible for instituting control and prevention measures(US CDC, 2001). The steps of different surveillance systems are different, which makes it difficult to develop a general mathematical equation to calculate timeliness(Dailey, Watkins, & Olant, 2007). Usually, timeliness is evaluated in the surveillance of infectious diseases, and different countries might adopt different indicators to evaluate timeliness, such as time lags used in a Korean study(Yoo et al., 2009) and time intervals used in studies in the US(Hedberg et al., 2008; Jajosky & Grosedlose, 2004) and Sweden(Jansson et al., 2004).

The key purpose of timeliness evaluation is to understand the steps in a surveillance system. In the US CDC guidelines, there is a simplified example of the steps in a surveillance system (Figure 6). From this figure, we can identify the steps, after which we can analyze time intervals or time lags. The time interval of the onset

of events and the receipt of reports was analyzed as the timeliness of VAERS(Singleton et al., 1999).

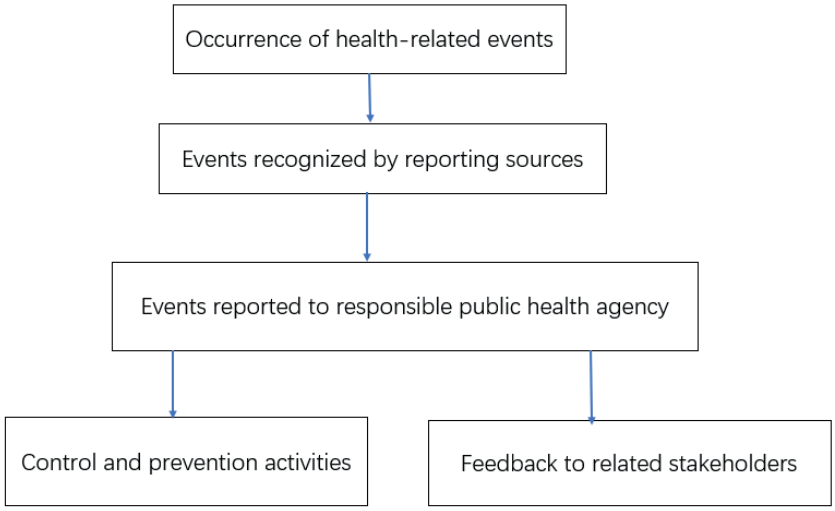

Figure 6 Simplified steps in a surveillance system

The timeliness of a surveillance system can be improved by using electronic data collection and via the Internet(US CDC, 2001; Ward et al., 2005).

Data quality

Data quality reflects the completeness and validity of the data recorded in a public health surveillance system(US CDC, 2001). The completeness of disease surveillance has been evaluated exclusively for infectious diseases(Doyle, Glynn, & Groseclose, 2002) and Acquired Immune Deficiency Syndrome reporting(Klevens et al., 2001). In these evaluations, completeness was calculated as a proportion, dividing the number of cases reported into a surveillance system by the total number of cases identified through other data sources, using active case detection, capture-recapture methods(Doyle et al., 2002), or different secondary data sources(Cronk et al., 2003; A. B. Curtis et al., 2001).

For validity, Leal et al.(Leal & Laupland, 2008) systematically reviewed the validity of electronic surveillance systems, and the sensitivity and specificity of electronic versus conventional surveillance was reported. The evaluation guidelines also recommend that sensitivity and PVP are useful in assessing data quality.

According to the US CDC guidelines, the percentage of "unknown" or "blank" responses to items on surveillance forms is also a more straightforward and easy

measure of data quality. Data of a high quality will have a low percentage of such responses. In the evaluation of the Australian Sentinel Practice Research Network (ASPREN) surveillance for an influenza-like illness, the data quality assessment included issues with data recording (i.e., missing variables like the age and condition categories)(Clothier, Fielding, & Kelly, 2005). The acceptability and representativeness of a public health surveillance system is also related to data quality(US CDC, 2001).

Representativeness

A surveillance system that is representative accurately describes the occurrence of a health-related event over time and its distribution in the population by place and person(US CDC, 2001). Generally, it can be measured by comparing the characteristics of the reported events to another source of data (e.g., a random sample survey)(Declich & Carter, 1994). Some studies have evaluated representativeness by comparing surveillance data to survey data that has been assumed to cover all actual cases(Kang et al., 2012; lin Li & qing Chen, 2009), or by comparing missing data with cases captured by surveillance(Macarthur & Pless, 1999a; Macarthur & Pless, 1999b; Russell & Conroy, 1991).

Representativeness is important for the generalizability of information. It is related to underreporting when it is not uniform or random(Declich & Carter, 1994). Several factors can influence case reporting, for instance, severe illnesses and hospitalizations are more likely to be reported than mild cases, and certain cases tend to have a higher reporting than others in certain health care settings(Declich & Carter, 1994). This is also applicable for AEFI surveillance. Serious events and events occurring within shorter intervals from the time of vaccination tend to be reported more than others(Singleton et al., 1999). For certain vaccines, especially for influenza vaccines, during the vaccination season, there would be a temporary increase in the reporting of AEFIs associated with the influenza vaccine. Without general census data on AEFIs, which serves as the background, combined with the above-mentioned influencing factors, it is difficult to assess the representativeness of AEFI surveillance systems.

Geographic representativeness is also an indicator of data generalizability. Increasing the geographic areas covered by registries or surveillance systems would also increase their representativeness(L. H. Curtis et al., 2009). In the evaluation of the ASPREN surveillance for influenza-like illnesses, the geographic representativeness of GP recruitment was assessed(Clothier et al., 2005; Clothier & Turner, 2006).

Acceptability

Acceptability reflects the willingness of individuals and organizations to participate in a system(US CDC, 2001). To assess acceptability, it is necessary to consider persons with the health-related events as well as those reporting the cases. According to the guidelines, quantitative measures of acceptability include subject or agency participation rates; interview completion rates and question refusal rates; completeness of report forms; facility reporting rates; and timeliness of data reporting.

The percentage of unknown or blank responses to items on surveillance forms, which is a straightforward and easy measure of data quality, could also represent the completeness of report forms. Moreover, the timeliness of data reporting can also be a measure to evaluate the timeliness of a surveillance system.

2.4 Using passive surveillance data to evaluate vaccine safety

Nationwide AEFI passive surveillance is designed to monitor vaccine safety and conduct timely investigations of suspected adverse events to support the appropriate actions(WHO/WPRO, 2013).

2.4.1 VAPP in CNAEFIS

The OPV, which contains live, attenuated poliovirus strain types I, II, and III, has served as the primary tool for eradicating polio worldwide(Minor, 2009; WHO, 2016). Since their introduction, poliovirus vaccines have had a dramatic impact on the incidence of polio in developed countries(Minor, 2009). The OPV was developed in 1959 and its manufacturing began in 1962 in China, as it was felt that an oral vaccine would more closely imitate natural infections due to the similarity in the route of ingestion; thus, it was believed it would potentially interrupt transmission much more effectively(Minor, 2009).

China reported 20,000–43,000 polio cases each year in the early 1960s, making it a major affected area(Minor, 2009). The Chinese NIP began in 1978, and China started to implement the planned immunization schedule in which the OPV was recommended for children in certain age brackets(Zheng et al., 2010). According to the schedule, the recommended ages at which the OPV was to be administered were 2 months, 3 months, 4 months, and 4 years old. In order to eliminate the polio cases, since 1994, the polio vaccine supplementary immunization activity launched every

year targeted children under 4 years old, and the estimated covered more than 800 million children(Liang, 2003). Subsequently, the number of polio cases declined dramatically and, in 2000, WHO's WPRO certified the nation as being polio-free. There have been no reported indigenous wild poliovirus cases in China since 1994(W.-Z. Yu et al., 2014). In 2011, an outbreak of imported wild-type poliovirus occurred in the Xinjiang Uygur Autonomous Region in northwest China. Supplementary immunization activity was launched and five rounds of OPV vaccination were administered to children and adults. The outbreak ended 1.5 months after a laboratory confirmation of the index case(Luo et al., 2013), and China was again certified by WHO as being polio-free(W.-Z. Yu et al., 2014).

Despite the great advantages of the OPV in preventing wild poliovirus, a reversion of the attenuating mutations during OPV replication could lead to an increase in neurovirulence, thus triggering abnormal reactions and even serious cases(Minor, 2009).

In polio eradication environments like China, VAPP, which is the only serious adverse event associated with OPV(WHO, 2016), became a public health problem. In the second half of 2005, parents from different provinces sought medical treatment in Beijing for their children who had developed abnormal limbs(Zuo et al., 2010). The Chinese government established several laws and policies aimed to compensate VAPP patients. As neonatal immunodeficiency is a rare but natural part of infancy, "one in a million" victims cannot be avoided when using OPV.

VAPP is one of the most important adverse effects of the vaccines that are currently in use globally. With the near disappearance of wild-type polio, VAPP has emerged as the greatest cause of paralysis from polioviruses. One of the goals of the Global Polio Eradication Initiative's Polio Endgame Strategic Plan 2013–2018(Global Polio Eradication Initivative, 2012) is the reduction of VAPP. The WHO polio vaccine position paper indicates that in countries where VAPP is a concern, a sequential inactive poliovirus vaccine (IPV)/OPV schedule can be adopted. In response to WHO's planned global action of switching from trivalent OPV (tOPV) to bivalent OPV (bOPV) in April 2016, which was aimed at mitigating VAPP following a pilot study with IPV in 2015, the attenuated poliovirus vaccine has been switched from tOPV to bOPV, and IPV was included as the first polio vaccination dose across China as of May 1, 2016. Consequently, it was expected that VAPP cases would decrease significantly and ultimately disappear. Since VAPP is a serious and confirmed reaction to the live attenuated polio vaccine and recipient VAPP could be captured by CNAEFIS, the analysis of VAPP in CNAEFIS could

give some clue regarding the vaccine safety of the live attenuated polio vaccine used in China.

2.4.2 Fatalities in CNAEFIS

Chinese EPI, which was started in late 2007(Zheng et al., 2010), includes 14 vaccines. As part of an expanded immunization program, about 22 vaccination doses are administered in the first year of life in China(Guo et al., 2013). Recently, concerns have been raised about AEFIs and vaccine safety(Guo et al., 2013). Fatalities that occur after immunization, particularly neonatal or infant deaths, frequently attract media attention and become a cause of public concern. However, vaccinations are common during childhood, and they may not be the direct cause of reported pediatric fatalities.

Generally, parents have their children vaccinated when they are in relatively good health. In cases where infants die shortly after immunization, parents and even health providers may view the vaccine as the cause or at least as a contributory factor to the death(McGarthy et al., 2013). Although vaccines play a vital role in preventing diseases in children, vaccine hesitancy has become an issue not only in high-income counties, such as the US and UK but also in LMICs(W. Yu et al., 2016; Larson et al., 2013). Due to vaccine hesitancy, vaccination coverage may not be high enough to build herd immunity and prevent disease outbreaks among the population (Brown et al., 2012; Casiday, 2006). Experts have placed the reasons for parental refusal to have their children vaccinated into the following four categories: religious beliefs, personal beliefs, philosophical rationales, and safety concerns, with parents expressing a desire for more information from healthcare providers(McKee & Bohannon, 2016). Among these, safety concerns accounted for most parental refusals(McKee & Bohannon, 2016) . The events in December 2013 in Mainland China provide a typical example of how such concerns arise(CFDA & MoH, n.d.). Media reports of 17 infant deaths, including 1 case of anaphylactic shock following HepB vaccination, raised widespread public concern in China(M.-N. Li, Liu, & Zhang, 2014; W. Yu et al., 2016), and HepB vaccinations were suspended during the ensuing investigation. After prudent investigation, China FDA claimed that the babies' deaths were not related to the vaccine. There were also various problems following the vaccine, including severe pneumonia, suffocation, kidney failure, severe diarrhea and congenital heart disease(W. Yu et al., 2016), (M.-N. Li et al., 2014; Yan et al., 2015). However, this "Hepatitis B vaccine event" caused a vaccine

confidence crisis among parents. A telephone survey showed that before the event, 85% of respondents regarded domestic vaccines as safe and that this decreased to just 26.7% during the event(W. Yu et al., 2016). Although confidence increased after the investigation, it remained lower than before the event(W. Yu et al., 2016). The analysis of fatalities reported in CNAEFIS could provide evidence for vaccine safety in China.

2.4.3 JE vaccines safety

Japanese Encephalitis (JE) is a mosquito-borne acute viral infection of the central nervous system caused by a flavivirus(Wang, Li, Liang, & Liang, 2009). JE is the most important cause of vaccine-preventable viral encephalitis in nearly all Asian countries, whether temperate, subtropical, or tropical, and it has expanded to new areas through the importation of infected-mosquito vectors. Currently, an estimated 3 billion people living in 24 countries, mainly in South-East Asia and WPR are considered at risk of JE(WHO, 2015b). The inactivated JE vaccine (JEV-I) was developed in China and has been used since the 1970s, and the live-attenuated vaccine (JEV-L) has been in use since the beginning of the 1990s(Wang et al., 2009). Since 2007, JE vaccines have been included in the EPI in Mainland China(Wang et al., 2009). With the decline in the number of JE cases in China, the public has become more concerned with the adverse events following JE vaccination.

The safety of JE vaccines manufactured in China and abroad has been evaluated in previous clinical and post-marketing studies(Nakayama & Onoda, 2007). The vaccine safety review of JE vaccines by WHO found that they have acceptable safety profiles, and data from multiple studies (including multicenter randomized controlled trials and randomized trials) have shown the same conclusion(WHO, 2015b; D. Liu et al., 2015; Liang et al., 2011).

However, the JE vaccine used in China was mainly produced by domestic manufacturers, and a JEV-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 in the Chinese EPI and, consequently, its large-scale use. Therefore, the JE vaccines was chosen as an example to assess vaccine safety using passive AEFI surveillance data.

2.5 Methods of signal detection using passive surveillance data

2.5.1 Signals

Vaccine pharmacovigilance includes a vaccine safety study conducted during clinical trials and in the post-licensure period(CIOMS & WHO, 2012). One primary aim of passive AEFI surveillance is to identify signals after the vaccine products have been marketed. The rapid detection and evaluation of safety signals is essential to ensure the continued safety of vaccines(CIOMS & WHO, 2012). In fact, a signal was extended from the drug to the vaccine in pharmacovigilance. Dr. Hauben and Dr. Aronson systemically reviewed the definition of a signal in pharmacovigilance(Hauben & Aronson, 2009) and found that WHO, Council for International Organizations of Medical Sciences (CIMOS), and other study groups had slightly different definitions: WHO defined a signal as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented"; CIMOS defined a signal as "a report or reports of an event that may or may not have a causal relationship to one or more drugs; it alerts health professionals and should be explored further"; and the US FDA defines a signal as "a concern about an apparent excess of an adverse event compared to what would be expected." Despite the different definitions, there are two common points: i) the study objective is drug/vaccine-events/diseases pair association; ii) the possible causal relationship needs further investigation(Almenoff et al., 2005).

Before powerful computer technology was available, signal detection solely relied on a case-by-case study(Egberts, 2007). An experienced assessor had to review every single case report in the database, assess the likelihood of whether the event was caused by the drug, and try to detect whether the case report was somehow unusual or strange(Egberts, 2007). However, with the development of computer science and the growing database of surveillance systems, quantitative signal detection became possible, and it is now possible to get a complete picture of all the cases in a database. Dr. Egbert(Egberts, 2007) concludes that the quantitative assessment of signal detection is all about disproportionality, and he enquires, "Is what we observe different from what we expect?"

2.5.2 Denominator-based methods

In passive AEFI surveillance, there are two methods of signal detection(Hauben & Zhou, 2003): denominator-based methods and numerator-based methods. Denominator-based methods detect temporal changes in reporting rates or frequencies by constructing a probability model and a corresponding test statistic to assess the probability that the observed temporal changes reflect random sampling variability(Hauben & Zhou, 2003). In numerator-based methods, no external data sets are needed, and data mining algorithms (DMAs) are used to seek interesting or valuable information within a database(Hauben et al., 2005).

Dr. Hauben (Hauben & Zhou, 2003) concluded that there are several techniques of implementing denominator-based methods for signal detection, such as cumulative sum techniques, time scans, and Poisson methods. In passive surveillance, the application of these methods is difficult, since systems like VAERS rely on voluntary submissions. Thus, the underreporting of events represents an inherent system limitation(Varricchio et al., 2004) along with different resources of vaccination doses (distributed or administered) and unknown background information. All of this makes it difficult to compare the observed to the expected rates and among different settings. Since the existing vaccine safety surveillance systems mostly rely on the passive reporting of events suspected by reporters to be vaccine related(Postila & Kilpi, 2004), different surveillance definitions, reporting requirements, and settings make it difficult to compare different countries(Schumacher, Bourquin, & Heininger, 2010). Any missing denominator data or the use of a different proxy of denominator data also creates a barrier to comparison. For instance, in the US, the net distributed doses were used as denominator data(Zhou et al., 2003), while in Australia(Mahajan et al., 2014), Switzerland(Schumacher et al., 2010), and Denmark(Aagaard, Hansen, & Hansen, 2011), the number of doses administered was used as the denominator data. Another big obstacle is the background rates and lack of control groups(S. B. Black et al., 2009). Overall, there are several limitations in denominator-based methods, but the ongoing analysis of AEFI surveillance data could generate the baseline and provide useful information on vaccine safety. In CNAEFIS, the annual AEFI surveillance data has been analyzed since 2005, and the administered vaccine doses have been used to estimate the incidence rates of AEFIs(D. Liu, et al., 2007; Wu et al., 2013; Wu et al., 2012; Ye, et al., 2015). However, few signals were detected during these years, given the lack of control groups or background rates.

2.5.3 Disproportionality analysis

A commonly used numerator-based technique for signal detection is disproportionality analysis (DPAs or DMA)(Johnson et al., 2012). There are several review papers on different measures of DPAs(Harpaz et al., 2012; Hauben et al., 2005; Hauben & Zhou, 2003; Iskander et al., 2006; Johnson et al., 2012; Suling & Pigeot, 2012), and the commonly used statistical measures are Proportional Reporting Ratios (PRR), Reporting Odds Ratios (ROR), Bayesian Confidence Propagation Neural Network (BCPNN), and the Gamma-Poisson Shrinker (GPS) algorithm of Empirical Bayes Screening (EBS)(Hauben & Zhou, 2003). The theory behind those four methods is similar: use a frequency analysis of 2 × 2 contingency tables (Table 4) to estimate surrogate measures of statistical association between specific drug-event combinations mentioned in spontaneous reports(Harpaz et al., 2012). They intend to quantify the degree to which a drug-event combination co-occurs "disproportionally" compared to what would be expected if there were no association(Harpaz et al., 2012). The signals detected by DPAs were mainly dependent on statistical calculations, devoid of any clinical context; therefore, instead of signals or safety signals, "signals of disproportionate reporting" (SDR) were used(EMA, 2006; Hauben & Reich, 2005).

Table 4 2 × 2 Contingency table* used in SRS-based DPA (et al Rave Harpaz, William DuMouchel, Nigam H. Shah, 2012)

	With target adverse events	**Without target adverse events**	
With target drugs or vaccines	A	B	N=A+B
Without target drugs and vaccines	C	D	C+D
	M=A+C	B+D	T=A+B+C+D

*Reports are classified according to the presence/absence of specific adverse event combinations. Each cell contains the report counts.

In passive surveillance, based on the 2 × 2 tables above (Table 4), different algorithms (i.e., PRR, ROR, BCPNN, and GPS) could be used to generate SDRs. Since there is no "gold standard" for algorithms, different methods have been used in different passive systems(Hauben et al., 2005; Suling & Pigeot, 2012) (Table 5).

Table 5 Common DPAs and their related result measures

DPAs	Measure of association (based on Table 4)
PRR	PRR = $\frac{a/(a+b)}{c/(c+d)}$
ROR	ROR = $\frac{a/c}{b/d}$
BCPNN	Information Component (IC) = $log_2 RRR$ RRR refers to Relatively Reporting Ratio and RRR = $\frac{P_{(AE\|drug)}}{P_{(AE)}}$
GPS	Empirical Bayesian Geometric Mean (EBGM) EBGM = $e^{E(log(\lambda))}$ The observed AE may be assumed as a realization of a Poisson-distributed random variable, and the RRR is defined as λ = $\frac{\mu}{E}$ and $\hat{E} = \frac{c \times b}{d}$

The PRR were used in the ADR online information tracking (ADROIT) database, also known as the YCS of the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK(Evans, Waller, & Davis, 2001) and the EudraVigilance data of EMA(EMA, 2006). The BCPNN (Bate et al., 1998; Orre et al., 2000)and ROR(Bruin et al., 2005) were used in the ADR monitoring database of UMC WHO. The GPS and PRR were also used in the US ADR surveillance system(O'Neill & Szarfman, 2001) and VAERS(Iskander et al., 2006). Although some publications use the new names of DPAs, they are all in fact the same method, for instance, "Screened PRR" (sPRR) is only PRR with certain screening SDR criteria. Another example: "EBGM" and "5th percentile of EBGM" (EB05) are both GPS-type DPAs(Banks et al., 2005). Usually, pharmacovigilance researchers classify the four algorithms into two categories: i) simple, classical, or frequentist, such as PRR and ROR; ii) Bayesian methods, such as BCPNN and GPS(Hauben et al., 2005; Stephenson & Hauben, 2007). Apart from these four algorithms, there are other DPAs that have also been used, such as the PROFILE analysis (i.e., Probability Filtering), which was also based on a 2 × 2 contingency table, using Fisher's exact one-tailed right to calculate association, and mainly in the Australian ADR database(Burcell & Barty, 2002).

Not only are different algorithms used, the threshold criteria for screening SDRs also differ. In EMA's EudraVigilance data analysis system(EMA, 2006), two criteria apply to define an SDR: i) when the PRR is displayed with its 95% confidence interval (CI)—the lower bound of the 95% CI≥1 and the number of individual cases (i.e., a in Table 5) ≥3; ii) when the PRR is displayed with the χ2 statistic—PRR>2, χ2>4 and a≥3. In US VAERS, EB05 >2 was used to detect SDRs in some studies(Moro et al., 2015). Dr. Deshpande et al.(Deshpande, Gogolak, & Smith, 2010) found more than 100 English language articles, editorials, and letters on the topic of data mining of adverse event databases to identify potential safety signals of

pharmacological products, including drugs, biologicals, and vaccines, and different thresholds were used among those algorithms (Table 6).

Table 6 Threshold criteria used in different algorithms in pharmacovigilance literature (Deshpande et al., 2010)

DPAs	Threshold criteria used in the literature
PRR	PRR>1;
	PRR>3,$\chi 2 \geq 4$,$a \geq 4$;
	Lower than 95% CI for PRR >1, $a \geq 2$.
ROR	ROR>1;Lower than 95% CI for ROR >1;
	Lower than 95% CI for ROR >2, a>2.
BCPNN	IC >0;
	IC – 2 SD >0.
GPS/MPGS	5th percentile of EBGM (EB05)≥ 2,a>0;
	EB05>2, a >0;
	EBGM/2>0, a>0.

Since there was no "gold standard" for choosing algorithms and their related thresholds, several researchers have compared these methods and thresholds. There has been disagreement on ROR and PRR(Rothman et al., 2004; Waller, 2004) and several studies on the comparison of these DPAs(Almenoff et al., 2006; Berlin et al., 2012; Harvey, Turville, & Barty, 2004; Kubota, Koide, & Hirai, 2004; C. Li et al., 2008; Puijenbroek et al., 2002). Van Puijenbroek demonstrated that when there are ≥ 4 cases (i.e., $a \geq 4$), both SDRs detected by Bayesian and non-Bayesian methods are similar(Hauben et al., 2005; Puijenbroek et al., 2002). These algorithms have both advantages and disadvantages, as Dr. Hauben concluded in his review articles (Table 7)(Hauben et al., 2005).

Table 7 Characteristics of common algorithms based on DPAs (Hauben et al., 2005)

	"Simple"/frequentist	**Bayesian**
Algorithms	PRR and ROR	BCPNN and GPS/MGPS
Advantages	More sensitive	More specific
	Clear, easy to use and understand	Numerous data mining settings and configurations maximize exploratory capacity
	Identifies virtually all SDRs identified by Bayesian methods	
	Natural metric for logistic regression analysis	Configured to perform higher order analysis (e. g., drug-drug interactions, complex medical syndromes)
Disadvantages	Lower specificity leading to overabundance of SDRs that may require additional triage criteria for practical implementation	Lower sensitivity
		Numerous data mining settings and configurations raise issues of confirmation bias and multiple comparisons

DPAs for SDR detection were not intended to be used in isolation(Almenoff et al., 2005). They have their pitfalls, which should be considered when they are used for signal detection. According to Dr. Stephenson and Dr. Hauben, the following points should be considered when using these methods for SDR detection: i) evidence for the predictive value of current data mining methods is lacking; ii) limitation of passive surveillance data, such as underreporting and poor data quality, will have an impact on the usefulness of data mining; iii) the sampling framework for passive surveillance is problematic; iv) there are intrinsic methodological limitations in data mining, such as it being susceptible to confounding; v) it is important to take a holistic approach to the interpretation of data mining methods and signal detection(Stephenson & Hauben, 2007). Therefore, currently, in post-marketing surveillance systems, the traditional methods of signal detection, including literature searching, case-by-case analysis, and denominator-based analysis of incidence rates, should be integrated with the newly computer-enhanced DPAs(Almenoff et al., 2005). Though the DPA methods were first used in SDR detection in drug pharmacovigilance, they were gradually introduced into vaccine pharmacovigilance as well(Almenoff et al., 2005). In US VAERS, DPAs were already introduced for signal detection(Banks et al., 2005; Leroy et al., 2012b; Moro et al., 2015; Manette T Niu, Erwin, & Braun, 2001; Slade et al., 2009). We have applied them to the CNAEFIS data as complementary techniques to assess vaccine safety.

3 OBJECTIVES OF THE STUDY

The overall aim of this thesis was to a) describe and evaluate the performance of the national adverse events following the immunization surveillance system in China during 2008–2015, to identify parts of vaccine safety concerns and ways to strengthen vaccine safety surveillance in China; b) to assess specific issues associated with vaccine safety by using this surveillance data.

Specific objectives:

I. To describe the characteristics and evaluate the performance of the National Adverse Events Following Immunization (AEFI) surveillance system in China.

1.1 To provide an overview of the passive surveillance system for AEFIs in China (Study I)

1.2 To summarize routine analyses of data collected in the Chinese Online National AEFI Information System (CNAEFIS), 2008–2013 (Supplemental published reports 1st-6th)

1.3 To assess the performance attributes of CNAEFIS according to standard guidelines for evaluating public health surveillance systems.

II. To assess specific issues associated with vaccine safety by using the following Chinese national surveillance data:

2.1 Case characteristics and occurrence of cases of recipient vaccine-associated paralytic poliomyelitis (VAPP) during 2010–2015 (Study II)

2.2 Causality assessment of reported associations of fatalities with vaccinations during 2010–2015. (Study III)

2.3 Monitoring the post-licensure vaccine safety of JE vaccines. (Study IV)

4 MATERIALS AND METHODS

4.1 Study settings

Mainland China has 32 provinces (including Xinjiang Corps), with an estimated population of 1.3 billion and more than 16 million births every year. China initiated the National EPI in 1978. Currently, there are about 14 vaccines targeting 15 VPDs in the NIP. The vaccines included are funded by the central government and administered to target children free of charge. There are still vaccines used outside the national immunization schedule in the private market, produced by manufacturers based on market demand, and these can be purchased by consumers on a voluntary basis. All vaccines are to be administered in vaccination clinics approved by the local government and supervised by the local CDC. The nationwide AEFI surveillance covers all vaccines marketed in the mainland of China.

4.2 Data resources

All AEFI data were extracted from the online CNAEFIS database.

AEFI surveillance covers all vaccines marketed in Mainland China, with the scope of reporting shown in Table 8. Healthcare facilities, vaccination clinics, CDCs at all four administrative levels (i.e. National-, provincial-, prefecture-, and county- level), ADR monitoring agencies, and vaccine manufacturers' executive staff are all responsible reporting units and reporters of AEFIs. The reporting of AEFIs is implemented in line with the principle of localized management. The public or the guardians (parents) can notify any of these authorized reporters about an AEFI. Cases are gathered by local, county-level CDCs, which are responsible for completing AEFI Case Reporting Cards (Appendix 1) and submitting the data to CNAEFIS. Duplicate reports are identified and de-duplicated centrally in CNAEFIS. Once the case information is entered, it can be viewed by staff at all administrative levels of the CDCs and ADRs.

Table 8 Scope of reporting* (Paper I)

AEFI onset time since vaccination	Specific AEFI
Within 24 hours	Anaphylactic shock, allergic reactions without shock (hives, rash, laryngeal edema, etc.), toxic shock syndrome, syncope, hysteria
Within 5 days	Fever (axillary temperature ≥ 38.6°C), angioedema, systemic purulent infection (toxemia, septicemia, sepsis), redness and swelling at the injection site (diameter > 2.5cm), induration (diameter > 2.5cm), localized purulent infection (localized abscess, lymphangitis, lymphadenitis, or cellulitis)
Within 15 days	Measles-like or scarlet-fever-like rash, Henoch Schonlein purpura, localized allergic necrotic reaction (Arthus reaction), febrile convulsion, epilepsy, polyneuritis, encephalopathy, encephalitis, and meningitis
Within 6 weeks	Thrombocytopenic purpura, Guillain-Barré Syndrome, vaccine-associated paralytic poliomyelitis
Within 3 months	Brachial neuritis, sterile abscess at the injection site
1–12 months after BCG vaccination	Lymphadenitis or lymphangitis, osteomyelitis, systemic disseminated BCG infection
Unspecified time frame	Other serious AEFIs suspected to be related to vaccination

* From National AEFI surveillance guideline (2010)

All AEFIs are to be investigated, except for common adverse reactions which have a clear diagnosis (e.g., fever, redness and swelling at the injection site, or induration). County CDCs start their investigation by collecting the relevant data and completing an AEFI Case Investigation Form (Appendix 2), which is subsequently entered CNAEFIS. For deaths, serious AEFIs, AEFI clusters, and AEFIs of significant public concern that are suspected to be related to immunization, upon receiving the CNAEFIS reports, the prefectural or provincial CDCs must immediately organize an AEFI expert panel for investigation.

As a key part of an investigation, county CDCs organize a group of relevant experts in clinical medicine, epidemiology, laboratory practices, pharmacy, vaccinology, vaccine regulation, and other fields relevant to the case. This group of experts is responsible for making a diagnosis and assessing the causality of the AEFI. For deaths, serious AEFIs, AEFI clusters, and AEFIs of significant public concern, the higher-level prefectural or provincial CDCs organize an AEFI Investigation and Diagnosis Expert Panel to conduct a diagnostic and causality assessment. The flows of reporting and investigation are shown diagrammatically in Figure 7.

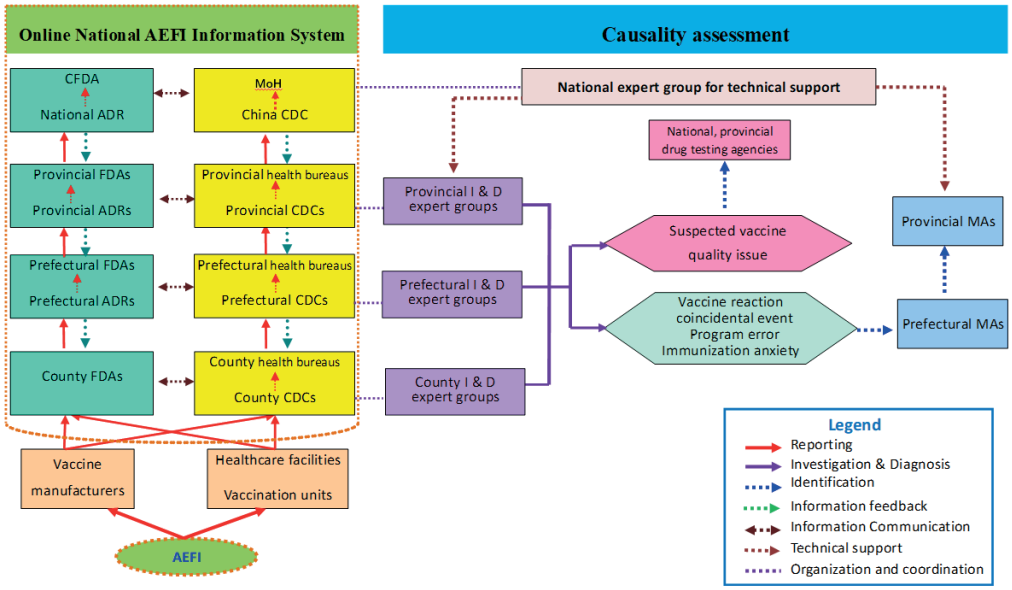

Figure 7 AEFI reporting, investigation, and causality assessment flow* (Paper I)

*I&D: investigation and Diagnosis

4.3 Case definitions

Case definition of AEFI

In CNAEFIS, an AEFI case is defined as a reaction or an event occurring after vaccine administration that is suspected to be related to the vaccination.

Serious AEFIs are defined as rare adverse reactions, including death and long-term disabilities. Those diseases include allergic shock, allergic laryngeal edema, allergic purpura, thrombocytopenic purpura, localized allergic necrosis reaction (Arthus reaction), febrile convulsion, epilepsy, brachial plexus neuritis, polyneuritis, Guillain-Barré syndrome (GBS), encephalopathy, encephalitis and meningitis, vaccine-related paralytic polio (VAPP), BCG osteomyelitis, systemic disseminated BCG infection, etc.

Following investigation and causality assessment, AEFI cases are classified into one of five categories (Table 9). AEFIs are classified as serious if they are any of the following: death, life-threatening condition, permanent or significant disability, or damage to organs or bodily functions. Serious AEFIs 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-Barré Syndrome, encephalopathy, encephalitis and meningitis, VAPP, BCG osteomyelitis, systemic disseminated BCG infection, syncope, toxic shock syndrome, and systemic purulent infection.

Table 9 Cause-specific classification of AEFIs (Paper I)

Category	Definition
vaccine reaction following immunization	Unexpected harmful reactions or reactions unrelated to the expected purpose of the vaccination that occur after standard vaccination with a vaccine product, including common adverse reactions and rare adverse reactions. Common adverse reactions or common vaccine reactions are reactions caused by the inherent character of the vaccine after vaccination and that only impair body functions transiently. They mainly include fever and localized redness and swelling that may be accompanied by discomfort, fatigue, poor appetite, tiredness, etc. Rare adverse reactions or rare vaccine reactions are drug adverse reactions occurring during the process of or after a standard vaccination with a qualified vaccine that has caused damage to the tissues or organs or damage to the functioning of the vaccine recipient when all parties involved have made no medical errors. Included are reactions caused by the inherent character of the vaccine that might be related to the strain, purity, production technology, or added substances of the vaccine such as antiseptics, stabilizers, and adjuvants.
Vaccine quality event	Damage to tissues or organs and damage to functions of the vaccinated person due to substandard quality of the vaccine. Substandard quality refers to problems with the strain and purity of the vaccine, production technology, or added substances in the vaccine (excipients), exogenous factors. Also, if inspection and control of the vaccine were not consistent with national protocols or standards for vaccine production.
Program error	Damage to tissues or organs and damage to functions of the vaccine recipient due to violation of standard operational practices, vaccination procedures, guidelines for using the vaccine.

Category	Definition
Coincidental event	The vaccine recipient was in the incubation stage or preclinical stage of a certain condition, and the onset of the disease coincides with the vaccination by chance. Coincidental events are not caused by the inherent character of the vaccine.
Psychogenic reaction or injection reaction	Individual reactions or reactions of groups of individuals that occur during or after a vaccination due to the psychological responses of the vaccine recipients. Psychogenic reactions are not caused by the inherent character of the vaccine.

Vaccine schedules of JE vaccines in China

As JEV-L was the first Chinese produced vaccine product to be prequalified by WHO, and JEV-L and JEV-I were used simultaneously in the country, this vaccine was chosen to be studied. In Mainland China, both JEV-I and JEV-L have been included in the NIP since 2007. The JEV-L has a two-dose schedule and is administered at ages 8 months and 24 months, with an interval of at least 3 months. The JEV-I has a four-dose schedule and is administered as follows: 2 doses at 8 months with at least 7–10 days intervals, and subsequent doses at ages 2 years and 6 years.

Case definition of VAPP

In 2008, the MoH of the People's Republic of China issued two regulations on the diagnosis and verification of VAPP: "Instruction advice on diagnosis and treatment of vaccine associated paralytic poliomyelitis" (Wei Ban Yi Fa [2008] No. 17), and "Instruction advice on verification of VAPP and handling of remaining problems" (Wei Ban Fa [2008] No. 40). These regulations describe two types of VAPP: recipient and contact. Although contact VAPP is not included in CNAEFIS, recipient VAPP is defined as a case of i) fever occurring 4–35 days after vaccination, acute flaccid paralysis (AFP) occurring 6–40 days after vaccination, and a clinical diagnosis compatible with paralytic poliomyelitis; or ii) the isolation of vaccine-related poliovirus from stool samples, which are considered as supplementary conditions. Like other AEFI cases, VAPP is also now investigated by a panel of experts and receives a causality assessment based on the clinical and epidemiological characteristics of each case.

Case definition of AEFI-associated deaths

Included in this study are deaths reported in CNAEFIS that are suspected to be related to vaccinations. Neonatal deaths were cases who died within 28 days after birth.

4.4 Study designs

To evaluate the system performance of CNAEFIS and vaccine safety in China, we conducted descriptive epidemiological studies. In addition, we also conducted a signal detection for JE vaccines using both denominator-based methods and DPA.

4.4.1 Descriptive analysis

To study the system performance and safety of JE vaccines, we analyzed the national AEFI database from 2008–2013. For VAPP and reported in CNAEFIS, we conducted descriptive analyses on database from 2010–2015. Deaths which were suspected to be related to the vaccinations, with dates of death from 1st January 2010 to 31st December 2015, were extracted from CNAEFIS and included in the study.

In the descriptive analysis of the national AEFI database, the variables used included demographic variables (i.e., year of onset of AEFI, district, age, and gender), seriousness of AEFIs, classification (i.e., causality assessment), vaccine, and outcomes of AEFIs (Table 10).

Table 10 Variables of the quantitative analysis

Variables	Definitions or category
Year	The onset year of AEFIs in the database
Gender	Female, Male, Unknown
Age groups	≤1 year; 2–6 years; ≥7 years
Districts	Eastern area includes Beijing, Tianjin, Liaoning, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong and Guangdong. Middle area includes Hebei, Shanxi, Jilin, Heilongjiang, Anhui, Jiangxi, Henan, Hubei, Hunan and Hainan. Western area includes Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Tibet, Shaanxi, Gansu, Qinghai, Ningxia, Xinjiang, and Xinjiang Corps.
Seriousness	According to the national guidelines, since 2011, AEFI cases are classified into serious and non-serious.
Classification	After investigation and causality assessment by CDCs and expert panel of causality assessment, AEFI cases are classified into five groups: Vaccine reactions (includes common and rare vaccine reactions); Vaccine quality event; Program error; Coincidental event; Psychogenic reaction or injection reaction.
Vaccine	In every AEFI case, the maximum number of suspected vaccines is three; however, in this analysis, the first and most suspected vaccine will be included.
Outcome of AEFI cases	The outcomes of AEFI cases are classified as recovered or bettered, death, sequela, unknown.

In addition, for VAPP, we also analyzed the OPV vaccination history and serotype of the vaccine strains of each case. For AEFI-associated deaths, we also included other variables such as time interval from vaccination to onset of symptoms and concurrent vaccines administered.

Since there are two types of JE vaccines used in China, for its safety assessment, we analyzed AEFI reports submitted from 2008–2013 for subjects vaccinated with JEV-L or JEV-I. In CNAEFIS, a maximum of three suspected vaccines can be reported at a 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.

4.4.2 Performance attributes

According to the literature review on the system attributes of surveillance systems, several attributes could be analyzed using only the AEFIs database in CNAEFIS and no external information. Since we did not have cost information on establishing and maintaining this surveillance system, the utility and cost evaluation of this surveillance was not included in this analysis. These attributes could reflect the following indicators or analyses:

Sensitivity & PVP

Reporting sensitivity is calculated as the proportion of events in a specific population that are actually reported. PVP is the proportion of reported cases that actually have the health-related event under surveillance. The calculation of sensitivity and PVP can be seen in Table 11.

Table 11 Calculation of sensitivity and PVP in CNAEFIS

Detected by AEFI surveillance	Condition present		
	Yes	No	
Yes	True positive A	False positive B	A + B
No	False negative C	True negative D	C + D
	A + C	B + D	Total

Sensitivity = Number of vaccine reactions (after causality assessment) (A) / Number of Expected Reports (A + C) *100%

PVP = Number of vaccine reactions (after causality assessment) (A)/Number of all AEFIs detected by CNAEFIS (A + B) *100%

Nine pairs of vaccine-diseases events were selected: BCG-Suppurative lymphadenitis; BCG-Disseminated BCG infections; HepB-Anaphylaxis; OPV-VAPP; measles containing vaccines (MCV)-Febrile seizures; MCV-Thrombocytopenia; Varicella live attenuated Vaccine (VarV)-Febrile seizures; seasonal influenza inactive Vaccine (InfV)-Guillain-Barré Syndrome (GBS); InfV-Anaphylaxis.

The number of vaccine reactions (A) and total number of AEFIs detected by CNAEFIS (A + B) were extracted from the CNAEFIS database. The number of expected reports (A + C) were estimated by calculating incidence rate of events in the literature × administered doses of certain vaccines.

In China, BCG, HepB, OPV, and parts of MCV, which includes MV, measles-mumps attenuated live vaccine (MM), measles-rubella combined vaccine (MR), and MMR belong to Group I, which is covered by the government, which means parents can freely and easily give their children these vaccines. VarV and InfV were common vaccines in Group II, which is not free, and parents therefore have to pay for these vaccinations. Since administration doses of vaccines in Group II were not collect before 2010, we only included data from 2010–2013 for MCV, VarV, and InfV. Incidence rates for selected vaccine reactions following vaccination were estimated based on a review of the WHO guidelines: i) Immunization Safety Surveillance—Guidelines for Immunization Program Managers on the Surveillance of Adverse Events Following Immunization (Second Edition)(WHO/WPRO, 2013); and ii) Supplementary Information on Vaccine Safety: Part 2—Background Rates of Adverse Events following Immunization(WHO, 2000).

Timeliness

The variables were used, and the time intervals were calculated according to the flowchart. Table 12 presents the definitions of the different variables.

Table 12 Definition of different time variable in CNAEFIS

Variables	Definition
Onset date	The onset date of the disease or first symptom will be enquired about when AEFI patients contact the responsible nurses or physicians.
Reporting date	The date of the AEFI patients or guardian reporting the case to the responsible nurses or physicians.
Investigation date	The date when investigation started, if the cases needed to be investigated by the CDCs.

The time interval analysis includes the reporting time interval and the investigation time interval.

Reporting time interval = Reporting date – Onset date;

Investigate time interval = Investigate date – Reporting date.

Time lag: If the time interval was more than 2 days, the case will be identified as a time lag case.

The range and median days of time interval will be calculated, and the proportion of time lag will be analyzed.

Proportion of unknowns or errors in the variables

The variables and criteria of errors or unknowns are displayed in Table 13. The proportion of errors or unknown cases was analyzed.

Table 13 Indicators in the analysis and criteria of unknowns or errors

Indicators	Related key variables	Criteria of unknowns or errors
Age	Vaccination date; Birth date	If the age is unknown (either vaccination date or onset date is missing), or >120 years old, or <0 year, the case will be marked as an error case.
Time interval between vaccination date and onset date	Vaccination date; Onset date	Time interval between vaccination and onset = Onset data – vaccination date If this time interval < 0, the case will be marked as an error case.
Vaccine dose	Vaccine dose (the first suspected vaccine)	If the vaccine dose >30, the case will be marked as an error case.
Classification after causality assessment	Classification	If the classification of causality assessment is unknown, the case will be marked as an error case.
Outcome	Outcome	If the outcome of the case was unknown, the case will be marked as an error case.

Representativeness

At least one AEFI is reported into the CNAEFIS within one year by county, this county will be the county reported cases. The proportion of reported cases in 2008–2013 will be considered as geographic representativeness. The 32 provinces (including Xinjiang Corps) will be divided into three categories according to their location: i) Eastern (including Beijing, Tianjin, Liaoning, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong, and Guangdong); ii) Middle (including Hebei, Shanxi, Jilin, Heilongjiang, Anhui, Jiangxi, Henan, Hubei, Hunan, and Hainan); iii) Western

(including Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Tibet, Shaanxi, Gansu, Qinghai, Ningxia, Xinjiang, and Xinjiang Corps).

4.4.3 Denominators for incidence estimation

Denominators for performance evaluation

According to the WHO GACVS(WHO, 2015a), the ratio of AEFI reports per 100,000 surviving infants per year is used as a general AEFI indicator to assess the progress in the development of AEFI surveillance systems. The surviving infants per year were calculated by total population × birth rate × (1-infant mortality rates). The total population, birth rate and infant mortality rates were downloaded from the website of Chinese National Bureau of Statistics.

Denominators for risk estimation

Vaccination doctors or nurses collect information on vaccination doses and send monthly reports to the national CDCs. The CDCs then report the data to the municipal CDCs who in turn report to provincial CDCs. China CDC collects administered vaccination data from all provincial CDCs(Zuo et al., 2010; Landaverde et al., 2014). Before 2010, only doses of vaccines provided by the government for free were reported. Since 2010, however, the vaccination information system has been collecting 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.

For VAPP risk calculations, two methods were used(Platt, Estivariz, & Sutter, 2014): VAPP per million administered OPV doses, and VAPP per million births. The risk of recipient VAPP per administered OPV doses was calculated using the number of recipients VAPP cases reported during the study period divided by the total number of OPV doses administered during the same period. The OPV-administered doses were collected from a Chinese immunization information system, which collects immunization doses of all vaccines in the national immunization schedules, including OPV. However, the immunization doses of OPV in supplementary immunization activities launched at the provincial level are not collected in this system. VAPP per million births is calculated using the number of recipients VAPP cases divided by the number of estimated births during the same period. The estimated births are calculated by multiplying the total population by the birth rate. Both total population and birth rate were secured from the website of Chinese National Bureau of Statistics (http://data.stats.gov.cn/easyquary.htm?cn=C01,

accessed: 2016.10.15). The data from 2010 were census data, while data from other years were from annual sampling surveys.

We used the following denominators to estimate the risk of AEFI-associated deaths: 1) administered doses collected from vaccination clinics during the study period, 2) population data from the National Bureau of Statistics of the People's Republic of China, and 3) neonatal death rates after vaccination. For denominator 1 and 2, the numerator was AEFI-associated deaths reported to CNAEFIS during the same period. The rates were calculated per million administered vaccination doses or per million population. For denominator 3, we used administered doses for first dose of Hepatitis B vaccines (HepB) which administered within 24h after birth and vaccination coverage to estimate the number of live births. The numerator was cases who died within 28 days after birth.

4.4.4 Disproportionality analysis of JE vaccines

For the detection of SDRs, we used PRR, BCPNN, and GPS. The threshold of PRR was LB95 (PRR) ≥1 & a >3; for BCPNN it was the lower limit of 95% CI of IC >1 & a>3; for GPS it was EB05>2 & n>3.

Since DPAs require pairs consisting of a vaccine and a diagnosis, we excluded cases without enough clinical diagnoses. For cases diagnosed as common and minor adverse reactions, with mixed symptoms of fever, local redness, local swelling, and other minor local or systematic symptoms, we used the common reaction as one diagnosis. We also excluded cases of concurrent vaccines.

4.5 Statistical analysis

All calculations were performed using R software, version i386 3.2.3, and the epitools package was used to calculate CIs. 95% CIs were obtained using Wilson's formula, which approximates the exact method for Poisson rates (study II, III and IV). With the package PhVID, SDRs were calculated by R (version i386 3.0.3; accessed: http://www.r-project.org/).

4.6 Ethical considerations

The study protocol was reviewed and approved by the China CDC. Informed consent is routinely obtained from all vaccine recipients in China. When vaccine recipients visit vaccination clinics, nurses will do a general health screening and provide an informed consent to the individual or caregiver before vaccine administration. Like VAERS in US, CNAEFIS is considered part of a public health activity, and MoH and CDC are public health authorities collecting this data, thus informed consent was not required in case of the passive reporting of AEFIs. The identities of all individuals and establishments in CNAEFIS were kept confidential.

5 RESULTS

5.1 Overview of CNAEFIS

Since the establishment of CNAEFIS, AEFI data have been used extensively by the Chinese national vaccine regulatory authorities (primarily, CFDA and MOH) to study the safety of vaccines used in China. For example, using AEFI data from CNAEFIS, NIP and ADR analyzed safety data for the novel 2009 A(H1N1) influenza vaccine and the JEV-L vaccine, both of which were manufactured in China. An important purpose of passive AEFI surveillance is to detect emerging vaccine safety signals. With the development of CNAEFIS, NIP scientists detected an increased incidence of anaphylactic shock after the administering of a manufacturer's HepA live attenuated vaccine in 2011 and 2012 (unpublished data). Although there was not enough evidence to show that this vaccine did cause an increased incidence of anaphylaxis shock, following discussions between the CFDA and the manufacturer, the manufacturer decided to withdraw its product from the market pending further investigation.

The identification of vaccination medical practice errors and related adverse reactions is of great importance, because these errors are preventable and have the potential to derail the benefits of the immunization program. Between 2008 and 2013, about 1% of AEFI cases in CNAEFIS were identified as program errors, primarily related to the MMR and BCG vaccinations.

5.1.1 Descriptive analysis of CNAEFIS database, 2008–2013

5.1.1.1 Reporting over time

From 2008 and 2013, CNAEFIS received 439,693 AEFIs reports, with an average of 457 reports per 100,000 surviving infants per year. The number of AEFIs has increased by more than 30% every year since 2009. The AEFI general program indicator—the ratio of AEFIs per 100,000 surviving infants per year— increased about six-fold from 2008–2013 (Figure 8).

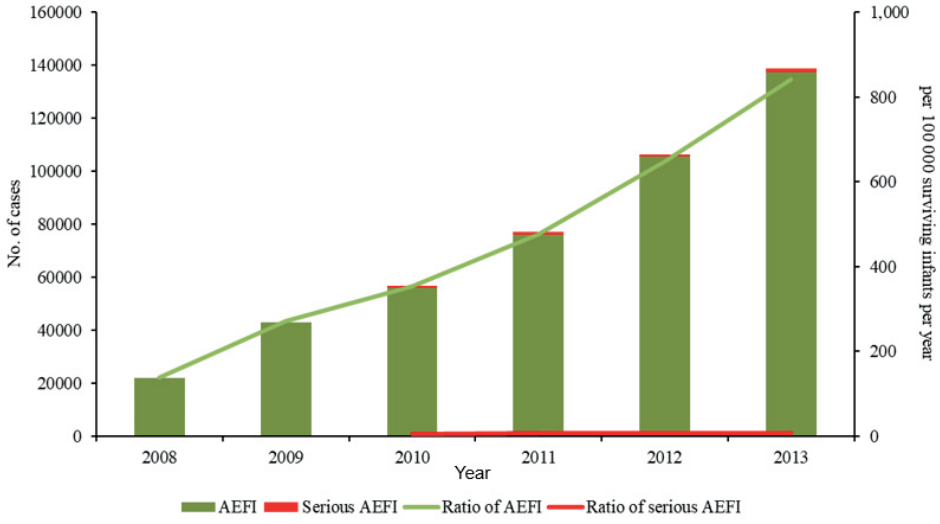

Figure 8 AEFI/ serious AEFI and ratio of AEFIs/serious AEFI per 100,000 surviving infants per year, 2008–2013

Since 2010, AEFI cases have been divided into serious and non-serious. An average of 973 (range of 892–1152) AEFIs were identified as serious per year during 2011–2013, with no significant difference among the annual ratios of serious AEFIs per 100,000 surviving infants ($\chi 2 = 0.2751$; $P = 0.8715$).

5.1.1.2 Age and gender distribution

Since most immunizations are administrated to infants and young children, more than 60% of AEFIs were reported among ≤1-year-olds. Age distribution by year was similar, except in 2009 when the A(H1N1) influenza vaccination campaign also targeted adults. The proportion of AEFIs among ≥7-year-old was higher than other years (Figure 9). The ratio of male to female was 1.4:1 (range 1.4:1–1.3:1).

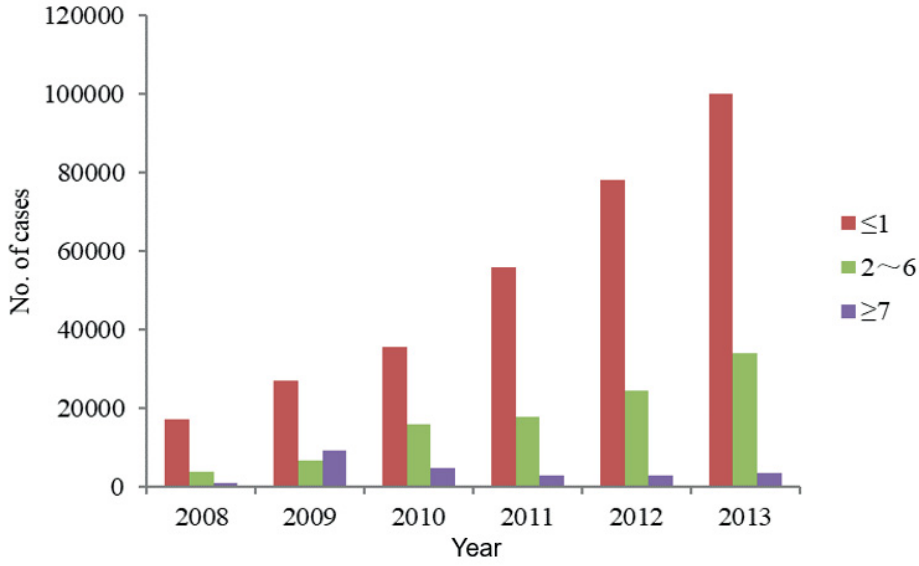

Figure 9 AEFIs by age group, 2008–2013

5.1.1.3 Vaccine distribution

Due to the Chinese national immunization schedule and total of two to four doses of some vaccines, the most frequent AEFI were reported after DTP (including Diphtheria, Tetanus, and Acellular Pertussis combined vaccine [DTaP] and DTwP) vaccination. Routine MCV immunization schedule is 2 doses for children. However, in September 2010, China launched a national MCV SIA and vaccinated more than 100 million children during the 10-day campaign. Also, with the development of the measles elimination program in China, MCV SIAs were conducted at the subnational levels from 2011–2013. These events led to MCV being listed on the vaccine with second most frequent AEFI reports (Figure 10).

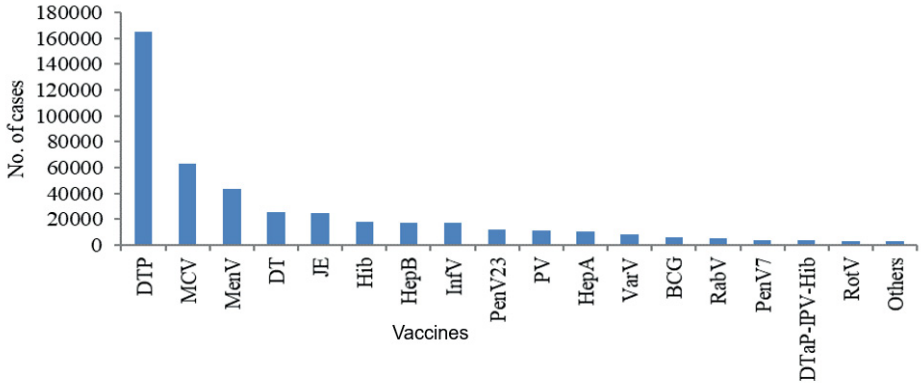

Figure 10 AEFIs by vaccine*, 2008–2013

**DTP: Diphtheria Tetanus and Pertussis Combined Vaccine; MCV: Measles Containing Vaccine; MenV: Meningococcal Vaccine; DT: Diphtheria and Tetanus combined vaccine; JE: Japanese Encephalitis vaccine; Hib: Haemophilus Influenza Type B Polysaccharide Conjugate Vaccine; HepB: Hepatitis B vaccine; InfV: Influenza Vaccine (including 2009 A(H1N1) influenza vaccine); PenV23: 23-valent Pneumococcal Polysaccharide Vaccine; PV: Poliomyelitis Vaccine; HepA: Hepatitis A vaccine; VarV: Varicella Vaccine; BCG: Bacilli Calmette-Guérin Vaccine; RabV: Rabies Vaccine for human use; RotV: Rotavirus Vaccine.*

5.1.1.4 Classification of causality assessment distribution

Most of the AEFIs reported were common vaccine reactions, such as fever, local redness, and local duration (Figure 11). An average of 8.8% (range: 6.5%–13.5%) of AEFIs were classified as rare vaccine reactions following an investigation and a causality assessment. No vaccine quality events were reported.

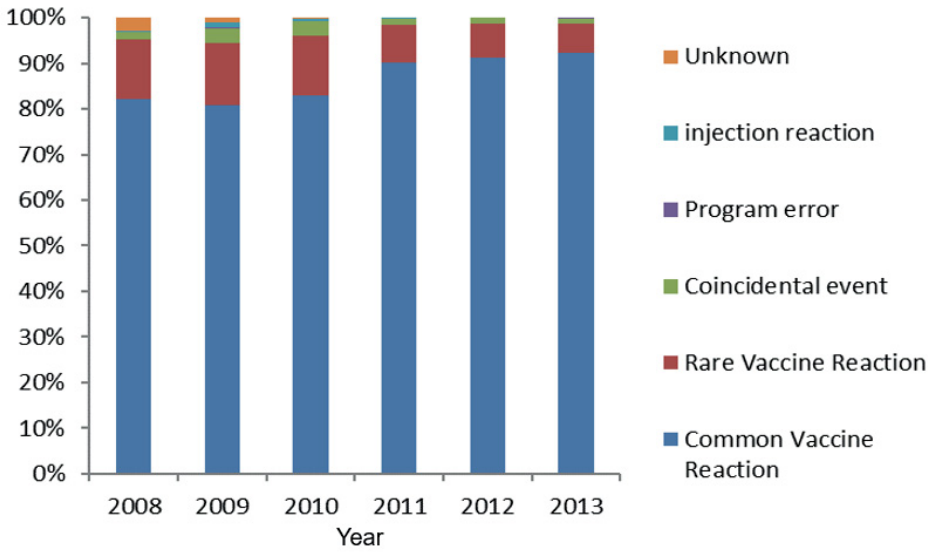

Figure 11 AEFIs by classification, 2008–2013

A total of 155 program error-related AEFIs were reported over 6 years from 2008–2013. In 155 of the program error cases, 102 (65.8%) AEFIs were related to the BCG vaccination.

5.1.1.5 Outcomes of AEFI cases

Of all AEFIs, 98.4% (432,645) recovered or improved without sequale. 0.1% (304) AEFIs were with sequele. 0.1% (614) cases died, and 1.4% (6130) cases were unknown or lost to follow-up.

The annual number of AEFI-associated deaths ranged from 30 in 2008 to 166 in 2013, on average of 102 deaths per year. In all fatal cases, 17 different vaccines were involved, with the most frequent vaccines being HepB, BCG, DTP, OPV, and MCV (Figure 12).

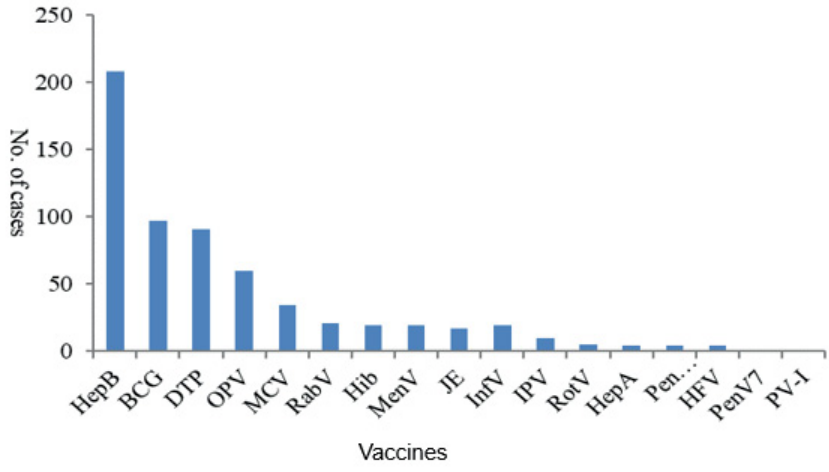

Figure 12 Number of AEFI-associated deaths by vaccine, 2008–2013

5.1.2 System attributes of CNAEFIS

5.1.2.1 Simplicity

The surveillance flowchart is shown in Figure 7. The vaccine recipients or their guardians are advised to report AEFIs by calling or visiting the vaccination clinic or local county CDC where they received the vaccine. The physicians in vaccination clinics or county CDCs will gather information according to the AEFI reporting form (Appendix 1) and give their professional advice to the patients. The trained staff in county CDCs, usually in the immunization department, will verify the information and enter it into the CNAEFIS database. There are also built-in quality control mechanisms when the data is entered into the online system. If there is a need to start an investigation, the online system will generate the investigation form accordingly and send reminders to the county CDC to start investigating. If the cases are investigated, the members of the investigation panel must follow the national guidelines, and all the information in the AEFI investigation form (Appendix 2) is to be entered into the database. For serious cases, the trained staff in prefectural and provincial CDCs must recheck the case information.

The reporters are expected to gather all information related to the reporting and investigation in accordance with the reporting and investigation forms. The quality check is to be done by the online system and the higher-level CDCs. The use of this online system is easy; however, the investigation and causality assessment are difficult. For serious cases, this process is done by an expert panel. Sometimes, several meetings of the panel will be organized, and more complex clinical materials and examinations will be collected so as to generate the final result.

5.1.2.2 Flexibility

There are restrictions on how many vaccines can be included in one CNAEFIS report. The maximum number of suspected vaccines for one case is 3 concurrent vaccines. There are no restrictions on which events should be included in a report. In the analysis, the most serious events will be chosen. When new vaccines are introduced, the NIP's administrator will simply add it to the database, and this would then become available to all levels of CDCs.

Flexibility can be evaluated by retrospectively observing how a system has responded to a new demand. In the initial development period, CNAEFIS served as the AEFI surveillance system for the pandemic A(H1N1) influenza vaccination in 2009 and the measles SIAs in 2010. During the 2009 pandemic influenza vaccination campaign, the CNAEFIS collected information on 8067 AEFIs from 89.6 million doses of vaccine from September 21, 2009, through March 21, 2010(Liang et al., 2011). In September 2010, over 10 days of measles SIA, there were 15,330 reported cases of AEFIs(Wu et al., 2012). The CNAEFIS experienced these two immunization campaigns after its establishment, which could demonstrate its flexibility. Currently, the data linkage between CNAEFIS and the immunization registry is under consideration.

5.1.2.3 Sensitivity and PVP

In CNAEFIS, true vaccine reactions can be derived through a causality assessment(China MoH & China FDA, 2010). Nine pairs of vaccine-adverse reactions were studied. The administered doses varied by vaccine from 8 million per year (VarV) to 72.2 million per year (OPV). A total of 3835 AEFI cases were included in this study from reports submitted in 2008–2013, of which 3727 were

judged to be vaccine reactions. Most of the reports were related to BCG suppurative lymphadenitis (Table 14).

Table 14 Administered doses, expected incidence rates, and frequency of selected AEFIs and vaccine adverse events in China, 2008–2013

Vaccines	Events	Administered doses # (millions)	Expected incidence * (/doses)	AEFIs		Rare vaccine reactions	
				2008–2009	2010–2013	2008–2009	2010–2013
BCG	Suppurative lymphadenitis	101	10/104	685	2634	671	2610
	Disseminated BCG infections		1.56/106	3	34	3	34
HepB	Anaphylaxis	343	1.1/106	8	19	5	18
OPV	VAPP	433	2-4/106	25	88	25	88
MCV	Febrile seizures	263	3/103	-	165	-	134
	Thrombocytopenia		3/104	-	130	-	105
VarV	Febrile seizures	32	4-9/104	-	33	-	25
InfV	GBS	46	1-2/106	-	5	-	3
	Anaphylaxis		0.7/106	-	6	-	6

For BCG, HepB, and OPV, the administered doses were calculated from 2008–2013. For other vaccines, the administered doses were calculated from 2010–2013.

*WHO guidelines(WHO/WPRO, 2013),(WHO, 2000)

Reporting sensitivity varied with the vaccine and the related reactions (Table 15). From 2008–2013, the sensitivity increased for all. Among all the reactions studied, disseminated BCG infections and VAPP were specific reactions related to BCG and OPV. Therefore, the AEFI cases of disseminated BCG infections and VAPP were all classified as vaccine reactions after a causality assessment, and the PVP was 100% from 2008–2013 (Table 15). There were no statistical differences among all the nine pairs in both periods of 2008–2013 and 2010–2013.

Table 15 Reporting sensitivity (%) and PVP (%) of selected outcomes in CNAEFIS, 2008–2013

Vaccines	Events	2008		2009		2010		2011		2012		2013	
		S	P	S	P	S	P	S	P	S	P	S	P
BCG	Suppurative lymphadenitis	1.6	99.6	2.5	96.9	3.0	98.2	4.5	99.1	4.4	99.4	3.2	99.4
	Disseminated BCG infections	4.0	100	7.8	100	15.3	100	41.4	100	24.6	100	44.9	100
HepB	Anaphylaxis	3.8	100	5.5	50.0	6.1	100	6.0	100	7.2	100	7.3	83.3
OPV	VAPP	4.4	100	5.5	100	5.3	100	9.3	100	4.8	100	8.7	100
MCV	Febrile seizures	-	-	-	-	0.02	79.0	0.02	80.8	0.01	88.2	0.01	86.4
	Thrombocytopenia	-	-	-	-	0.1	79.6	0.1	89.5	0.2	73.3	0.2	84.4
VarV	Febrile seizures	-	-	-	-	0.04	100	0.1	88.9	0.1	60.0	0.1	75.0
InfV	GBS	-	-	-	-	5.2	100	8.1	100	0	0	0	0
	Anaphylaxis	-	-	-	-	0	0	23.0	100	25.2	100	23.4	100

#S:Sensitivity; P: PVP.

5.1.2.4 Timeliness

CNAEFIS adopted an online reporting scheme to timely captured all AEFIs. Besides the online scheme, the time interval between reporting and event onset, reporting and investigation, could also show the timeliness of CNAEFIS. All reports were submitted within 2 years of the event onset by reporters, with the range of reporting time intervals in 2008–2013 being 0–730 days (Table 16). The median of all reporting time intervals in 6 years was 1 day. The timeliness of reporting has certainly improved, and the proportion of time lags (reported more than 2 days after event onset) was decreased from 25.7% in 2008 to 16.7% in 2013.

Table 16 Reporting time intervals in CNAEFIS, 2008–2013

Reporting time interval (days)	2008	2009	2010	2011	2012	2013
Range	0-420	0-323	0-618	0-671	0-481	0-537
Median	1	1	1	1	1	1
Mean	5.9	5.2	4.7	4.2	3.6	3.3
Proportion of time lags	25.7	25.9	21.8	20.4	18.3	16.6

The national guidelines lay out certain requirements regarding the timeliness of investigations: Any AEFIs except common adverse reactions with a clear diagnosis (e.g., fever, redness and swelling at the injection site, scleroma) should be investigated. For AEFIs that need to be investigated, the county CDC should start

the investigation and collect the relevant data within 48 hours of receiving the report. The surveillance indicators in the national guidelines require that the rate of AEFIs that need investigation within 48 hours after reporting ≥ 90% (at the provincial level in 1 year).

All cases needing investigation were investigated within almost 1 year, with the longest time interval being 367 days in 2012 (Table 17). 99.9% of the investigations were started with 100 days after reported into the CNAEFIS. The median of the investigation time interval in 3 years was 0 days, and the proportion of time lags also decreased with time from 1.1% in 2011 to 0.5% in 2013.

Table 17 Investigation time intervals in CNAEFIS, 2011–2013

Investigation time interval (days)	2011	2012	2013
Range	0–206	0–367	0–179
Median	0	0	0
Mean	0.3	0.3	0.4
Proportion of time lags	1.1	0.9	0.5

5.1.2.5 Data quality

Proportions of unknowns or errors in key variables

In CNAEFIS, there are several key variables in the reporting and investigation forms; therefore, the proportion of missing/unknown/error values of key variables could be proxy indicators for an indirect measure of data quality. This analysis included 6 key variables: date of vaccination, birth date, onset date, dose of suspected vaccine, classification, and outcome. As the CNAEFIS developed, several quality controls were added to it, such as the time interval checked when entering the information online. For the age check, there was no error or unknown (missing) value. The proportions of other indicators, such as vaccination doses and time intervals between vaccination date and onset date, decreased from 2008–2013 (Table 18).

To improve the data quality of the AEFI surveillance, during the annual national AEFI surveillance meetings or workshops, a key session was conducted on data quality recheck. Also, follow-ups of serious cases were required by the provincial CDCs. The proportions of unknowns or errors in the causality assessment classification and outcomes also decreased over 6 years (Table 18).

Table 18 Percentage of unknowns or errors of key variables in CNAEFIS, 2008–2013

Unknowns or errors	2008	2009	2010	2011	2012	2013
Time interval between vaccination date and onset date	0.4	0	0.01	0.01	0	0
Vaccination doses	0.4	0.01	0.02	0.01	0.004	0.004
Causality assessment classification	3.1	0.9	0.3	0.1	0.03	0.04
Outcome	9.1	1.9	1.6	0.8	0.8	0.7

5.1.2.6 Representativeness

In CNAEFIS, the proportion of countries reporting AEFI cases could be an indicator of geographic representativeness. The proportion of counties that reported AEFIs in 2008 was 34.3%, which increased to 94.6% in 2013. In the eastern and middle areas, the proportions of cases reported by counties were over 90% since 2010 and steadily increasing to 100%. The proportion of reports from the western area also increased over 6 years, reaching 87.5% in 2013 (Figure 13).

In CNAEFIS, the agency responsible for reporting was the county CDC. Usually, only one CDC institute is set up in each county to perform all disease control and prevention work. Therefore, the proportion of counties reporting cases of AEFIs is also the county's CDC participation rate, which reflects acceptability among CDCs.

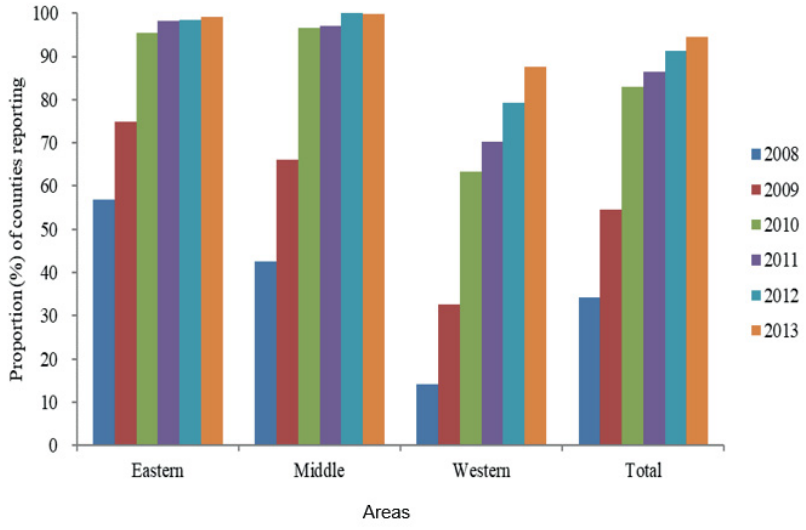

Figure 13 Proportion of counties with at least one AEFI report by year and geographic areas, 2008–2013

5.2 Recipient VAPP in CNAEFIS, 2010–2015 (Study II)

5.2.1 Characteristics of VAPP cases

A total of 157 recipient VAPP cases were reported in CNAEFIS during 2010–2015. The male to female ratio was 8.2:1, and 151 cases (96.2%) were of children less than 6 months of age. 24 of the 31 provinces and the Xinjiang Production and Construction Crops in China reported recipient VAPP; 51.6% (81 cases) were reported from eastern regions, 38.9% (61 cases) from middle regions, and 9.6% (15 cases) from western regions. The number of recipients VAPP cases by year, gender, and age are summarized in Table 20. Perianal abscess was reported in 24.8% (39) of the 157 recipient VAPP cases, all of which were male infants.

Table 19 Number of recipients VAPP cases by gender and age, 2010–2015, China

	2010		2011		2012		2013		2014		2015		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Gender														
Male	23	100	30	93.8	17	77.3	35	87.5	21	87.5	14	87.5	140	89.2
Female	0	0	2	6.2	5	22.7	5	12.5	3	12.5	2	12.5	17	10.8
Age (Month)														
1–3 months	17	73.9	24	75.0	17	77.3	29	72.5	21	87.5	14	87.5	122	77.7
4–6 months	5	21.7	7	21.9	4	18.2	8	20.0	3	12.5	2	12.5	29	18.5
>6 months	1	4.4	1	3.1	1	4.5	3	7.5	0	0	0	0	6	3.8
Total	23		32		22		40		24		16		157	

The vaccine associated with all recipient VAPP cases in CNAEFIS from 2010–2015 was tOPV, which was recommended in the national immunization schedule during the study period. Among all 157 recipient VAPP cases, 89.8% (141) of the cases occurred after the infants received their first dose of OPV; 7.6% (12) cases occurred after the second dose; and 2.6% (4) cases occurred after the third or more doses. None of the recipient VAPP cases had a history of IPV vaccination.

Information on the serotype of poliovirus isolation was reported in 139 cases (88.5%). The type II poliovirus vaccine strain was isolated from 27 cases; type III was isolated from 25 cases; type I was isolated from 16 cases; and multiple serotypes were isolated from 25 cases. Three recipient VAPP cases reported vaccine strain isolation but did not report any of the specific serotypes. 15 cases did not report

results of vaccine strain isolation. The results of serotype isolation from 46 cases (29.3%) were negative (Table 20).

Table 20 Number of recipients VAPP cases by OPV vaccination history and serotype of vaccine strains, 2010–2015, China

	2010		2011		2012		2013		2014		2015		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
OPV vaccination history														
1st dose	22	95.6	29	90.6	20	90.9	34	85.0	21	87.5	15	93.8	141	89.8
2nd dose	0	0.0	3	9.4	2	9.1	3	7.5	3	12.5	1	6.2	12	7.6
≥ 3 doses	1	4.4	0	0.0	0	0.0	3	7.5	0	0.0	0	0.0	4	2.6
Serotype of vaccine strains														
II	4	17.4	6	18.7	2	9.1	5	12.5	6	25.0	4	25.0	27	17.2
III	2	8.7	9	28.1	1	4.5	6	15.0	4	16.7	3	18.8	25	15.9
I	4	17.4	3	9.4	2	9.1	4	10.0	1	4.2	2	12.5	16	10.2
II + III	3	13.0	2	6.3	3	13.6	3	7.5	1	4.2	2	12.5	14	8.9
I + III	1	4.4	0	0.0	1	4.5	2	5.0	1	4.2	0	0.0	5	3.2
I + II + III	0	0.0	0	0.0	1	4.5	1	2.5	2	8.3	0	0.0	4	2.6
I + II	0	0.0	0	0.0	0	0.0	1	2.5	0	0.0	1	6.2	2	1.3
Negative	6	26.1	7	21.9	8	36.4	14	35.0	7	29.2	4	25.0	46	29.3
Unclassified*	0	0.0	1	3.1	2	9.1	0	0.0	0	0.0	0	0.0	3	1.9
Unreported	3	13.0	4	12.5	2	9.1	4	10.0	2	8.3	0	0.0	15	9.6
Total	23		32		22		40		24		16		157	

*Unclassified: These cases reported positive results but not specific serotypes.

Of the 157 cases, 118 (75%) reported fever between 3–35 days following the vaccination, while the others did not provide enough temperature information to assess fever. One recipient VAPP case died and another recovered; the remaining 155 cases experienced physical disabilities—107 cases reported residual paralysis on the 60-day follow-up visit, of which 55.1% (59) cases involved a single limb.

5.2.2 Rate calculation

Using the administered OPV vaccination doses as the denominators, the incidence of recipient VAPP in the study period was 0.4 per million OPV doses with a range of 0.2 per million OPV doses–0.6 per million OPV doses in 2013. If we use the total population and birth rates to approximate the number of births, the recipient VAPP

per million births can be estimated; accordingly, the recipient VAPP per million births ranged from 1.0–2.4 in 2010–2015 (Table 21).

Table 21 Risk of recipient VAPP in China by year, 2010–2015

	Recipient VAPP	Million OPV doses	Recipient VAPP per million OPV doses	95% CI	Total population (million)	Birth rates (%)	Estimated births (in millions)	Recipient VAPP per million births	95% CI
2010	23	66.6	0.3	0.2–0.5	1340.9	11.9	16.0	1.4	0.9–2.2
2011	32	69.6	0.5	0.3–0.6	1347.4	11.9	16.1	2. 0	1.4–2.8
2012	22	73.1	0.3	0.2–0.5	1354.0	12.1	16.4	1.3	0.8–2.0
2013	40	72.5	0.6	0.4–0. 8	1360.7	12.1	16.4	2.4	1.7–3.3
2014	24	71.9	0.3	0.2–0.5	1367.8	12.4	16.9	1.4	0.9–2.1
2015	16	70.1	0.2	0.1–0.4	1374.6	12.1	16.6	1.0	0.6–1.6
Total	157	423.8	0.4	0.3–0.4	-	-	98.4	1.6	1.4–1.9

After the first dose, 141 recipient VAPP cases occurred, with an incidence of 1.3 per million doses, which is 1 in 764,107 vaccinations. The risk after the first dose was substantially higher than after the second and third doses (Table 22). For the second dose, the risk was about 1 in 9 million doses, while it was 1 in 27 million doses for the third dose or more.

Table 22 Risk of recipient VAPP cases in China by dose, 2010–2015

	No. of cases	Vaccination doses	Incidence rates (per million doses)	95% CI
1st dose	141	107.7	1.3	1.1–1.5
2nd dose	12	108.1	0.1	0.1–0.2
≥ 3rd dose	4	107.7	0.04	0.01–0.1

5.3 AEFI-associated deaths in CNAEFIS, 2010–2015 (Study III)

5.3.1 Demographic distribution of deaths following vaccination

A total of 753 AEFI-associated deaths were reported during 2010–2015. AEFI-related deaths peaked in 2013–2014 (Figure 14). The proportion of neonatal deaths varied from 5.0% (2010, 2011) to 16.5% (2013). In 2012–2014, the proportion exceeded 10.0%. All deaths were reported from locations within mainland of China.

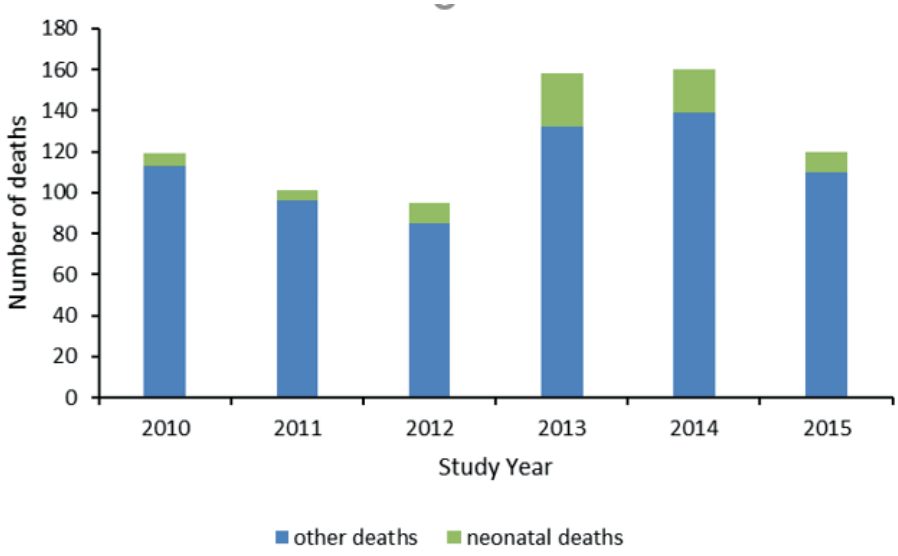

Figure 14 Reports of AEFI-associated deaths by year, 2010-2015

During the first quarter of the year (January to March), there were 249 (33.1%) AEFI-associated deaths, followed by 234 (31.1%) during the fourth quarter, 140 (18.6%) and 130 (17.3%) during the third and second quarters, respectively. Fifty-one AEFI-associated deaths were reported in December 2013, and 34 (66.7%) of these were related to HepB vaccine, administered alone or with other vaccines (Figure 15).

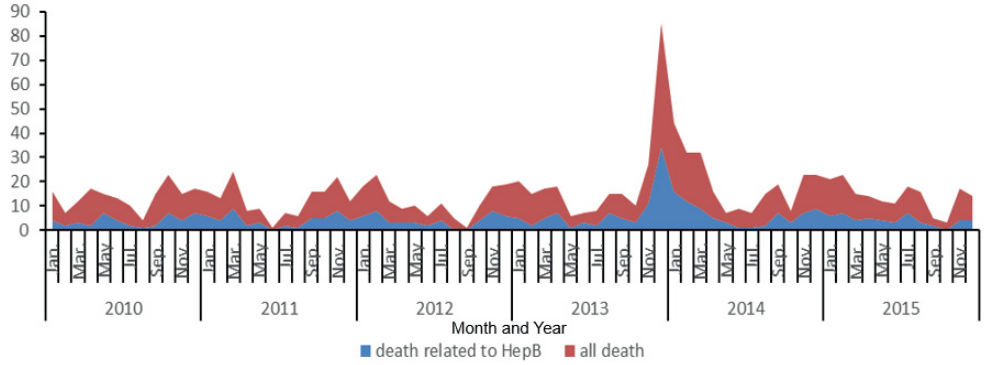

Figure 15 Seasonal distribution of AEFI-associated deaths, 2010-2015

Of AEFI-associated death reports, 293 (38.9%) were females, 635 (84.3%) were aged <1 year, and 82 (10.9%) cases were aged 1–4 years (Table 23). The median age

in the group aged <1 year was 68 days, and the median age in the group aged 1–4 years was 1 year old.

Table 23 AEFI-associated deaths by year of death, age and gender, 2010-2015

	<1		1–4		5–9		10–17		18–64		≥65		Total	
	N	Female %	N	Female %	N	Female %	N	Female %	N	Female %	N	Female %	N	Female %
2010	84	44.05	20	50.00	3	0	2	50.00	9	44.44	1	0	119	43.70
2011	90	44.44	8	37.50	1	0			1	100	1	100	101	44.55
2012	79	27.85	12	25.00	2	50.00			1	0.00	1	0	95	27.37
2013	139	36.69	13	38.46			2	0	2	50.00	2	50.00	158	36.71
2014	141	39.01	15	40.00	3	0					1	100	160	38.75
2015	102	42.16	14	42.86	1	100			2	0.00	1	0	120	41.67
Total	635	39.06	82	40.24	10	20.00	4	25.00	15	40.00	7	42.86	753	38.91

Sixty-Nine different vaccines or vaccine combinations were associated with reported deaths. The most common vaccines or vaccine combinations were 1) HepB (alone) (182, 24.2%), 2) Bacillus Calmette Guerin (BCG) and HepB (116, 15.4%), 3) oral poliomyelitis vaccine (OPV) and diphtheria, tetanus and acellular pertussis combined vaccine (DTaP) (84, 11.2%), 4) BCG (alone) (61, 8.1%), and 5) DTaP (alone) (31, 4.1%) (Table 24).

Table 24 AEFI-associated deaths by vaccine and vaccine combination, and the causality assessment classification, 2010-2015

Vaccines and vaccine combinations	Vaccine reaction	Immunization error	Coincidental events	Indeterminate	Total
HepB	13		163	6	182
BCG + HepB	16	1	92	7	116
OPV + DTaP	13		65	6	84
BCG	34		24	3	61
DTaP	7		22	2	31
OPV			26	1	27
HepB + OPV	2		17		19
RabV	7		8	3	18
JEV-L	4		12	1	17
OPV + DTaP + Hib	1		12		13
61 other vaccines and vaccine combinations	23		153	9	185
Total	120	1	594	38	753

5.3.2 Results of the causality assessments

Autopsies were conducted in 257 (34.1%) cases. According to the causality assessment, 120 (15.9%) deaths were classified as vaccine reactions, 594 (78.9%) deaths were due to coincidental events, 38 (5.1%) deaths were classified as indeterminate, and 1 (0.1%) death was due to an immunization error-related reaction. No deaths were classified as due to vaccine quality defect-related reactions or immunization anxiety-related reactions during the study period (Table 24).

5.3.2.1 Vaccine reactions and deaths

One hundred-twenty deaths were classified as vaccine-related reactions, with an estimated rate of 0.04 per million doses, using the all vaccination doses as the denominator. Anaphylactic reactions accounted for 55 cases, in which 53 cases occurred within 1 day after vaccination. Anaphylactic reactions take 45.8% of vaccine-related reactions, with estimated rates of 0.02 per million vaccination doses. Nineteen vaccines or vaccine combinations were related to anaphylactic reactions. The average numbers of deaths per year due to anaphylactic reactions post-vaccination was about 9 (range: 6–13 cases). The most common vaccine and vaccine combinations associated with vaccine reactions were HepB (by itself) (12 cases), OPV and DTaP (10 cases), BCG and HepB (9 cases).

There were 39 BCG-related deaths (estimated rate: 0.37 per million BCG vaccination doses, including 34 BCG-alone cases and 7 BCG+HepB concurrently vaccinated cases). Thirty BCG-related deaths were classified as the result of disseminated BCG infections, and nine cases were due to BCG lymphadenitis or other infections (recurring). One death due to vaccine associated Vaccine-Associated Paralytic Poliomyelitis (VAPP) was reported. One case of hemorrhagic measles was reported in which the autopsy and laboratory findings confirmed that this was related to the vaccine virus.

Thirteen deaths were attributed to neurological, illness, of which six cases were meningitis (aseptic or viral), four cases were acute disseminated encephalomyelitis, two cases were encephalopathy, and one case was epilepsy. Seven vaccines and vaccine combinations were administered in these cases, of which the rabies vaccine was the most common vaccine, accounting for five deaths. The average number of deaths per year was three, with a range of two to four in the study period.

Nine deaths were confirmed as status thymicolymphaticus (STL) after autopsies. Other two cases were diagnosed as malaise and vomiting post vaccination, and both

died of aspiration asphyxia. In all above 11 cases, vaccination was not the direct cause of death. However, in the causality assessment, the expert committee concluded that vaccination contributed to these deaths and classified the deaths as vaccine-related reactions.

5.3.2.2 Immunization errors

Only one death was classified as immunization error-related reaction. In this case, the baby had been diagnosed with severe malnutrition prior to immunization, and the immunization nurse had failed to perform a physical examination when the parents requested that the infant be vaccinated. The direct cause of death was severe malnutrition, respiratory failure, and cardiac failure, not vaccine related.

5.3.2.3 Coincidental events

After causality assessment, 594 deaths were classified as coincidental events. The most common causes of death were asphyxia, sudden infant death syndrome (SIDS), pneumonia (neonatal and infant), congenital heart diseases, and vitamin K deficiency (which could lead to internal bleeding). In these cases, 577 (97.1%) deaths occurred within 15 days after vaccination. Sixty vaccines and vaccine combinations were administered, the most common were HepB (alone) (163 cases), BCG and HepB (92 cases), OPV and DTaP (65 cases), OPV (alone) (26 cases), and BCG (alone) (24 cases). In 574 (96.6%) cases, the patients aged < 5 years.

5.3.2.4 Indeterminate cause of death

During 2010–2015, 38 deaths were classified as due to indeterminate causes. There was no clear clinical diagnosis in 25 (65.8%) cases, and for the rest cases there was insufficient evidence available to conduct the causality assessment. All 38 deaths occurred within one-week post-vaccination, and 34 (89.5%) cases aged < 5 years.

5.3.3 Risk estimation of deaths after vaccination

Using all administered doses as the denominator, the average rate of AEFI-associated death was 0.26 per million vaccination doses (range: 0.20-0.32) during the study years. Using population data as the denominator, the average rate was 0.09 per million population (range: 0.07-0.12) (Table 25).

Table 25 Estimated overall AEFI-associated death rates using different denominators, 2010-2015

Year	No. of deaths	All vaccination doses (in millions)	Estimated rate by vaccination dose		Total population (in millions)	Estimated rates by total population	
			Death rate (per million vaccination doses)	95% CI		Death rate (per million population)	95% CI
2010	119	427.88	0.28	0.23–0.33	1340.91	0.09	0.07–0.11
2011	101	461.44	0.22	0.18–0.27	1347.35	0.07	0.06–0.09
2012	95	478.97	0.20	0.16–0.24	1354.04	0.07	0.06–0.09
2013	158	489.21	0.32	0.27–0.38	1360.72	0.12	0.10–0.14
2014	160	495.74	0.32	0.27–0.38	1367.82	0.12	0.10–0.14
2015	120	504.23	0.24	0.20–0.28	1374.62	0.09	0.07–0.10
Total	753	2857.49	0.26	0.25–0.28	8145.46	0.09	0.09–0.10

Neonatal deaths accounted for 10.4% (78 cases) of all reported AEFI-associated deaths. The highest rate of reported neonatal deaths after vaccination occurred in 2013 (1.48 per million live births). The rate of neonatal deaths after vaccination in 2010–2011 was significantly different from 2013–2014(Table 26).

Table 26 Estimated neonatal deaths rates after vaccination, 2010-2015

Year	No. of Neonatal death	Vaccination dose of 1st dose of HepB (in millions)	Vaccination coverage %	Estimation of live births (in millions)	Neonatal death rates (per million births)	95% CI
2010	6	17.16	99.81	17.19	0.35	0.13–0.76
2011	5	17.5	99.86	17.53	0.29	0.09–0.67
2012	10	18.68	99.87	18.71	0.53	0.26–0.98
2013	26	17.48	99.77	17.52	1.48	0.97–2.17
2014	21	15.18	99.84	15.2	1.38	0.86–2.11
2015	10	15.75	99.87	15.77	0.63	0.30–1.17
Total	78	101.75	-	101.91	0.77	0.61–0.96

During 2013–2014, 47 neonatal deaths were reported and 44 (93.6%) of those were related to HepB (with concurrent vaccines). In the causality assessment

however, only one of the reported deaths was considered causally related to vaccination. During 2010-2015, we identified 182 reports of AEFI-associated deaths after vaccination with HepB was the only vaccine used. Of these, 13 were causally related to vaccination in the causality assessment. The annual numbers of causally related deaths during the period were 2,3,2,1,3,2, respectively.

5.4 Post-marketing vaccine safety of JE vaccines (Study IV)

5.4.1 AEFIs following JEV-L and JEV-I

A total of 34,879 AEFI cases associated with JE vaccines were collected by CNAEFIS, 2008–2013; 95.2% (33,186) cases were related to JEV-L. JE vaccines were administered concurrently with one or more other vaccines in 13,592 (39.0%) of cases (39.9% for JEV-L and 19.9% for JEV-I, respectively). Both for JEV-L and JEV-I, the most common concurrently administered vaccine was measles containing vaccines, with a proportion of 24.8% for JEV-L (8226 cases in 33,186 JEV-L-related cases) and 17.5% for JEV-I (297 cases in 1693 JEV-I-related cases).

JEV-L was listed as the first suspected vaccine in 23,627 (71.2% of the JEV-L-associated AEFI cases). JEV-I was the first suspected vaccine in 1357 (80.2% of JEV-I-associated cases) ($p < 0.05$). There were more cases in males than in females, with a sex ratio of 1.3:1. More cases occurred in 1 years of age, with 66.4% of JEV-L and 60.8% of JEV-I (Table 27). Of all 34,879 AEFI cases, 361 (1.0%) AEFI cases were defined as serious. There were 146.7 million vaccination doses collected of JE vaccines from 2010 to 2013, in which 95.1% (139.5 million doses) was JEV-L. Since both JEV-L and JEV-I could be used as NIP vaccines and voluntary vaccines, among all JE vaccination doses, 91.5% (134.3 million doses) were used as NIP vaccines, including 133.1 million of JEV-L and 1.2 million of JEV-I. Using the doses administered from 2010 to 2013 as denominators, the overall reporting rates of AEFIs per million were 214.4 for JEV-L and 176.9 for JEV-I (RR: 1.2, 95% CI: 1.1–1.3). the annual reporting rates increased substantially from 2010 to 2013 (Table 28). During 2010–2013, 271 serious AEFIs were reported. The overall reporting rates of serious AEFIs were 1.8 per million doses for JEV-L and 2.8 per million doses for JEV-I (RR: 0.7, 95% CI: 0.4–1.0).

Table 27 Characteristics of AEFIs after JEV-L and JEV-I vaccination, China, 2008-2013

		JEV-L				JEV-I			
		As most suspected* N=23627 (%)		others N=9559(%)		As most suspected N=1357(%)		Others N=336(%)	
Serious	Serious	244	1.03	66	0.69	51	3.76	0	0.00
	Non-serious	23383	98.97	9493	99.31	1306	96.24	336	100.00
Gender	Male	13444	56.90	5358	56.05	768	56.60	190	56.55
	Female	10183	43.10	4201	43.95	589	43.40	146	43.45
Age group	≤1yr	13306	56.32	8712	91.14	710	52.32	320	95.24
	2-6yrs	10036	42.48	825	8.63	511	37.66	14	4.17
	≥7yrs	285	1.21	22	0.23	136	10.02	2	0.60

* There were at most three suspected vaccines were reported in one AEFI cases, the reporters will put one vaccine as the most suspected vaccines. JE as most suspected means JE was most suspected related to adverse events in the reports.

Table 28 Number and estimated AEFI reporting rates of after JEV-L and JEV-I by severity* of AEFI, China, 2010-2013

AEFI	JEV-L				JEV-I				Rate ratios	
	Non-serious		Serious		Non-serious		Serious		Non-serious	Serious
	No. of cases	Reporting rates**	No. of cases	Reporting rates	No. of cases	Reporting rates	No. of cases	Reporting rates	(95% CI)	
2010	2428	75.97	43	1.35	96	33.99	5	1.77	2.23 (1.83-2.76)	0.74 (0.32-2.17)
2011	5816	168.51	41	1.19	102	124.86	1	1.22	1.35 (1.12-1.65)	0.85 (0.19-19.85)
2012	8495	240.25	69	1.95	756	294.80	13	5.07	0.82 (0.76-0.88)	0.38 (0.22-0.72)
2013	12908	343.11	98	2.60	308	295.79	1	0.96	1.16 (1.04-1.30)	2.37 (0.54-54.72)
2010-2013	29647	212.60	251	1.80	1262	174.15	20	2.76	1.22 (1.15-1.29)	0.65 (0.42-1.05)

*The severity of AEFI were classified according to national AEFI guidelines. Serious AEFIs 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.

**Reporting rates: per million vaccination doses given

5.4.2 Clinical diagnosis of AEFIs

Of the 29,831 non-serious AEFIs, (86.4%) were diagnosed as common and minor adverse reactions, such as fever, local redness, and swelling. Among serious AEFIs, the most frequently reported clinical diagnosis were febrile convulsion (132, 36.6%), thrombocytopenic purpura (39, 10.8%), encephalitis and meningitis (29, 8.0%), Henoch-Schönlein purpura (28, 7.8%), and anaphylactic shock (25, 6.9%) (Table 29). 22 death cases were reported during the study period, only 4 cases were classified as related to vaccination due to anaphylactic shock.

Table 29 Clinical Diagnosis of serious AEFI after the immunization of JEV-L and JEV-I, China, 2008-2013

	JEV-L				JEV-I*	
Clinical diagnosis	**First suspected, N=244 (%)**		**Not first suspected, N=66(%)**		**First suspected, N=51 (%)**	
Febrile Convulsion	83	34.02	16	24.24	33	64.71
Thrombocytopenic Purpura	22	9.02	15	22.73	2	3.92
Encephalitis and Meningitis	23	9.43	5	7.58	1	1.96
Henoch-Schönlein Purpura	18	7.38	6	9.09	4	7.84
Anaphylactic Shock	21	8.61	1	1.52	3	5.88
Apsychia	11	4.51	4	6.06	5	9.80
Seizure	16	6.56	1	1.52	1	1.96
Laryngeal Edema	4	1.64	1	1.52	1	1.96
Acute disseminated encephalomyelitis (ADEM)	5	2.05	0	0.00	0	0.00
Arthus Reaction	3	1.23	1	1.52	0	0.00
Guillain Barre Syndrome (GBS)	1	0.41	1	1.52	0	0.00
Others	37	15.16	15	22.73	1	1.96

*For JEV-I, there was no cases coded as serious AEFIs when administered in combination with other vaccines.

5.4.3 SDR detection of JEV-L and JEV-I

A total of 20,988 AEFIs with complete information on vaccine and diagnosis were included in the disproportionality analysis. All three methods, PRR, EB, and BCPNN, suggested JEV-I and febrile convulsion as the suspected SDRs (Table 29). For JEV-L, there was no diagnosis with disproportionally higher reporting. Based on the results of Table 30, using the administered doses from 2010 to 2013 as the denominator, the estimated reporting rates of febrile convulsion after JEV-L (as the

only vaccine suspected) and JEV-I (as the only vaccine suspected) were calculated: 0.3 per million doses for JEV-L and 0.4 per million doses for JEV-I (p = 0.5).

Table 30 Suspected SDR of JE vaccines using 3 DPA methods, China, 2008-2013*

Methods (Criteria)	Results
PRR (Lower limit of 95% CI of PRR >1 & n >3)	JEV-I- Febrile Convulsion PRR=7.44, Lower limit of 95% CI =1.59
EB (EB05>2 & n>3)	JEV-I- Febrile Convulsion EB05=3.27
BCPNN (Lower limit of 95% CI of IC >1 & n>3)	JEV-I- Febrile Convulsion Lower limit of 95% CI of IC=1.64

*PRR: Proportional Reporting Ratios
EB05: single sided 5% Empirical Bayesian Geometric Mean (EBGM)
BCONN: Bayesian Confidence Propagation Neural Network

6 DISCUSSION

National AEFI surveillance is a key component of vaccine safety evaluation. China CDC developed CNAEFIS, which has served as the national passive surveillance system since 2005. So far, it has successfully captured more than 300,000 AEFI cases, providing a robust database for vaccine safety evaluation in the Mainland of China. Experience and evidence drawn from CNAEFIS has been a vital resource for decision-making by Chinese Vaccine Regulatory Agency and related stakeholders.

6.1 Study strengths and limitations

National AEFI surveillance is a key part of public health surveillance and it could provide evidence for vaccine safety evaluations. CNAEFIS covers all the vaccines used in Mainland China, whether manufactured in China or abroad, whether used in NIP or in the free market (purchased and used by parents or adults). China is one of the most populous countries in the world, with vaccines being used and manufactured by the billion every year. Thus, the massive amounts of AEFI data in CNAEFIS could provide valuable information on vaccine safety in Mainland China, India and some African counties which also used Chinese manufactured vaccines.

Based on national laws and national AEFI guidelines issued by MoH and CFDA, CNAEFIS is the primary tool to collect AEFI cases nationally. The case verification from county, prefectural and provincial CDCs and experts committee of causality assessment strength the data quality, especially for rare and serious cases. The analysis of reporting over time and epidemiological distribution illustrates the progress made with vaccine safety monitoring during study years in China.

To evaluation the vaccine safety in China, three examples were chosen in our analysis with various reasons. VAPP is the rare and most serious vaccine reactions following Oral polio vaccines, which is used in China for more than 30 years, and risk estimation showed that the incidence of recipient VAPP in China was consistent with international studies, and with the polio vaccine switch program started in 2016, would diminish the VAPP further. Fatalities is also a serious event following immunization, especially among neonatal. The widely publicity of Hepatitis B

vaccines in the end of 2013, bring public concern on vaccine safety situation in China, and our analysis providing reassured information on vaccine safety and the peak of fatalities during the media reports was pure reporting boost. The two examples will be the important evidence to document how safe immunization risks in China.

Since JEV-L is the first vaccine to be prequalified by the WHO, which is produced by domestic vaccine manufactures in China, the safety evaluation of this vaccine could benefit not only inside China, but also internationally, especially India, Thailand and some Africa counties that imported this vaccine.

Limitations

An important limitation of this analysis is that CNAEFIS is a passive surveillance system with low sensitivity and the potential underreporting of AEFI cases, which could result in reporting bias(Singleton et al., 1999). Reporting of adverse events might be influenced by a number of factors, such as clinical seriousness, temporal proximity to vaccination and vaccination providers' awareness and obligation to report(Rosenthal & Chen, 1995). More serious the cases are, and shorter time interval between vaccination and occurrence, more likely vaccines could be suspected by parents and health providers. Also, the increase of reporting AEFI cases might be related to vaccination campaigns during which more vaccination doses were used, or after media reports and rose public's attention on vaccinations. Therefore, the vaccine safety signal detected by passive surveillance should be considered with caution and used a clue for further studies.

National AEFI surveillance data is different with researcher-collected data, with all vaccination doses were covered and there are no statistical analyses focusing on sampling errors. According to experts' analysis and conclusion(Thygesen & Ersboll, 2014), validity of epidemiological studies with inclusion of all persons in a population followed for decades, should be characterized as completeness and validity of variables included. The completeness is whether all individuals (with vaccinations in our study) are included. The validity of the variables include is whether the information on vaccinated persons are collected and whether the information collected is correct.

In Study I, the only available data on AEFIs in China is currently the CNAEFIS, and no another surveillance system dataset is available for comparison. Continuous improvement and investigation are needed for more detailed information and assessment of the surveillance system. In the future, data completeness could be

evaluated by comparing the AEFI database with another data source at local level, by capture-recapture method or, by comprehensive medical chart review. However, these would be very resource-intensive methods.

The demand for completeness and validity depends on the research questions. Usually, the population-based surveillance data has high completeness, however, the analytical studies to address specific vaccination safety question, such as vaccination as the exposure and diseases as the outcome, needs high validity(Thygesen & Ersboll, 2014).

In Study II, since only cases of recipient VAPP were reported, no contact cases were included in our analysis: This could lower the estimated risk for VAPP. Another limitation is that since some laboratory data were unavailable in CNAEFIS, cases were categorized as VAPP without serotype information, which influence the validity of the outcome assessment. In addition, since VAPP cases stand to receive government compensation, some cases were classified as VAPP even when the laboratory results of the serotypes were negative. Compensation is also given for vaccine-related reactions in Mainland China. When an expert panel finds no other cause of death in its causality assessment, it might conclude that the vaccine or vaccination was a trigger or contributor to the death. In such cases, the families of the deceased can apply for compensation. This policy might have increased the number of reports of vaccine-related reactions in the present VAPP and deaths study.

Also, one should be cautious when comparing related rates across countries by using the incidence estimates in our study. The limitation of denominator-based risk estimation includes different resources to identify the vaccine-administered doses and unknown background information, which make it difficult to compare the observed to the expected, as well as among different settings(Hauben & Zhou, 2003). In our study, the denominators used were estimated from different data resources and one should be cautious about comparing the estimated rates with immunization related death rates in other countries. In Study II, to eliminate wild poliovirus, many complementary polio vaccine campaigns were launched in Mainland China. Yet, information regarding these campaigns, including vaccination doses, was not completely reported during the study period. This could lead to underestimate denominators (administered doses will be underreported), thereupon lead to an overestimation of overall risk.

6.2 Methods considerations

The evaluation of a surveillance system could be divided into two: 1) utility and cost, 2) system attributes(US CDC, 2001). The completeness is closely related to sensitivity and positive predictive value(Thygesen & Ersboll, 2014). Completeness could be evaluated by different methods, such as comparing with another data source believed to be complete, or alternatively to calculate the expected number of cases by applying rates of similar populations or "gold standard". In our study, according to the review of attributes in the evaluation guidelines(US CDC, 2001), the sensitivity and positive predictive value are used for evaluated the completeness. Validity of the variables include is another dimension of population-based surveillances. Important measures for validity are sensitivity, specificity and predicative value (both positive and negative)(Thygesen & Ersboll, 2014). Commonly, the validity of a register is performed by case to case evaluation. In CNAEFIS, all serious cases, including death, serve disabilities, clusters, and cases with public concerns, would be investigated and causally assessed by prefectural level or provincial level expert committee.

Besides of sensitivity and PVP, we also use the demographic representativeness to show that how the CNAEFIS covered whole China. Based on the national AEFI surveillance guidelines, the events following immunization suspected should be reported, however, the nature of voluntary reporting makes underreporting more likely in this system. Through with several years of training, there were still some counties with no cases reported every year. The demographic representativeness could be a proxy indicator for reporting sensitives.

To evaluate vaccine safety, we conducted two levels of analysis: a descriptive analysis of AEFIs (Studies II–IV) and a disproportionate reporting analysis (Study IV). We calculated AEFI incidence rates using different denominators. Through comparison with historic data and published studies, emerging vaccine safety signals were detected. As serious AEFIs are very rare and it is difficult to know the background incidence rates, DPAs in the SDR detection could be used. Since both JEV-L and JEV-I are used in China, we mainly compared the vaccine safety of JEV-L and JEV-I instead of comparing them with all other vaccines in the DPAs. Since there are no DPA gold standard methods, we applied both Bayesian and non-Bayesian DPAs to screen SDRs.

6.3 Performance of National AEFI system

Study I comprise three parts: i) a review of the national AEFI surveillance system in Mainland China; ii) a descriptive analysis of AEFI surveillance data during 2008–2013; iii) an analysis of the system attributes of CNAEFIS. The descriptive analysis of CNAEFIS during 2008–2013 showed that about 440,000 AEFI cases were reported, with an average rate of 454 per 100,000 surviving infants per year. The number of annually reported cases increased by 30%, and the ratio of AEFI cases per 100,000 surviving infants per year also increased six-fold. However, the ratio of serious cases per 100,000 surviving infants per year remained steady for the 6 years. Consistent with NIP target population, the majority of reported AEFI cases were in children and occurred after administration of NIP vaccines. Most of the AEFIs were common vaccine reactions, and the proportion of rare vaccine reactions remained at about 8% every year. Program errors in CNAEFIS decreased, and most of them were related to the BCG vaccination. More than 98% of AEFI cases recovered or improved. About 0.1% of cases resulted in death and various vaccines were involved.

As a public health surveillance system, CNAEFIS is simple to use and adaptable to new situations and requirements. Much like other SRSs, the sensitivity of CNAEFIS is relatively low and varies by vaccine and event type. However, its level of specificity is quite high. Cases were reported and investigated in a timely manner, and timeliness increased every year. Though the estimated incidence rates of certain vaccines in CNAEFIS were still lower than when enhanced or active reporting was implemented(Yue et al., 2012), its completeness increased each year. With the development of quality control mechanisms, unknown, missing, or errors in key information decreased and were adjusted to some extent. The geographic representativeness of CNAEFIS has also increased in each of the 6 years.

Our analysis shows that CNAEFIS has the capability to continuously collect AEFI information in China since its establishment. It also makes it simple to report and generate valuable post-marketing information. However, conclusive evaluation of vaccine safety is difficult, as the investigation and causality assessment are labor intensive and require collection of clinical information in most cases. The flexibility of CNAEFIS is good and it could adapt to mass immunization campaigns and new conditions such as the launch of new vaccines. We thus can conclude that CNAEFIS is a low-sensitivity and high-specificity surveillance system. Despite this low sensitivity, it is a useful system as long as the sensitivity remains reasonably consistent over time(Rosenthal & Chen, 1995). As a national passive surveillance system in a

country with limited resources, the high PVP of the CNAEFIS reports seems reasonable, although it varied by vaccine.

The reporting time interval from onset date to reporting of cases to county CDCs or the responsible reporters not only reveals the timeliness of reporting but also illustrates the reporting behavior of vaccine recipients or their guardians. The reporting time lag has decreased from 2008–2013, suggesting that the public is paying more and more attention to vaccine safety. The investigation time interval has also decreased, and this is solely due to the work of the CDCs and the expert panels. An indicator for data quality is the key variable check: With built-in quality control mechanisms, training sessions, and error checks every year, the missing, unknown, or incorrect key variables have decreased. Also, for causality and outcome assessment, follow-up by the CDCs is important to reduce unknown or missing values.

At its grassroots, the CDC in China functions at the county level, playing an important role in AEFI surveillance. The county CDCs are responsible for receiving reports and entering the data into the database, performing case verification, and starting the initial investigation. The proportion of cases reported by county CDCs could thus be an indirect indicator of the representativeness of CNAEFIS. With the unequal development of CDCs in the eastern, middle, and western areas, the proportions of cases reported by county CDCs are also unequal. From 2010, the proportion of reported cases by county CDCs from the eastern and middle areas was over 90%; however, the proportion from the western area was lower than 90% in 2013, suggesting that that there are geographic differences in CDC's investigation capacities.

Although AEFI surveillance in China is passive, it does have several advantageous characteristics. CNAEFIS is supported by national vaccination and immunization laws and regulations, and China CDC's national AEFI surveillance guidelines are the official standards for conducting AEFI surveillance. The reporting of AEFIs is mandatory for all health professionals and vaccine providers. CNAEFIS is the primary tool to collect AEFI data so that these data can be used rapidly, efficiently, effectively, and conveniently. The system is online and is designed to ensure data quality through data verification at all levels of CDCs, especially for rare and serious cases.

China also has a mechanism to arrange for panels of AEFI experts to participate in investigations and conduct causality assessments. The immunization program in China is unified and vertically integrated, and all provinces, prefectures, and counties have CDCs that participate in the vaccine safety surveillance system. The AEFI

Surveillance and Management Division was established in January 2009 in China CDC NIP, and, by 2014, several province-level CDCs had also established AEFI surveillance divisions. China CDC NIP has an ongoing training plan for AEFI surveillance staff and physicians to build and sustain their capacity of AEFI surveillance. Since 2005, training workshops and conferences on AEFI surveillance have been conducted at least annually. Such programs will continue to help ensure that there is no dearth of highly qualified staff for AEFI surveillance in China.

An analysis of the national AEFI surveillance is published monthly in the NIP Bulletin, which is distributed to all the CDCs and shared with ADRs. Analyses of AEFI surveillance data are published annually in the Chinese Journal of Vaccine and Immunization. Analyses of AEFI data reported during special immunization campaigns, such as measles SIAs and the A(H1N1) influenza response vaccination campaign, have also been published in Chinese and other international scientific journals. For example, an early paper on a post-marketing safety surveillance of the 2009 A(H1N1) influenza vaccine was published shortly after the vaccination campaign in China.

In addition to information shared among CDCs and other vaccination stakeholders, vaccine safety information is released to the public through press releases and news announcements by MOH. Since 2013, annual national AEFI surveillance information has been released jointly by MOH and CFDA to the public through their websites, providing AEFI surveillance summary and safety evaluation on vaccines given to children.

The personal identification information, including names, telephone numbers, address were blocked and could not be viewed by prefectural level, provincial level and national level CDCs and all levels of ADRs to protect database. Since AEFI reporting forms and investigation forms were collected and entered the online CNAEFIS by staff in points of vaccination and county level CDCs, those users could only view the personal data they entered and for purpose of following-ups.

6.4 Recipient VAPP in China

In Study II, using data from the national passive AEFI surveillance system in China, we estimated that the risk of recipient VAPP was 0.4 per million administered OPV doses. The NIP began in 1978, and tOPV has been used for more than 35 years(Zheng et al., 2010). VAPP data reported in CNAEFIS complements routine Acute Flaccid Paralysis surveillance and provides an estimate of the baseline risk of

VAPP before China switches to the bivalent polio vaccine. In previous studies, VAPP cases were more frequently reported in males and in children under 5 years of age(Landaverde et al., 2014). However, in our study, the gender imbalance in VAPP reports was striking (8:1) for unclear reasons. This could be related to several issues, including surveillance or reporting artifact—in the whole passive AEFI surveillance, more AEFIs were reported for males than females, with a ratio of 1.4:1(Wu et al., 2012; Wu et al., 2014; Jiakai Ye et al., 2016). Also, as immunity to poliovirus is largely antibody-mediated, persons with antibody deficiencies are much more susceptible to VAPP than immune-competent individuals(MacLennan et al., 2004). However, considering that only part of the reported VAPP cases were immune deficient, and not all relevant immune deficiency syndromes are x-linked, immune deficiency may only explain part of the gender difference. One study in a children's hospital in Beijing(J. Zhang, et al., 2013) found that among patients suffering from primary immunodeficiency diseases (PID), the ratio of boys to girls was 4.4:1. The same study found that in 174 patients with PID over 11 years, the median age of onset of antibody deficiency was 12 months(J. Zhang et al., 2013). Therefore, it is difficult to assess immune-competency in young infants as they are only 2 months old at the time of OPV vaccination. We also found that about 25% of VAPP cases had perianal abscesses and they were all male. The possible relationship between gender, perianal abscesses, and VAPP requires further study.

The age distribution of VAPP cases is obviously associated with the OPV vaccine schedule, with the recommended age for OPV doses being 2, 3, and 4 months of age. The majority of recipient VAPP cases occurred after the first dose. A literature review of the VAPP burden indicated that in low-income countries, the number of VAPP cases is highest among children aged 1–4 years, whereas in middle- and high-income countries, the risk of VAPP is highest among children under 1 year of age(Landaverde et al., 2014). The reason for this was assumed to be related to the prevalence of protective maternal antibodies and the high coverage provided by the first dose of OPV; accordingly, VAPP was high in the under 1-year age group. In high-income countries, high OPV immunogenicity and the delivery of the first dose of OPV after 2 months (when maternal antibody levels have decreased) might have been associated with the risk of VAPP following the first dose. Because of oral administration, the coverage of OPV is generally higher than that of other vaccines, and it has been reported to be as high as 99% in China according to national immunization coverage surveillance data(Cui et al., 2016).

Improved reporting capacity for AEFIs might have affected the geographic distribution of VAPP cases. Since CNAEFIS developed rapidly after national AEFI

guidelines were issued in 2010, AEFI surveillance in different regions in China might have been implemented unevenly. Like all reported AEFI cases, most cases of recipient VAPP were from the eastern regions, followed by the middle and western regions. In addition to the capability of AEFI surveillance, differential reporting might also be related to economic status and population distribution. After 2012, the central government issued financial support for AEFI investigation and causality assessment, which could enhance the number of recipients VAPP cases reported in CNAEFIS. The decline in recipient VAPP in 2015 might be related to the policy change in July 2015 in which six pilot provinces in China introduced IPV to replace tOPV as the first dose. Also, the domestically manufactured IPV-Sabin strains were introduced in the market in 2015. In the vaccine serotype analysis, type II accounted for about one-third (27/93) of all cases, as seen in other studies(Landaverde et al., 2014).

Our study suggested that the incidence of VAPP in China was similar to that of other countries. In studies from different countries, the estimated incidence of recipient VAPP has ranged from 0.33 to 19.08 cases per million births(Minor, 2009). Using the total population and birth rates from the National Bureau of Statistics to estimate the number of live births, the approximate recipient VAPP per million births during 2010–2015 was 1.34–2.34; similar to that of the US (1.91; 1961–1972), Cuba (2.91; 1963–2006), and England/Wales (1.68; 1985–1991)(Landaverde et al., 2014; Platt et al., 2014). In our analysis, using vaccines administered doses as the denominator, the recipient VAPP per million vaccination doses was 0.4 per million OPV doses or about 1 case per 2.67 million vaccines administered doses. This is similar to countries such as Japan (1 recipient VAPP case per 2.3 million doses in 1971–2000), India (1 recipient VAPP case per 2.8 million doses in 1999), and Brazil (1 recipient VAPP case per 2.39 million doses in 1989–1995)(Landaverde et al., 2014). In contrast, the VAPP risk was estimated as 1 case per 750,000 vaccine recipients in the U.S., and 1 per 400,000 in Norway, England, and Wales(Zuo et al., 2010); however, these rates include both recipient and contact VAPP. Without data on contact VAPP, the rates estimated from CNAEFIS could not be compared with these countries. Based on the vaccine doses, we could estimate the incidence of recipient VAPP after 3 doses. In our analysis, the risk after the first dose was highest (1.31 per million vaccine doses), which was about one in 760,000 vaccine doses, similar to international studies (one in 750,000 doses)(WHO, 2016). The risk after the second and third doses was significantly lower than after the first dose—about 1 in 9 million for the second dose and 1 in 26 million for the third dose, consistent with the WHO estimate(WHO, 2016).

6.5 Deaths reported in CNAEFIS

During six years of AEFI surveillance in mainland China, more than three quarters of reported AEFI-associated deaths were due to coincidental events, and only 16% could be attributed to vaccination by causality assessment. Most of those determined to be causally related to vaccination were related to anaphylactic reactions and disseminated BCG diseases. Although the reporting rates of neonatal deaths increased during 2013-2014, deaths that causally related to HepB were very rare during the study years.

Overall, our study provides reassuring information about the small risk of deaths following immunization. Although 5% AEFI-associated deaths were indeterminate cause, the AEFI investigation and causality assessment process provided valuable information to evaluate vaccine safety in China. The reporting peak of AEFI-associated deaths in late 2013 to early 2014, illustrates the sensitivity of passive reporting of serious AEFI to public information and the caution that should be exercised in interpreting peaks in serious AEFI reporting. Our analysis also illustrates progress made with vaccine safety monitoring during recent years in China.

Regarding the seasonal distribution of deaths during the study period, except for 2013, deaths were more common in winter than in summer months, consistent with findings of similar studies elsewhere(McGarthy et al., 2013). The results showed that children aged <5 years accounted for 95% of AEFI-associated death, which is consistent with Vaccine Adverse Event Reporting System (VAERS) data in the U.S(Moro et al., 2015) and the National Immunization Schedule in China. There were also more male than female deaths. This finding is consistent with data reported in the All Cause of Death Surveillance System in China (Chinese Center for Diseases Control and Prevention, 2013). Of the AEFI-associated deaths, 78.9% were classified as coincidental events. The reported causes of death were consistent with common causes of mortality nationally (Jianli Ye et al., 2012; Ren & Pang, 2016). According to the National Bureau of Statistics of the People's Republic of China, all-cause neonatal death rates during 2010-2014 were 5.9–8.3‰. The estimated neonatal death rates in this study were lower than all-cause neonatal death rates in the general population, suggesting no association of vaccinations with an increased risk of death at the population level.

Generally, parents have their children vaccinated when they are in relatively good health. In situations where the infant dies shortly after immunization, parents and even health providers may blame vaccine(Moro et al., 2015). Although vaccines play a vital role in preventing diseases in children, vaccine hesitancy has become an issue

in many counties, including China(W. Yu et al., 2016; Larson et al., 2013). Events in December 2013 in Hunan province of mainland China provide an example of how such concerns was arise (China Ministry of Health website.). Media reports of 17 infant deaths, including one case of anaphylactic shock following HepB vaccination, raised widespread public concern in China (W. Yu et al., 2016; M.-N. Li et al., 2014). After investigation, The China Food and Drug Administration reported that the deaths were not related to the vaccine, but instead with a variety of problems, including severe pneumonia, suffocation, kidney failure, severe diarrhea and congenital heart disease(W. Yu et al., 2016; M.-N. Li et al., 2014; Yan et al., 2015). In passive surveillance systems, the behavior of parents and vaccine providers behavior may influence the number of reports. This publicity may have increased public awareness and led to a tendency to report deaths after immunization during 2013-2014. Our analysis showed a reporting peak during 2013-2014, in which 94% of the neonatal deaths were reported to be related with HepB. However, vaccine reactions determined to be causally related to HepB were rare during the study years. Although the overall number of all AEFI reports in CNAEFIS increased from 2010 to 2015, the number of serious AEFIs (events causing a potential risk to the health/life of a recipient leading to prolonged hospitalization, disability/incapacity, congenital abnormalities/birth defects or death) has remained constant(Wu et al., 2012; Wu et al., 2013; Wu et al., 2014; Jiakai Ye et al., 2015; Jiakai Ye et al., 2016).

Causality assessments in China are performed in accordance to WHO guidelines (China MoH & China FDA, 2010; M. S. Gold et al., 2016). The documented causes of death that could possibly occur due to the inherent properties of a vaccine are limited and include anaphylaxis, viscerotrophic disease following yellow fever vaccine, disseminated attenuated live vaccine agent infection in severely immune-compromised individuals and death from intussusception following RotV (M. S. Gold et al., 2016). In China, yellow fever vaccine is not recommended, and RotV differ from those used internationally. In our study, the most common causes of vaccine-related reactions and deaths were anaphylaxis and disseminated BCG infections. BCG is recommended at birth, without screening to determine the status of the immune system at that time. In our study, several deaths were due to neurological diseases. There was no solid evidence that these neurological diseases were caused by the vaccines or vaccination, although some studies reported temporal associations of such diseases with various immunizations(Sejvar et al., 2007; Tapiainen et al., 2007). When no etiologic agent is identified, and the person was healthy prior to immunization, a suspicion may arise in the causality assessment that the vaccine contributed to the death. Several cases with STL was also assessed to be

causally related to vaccination during surveillance. STL is associated with immune system dysfunction, which occurs mostly in young children and young people. It is characterized by thymus hypertrophy, systemic lymphoid tissue proliferation (lymph nodes, respiratory and digestive tract lymphoid tissue and splenic lymph follicles), small heart, narrow circumference of aorta origin, adrenal and gonadal dysplasia, pale skin, rich subcutaneous fat, and late development of secondary sexual characteristics. Such a person may die suddenly when subjected to a mild stimulus, such as minor trauma, argument, sudden fright, anesthesia or injection. This kind of clinical state is difficult to recognize during one's lifetime and usually diagnosed by autopsy after death. As reported previously, mild immune stimulation, such as that produced by minor trauma or immunizations, could give rise to sudden death among individuals with STL (X. Zhang et al., 2011). The expert committee concluded that it triggered these deaths, even when neither the vaccine nor the vaccination was the direct cause. Case causality assessments are extremely difficult. Strengthening the capacity of AEFI investigation and causality assessment is very important in the field of vaccine safety surveillance and evaluation in China. In 2018, WHO issued revised classification for causality assessment(WHO, 2018a) which could be adopted and modified for the Chinese setting in future.

6.6 Evaluation of JE vaccines

In Study IV, although the number and reporting rates of AEFIs following live attenuated and inactivated JE vaccines increased during the study period, there was no statistical difference between the two vaccines overall, or for serious AEFIs. Serious AEFIs only account for 1% of all AEFIs. The increased trend in AEFI reporting rates following JE vaccines might be related to the development of improved reporting. The increasing trends were similar for reporting rates of all AEFIs during the same period.

Study IV included two JE vaccines used internationally: JEV-L and JEV-I. Different JE vaccines have been used in other countries. For example, the US used an inactivated mouse brain-derived JE vaccine (JEV-I) for travelers (most of whom were adults) from 1992–2009, while Japan used JEV-I for children. Takahashi(Takahashi et al., 2000) reviewed the post-marketing surveillance of JEV-I in Japan and the US and found that the adverse event rate was 2.8 per 100,000 doses in Japan and 15 per 100,000 doses in the US. Although the surveillance system, reporting scope, and denominators used were slightly different in China and other

countries, our reported AEFI rate for JEV-I was 17.6 per 100,000 vaccination doses, not substantially different from the US. JEV-L was widely used in WPR and Asia (China, Korea, and India), but very little systematic data are available on the adverse effects of JEV-L in these countries. An analysis of a post-marketing surveillance of JEV-L from 2009–2012 by the Chinese National Centre for Adverse Drug Reaction (ADR) Monitoring(WHO, 2015b) showed that of the 6024 AEFIs, only 70 were considered severe. The WHO advisory committee (GACVS) reviewed these data and noted that although no safety signals were identified, the number of events recorded in the AEFI reporting system was low given that >70 million doses of vaccines had been administered (WHO, 2015b).

Following WHO's positive assessment of Chinese Vaccine National Regulatory Authority in 2011 and with the rise of vaccine manufacturing in China, JEV-L was the first vaccine in China to be prequalified by WHO. Through ongoing surveillance and data mining analysis, we were able to monitor the vaccine safety of JEV-L produced and used in China.

In a previous analysis of CNAEFIS data, only JE vaccines alone, listed as the most suspected vaccine, were included in the study(D. Liu et al., 2008). However, in our study, at least one-third of AEFIs occurred when vaccines were administered concurrently. Furthermore, in the ≤1-year age group, the target group of NIP. more than half the AEFIs related to JEV-L were related to JEV-L in combination with other vaccines. In these situations, it was not possible to determine the vaccine responsible for some adverse events such as allergic reactions. Therefore, we included in the analysis all AEFIs related to JE in the CNAEFIS database.

The gender distribution of AEFIs related to JEV-L and JEV-I was similar to that of other vaccines(Wu et al., 2013)—the male to female sex ratio was>1. Most of the cases occurred among ≤1-year-olds, consistent with the Chinese immunization schedule for EPI vaccines. Most AEFIs were relatively mild and self-limiting, with a diagnosis of common and minor adverse reactions, including fever, local redness and swelling, and local induration.

The three measures of disproportionality analysis, including Proportional Reporting Ratios (PRR), Gamma-Poisson Shrinker algorithm (GPS), and Bayesian Confidence Propagation Neural Network (BCPNN) analyses, detected no SDR for JEV-L compared with JEV-I. Combined with the comparison of incidence rates between JEV-L and JEV-I, suggests no vaccine safety concern regarding JEV-L.

Febrile convulsions are the most common type of seizure in children, affecting 2–5% of children in North America and Europe and 6–9% of children in Japan(Daoud, 2004; Jones & Jacobsen, 2007). It usually occurs between 3 months

and 5 years of age, with a peak incidence at 18 months.(Waruiru & Appleton, 2004) This is also the target age for vaccinations, including JEV-L and JEV-I. Through some risk factors, such as family history and exposure to infectious illnesses, were found to be related to febrile convulsions in children, in general, about 50% of children who presented with febrile convulsion will have no identified risk factors(Waruiru & Appleton, 2004). Elevated body temperature is frequently observed following immunization, and febrile seizures are the most common type of non-epileptic seizure observed following immunization(Sun et al., 2012). Signals for possible association of febrile convulsion with vaccination were found following MMR, DTP, and InfV in the US and Australia(Leroy et al., 2012a; Cendes & Sankar, 2011; Jacobsen et al., 2009; Sun et al., 2012). In our study, by using the three data-mining methods, disproportionate reporting was detected for JEV-I and febrile convulsion compared with JEV-L, suggests that there were disproportionate reports of febrile convulsion after JEV-I compared to JEV-L.

7 CONCLUSIONS AND RECOMMENDATIONS

Although clinical trials and various regulatory processes assess safety and efficacy of vaccines, rare vaccine adverse events among large populations can only be captured through post-licensure monitoring of AEFIs. National passive AEFI surveillance is an important part of the public health surveillance system in Mainland China. Having undergone several years of development, CNAEFIS, the national AEFI surveillance system, has functioned well in accordance with the national AEFI guidelines issued in 2010. CNAEFIS as a public health surveillance system is simple to use and can adapt to new situations and requirements. Like other spontaneous reporting systems, the sensitivity of CNAEFIS is relatively low and varies by type of vaccine and event; however, its specificity is high. The geographic representativeness has also increased in the past 6 years. All three vaccine safety evaluation studies in this thesis provide a snapshot of the vaccine safety situation in Mainland China. Study II showed that recipient VAPP in China was a rare adverse consequence of receiving OPV, similar to that found in studies in other countries, and that the risk of recipient VAPP calculated using either estimated births or vaccination doses was also comparable to that reported in studies from the US and Japan. As polio's global eradication approaches, VAPP will become increasingly unacceptable. After the introduction of IPV and the replacement of tOPV, the burden of VAPP should diminish further. The AEFI-associated deaths study showed that the risk of deaths following vaccination was extremely small and did not identify specific safety concerns with vaccines used in China. The JE vaccine safety study did not show any apparent safety concerns regarding JE vaccines in Mainland China.

The epidemiology distribution of national AEFI surveillance during recent years and the three examples of VAPP, deaths and JE vaccines safety, illustrated that the progress of vaccine safety surveillance made nationally, and provide important evidence to document how safe immunization risks in mainland of China.

7.1 Strengthening vaccine safety surveillance and evaluation in China

Vaccines are among the safest medical products in use. However, parents will naturally become concerned when serious adverse events occur after vaccination, even though the event may only be temporally related to immunization(E. R. Miller et al., 2015). A functional vaccine safety surveillance system and thorough AEFI investigation for causality assessment can provide valuable information for both national regulatory authorities and the public (M. S. Gold et al., 2016). Based on the systems of the CDC/NIP and through fruitful collaborations with Chinese NRA, CNAEFIS has operated smoothly in the sphere of AEFI surveillance since 2010. The AEFI surveillance system was a project of cooperation with standard national guidelines and support from Chinese MoH; the national immunization technical expert committee; and the operation of national, provincial, prefectural, and county CDCs and physicians in vaccination clinics. Based on the national AEFI surveillance guidelines, all information gathered from AEFI reporting, investigation, and causality assessment have been compiled in this online system. Post marketing vaccine safety surveillance and evaluation is an important function of vaccines National Regulatory Authority (NRA. Based on the guideline, AEFI data analysis is a collaborative work of the China CDC and the China adverse drug reaction surveillance center (CDR), which oversees national adverse drug reaction surveillance. All the stakeholders, including CDC, CDR, MoH, CFDA and related administrative bodies, would share safety evaluation information and communicate routinely based on surveillance data. Through this close collaboration, the CNAEFIS can run smoothly and gather the database for post marketing vaccine evaluation in China. Since the national guidelines of AEFI surveillance were issued over 5 years ago, with the development of AEFI surveillance and vaccine safety research, along with advice from the WHO NRA reassessment in 2014, Chinese MoH and FDA are considering revisions to the guideline.

Our evaluation shows that several issues should be considered when revising the national guidelines to improve the CNAEFIS: First, the definition/scope of reportable cases should clearer and related to different vaccines. The scope of reporting in CNAEFIS could follow the structure of reporting events in the US VAERS which is more precise and related to vaccines. Therefore, it would also be easier to operate for local physicians and nurses. Second, For CNAEFIS itself, a combination of test-based and coded medication conditions in the database makes it hard to analyze the data, and it is not as precise as the standard coding system, for

instance, MedDRA, which is used by VAERS. It is extremely labor-intensive to analyze test-based information, and the unstandardized coding system could also influence the results of the data-mining of safety signals. MedDRA is used internationally to standardize diagnoses and symptoms. This should also be adopted in data analysis in CNAEFIS. Third, standardized case definitions have also not been used in CNAEFIS, and this has affected AEFI classification, which is based on causality assessment. There are more than 30 globally accepted case definitions by the Brighton Collaboration with WHO that provide clear criteria for degrees of diagnostic certainty.(Bonhoeffer et al., 2004) These could also be introduced in the CNAEFIS, as appropriate. Fourth, since reporting from different areas of China has been uneven, further quality improvement work, such as training, education and supervision, should be offered to the weaker areas.

For case investigation and causality assessment, consistency among different levels of the expert panels in charge of causality assessment should be evaluated and improved. Through Case causality assessments are extremely difficult, all the serious cases should be assessment by experts committee(China MoH & China FDA, 2010). Although the process of gathering information for investigation and causality assessment has been described in the national guidelines, the level of consistency in the workings of different levels of expert panels is not known. In our studies on recipient VAPP and fatalities in CNAEFIS, the clinical diagnosis the diseases and causality assessment which linked disease to vaccination, could influence the validity of the study. Since China has a large population, and there is 32 provincial level- and more than 400 prefectural level- AEFI experts committees, the causality assessment quality of expert committees is varied, even based on the same national principle. Also, the national compensation policy(China MoH & China FDA, 2010), which the victims related to vaccine-related reaction, could apply the economic compensation form the government or the manufactures, also affected the impartiality of causality assessment. Strength the capacity of AEFI investigation and causality assessment is an important work in field of vaccine safety surveillance and evaluation in China. The WHO had issued AEFI causality assessment: user manual for the revised WHO classification in 2018(WHO, 2018b) which could be adopted and modified for Chinese setting for future.

7.2 Implications for future studies on vaccine safety

The vaccine safety evaluation of recipient VAPP, fatalities, and JE vaccines indicate that AEFI surveillance data could provide valuable information on vaccine safety and generate evidence for policy making and immunization program development. As a passive surveillance system is aimed for vaccine safety signal detection and generating hypotheses, the analytic method could be further developed in CNAEFIS. Based on Study IV's JE vaccines analysis, besides traditional risk estimation using different denominators, a disproportionality reporting analysis is also recommended for signal detection using passive AEFI surveillance data, especially since this method needs no external data. Although we should be cautious about the signals it generates, it could be introduced as a compensatory method of analysis when using AEFI surveillance data to evaluate vaccine safety.

The AEFI surveillance data however can only provide information on cases after vaccination, whereas we need external information on controls, i.e., patients who have not been vaccinated. Various epidemiological methods, such as self-control case series, case control studies and cohort studies, could be implemented and applied to assess vaccine safety. We recommend further studies aimed at determining the effects of concurrent vaccination with JE vaccines and adopting more sensitive methods to detect signals.

Since live attenuated polio vaccines continue to be used in Mainland China, recipient VAPP is certainly a concern of the public and the immunization programs. This concern must continue to be addressed and investigated in the future. The JE vaccines safety analysis shows that there is a rise in JEV-I and febrile seizure cases compared to JEV-L, which might be a safety signal for future studies.

The CNAEFIS covers all vaccines used in Mainland China, but we only illustrated three examples, which were key concern during the study years. With the development immunization program, new vaccines might be introduced into immunization schedules that will be paid for by the government, such as a second dose of inactivated polio vaccines, varicella live attenuated vaccines, and seasonal influenza vaccines. Evaluating the safety of these vaccines will be done by using passive AEFI surveillance systems.

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10 APPENDIXS

Appendix 1 AEFI Case Reporting Form

Code	□□□□□□□□□□□□□□□
Name*	
Sex*	1. Male 2. Female
DOB*	□□□□/□□/□□
Occupation	
Present address	
Tel	
Guardian	

Suspicious vaccine and vaccination (start from the most suspicious vaccine)

	Vaccine name *	specifications (dose/vial or pill)	Manufacturer *	Vaccine batch No.*	Date of vaccination*	Vaccination format*	Vaccination dose*	Vaccination dosage (ml or pill)*	Vaccination route*	Vaccination site*
1										
2										
3										

Onset date*	□□□□/□□/□□
Detection date*	□□□□/□□/□□
Where to seek medical care	
Clinical process*	
Fever (axillary temperature ℃)*	1. 37.1-37.5 2. 37.6-38.5 3. ≥38.6 4. none
Localized redness and swelling (diameter in cm)*	1. ≤2.5 2. 2.6-5.0 3. > 5.0 4. none
Localized scleroma (diameter in cm)*	1. ≤2.5 2. 2.6-5.0 3. > 5.0 4. none
Primary clinical diagnosis	
Hospitalized*	1. yes 2. no
Patient outcome*	1. cured 2. improved 3. sequelae 4. death 5. unknown
Primary classification*	1. common adverse reactions 2. to be defined
Identified by:	1. passive surveillance 2 .active surveillance
Reporting date*	□□□□/□□/□□
Reporting unit *	
Reporter	
Tel	

Note: * key items.

Appendix 2 AEFI Case Investigation Form

A. Basic information

Code	□□□□□□□□□□□□□□
Name*	
Sex*	1. Male 2. Female
DOB*	□□□□/□□/□□
Occupation	
Present address	
Tel	
Guardian	

B. Past history

Any disease in the past before vaccination?	1. yes 2. no 3. unknown
If yes, disease name	
Any allergies in the past before the vaccination?	1. yes 2. no 3. unknown
If yes, name of allergic	
Family history	1. yes 2. no 3. unknown
If yes, name of disease	
Past history of adverse reactions	1. yes 2. no 3. unknown
If yes, onset date	□□□□/□□/□□
Vaccine name	
Clinical diagnosis	

C. The suspicious vaccine (start from the most suspicious vaccine)

	vaccine 1	vaccine 2	vaccine 3
Vaccine name*			
Specifications (dose/vial or pill)			
Manufacturer*			
Vaccine batch number*			
Valid until			
Having batch release certificate?			
Appearance of vaccine normal?			
Storage container			
Storage temperature (ºC)			
Delivery date for testing			
Having passed the inspection and control?			

D. The diluent

	vaccine 1	vaccine 2	vaccine 3
Name of diluent			
Specifications (ml/vial)			
Manufacturer			

Batch number			
Valid until			
Appearance of diluent normal?			
Storage container			
Storage temperature (ºC)			
Delivery date for testing			
Having passed the inspection and control?			

E. Syringe

	vaccine 1	vaccine 2	vaccine 3
Syringe name			
Syringe type			
Specifications (ml/vial)			
Manufacturer			
Syringe batch number			
Valid until			
Delivery date for testing			
Having passed the inspection and control?			

F. vaccination

	vaccine 1	vaccine 2	vaccine 3
Vaccination date*			
Vaccination format*			
Vaccination dose*			
Vaccination dosage (ml or pill)*			
Vaccination route*			
Vaccination site*			
Vaccinating unit			
Vaccination address			
Vaccinator			
Having vaccination training certificate?			
Vaccination performed correctly?			

G. Clinical information

Onset date*	□□□□/□□/□□
Detection date/date seeing medical care*	□□□□/□□/□□
Where to seek medical care	
Clinical process*	

fever (axillary temperature ºC) *	1. 37.1-37.5 2. 37.6-38.5 3. ≥38.6 4. none□
Localized redness and swelling (diameter in cm)*	1. ≤2.5 2. 2.6-5.0 3. > 5.0 4. none
Localized scleroma (diameter in cm)*	1. ≤2.5 2. 2.6-5.0 3. > 5.0 4. none
Primary clinical diagnosis	
Hospitalized*	1. yes 2. no
If yes, name of hospital	
Medical record number	
Admission date	□□□□/□□/□□
Discharge date	□□□□/□□/□□
Patient outcome*	1. cured 2 .improved 3. sequelae 4. death 5. unknown
If death, date of death	□□□□/□□/□□
Autopsy done?	1. yes 2. no
Conclusion from the autopsy	

H. Other information

Vaccine distribution and vaccination implementation process	
Vaccine doses of the same type and same batch that have been vaccinated and occurrence of adverse reactions	
Local incidence of similar disease	

I. Reporting and investigation

Identified by	1. passive surveillance 2. active surveillance□
Reporting date*	□□□□/□□/□□
Reporting unit *	
Reporter	
Tel	
Investigation date*	□□□□/□□/□□
Investigation unit	
Investigator	

J. Conclusion

Conclusion made by*	1. medical association 2. Investigation and Diagnosis Expert Panel 3. CDC 4. healthcare facility
Level*	1. provincial 2. prefectural 3. county
Type of reactions*	1. common adverse reactions 2. rare adverse reactions 3. vaccine Quality Event 4. Program Error 5. Coincidental event 6. psychogenic reaction 7. to be defined
If it is an adverse reaction, severity of damage to the body	_____ (refer to the "Criteria for Classifying Medical Accidents")
Final clinical diagnosis*	

Whether a serious AEFI?	1. yes 2. no
Whether a AEFI cluster?	1. yes 2. no
If yes, code of the AEFI cluster?	□□□□□□□□□□□□

Notes: * key items.

ORIGINAL PUBLICATIONS

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Surveillance of adverse events following immunization in China: Past, present, and future

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Surveillance of adverse events following immunization in China: Past, present, and future

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ABSTRACT

Surveillance for adverse events following immunization (AEFI) is an important component of any national immunization program. In the People's Republic of China (China), a populous, middle-income country, development of an AEFI surveillance system began in 2005. In 2008, the AEFI surveillance system was implemented as a nationwide, online system and called the Chinese National AEFI Information System (CNAEFIS). Since then, CNAEFIS has provided useful, national-level data on vaccine safety. National AEFI surveillance guidelines were issued jointly by the Ministry of Health and the China Food and Drug Administration in 2010. This article reviews the development, status, and key aspects of the Chinese AEFI surveillance system, and describes challenges and future plans for vaccine safety assessment in China.

1. Introduction

Vaccines are considered one of the most effective interventions to improve global public health [1]. However, due to successes of vaccines, vaccine-preventable diseases (VPDs) have become less frequent, or even rare, and public attention often shifts from VPDs to the safety of vaccines and adverse events associated with vaccines. Widespread concern about the occurrence of adverse events following immunization may lead to a loss of confidence in the safety of vaccines, low vaccination coverage, and even a resurgence of VPDs [2]. The safety of vaccines is evaluated extensively through pre-licensure animal studies and human clinical trials, and through post-licensure surveillance [3]. Safety monitoring in post-licensure surveillance has relied primarily on passive reporting systems and epidemiological studies [3,4].

China is one of the most populous, rapidly-developing countries in the world, with an annual birth cohort of over 16 million; China uses an average of more than 500 million vaccine doses annually [5]. China's National Expanded Program on Immunization started in 1978 and provides government-purchased vaccine at no cost to parents for all children under 7 years of age, regardless of socioeconomic status [6]. Since 2008, the National Immunization Program (NIP) has included 14 types of vaccines targeting 15 VPDs (Table 1) [6]. China's large demand for vaccines is fulfilled by more than 60 vaccine presentations that are licensed for the Chinese market; more than 80% of these vaccines are made domestically and are administered through NIP [7]. Conducting adequate pharmacovigilance for this large number of vaccines and the hundreds of millions of vaccine doses administered requires a credible system to monitor adverse reactions, detect and respond to emerging vaccine safety signals, and address concerns of the public and the media [7]. The purpose of this article is to review the development and status of the Chinese AEFI surveillance system, and to discuss challenges and future plans for vaccine safety assessment in China.

2. History of AEFI surveillance in China

Although the China Ministry of Health (MOH), issued guidance for handling vaccine adverse reactions in 1980 [8], nationwide AEFI surveillance was not implemented until 2005. In March, 2005, with the technical support of the World Health Origination (WHO), the Chinese Center for Disease Control and Prevention (CDC) launched a pilot study of passive surveillance for AEFI in 10 of China's 31 provinces [9]. These 10 provinces used a unified set of guidelines, which were based on the WHO AEFI surveillance guidelines [10].

Following development of the AEFI surveillance guidelines and with technical support from China CDC, several additional provinces joined the safety system pilot. By 2006, the 10 original pilot provinces and 6 additional provinces reported AEFI cases to the surveillance system [11]. To further enhance surveillance, in

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0264-410X/

Table 1
National Immunization Program vaccines and targeted VPDs.

Vaccine	VPD
Hepatitis B vaccine (HepB)[#]	Hepatitis B
Bacilli Calmette-Guérin vaccine (BCG)[#]	Tuberculosis
Oral poliomyelitis attenuated live vaccine (OPV)[#]	Polio
Diphtheria tetanus and acellular pertussis combined vaccine (DTP)[#]	Diphtheria, tetanus, and pertussis
Diphtheria and tetanus combined vaccine (DT)	Diphtheria and tetanus
Measles attenuated live vaccine (MV)[#]	Measles, mumps, and rubella
Measles mumps and rubella combined attenuated live vaccine (MMR) (including measles and rubella combined attenuated live vaccine and measles and mumps attenuated live vaccine)	
Japanese encephalitis attenuated live vaccine (JE-live)	Japanese encephalitis
Group A meningococcal polysaccharide vaccine (MPV-A)	Meningococcal meningitis
Group A and C meningococcal polysaccharide vaccine (MPV-AC)	
Hepatitis A attenuated live vaccine	Haptitis A
Hemorrhagic fever with renal syndrome vaccine (HFV)[*]	Hemorrhagic fever with renal syndrome
Anthrax vaccine[*]	Anthrax
Leptospira vaccine[*]	Leptospira

[#] Included in the original National Immunization Program.
[*] High risk individuals only.

2007 and 2008 China CDC supported 5 counties to conduct intensive AEFI surveillance using an online AEFI information system [12]. During this time, China CDC launched a series of AEFI surveillance training workshops to promote AEFI reporting. In 2008, the online China National AEFI Information System (CNAEFIS) was expanded to cover all 31 provinces in China [13].

CNAEFIS played a key role in the collection of AEFI reports during the large influenza vaccination campaign response to the 2009 A(H1N1) influenza pandemic [14], leading to further improvement of AEFI surveillance in China. In June 2010, MOH and China Food and Drug Administration (CFDA) jointly issued national AEFI guidance [15]. According to this guidance, CNAEFIS (http://219.141.175.204/) became the official AEFI information system, and was to be owned and maintained by China CDC. In order to support vaccine regulatory oversight, AEFI data collected through CNAEFIS are shared routinely with Adverse Drug Reaction monitoring centers (ADR) in China.

Since 2005, the number of AEFI cases reported to the surveillance system has increased by approximately 30% year by year. By 2013, CNAEFIS had over 300,000 AEFI reports, and more than 90% of China's 3100 counties were reporting AEFI cases to CNAEFIS (Fig. 1).

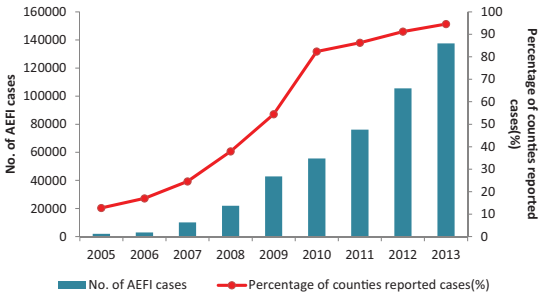

Fig. 1. Number of AEFI cases and percentage of reporting counties in China, 2005–2013

Table 2
Scope of reporting.

AEFI onset time since vaccination	Specific AEFI
Within 24 h	Anaphylactic shock, allergic reactions without shock (hives, rash, laryngeal edema, etc.), toxic shock syndrome, syncope, hysteria
Within 5 days	Fever (axillary temperature ≥38.6 °C), angioedema, systemic purulent infection (toxemia, septicemia, sepsis), redness and swelling at the injection site (diameter >2.5 cm), induration (diameter >2.5 cm), localized purulent infection (localized abscess, lymphangitis, lymphadenitis, or cellulitis)
Within 15 days	Measles-like or scarlet-fever-like rash, Henoch Schonlein purpura, localized allergic necrotic reaction (Arthus reaction), febrile convulsion, epilepsy, polyneuritis, encephalopathy, encephalitis, and meningitis
Within 6 weeks	Thrombocytopenic purpura, Guillain-Barre syndrome, vaccine-associated paralytic poliomyelitis.
Within 3 months	Brachial neuritis, sterile abscess in the injection site
1–12 months after BCG vaccination	Lymphadenitis or lymphangitis, osteomyelitis, systemic disseminated BCG infection
Unspecified time frame	Other serious AEFI suspected to be related to a vaccination

3. Description of AEFI surveillance in China

CNAEFIS is operated in accordance with China's national AEFI guidelines [15]. These guidelines are, in turn, supported by the Law on the Prevention and Treatment of Infectious Diseases of the People's Republic of China [16], the Pharmaceutical Administration Law of the People's Republic of China [17], the Administrative Regulation on the Circulation of Vaccines and Vaccination [18], the Regulations on Preparedness for and Responses to Public Health Emergencies [19], and other laws and regulations, with reference to WHO's guidelines on AEFIs [10], and with the intent to improve vaccine safety and immunization service quality.

An AEFI case is defined as a reaction or an event following vaccination that is suspected to be related to the vaccination. AEFI surveillance covers all vaccines marketed in mainland China, with a scope of reporting as shown in Table 2. Healthcare facilities, vaccination clinics, Centers for Disease Control and Prevention at all 4 administrative levels, adverse drug reaction (ADR) monitoring agencies, and vaccine manufacturers executive staff are all responsible reporting units and reporters of AEFIs. The reporting of AEFIs is implemented in line with the principle of localized management. The public or the guardian (parents) can notify any of the above authorized reporters to report an AEFI. Cases are gathered by local, county-level CDCs, which are responsible for completing AEFI Case Reporting Cards and submitting data to CNAEFIS. Duplicate reports are identified and de-duplicated centrally in CNAEFIS. Once case information is entered, it can be viewed by all administrative levels of CDCs and ADRs.

All AEFIs are to be investigated, with the exception of common adverse reactions that have a clear diagnosis (e.g., fever, redness, and swelling on the injection site; induration). County CDCs start investigations by collecting relevant data and completing an AEFI Case Investigation Form, which is subsequently entered into CNAEFIS. For deaths, serious AEFIs, AEFI clusters, and AEFIs of significant public concerns that are suspected to be related to immunization, upon receiving CNAEFIS reports, prefectural or provincial CDC must immediately organize an AEFI expert panel for investigation.

As a key part of an investigation, county CDCs organize a set of relevant experts in clinical medicine, epidemiology, laboratory practices, pharmacy, vaccinology, vaccine regulation, and other fields relevant to the case. This set of experts is charged with making

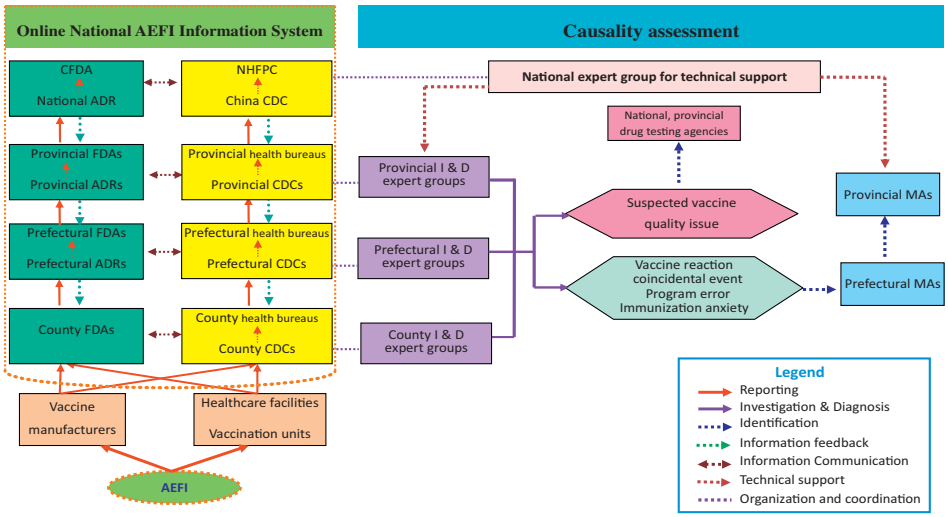

Fig. 2. AEFI reporting, investigation, and causality assessment flow chart

a diagnosis and assessing causality of the AEFI. For deaths, serious AEFIs, AEFI clusters, and AEFIs of significant public concern, the higher-level prefectural or provincial CDCs organize an AEFI Investigation and Diagnosis Expert Panel to conduct diagnostic and causality assessment. Reporting and investigation flow charts are shown diagrammatically in Fig. 2.

Following investigation and causality assessment, AEFI cases are classified into 1 of 5 categories (Table 3). AEFIs are classified as serious if they are any of the following: death, life-threatening condition, permanent or significant disability, or damage to organs or body functions. Serious AEFIs 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, vaccine-associated paralytic poliomyelitis, BCG osteomyelitis, systemic disseminated BCG infection, syncope, toxic shock syndrome, and systemic purulent infection.

Analysis of national AEFI surveillance is published monthly in the National Immunization Program Bulletin, which is distributed to CDCs and shared with ADRs. Analyses of AEFI surveillance data are published annually in the Chinese Journal of Vaccine and Immunization [11,13,20–23]. Analyses of AEFI data reported during special immunization campaigns, such as measles supplementary immunization activities (SIAs) [24] and the A(H1N1) influenza response vaccination campaign [14], have also been published in Chinese and international scientific journals. For example, an early paper on post-marketing safety surveillance of the 2009 A(H1N1) influenza vaccine was published shortly after the vaccination campaign in China [14].

In addition to information shared among CDCs and other vaccination stakeholders, vaccine safety information is released to the public through press releases and news announcements by MOH. Beginning in 2013, annual national AEFI surveillance information is released jointly by MOH and CFDA to the general public through websites (http://www.chinacdc.cn/jkzt/ymyjz/ymyjjz_6758/201412/t20141230_108607.htm), providing information on the safety of vaccines given to children.

Since the establishment of CNAEFIS, AEFI data have been used extensively by the Chinese national vaccine regulatory authorities (primarily CFDA and MOH) to study the safety of vaccines used in China. For example, using AEFI data in CNAEFIS, NIP and ADR analyzed safety data for the novel 2009 A(H1N1) influenza vaccine [14] and the JE live-attenuated vaccine, both of which were manufactured in China [25]. An important purpose of passive AEFI surveillance is to detect emerging vaccine safety signals. With the development of CNAEFIS, NIP scientists detected an increased incidence of anaphylactic shock after vaccination with a manufacturer's hepatitis A live attenuated vaccine in 2011 and 2012 (unpublished data). Although there was not enough evidence to show that an increased incidence of anaphylaxis shock was caused by this particular hepatitis A vaccine (still under investigation), following discussions between CFDA and the manufacture, the manufacture decided to withdraw their product from the market pending further investigation.

The identification of vaccination medical practice errors and related adverse reactions is of great importance because these errors are preventable and have potential to derail the benefit of the immunization program. Between 2008 and 2013, about 1% AEFI cases in CNAEFIS have been identified as program errors, primarily related to MMR and BCG vaccination.

Although AEFI surveillance in China is passive, it does have several advantageous characteristics. CNAEFIS is supported by national vaccination and immunization laws and regulations, and China CDC's national AEFI surveillance guidelines are the official standards for conducting AEFI surveillance. The reporting of AEFIs is mandatory for all health professionals and vaccine providers. CNAEFIS is the primary tool to collect AEFI data so that these data can be used rapidly, efficiently, effectively and conveniently. The system is an online system that is designed to ensure data quality through data verification at all levels of CDCs, especially for rare and serious cases.

China has a mechanism to arrange for panels of AEFI experts to participate in investigations and conduct causality assessments. The immunization program in China is a unified, vertically integrated immunization program, and all provinces, prefectures, and counties have CDCs that participate in the vaccine safety surveillance system. In China CDC NIP, the AEFI Surveillance and Management Division was established in January of 2009, and by 2014, several province-level CDCs also established AEFI surveillance divisions. China CDC NIP has an ongoing training plan for AEFI

Table 3
Cause-specific classification of AEFIs.

Category	Definition
Adverse reaction following immunization or vaccine reaction following immunization	Unexpected harmful reactions or reactions unrelated to the expected purpose of the vaccination that occur after standard vaccination with a vaccine product, including common adverse reactions and rare adverse reactions Common adverse reaction or common vaccine reaction: reactions caused by the inherent character of the vaccine after vaccination, and that only impair body functions transiently. They mainly include fever and localized redness and swelling that may be accompanied by discomfort, fatigue, poor appetite, tiredness, etc. Rare adverse reaction or rare vaccine reaction: Drug adverse reactions occurring during the process of, or after a standard vaccination with a qualified vaccine that caused damage to tissues or organs, or damage to functions of the vaccine recipient, when all parties involved have made no medical errors. Included are reactions caused by the inherent character of the vaccine that might be related to the strain, purity, production technology, or added substances of the vaccine such as antiseptics, stabilizers, and adjuvants
Vaccine quality event	Damage to tissues or organs, and damage to functions of the vaccinated person due to substandard quality of the vaccine. Substandard quality refers to problems with the strain and purity of the vaccine, production technology, or with added substances in the vaccine (excipients), exogenous factors, and if inspection and control of the vaccine were not consistent with national protocols or standards for vaccine production
Program error	Damage to tissues or organs, and damage to functions of the vaccine recipient due to violation of standard operational practices, vaccination procedures, guidelines for using the vaccine
Coincidental event	The vaccine recipient was in the incubation stage or preclinical stage of a certain condition, and the onset of the disease coincides with the vaccination by chance. Coincidental events are not caused by the inherent character of the vaccine
Psychogenic reaction or injection reaction	Individual reactions or reactions of groups of individuals that occur during or after the vaccination due to the psychological responses of the vaccinees. Psychogenic reactions are not caused by the inherent character of the vaccine

surveillance staff and physicians to build and sustain the capacity of AEFI surveillance. Since 2005, training workshops or conferences on AEFI surveillance have been conducted at least annually. This AEFI training program will be continued to help ensure highly qualified staff for AEFI surveillance in China.

4. Challenges and future work

Passive vaccine safety surveillance is cost-effective [3,4], and CNAEFIS is able to collect timely national AEFI data and detect rare and severe events. With a growing number of years of experience and data, CNAEFIS is providing a baseline of AEFI information in a very populous country. Using vaccine doses administered data that are available in China, CNAEFIS may also be able to detect changes in reporting rates of known adverse events to help determine whether changes in established rates reflect uneven reporting.

A disadvantage of CNAEFIS's passive surveillance, as with other countries' passive systems such as the national AEFI reporting surveillance in Australia [26] and the Vaccine Adverse Event Reporting System (VAERS) in the United States [27], is under-reporting and reporting bias. An evaluation of CNAEFIS as a public health surveillance system is being conducted, and involves the assessment of 9 system attributes, including simplicity, flexibility, data quality, acceptability, sensitivity, predictive value positive, representativeness, timeliness, and stability, to ensure that AEFI are being monitored efficiently and effectively. Although vaccine doses administered data are also collected by NIP [28], calculations of the incidence rates of AEFIs in passive surveillance system have inherent biases [29], necessitating a cautious interpretation of rates. To strengthen passive AEFI surveillance, China CDC launched an intensive surveillance effort in 5 counties for several vaccines, including measles–mumps–rubella combined vaccine (MMR) and hepatitis A vaccine (HepA), from August 2007 to July 2009 [12]. Annual training programs have been used to build reporting and analytic capacity of AEFI staff, healthcare providers, and diagnostic AEFI expert panels, in order to enhance AEFI surveillance development.

In addition to the need to continually improve passive AEFI surveillance, there are several qualitative changes to surveillance that could be considered to better understand vaccine safety in China. These qualitative changes include use of new data mining methods for signal detection that are compatible with the CNAEFIS database, active surveillance, and clinical data linkage for more robust causality assessment.

For recording AEFI cases, CNAEFIS uses a combination of coded diagnoses and text-based medical conditions. For example, medical conditions, such as fever, local redness, swelling, local induration and clinical diagnosis are symbol-coded events, while other clinical information is recorded as in free text in CNAEFIS. Compared with VAERS, which adopted MedDRA (Medical Dictionary for Regulatory Activities) and with the WHO Uppsala Monitoring Centre (UMC), which adopted WHO-ART (Adverse Reaction Terminology), CNAEFIS's text-based information is not as precise CNAEFIS's coded data. Without a standardized coding system, it is more challenging to conduct automated search for related cases [30]. As a consequence, whenever new variables and codes are adopted, web-based CNAEFIS text fields must be updated. Beginning in 2012, China CDC started to upgrade CNAEFIS, adding new information from AEFI reports using coded medical symbols and clinical diagnoses, and linking AEFI cases to immunization administration registration data. The new CNAEFIS will be used in 2015, with the website of www.nipis.chinacdc.cn. Linkage between CNAEFIS and immunization administration registration data will improve rate determinations and causality assessments.

For the purpose of vaccine injury compensation [31], an expert panel reviews AEFI case investigation information and conducts an individual causality assessment–an explicit linkage that is different from many other countries' vaccine safety surveillance systems and injury compensation programs. However, standardized case definitions have not been used in CNAEFIS, and this has affected AEFI classification, report reviews, and even causality assessment. The Brighton Collaboration with WHO (website: https://brightoncollaboration.org/public) has developed more than 30 globally-accepted case definitions that provide criteria for degrees of diagnostic certainty [32]. Experts in China have attempted to apply the Brighton Collaboration case definitions for AEFI surveillance [33], and China CDC is determining how to apply the Brighton Collaboration case definitions in China's system. With the support of WHO, China CDC is gradually developing its own case definitions as a reference for AEFI investigation and causality assessment that are based on Brighton Collaboration case definitions. In 2013, WHO updated its causality assessment methodology and its guidelines for program managers for immunization safety surveillance [34]. Following a China AEFI causality assessment training workshop supported by WHO in 2012, China CDC is working to apply the updated WHO methodology for causality assessment [34], including the updated algorithms and classifications.

One of the primary goal of AEFI passive surveillance is to detect vaccine safety signals and generate hypotheses for further studies [35]. Vaccine safety signals provide data for action. Although CDCs are only the users of vaccines and not responsible for the

manufacturing quality of vaccines, when abnormal vaccine safety signals are detected, CDCs are the frontline guardians to protect vaccinated individuals and the public. Using vaccine doses administered as a denominator, AEFI incidence rates are calculated. Through comparison with historic data and published studies, emerging vaccine safety signals are detected. However, since serious AEFIs are, fortunately, very rare – as examples, acute disseminated encephalomyelitis (ADEM) and Guillain–Barre syndrome (GBS) – it could be difficult to detect emerging signals, especially if vaccine lot information is not included in doses administered data. China CDC is learning new methods for vaccine safety signal identification for action. In the US CDC, a new data mining method, Proportional Reporting Ratio (PRR), has been used to screen VAERS data and generate signals, including signals from seasonal influenza vaccines and from newly licensed vaccines [29,36]. WHO UMC has used a similar data mining method, Bayesian Confidence Propagation Neural Network (BCPNN) [37]. China CDC has studied these new data mining methods, and plans to apply them in CNAEFIS for signal screening and for triggering follow-up actions.

To overcome challenges of using passively-acquired surveillance for validation of potential signals, some experts have advised the inclusion of active surveillance into AEFI surveillance. Active surveillance has potential to determine whether an adverse event is causally linked to vaccination (population causality assessment), and, if a causal relation is identified, the rate of the event or the vaccine's attribute risk [3,38] can be estimated. A recently-published article reviewed active adverse event surveillance systems worldwide [39]. Nine active systems were reviewed, including the US, Canadian, some European countries, and Asian countries' systems. Due to differences in healthcare systems, these active surveillance systems differed substantially from each other. Each had its own strengths and weakness, which indicated to us that we should create our own active surveillance according to Chinese situation. Following the positive reassessment by WHO of China's vaccine National Regulatory Authority in 2014, China CDC has started to determine how to build active vaccine safety surveillance that will work effectively in the Chinese healthcare system.

To offset passive AEFI surveillance's underreporting and inability to establish a causal relationship between vaccination and a specific adverse event, clinical data linkage has been used to assess vaccine safety by some developed countries, such as US, Australia and some parts of Vietnam [40–42]. In China, by 2007, most national- and provincial-level hospitals owned a local Hospital Information System (HIS), and about 38% of county-level hospitals had various types of HISs, according to the statistical data of the Ministry of Health in mainland of China [43]. Electronic Medical Records (EMR), which are key components of an HIS, contain information concerning patients' hospitalizations. The presence of these HISs, in conjunction with immunization information systems in China's CDCs, make it possible in theory to develop a data linkage system in China in the near future.

5. Conclusions

National AEFI surveillance is a key component of vaccine safety evaluation. China CDC developed CNAEFIS, which has served as the national passive surveillance system since 2005. So far, it has successfully captured more than 300,000 AEFI cases, providing a fundamental database for vaccine safety evaluation in mainland China. Experience and evidence drawn from CNAEFIS has been a vital resource for decision making by China's vaccine National Regulatory Authority and related stakeholders. In the future, strengthening the capacity and capabilities of passive surveillance, and developing new, active vaccine safety surveillance and analytical methods will be priorities for the Chinese AEFI surveillance program.

Conflict of interest statement

Authors declare there are no conflicts of interest.

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PUBLICATION II

Recipient vaccine-associated paralytic poliomyelitis in China, 2010–2015

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Recipient vaccine-associated paralytic poliomyelitis in China, 2010–2015

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ABSTRACT

Introduction: Vaccine-associated paralytic poliomyelitis (VAPP) is one of the most important adverse effects of vaccines that are in current use globally. The Chinese national adverse event following immunization information system (CNAEFIS) is a passive surveillance system which collects data on VAPP.
Aims: To describe the epidemiological characteristics of VAPP and estimate the risk of recipient VAPP in China.
Methods: We retrieved information from reported cases of recipient VAPP from CNAEFIS from 2010 to 2015, examined the demographic characteristics of the cases, and used administrative data on vaccination doses and the estimated number of births as denominators to calculate VAPP incidence.
Results: During 2010–2015, 157 cases of recipient VAPP were reported to CNAEFIS (male-to-female ratio, 8.2:1); 151 cases (96.2%) were less than six months old. All cases were associated with trivalent OPV (tOPV), and 89.8% occurred after the receipt of first dose. Of the 157 recipient VAPP cases, type II, type III, and type I poliovirus vaccine strains were isolated from 27 (17.2%) , 25 (15.9%) , and 16 (10.2%) cases, respectively. One case died and one case recovered completely; the other 155 cases had various physical disabilities, such as monolateral or bilateral limping. Using the administered doses of OPV as the denominator, the incidence of recipient VAPP during the study period was estimated at 0.4 per million doses. The estimated recipient VAPP per million births ranged from 1.0 to 2.4 during 2010–2015.
Conclusion: The epidemiological characteristics of recipient VAPP cases in China, such as age distribution, were comparable to those in previous studies from other countries. The risk of recipient VAPP, using either estimated births or vaccination doses, was comparable to that in the US and Japan. We recommend using an inactive poliovirus vaccine to decrease the number of recipient VAPP cases in China.

1. Introduction

The oral poliovirus vaccine (OPV), which contains live, attenuated poliovirus strains types I, II, and III, has served as the primary tool for eradicating polio worldwide [1,2]. Poliovirus vaccines have had a dramatic effect on the incidence of polio in developed countries since their introduction [2]. OPV was developed in 1959 and manufacturing began in 1962 in China, as it was felt that an oral vaccine would more closely imitate natural infections due to its similar route of ingestion, and would thus potentially interrupt transmission much more effectively [2].

China reported 20,000–43,000 polio cases each year in the early 1960s, making it a major affected area [3]. Chinese national immunization program began in 1978, and China started to implement the planned immunization schedule, in which OPV was recommended to children in certain age brackets [4]; according to the schedule, the recommended ages for OPV were two months, three months, four months, and four years for each dose. Subsequently, the number of polio cases declined dramatically, and in 2000, the West Pacific Regional Office (WPRO) of the World Health Organization (WHO) certified the nation to be polio-free. There have been no reported indigenous wild poliovirus cases in China since 1994 [5]. In 2011, an outbreak of imported wild-type poliovirus occurred in the Xinjiang Uygur Autonomous Region in northwest China.

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Supplementary immunization activity was launched and five rounds of OPV vaccination were conducted among children and adults; the outbreak ended 1.5 months after laboratory confirmation of the index case [6], and China was again certified by the WHO as being polio-free [5].

Despite the great advantages of OPV in preventing wild poliovirus, reversion of the attenuating mutations during OPV replication could lead to an increase in neurovirulence, thus triggering abnormal reactions and even serious cases [2].

In polio eradication environments, such as China, vaccine-associated paralytic poliomyelitis (VAPP), which is the only serious adverse event associated with OPV [1], became a public health problem. In the second half of 2005, parents from different provinces sought medical treatment in Beijing for their children, who had developed abnormal limbs [3]. The Chinese government issued several laws and policies aimed to compensate VAPP patients. As neonatal immunodeficiency is a rare but natural part of infancy, "one in a million" victims cannot be avoided when using OPV.

VAPP is one of the most important vaccine-caused adverse effects of vaccines that are in current use globally. With the near-disappearance of wild-type polio, VAPP emerged as the largest cause of paralysis from polioviruses. One of the reasons for the Global Polio Eradication Initiative's Polio Endgame Strategic Plan 2013–2018 is to reduce VAPP. The WHO polio vaccine position paper indicates that countries in which VAPP is a concern, a sequential inactive poliovirus vaccine (IPV)/OPV schedule can be adopted. In response to WHO's planned global action of switching from trivalent OPV (tOPV) to bivalent OPV (bOPV) in April 2016, which was aimed at mitigating VAPP after conducting a pilot study with IPV in 2015, the attenuated poliovirus vaccine has been switched from tOPV to bOPV and IPV was included as the first polio vaccination dose across China as of May 1, 2016. Consequently, it was expected that VAPP cases would decrease significantly and ultimately disappear in the near future. We reviewed data from national AEFI surveillance to (1) describe the epidemiological characteristics of recipient VAPP cases as adverse events following immunization in China, and (2) estimate the risk of contracting recipient VAPP during the study years.

2. Methods

2.1. Chinese national AEFI surveillance system (CNAEFIS) [7]

CNAEFIS is an online AEFI information reporting system. In June 2010, the Chinese Ministry of Health (MoH) and Chinese Food and Drug Administration (CFDA) jointly issued national AEFI guidelines for reporting and management [8], making the CNAEFIS the only and official vaccine safety surveillance system in mainland China.

According to national AEFI guidelines, an AEFI case for surveillance is defined as a reaction or event after vaccination that is suspected to be related to the vaccination. Healthcare facilities, vaccination units, centers for disease control and prevention (CDCs), adverse drug reaction (ADR) monitoring agencies, vaccine manufacturers, and their executive staff are the responsible reporting units for AEFI. The reporting of AEFI is implemented in line with the principle of localized management, although the public can also notify any of the reporters listed above. Case reports are compiled by local county CDCs, which can verify AEFI Case Reporting Cards and enter them into the CNAEFIS; from there, duplicate reports can be detected and deleted. Once cases are entered into the CNAEFIS, they can be viewed by all levels of CDCs and ADRs.

Any AEFI with the exception of common adverse reactions with a clear diagnosis (e.g., fever, redness and swelling at the injection site, induration) should be investigated. For an AEFI in need of investigation, county CDCs should begin by collecting relevant data and then complete the AEFI Case Investigation Form; it can then be reported to CNAEFIS.

2.2. Causality assessment in CNAEFIS

According to national AEFI guidelines [8], every level of the CDC, including county, prefectural, and provincial, should organize an AEFI Investigation and Diagnosis Expert Committee, which should include relevant experts in clinical medicine, epidemiology, laboratory practices, pharmacy, vaccinology, vaccine regulation, and related fields. This committee should be in charge of making diagnoses and determining the cause of the AEFI when needed. For deaths, severe disabilities, AEFI clusters, and an AEFI of significant public concern, prefectural or provincial CDCs should organize an AEFI Investigation and Diagnosis Expert Panel, which should include experts involved in the related committee, for diagnosis and causality assessment.

Similar to WHO vaccine safety surveillance guidelines [9,10], after the causality assessment, the AEFI should be classified into the following categories [7,8]: (1) vaccine-related reaction or vaccine product-related reaction; (2) vaccine quality reaction or vaccine quality defect-related reaction; (3) program error or immunization error-related reaction; (4) coincidental event; (5) psychogenic reaction or immunization anxiety-related reaction.

2.3. Case definition of VAPP in CNAEFIS

In 2008, the Ministry of Health of the People's Republic of China issued two regulations on the diagnosis and verification of VAPP: "Instruction advice on diagnosis and treatment of vaccine associated paralytic poliomyelitis" (Wei Ban Yi Fa [2008] No.17), and "Instruction advice on verification of VAPP and handling of remaining problems" (Wei Ban Fa [2008] No. 40).

In these regulations, there are two types of VAPP: recipient and contact. In CNAEFIS, contact VAPP is not included. Recipient VAPP, on the other hand, is defined as a case of (1) fever occurring 4–35 days after vaccination, acute flaccid paralysis (AFP) occurring 6–40 days after vaccination, and a clinical diagnosis compatible with paralytic poliomyelitis, or (2) Isolation of vaccine-related poliovirus from stool samples, which are used as supplementary conditions. Similar to other AEFI cases, recipient VAPP is also investigated by a panel of experts and receives a causality assessment based on the clinical and epidemiological characteristics of the cases.

2.4. Data analysis

For each case, we reviewed the date of occurrence, gender, age, address, OPV vaccination history, and serotype of vaccine strains.

For risk calculations, two methods were used [11]: VAPP per million administered OPV doses, and VAPP per million births. The risk of recipient VAPP per administered OPV doses was calculated by using the number of recipient VAPP cases reported during the study period divided by the total number of OPV doses administered during the same period. The OPV-administered doses were collected from a Chinese immunization information system, which collects immunization doses of all vaccines in national immunization schedules, including OPV. However, the immunization doses of OPV in supplementary immunization activities launched at the provincial level are not collected in this system. VAPP per million births was calculated by using the number of recipient VAPP cases divided by the number of estimated births during the same period.

The estimated births were calculated by multiplying the total population by birth rate. Both total population and birth rate were determined from China's National Bureau of Statistics website [12]. The data from 2010 were census data, while data from other years were from annual sampling surveys.

3. Results

3.1. Characteristics of VAPP cases

There were 157 recipient VAPP cases reported to CNAEFIS during 2010–2015. The male to female ratio was 8.2:1; 151 cases (96.2%) were children less than six months of age. Twenty-four of 31 provinces and the Xinjiang Production and Construction Crops in China reported recipient VAPP; 51.6% (81 cases) were reported from eastern regions, 38.9% (61 cases) from middle regions, and 9.6% (15 cases) from western regions. The number of recipient VAPP cases by year, gender, and age are summarized in Table 1. Perianal abscess was reported in 24.8% (39 cases) of the 157 recipient VAPP cases, all of whom were male infants.

The vaccines associated with all recipient VAPP cases in CNAEFIS from 2010 to 2015 were trivalent OPV (tOPV), which was recommended in the national immunization schedule during the study period. Among all 157 recipient VAPP cases, 89.8% (141 cases) occurred after the infants received their first dose of OPV; 7.6% (12 cases) occurred after the second dose; and 2.6% (4 cases) occurred after the third or more doses. None of the recipient VAPP cases had a history of IPV vaccination.

Information on the serotype of poliovirus isolation was reported in 139 cases (88.5%). The type II poliovirus vaccine strain was isolated from 27 cases; type III was isolated from 25 cases; type I was isolated from 16 cases; and multiple serotypes were isolated from 25 cases. Three recipient VAPP cases reported vaccine strain isolation, but did not report the specific serotypes. Fifteen cases did not report results of vaccine strain isolation. The results of serotype isolation from 46 cases (29.3%) were negative (Table 2).

Of 157 cases, 118 (75%) reported fever between 3 and 35 days after vaccination, while the others did not provide temperature information to assess fever. One recipient VAPP died and another recovered; the remaining 155 cases experienced physical disabilities: 107 cases reported residual paralysis at the 60-day follow-up visit, of which 55.1% (59 cases) involved a single limb.

3.2. Rate calculation

Using the administered OPV vaccination doses as the denominators, the incidence of recipient VAPP in the study period was 0.4 per million OPV doses with a range of 0.2 per million OPV doses–0.6 per million OPV doses in 2013. If we use total population and birth rates to approximate the number of births, the recipient VAPP per million births can be estimated; accordingly, the recipient VAPP per million births ranged from 1.0 to 2.4 in 2010–2015 (Table 3).

After the first dose, 141 recipient VAPP cases occurred, with an incidence of 1.3 per million doses, which is one in 764,107 vaccinations. The risk after the first dose was substantially higher than after the second and third doses (Table 4). For the second dose, the risk was about one in 9 million doses, while it was one in 27 million doses for the third dose or more.

4. Discussion

By using data from the national passive AEFI surveillance system in China, we estimated that the risk of recipient VAPP was 0.4 per million administered OPV doses. The Expanded Programme on Immunization began in 1978, and tOPV has been used for more than 35 years [4]. VAPP data reported in CNAEFIS complement routine AEFI surveillance and provide an estimate of the baseline risk of VAPP before switching to the bivalent polio vaccine in China.

VAPP cases were more frequently reported in males and children under five years of age in previous studies [13]. However, in our study there was a striking gender imbalance in the VAPP reports for which the reasons are unclear, but possibly related to different aspects. One is the surveillance or reporting artefact. In overall passive AEFI surveillance, there are slightly more AEFIs reported for males than females, with a ratio of 1.4:1 [14–17]. Also as immunity to poliovirus is largely antibody-mediated, persons with antibody deficiencies are much more susceptible to VAPP than immune-competent individuals [18]. However, considering that only part of the reported VAPP cases were immune deficient, and not all relevant immune deficiency syndromes are x-linked, immune deficiency may only explain part of the gender difference. One study in a children's hospital in Beijing [19] found that among primary immunodeficiency diseases (PID)patients, the ratio of boys to girls was 4.4: 1. The same study found that in 174 patients with PID for 11 years, the median age of onset of antibody deficiency was 12 months [19]. Therefore, it is difficult to assess immune-competency in a young infant as they are only two months old at the time of OPV vaccination. We also found that about 25% of VAPP cases had perianal abscess and they were all male. The possible relations of gender, perianal abscess and VAPP require further study.

The age distribution of VAPP cases is obviously associated with the OPV vaccine schedule, in which the recommended age for OPV doses are two, three, and four months of age. The majority of recipient VAPP cases occurred after the first dose. A literature review of VAPP burden indicated that in low-income countries, VAPP was highest in children 1–4 years of age; whereas in middle- and high-income countries, the risk of VAPP was highest in infants under one year old [13]. The reason for this was assumed to be related to the prevalence of protective maternal antibodies and the high coverage provided by the first dose of OPV; accordingly,

Table 1
Number of recipient VAPP by gender and age, 2010–2015, China.

	2010		2011		2012		2013		2014		2015		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Gender														
Male	23	100	30	93.8	17	77.3	35	87.5	21	87.5	14	87.5	140	89.2
Female	0	0	2	6.2	5	22.7	5	12.5	3	12.5	2	12.5	17	10.8
Age (Month)														
1–3 month	17	73.9	24	75.0	17	77.3	29	72.5	21	87.5	14	87.5	122	77.7
4–6 month	5	21.7	7	21.9	4	18.2	8	20.0	3	12.5	2	12.5	29	18.5
>6 month	1	4.4	1	3.1	1	4.5	3	7.5	0	0	0	0	6	3.8
Total	23		32		22		40		24		16		157	

Table 2
Number of recipient VAPP by OPV vaccination history, serotype of vaccine strains, 2010–2015, China.

	2010		2011		2012		2013		2014		2015		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
OPV vaccination history														
1st dose	22	95.6	29	90.6	20	90.9	34	85.0	21	87.5	15	93.8	141	89.8
2nd dose	0	0.0	3	9.4	2	9.1	3	7.5	3	12.5	1	6.2	12	7.6
≥3 doses	1	4.4	0	0.0	0	0.0	3	7.5	0	0.0	0	0.0	4	2.6
Serotype of vaccine strains														
II	4	17.4	6	18.7	2	9.1	5	12.5	6	25.0	4	25.0	27	17.2
III	2	8.7	9	28.1	1	4.5	6	15.0	4	16.7	3	18.8	25	15.9
I	4	17.4	3	9.4	2	9.1	4	10.0	1	4.2	2	12.5	16	10.2
II + III	3	13.0	2	6.3	3	13.6	3	7.5	1	4.2	2	12.5	14	8.9
I + III	1	4.4	0	0.0	1	4.5	2	5.0	1	4.2	0	0.0	5	3.2
I + II + III	0	0.0	0	0.0	1	4.5	1	2.5	2	8.3	0	0.0	4	2.6
I + II	0	0.0	0	0.0	0	0.0	1	2.5	0	0.0	1	6.2	2	1.3
Negative	6	26.1	7	21.9	8	36.4	14	35.0	7	29.2	4	25.0	46	29.3
Unclassified[a]	0	0.0	1	3.1	2	9.1	0	0.0	0	0.0	0	0.0	3	1.9
Unreported	3	13.0	4	12.5	2	9.1	4	10.0	2	8.3	0	0.0	15	9.6
Total	23		32		22		40		24		16		157	

[a] Unclassified: They reported the positive results, but did not reported the specific serotypes.

Table 3
Risk of recipient VAPP in China by year, 2010–2015, China.

	Recipient VAPP	Million OPV doses	Recipient VAPP per million OPV doses	95% CI	Total population (million)	Birth rates (‰)	Estimated births (million)	Recipient VAPP per million births	95% CI
2010	23	66.6	0.3	0.2–0.5	1340.9	11.9	16.0	1.4	0.9–2.2
2011	32	69.6	0.5	0.3–0.6	1347.4	11.9	16.1	2. 0	1.4–2.8
2012	22	73.1	0.3	0.2–0.5	1354.0	12.1	16.4	1.3	0.8–2.0
2013	40	72.5	0.6	0.4–0. 8	1360.7	12.1	16.4	2.4	1.7–3.3
2014	24	71.9	0.3	0.2–0.5	1367.8	12.4	16.9	1.4	0.9–2.1
2015	16	70.1	0.2	0.1–0.4	1374.6	12.1	16.6	1.0	0.6–1.6
Total	157	423.8	0.4	0.3–0.4	–	–	98.4	1.6	1.4–1.9

Table 4
Risk of recipient VAPP in China by dose, 2010–2015.

	No. of cases	Vaccination doses	Incidence rates (per million doses)	95% CI
1st dose	141	107.7	1.3	1.1–1.5
2nd dose	12	108.1	0.1	0.1–0.2
≥3rd dose	4	107.7	0.04	0.01–0.1

VAPP was high in the under one year age group. In high-income countries, high OPV immunogenicity and delivery of the first dose of OPV after two months (when maternal antibodies are lower) might increase the risk of VAPP following the first dose. Because of oral administration, the coverage of OPV is generally higher than other vaccines, and has been reported to be as high as 99% in China, according to national immunization coverage surveillance data [20].

Improved capacity for reporting AEFI might affect the geographic distribution of VAPP cases. Since CNAEFIS developed rapidly after national AEFI guidelines were issued in 2010, the capability of AEFI surveillance in different regions in China might have been implemented unevenly. Similar to all reported AEFI cases, cases of recipient VAPP were highest in eastern regions, followed by middle regions, and then western regions. In addition to the capability of AEFI surveillance, this finding might also be related to economic status and population distribution. After 2012, the central government issued financial support for AEFI investigation and causality assessment, which could enhance the number of recipient VAPP cases reported to CNAEFIS. The decline in recipient VAPP in 2015 might be related to the policy change in July 2015 in which six pilot provinces in China introduced IPV to replace tOPV as the first dose. Also, the domestically manufactured IPV-sabin strains were put into market for parents in 2015. In the vaccine serotype analysis, type II accounted for about one-third (27/93) of cases, similar to other studies [13]. Responding to the WHO's global recommendations, China withdrew tOPV, and IPV was included as the first polio vaccination dose, and bOPV as the subsequent doses, across China in May 2016. This action is expected to reduce VAPP cases by about 25–30% in the future.

The incidence of VAPP in China was similar to other countries. In various studies, the incidence of recipient VAPP in different countries has been estimated to range from 0.33 to 19.08 cases per million births [2]. Using the total population and birth rates from the National Bureau of Statistics to estimate the number of births, the approximate recipient VAPP per million births was 1.0–2.4 from 2010 to 2015, which was similar to the US (1961–1972) (1.91), Cuba (1963–2006) (2.91), and England/Wales (1985–1991) (1.68) [11,13]. In our analysis, using vaccination doses as the denominator, the recipient VAPP per million vaccination doses was 0.4 per million OPV doses, or about one case per 2.7 million vaccine doses. This is similar to countries such as Japan (one recipient VAPP case per 2.3 million doses in 1971–2000), India (one recipient VAPP case per 2.8 million doses in 1999), and Brazil

(one recipient case per 2.39 million doses in 1989–1995) [13]. In contrast, the VAPP risk was estimated as one case per 750,000 vaccinees in the US, and one per 400,000 in Norway, England, and Wales [2]; however, these rates included both recipient and contact VAPP. However, without contact VAPP, the rates estimated from CNAEFIS could not be compared with these countries. Based on the vaccination doses, we could estimate the incidence of recipient VAPP after three doses. In our analysis, the risk after the first dose was highest (1.3 per million vaccination doses), which was about one in 760,000 vaccination doses, similar to international studies (one in 750,000 doses) [9]. The risk after the second and third dose was significantly lower than after the first dose, about one in 9 million for the second dose and one in 26 million for the third dose, consistent with the WHO estimate [1,9].

5. Limitations

An important limitation of this analysis it that CNAEFIS is a passive surveillance system with low sensitivity and could potentially underreport recipient VAPP. As only recipient VAPP was reported, no contact cases were included in our analysis, which could lower the estimated risk of VAPP. Another limitation is that since some laboratory data were unavailable in CNAEFIS, cases were categorized as VAPP without serotype information. In addition, for compensation reasons (VAPP cases could receive government compensation), some cases were classified as VAPP even when the laboratory results on serotypes were negative. To eliminate wild poliovirus, many complementary polio vaccine campaigns have been launched in China, yet information regarding these campaigns, including vaccination dosage, was not completely reported during the study period. This error could lead to an overestimation of overall risk.

Despite these limitations, our analysis showed that the epidemiology of recipient VAPP in China, as a rare adverse consequence of receiving OPV, was similar with other international studies, and that the risk of recipient VAPP, using either estimated births or vaccination doses, was comparable to that reported in US and Japanese studies. As the global eradication of polio is approaching, VAPP will become increasingly unacceptable. After the introduction of IPV and the replacement of tOPV, the burden of VAPP should diminish further.

Potential conflicts of interest

All authors: No reported conflicts.

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PUBLICATION III

Deaths reported to national surveillance for adverse events following immunization in China, 2010–2015

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Deaths reported to national surveillance for adverse events following immunization in China, 2010–2015

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ABSTRACT

Background: The national Adverse Events Following Immunization (AEFI) surveillance system in China (CNAEFIS) has collected AEFI reports -including deaths following all vaccines used in China since 2008.
Aims: To review reports of AEFI-associated death cases from 2010 to 2015 to assess potential vaccine safety issues.
Methods: Descriptive analysis of epidemiologic characteristic of AEFI-associated death cases and standard causality assessment for reported causes of deaths. To estimate the risk of death after vaccination, we used population data, administered doses and live births to calculate denominators.
Results: During 2010–2015, 753 deaths were reported to CNAEFIS from mainland China. Highest numbers were reported in 2013 and 2014 when reporting peak of AEFI-associated deaths occurred after media reports concerning "death following Hepatitis B vaccination" in China. About 95% of deaths were in children <5 years of age and males accounted for 60%. Most common vaccines associated with reports of fatal AEFIs were vaccines in national immunization schedule. In causality assessment, 120 (16.0%) deaths were classified as vaccine-associated reactions such as anaphylactic reactions and disseminated BCG infections; 594 (78.9%) deaths were identified as coincidental events. The main causes of death were asphyxia, and Sudden Infant Death Syndrome. The overall estimated AEFI-associated death rates were: 0.26 per million vaccination doses administered and 0.09 per million population. The neonatal AEFI death rate was 0.77 per million live births.
Conclusions: These data provide reassuring information about the small risk of death following immunization. They also illustrate sensitivity of passive reporting to public information and that peaks in serious AEFI reports should be interpreted with caution. Continuous monitoring and scientific causality assessment for serious AEFIs, including AEFI-associated deaths is imperative to ensure public confidence in the immunization program.

1. Introduction

China initiated the National Expanded Program on Immunization (EPI) in 1978 and expanded it to cover 14 types of vaccines in National Immunization Schedule in late 2007 [1]. As part of the EPI in China, about 22 vaccine doses are administered during the first year of life [2]. With its 1.3 billion inhabitants and over 17 million annual newborns, China is one of the largest market and manufacturer for vaccines in the world [3]. On average, more than 500 million vaccine doses are administered every year [2]. Deaths that occur after immunization, particularly neonatal or infant deaths frequently attract media attention and cause public concern. Recently, concerns were raised about adverse events following immunization (AEFI) and vaccine safety [4]. After media reports of deaths following hepatitis B vaccine (HepB) administration in Hunan province of China in December 2013, concerns about the vaccine safety increased among parents and the public [4]. However, vaccinations during childhood are common, and determining whether or not they are associated with pediatric deaths is difficult.

All vaccines administered in mainland China are monitored and considered to be safe and effective by the National Regulatory Authority [3]. Since 2008, Chinese Center for Disease Control and

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Prevention (CCDC) has monitored AEFI reports, which are recorded using a passive AEFI nationwide surveillance program (Chinese AEFI Information System [CNAEFIS]) [5]. Since its implementation, the CNAEFIS has collected information on a large number of AEFI cases associated with vaccines used in China.

To understand the epidemiological characteristics, causes of death, and risk of death following vaccination in China, we reviewed and analyzed reports of deaths after immunization from 2010 to 2015.

2. Materials and methods

2.1. Data sources

The CNAEFIS is a nationwide passive surveillance system for AEFI [2,5]. In 2008, after 3 years of various pilot studies [6,7], the CNAEFIS became an online system covering all provinces. The AEFI surveillance of mass immunization campaigns, including the 2009 A(H1N1) influenza vaccine campaign during 2009–2010 influenza season [8] and measles vaccines campaign, which included more than 100 million children in 10 days in September 2010 [9] were covered by CNAEFIS, strengthening the reporting capacity. In June 2010, Chinese Ministry of Health and the Food and Drug Administration jointly issued a national AEFI guideline that made the CNAEFIS the sole and official surveillance system in mainland China [10].

According to the national AEFI guideline, an AEFI is defined as a reaction or an event after vaccination that is suspected to be related to vaccination. Healthcare facilities, vaccination units, local centers for disease control and prevention (CDCs), adverse drug reaction monitoring agencies, vaccine manufacturers, and their executive staff are responsible for reporting AEFIs. In addition, the public can notify any of these bodies. The data are collated by local county CDCs. These centers verify the AEFI Case Reporting information, which is then entered the CNAEFIS. Duplicate reports are detected and deleted by county-level, prefectural-level and provincial-level CDCs. Once a case is reported in the CNAEFIS, it can be viewed online by CDCs, and adverse drug reaction monitoring agencies [10].

2.2. Causality assessment

According to national AEFI guidelines [10], all deaths reported in the CNAEFIS must be investigated. County-level CDCs commence an investigation by collecting relevant data and completing the AEFI Case Investigation Form, which is entered in CNAEFIS. An ad hoc AEFI Investigation and Diagnosis Expert Committee is then established by the CDCs. The committee includes experts in clinical medicine, epidemiology, laboratory practices, pharmacy, vaccinology, vaccine regulation, and related fields, as needed. In cases of deaths, prefectural or provincial CDCs establish the AEFI Investigation and Diagnosis Expert Committee, which includes experts and committee members related to the case. This Committee then conducts the causality assessment [5,10].

After the causality assessment, the AEFI (including reports of deaths) is classified into one of the following categories [10]: (1) vaccine reactions or vaccine-related reactions, (2) vaccine quality reactions, (3) program errors or immunization errors, (4) coincidental events, or (5) psychogenic reactions or immunization anxiety-related reactions.

2.3. Data collection

Deaths which were suspected to be related to the vaccinations, with dates of death from 1st January 2010 to 31st December 2015, were extracted from CNAEFIS and included in the study. Information collected included age and gender of the patients, vaccines received, results and conclusions of the causality assessments, time intervals from vaccinations to onset of symptoms, clinical diagnoses, and concurrent vaccines administered.

2.4. Calculation of reporting rates

We used the following denominators to estimate the risk of AEFI-associated deaths: (1) administered doses collected from vaccination clinics during the study period, (2) population data from the National Bureau of Statistics of the People's Republic of China, and (3) neonatal death rates after vaccination. For denominator 1 and 2, the numerator was AEFI-associated deaths reported to CNAEFIS during the same period. The rates were calculated per million administered vaccination doses or per million population. For denominator 3, we used administered doses for first dose of HepB vaccine which administered within 24 h after birth and vaccination coverage to estimate the number of live births. The numerator was cases who died within 28 days after birth.

2.5. Statistical analysis

All calculations were performed by using R software, version i386 3.2.3; the epitools package was used to calculate confidence intervals for Poisson rates.

3. Results

3.1. Characteristics of AEFI-associated deaths

A total of 753 AEFI-associated deaths were reported during 2010–2015. AEFI-related deaths peaked in 2013–2014 (Fig. 1). The proportion of neonatal deaths varied from 5.0% (2010, 2011) to 16.5% (2013). In 2012–2014, the proportion exceeded 10.0%. All deaths were reported from locations within mainland of China.

During the first quarter of the year (January to March), there were 249 (33.1%) AEFI-associated deaths, followed by 234 (31.1%) during the fourth quarter, 140 (18.6%) and 130 (17.3%) during the third and second quarters, respectively. Fifty-one AEFI-associated deaths were reported in December 2013, and 34 (66.7%) of these were related to HepB vaccine, administered alone or with other vaccines (Fig. 2).

Of AEFI-associated death reports, 293 (38.9%) were females, 635 (84.3%) were aged <1 year, and 82 (10.9%) cases were aged 1–4 years (Table 1). The median age in the group aged <1 year was 68 days, and the median age in the group aged 1–4 years was 1 year old.

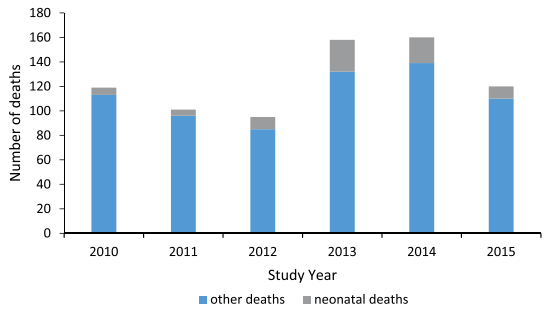

Fig. 1. Reports of AEFI-associated deaths by year, 2010–2015.

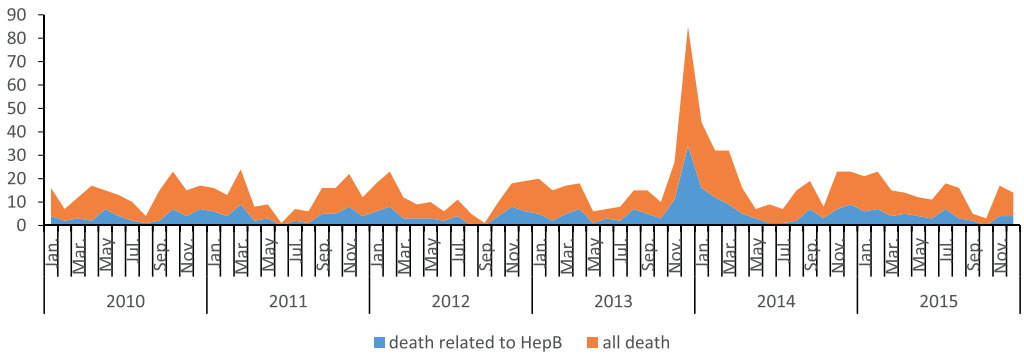

Fig. 2. Seasonal distribution of AEFI-associated deaths, 2010–2015.

Table1
AEFI-associated deaths by year of death, age and gender, 2010–2015.

	<1		1–4		5–9		10–17		18–64		≥65		Total	
	N	Female %	N	Female %	N	Female %	N	Female %	N	Female %	N	Female %	N	Female %
2010	84	44.05	20	50.00	3	0	2	50.00	9	44.44	1	0	119	43.70
2011	90	44.44	8	37.50	1	0			1	100	1	100	101	44.55
2012	79	27.85	12	25.00	2	50.00			1	0	1	0	95	27.37
2013	139	36.69	13	38.46			2	0	2	50.00	2	50.00	158	36.71
2014	141	39.01	15	40.00	3	0					1	100	160	38.75
2015	102	42.16	14	42.86	1	100			2	0	1	0	120	41.67
Total	635	39.06	82	40.24	10	20.00	4	25.00	15	40.00	7	42.86	753	38.91

Sixty-Nine different vaccines or vaccine combinations were associated with reported deaths. The most common vaccines or vaccine combinations were (1) HepB (alone) (182, 24.2%), (2) Bacillus Calmette Guerin (BCG) and HepB (116, 15.4%), (3) oral poliomyelitis vaccine (OPV) and diphtheria, tetanus and acellular pertussis combined vaccine (DTaP) (84, 11.2%), (4) BCG (alone) (61, 8.1%), and (5) DTaP (alone) (31, 4.1%) (Table 2).

3.2. Results of the causality assessments

Autopsies were conducted in 257 (34.1%) cases. According to the causality assessment, 120 (15.9%) deaths were classified as vaccine reactions, 594 (78.9%) deaths were due to coincidental events, 38 (5.1%) deaths were classified as indeterminate, and 1 (0.1%) death was due to an immunization error-related reaction. No deaths were classified as due to vaccine quality defect-related reactions or immunization anxiety-related reactions during the study period (Table 2)

3.2.1. Vaccine-related reactions

One hundred-twenty deaths were classified as vaccine-related reactions, with an estimated rate of 0.04 per million doses, using the all vaccination doses as the denominator. Anaphylactic reactions accounted for 55 cases, in which 53 cases occurred within 1 day after vaccination. Anaphylactic reactions take 45.8% of vaccine-related reactions, with estimated rates of 0.02 per million vaccination doses. Nineteen vaccines or vaccine combinations were related to anaphylactic reactions. The average numbers of deaths per year due to anaphylactic reactions post-vaccination was about 9 (range: 6–13 cases). The most common vaccine and vaccine combinations associated with vaccine reactions were HepB (alone) (12 cases), OPV and DTaP (10 cases), BCG and HepB (9 cases).

There were 39 BCG-related deaths (estimated rate: 0.37 per million BCG vaccination doses). Thirty BCG-related deaths were classified as the result of disseminated BCG infections, and nine cases were due to BCG lymphadenitis or other infections (recurring). One death due to vaccine associated Vaccine-Associated Paralytic Poliomyelitis (VAPP) was reported. One case of hemorrhagic measles was reported in which the autopsy and laboratory findings confirmed that this was related to the vaccine virus.

Thirteen deaths were attributed to neurological, illness, of which six cases were meningitis (aseptic or viral), four cases were acute disseminated encephalomyelitis, two cases were encephalopathy, and one case was epilepsy. Seven vaccines and vaccine combinations were administered in these cases, of which

Table 2
AEFI-associated deaths by vaccine and vaccine combination, and the causality assessment classification, 2010–2015.

Vaccines and vaccine combinations	Vaccine reaction	Immunization error	Coincidental events	Indeterminate	Total
HepB	13		163	6	182
BCG + HepB	16	1	92	7	116
OPV + DTaP	13		65	6	84
BCG	34		24	3	61
DTaP	7		22	2	31
OPV			26	1	27
HepB + OPV	2		17		19
RabV	7		8	3	18
JE-L	4		12	1	17
OPV + DTaP + Hib	1		12		13
Other 59 vaccines and vaccine combinations	23		153	9	185
Total	120	1	594	38	753

the rabies vaccine was the most common vaccine, accounting for five deaths. The average number of deaths per year was three, with a range of two to four in the study period.

Nine deaths were confirmed as status thymicolymphaticus (STL) after autopsies. Other two cases were diagnosed as malaise and vomiting post vaccination, and both died of aspiration asphyxia. In all above 11 cases, vaccination was not the direct cause of death. However, in the causality assessment, the expert committee concluded that vaccination contributed to these deaths and classified the deaths as vaccine-related reactions.

3.2.2. Immunization errors

Only one death was classified as immunization error-related reaction. In this case, the baby had been diagnosed with severe malnutrition prior to immunization, and the immunization nurse had failed to perform a physical examination when the parents requested that the infant be vaccinated. The direct cause of death was severe malnutrition, respiratory failure, and cardiac failure, not vaccine related.

3.2.3. Coincidental events

After causality assessment, 594 deaths were classified as coincidental events. The most common causes of death were asphyxia, sudden infant death syndrome (SIDS), pneumonia (neonatal and infant), congenital heart diseases, and vitamin K deficiency (which could lead to internal bleeding). In these cases, 577 (97.1%) deaths occurred within 15 days after vaccination. Sixty vaccines and vaccine combinations were administered, the most common were HepB (alone) (163 cases), BCG and HepB (92 cases), OPV and DTaP (65 cases), OPV (alone) (26 cases), and BCG (alone) (24 cases). In 574 (96.6%) cases, the patients aged <5 years.

3.2.4. Indeterminate cause of death

During 2010–2015, 38 deaths were classified as due to indeterminate causes. There was no clear clinical diagnosis in 25 (65.8%) cases, and for the rest cases there was insufficient evidence available to conduct the causality assessment. All 38 deaths occurred within one-week post-vaccination, and 34 (89.5%) cases aged <5 years.

3.3. Risk estimation of AEFI-associated deaths

Using all administered doses as the denominator, the average rate of AEFI-associated death was 0.26 per million vaccination doses (range: 0.20–0.32) during the study years. Using population data as the denominator, the average rate was 0.09 per million population (range: 0.07–0.12) (Table 3).

Neonatal deaths accounted for 10.4% (78 cases) of all reported AEFI-associated deaths. The highest rate of reported neonatal deaths after vaccination occurred in 2013 (1.48 per million live births) (Table 4). The rate of neonatal deaths after vaccination in 2010–2011 was significally different from 2013 to 2014 (Table 4). During 2013–2014, 47 neonatal deaths were reported and 44 (93.6%) of those were related to HepB (with concurrent vaccines). In the causality assessment however, only one of the reported deaths was considered causally related to vaccination.

During 2010–2015, we identified 182 reports of AEFI-associated deaths after vaccination with HepB was the only vaccine used. Of these, 13 were causally related to vaccination in the causality assessment. The annual numbers of causally related deaths during the period were 2,3,2,1,3,2, respectively.

4. Discussion

During six years of AEFI surveillance in mainland China, more than three quarters of reported AEFI-associated deaths were due to coincidental events, and only 16% could be attributed to vaccination by causality assessment. Most of those determined to be causally related to vaccination were related to anaphylactic reactions and disseminated BCG diseases. Although the reporting rates of neonatal deaths increased during 2013–2014, deaths that causally related to HepB were very rare during the study years.

Overall, our study provides reassuring information about the small risk of deaths following immunization. Although 5% AEFI-associated deaths were indeterminate cause, the AEFI investigation and causality assessment process provided valuable information to evaluate vaccine safety in China. The reporting peak of AEFI-associated deaths in late 2013 to early 2014, illustrates the sensitivity of passive reporting of serious AEFI to public information and the caution that should be exercised in interpreting peaks in serious AEFI reporting. Our analysis also illustrates progress made with vaccine safety monitoring during recent years in China.

Several limitations should be considered when interpreting the study findings. As CNAEFIS is a passive surveillance, it has inherent limitations, including reporting bias, and lack of control groups [11]. The limitation of denominator-based risk estimation includes different resources to identify the vaccine-administered doses and unknown background information, which make it difficult to compare the observed to the expected, as well as among different settings [12]. In our study, the denominators used were estimated from different data resources and one should be cautious about comparing the estimated rates with immunization related death rates in other countries. In China, compensation is available for reactions determined to be vaccine-related. When the expert panel finds no other cause of death, it might be concluding that the vaccine or vaccination was a contributor to the death in the causality assessment. In such cases, the families of the deceased are eligible to apply for compensation. This policy might increase the number of reports of vaccine-related reactions.

Regarding the seasonal distribution of deaths during the study period, except for 2013, deaths were more common in winter than in summer months, consistent with findings of similar studies elsewhere [13]. The results showed that children aged <5 years accounted for 95% of AEFI-associated death, which is consistent

Table 3
Estimated overall AEFI-associated death rates using different denominators, 2010–2015.

Year	No. of deaths	All vaccination doses (millions)	Estimated rates by vaccination doses		Total population (millions)	Estimated rates by total population	
			Deaths rates (per million vaccination doses)	95% *CI*		Deaths rates (per million population)	95% *CI*
2010	119	427.88	0.28	0.23–0.33	1340.91	0.09	0.07–0.11
2011	101	461.44	0.22	0.18–0.27	1347.35	0.07	0.06–0.09
2012	95	478.97	0.20	0.16–0.24	1354.04	0.07	0.06–0.09
2013	158	489.21	0.32	0.27–0.38	1360.72	0.12	0.10–0.14
2014	160	495.74	0.32	0.27–0.38	1367.82	0.12	0.10–0.14
2015	120	504.23	0.24	0.20–0.28	1374.62	0.09	0.07–0.10
Total	753	2857.49	0.26	0.25–0.28	8145.46	0.09	0.09–0.10

Table 4
Estimated neonatal deaths rates after vaccination, 2010–2015.

Year	No. of Neonatal death	Vaccination doses of 1st dose of Heptitis B (million doses)	Vaccination coverage %	Estimation of live birth (million live birth)	Neonatal death rates (per million birth)	95% CI
2010	6	17.16	99.81	17.19	0.35	0.13–0.76
2011	5	17.5	99.86	17.53	0.29	0.09–0.67
2012	10	18.68	99.87	18.71	0.53	0.26–0.98
2013	26	17.48	99.77	17.52	1.48	0.97–2.17
2014	21	15.18	99.84	15.2	1.38	0.86–2.11
2015	10	15.75	99.87	15.77	0.63	0.30–1.17
Total	78	101.75	–	101.91	0.77	0.61–0.96

with Vaccine Adverse Event Reporting System (VAERS) data in the U.S. [14] and the National Immunization Schedule in China. There were also more male than female deaths. This finding is consistent with data reported in the All Cause of Death Surveillance System in China [15]. Of the AEFI-associated deaths, 78.9% were classified as coincidental events. The reported causes of death were consistent with common causes of mortality nationally [16,17]. According to the National Bureau of Statistics of the People's Republic of China (http://data.stats.gov.cn/easyquery.htm?cn=C01), all-cause neonatal death rates during 2010–2014 were 5.9–8.3‰. The estimated neonatal death rates in this study were lower than all-cause neonatal death rates in the general population, suggesting no association of vaccinations with an increased risk of death at the population level.

Generally, parents have their children vaccinated when they are in relatively good health. In situations where the infant dies shortly after immunization, parents and even health providers may blame vaccine [13]. Although vaccines play a vital role in preventing diseases in children, vaccine hesitancy has become an issue in many counties, including China [18,19]. Events in December 2013 in Hunan province of mainland China provide an example of how such concerns was arise [20]. Media reports of 17 infant deaths, including one case of anaphylactic shock following HepB vaccination, raised widespread public concern in China [3,19]. After investigation, The China Food and Drug Administration reported that the deaths were not related to the vaccine, but instead with a variety of problems, including severe pneumonia, suffocation, kidney failure, severe diarrhea and congenital heart disease [3,19,20,21]. In passive surveillance systems, the behavior of parents and vaccine providers behavior may influence the number of reports. This publicity may have increased public awareness and led to a tendency to report deaths after immunization during 2013–2014. Our analysis showed a reporting peak during 2013–2014, in which 94% of the neonatal deaths were reported to be related with HepB. However, vaccine reactions determined to be causally related to HepB were rare during the study years. Although the overall number of all AEFI reports in CNAEFIS increased from 2010 to 2015, the number of serious AEFIs (events causing a potential risk to the health/life of a recipient leading to prolonged hospitalization, disability/incapacity, congenital abnormalities/birth defects or death) has remained constant [9,22–25].

Causality assessments in China are performed in accordance to WHO guidelines [10,26]. The documented causes of death that could possibly occur due to the inherent properties of a vaccine are limited and include anaphylaxis, viscerotrophic disease following yellow fever vaccine, disseminated attenuated live vaccine agent infection in severely immune-compromised individuals and death from intussusception following rotavirusvaccine [27]. In China, yellow fever vaccine is not recommended, and rotavirus vaccines differ from those used internationally. In our study, the most common causes of vaccine-related reactions and deaths were anaphylaxis and disseminated BCG infections. BCG is recommended at birth, without screening to determine the status of the immune system at that time. In our study, several deaths were due to neurological diseases. There was no solid evidence that these neurological diseases were caused by the vaccines or vaccination, although some studies reported temporal associations of such diseases with various immunizations [28,29]. When no etiologic agent is identified, and the person was healthy prior to immunization, a suspicion may arise in the causality assessment that the vaccine contributed to the death. Several cases with STL was also assessed to be causally related to vaccination during surveillance. STL is associated with immune system dysfunction. As reported previously, mild immune stimulation, such as that produced by minor trauma or immunizations, could give rise to sudden death among individuals with STL [30]. The expert committee concluded that it triggered these deaths, even when neither the vaccine nor the vaccination was the direct cause. Case causality assessments are extremely difficult. Strengthening the capacity of AEFI investigation and causality assessment is very important in the field of vaccine safety surveillance and evaluation in China. In 2018, WHO issued revised classification for causality assessment [31] which could be adopted and modified for the Chinese setting in future.

5. Conclusions

Vaccines are among the safest medical products in use. However, parents will naturally become concerned when serious adverse events occur after vaccination, even though the event may only be temporally related to immunization [32]. A functional vaccine safety surveillance system and thorough AEFI investigation for causality assessment can provide valuable information for both national regulatory authorities and the public [27]. Our study showed that the risk of death following vaccination was extremely small and did not identify specific safety concerns with vaccines used in China. Because passive surveillance might be stimulated by media reports and public concerns, continuous monitoring and scientific causality assessment of serious AEFI reports, including AEFI-associated deaths, is imperative to ensure public confidence in the immunization program.

Conflicts of interest

The authors declared that there is no conflict of interest.

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PUBLICATION IV

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

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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

symptoms, "common reaction" was used as a single diagnosis. Cases who had received concurrent vaccines were excluded.

3. Results

3.1. AEFI following JE-L and JE-I

A total of 34,879 AEFI cases associated with JE vaccines were collected by CNAEFIS, 2008–2013; 95.2% (33,186) cases were related to JE-L. JE vaccines were administered concurrently with one or more other vaccines in 13,592 (39.0%) of cases (39.9% for JE-L and 19.9% for JE-I, respectively). Both for JE-L and JE-I, the most common concurrently administered vaccine was measles-containing vaccines, with a proportion of 24.8% for JE-L (8226 cases in 33,186 JE-L-related cases) and 17.5% for JE-I (297 cases in 1693 JE-I-related cases).

JE-L was listed as the first suspected vaccine in 23,627 (71.2% of the JE-L-associated AEFI cases). JE-I was the first suspected vaccine in 1357 (80.2% of JE-I-associated cases) ($p < 0.05$).

There were more cases in males than in females, with a sex ratio of 1.3:1. More cases occurred in ≤1 years of age, with 66.4% of JE-L and 60.8% of JE-I (Table 1). Of all 34,879 AEFI cases, 361 (1.0%) AEFI cases were defined as serious.

There were 146.7 million vaccination doses collected of JE vaccines from 2010 to 2013, in which 95.1% (139.5 million doses) was JE-L. Since both JE-L and JE-I could be used as NIP vaccines and voluntary vaccines, among all JE vaccination doses, 91.5% (134.3 million doses) were used as NIP vaccines, including 133.1 million of JE-L and 1.2 million of JE-I. Using the doses administered from 2010 to 2013 as denominators, the overall reporting rates of AEFIs per million were 214.4 for JE-L and 176.9 for JE-I (RR: 1.2, 95% CI: 1.1–1.3). the annual reporting rates increased substantially from 2010 to 2013 (Table 2). During 2010–2013, 271 serious AEFIs were reported. The overall reporting rates of serious AEFIs were 1.8 per million doses for JE-L and 2.8 per million doses for JE-I (RR: 0.7, 95% CI: 0.4–1.0).

3.2. Clinical diagnosis of AEFIs

Of the 29,831 non-serious AEFIs, (86.4%) were diagnosed as common and minor adverse reactions, such as fever, local redness, and swelling.

Among serious AEFIs, the most frequently reported clinical diagnosis were febrile convulsion (132, 36.6%), thrombocytopenic purpura (39, 10.8%), encephalitis and meningitis (29, 8.0%), Henoch-Schönlein purpura (28, 7.8%), and anaphylactic shock (25, 6.9%). (Table 3) 22 death cases were reported during the study period, only 4 cases were classified as related to vaccination due to anaphylactic shock.

3.3. Disproportionality analysis

A total of 20,988 AEFIs with complete information on vaccine and diagnosis were included in the disproportionality analysis. All three methods, PRR, EB, and BCPNN, suggested JE-I and febrile convulsion as the suspected SDRs (Table 3). For JE-L, there was no diagnosis with disproportionally higher reporting.

Based on the results of Table 4, using the administered doses from 2010 to 2013 as the denominator, the estimated reporting rates of febrile convulsion after JE-L (as the only vaccine suspected) and JE-I (as the only vaccine suspected) were calculated: 0.3 per million doses for JE-L and 0.4 per million doses for JE-I ($p = 0.5$).

4. Discussion

We reviewed reported AEFIs after JE-L and JE-I in CNAEFIS by 3 levels of analysis: a description of the characteristics of AEFIs, disproportionate reporting between JE-L and JE-I and estimated reporting rates. The serious AEFIs only accounted for 1% of all reported AEFIs, and there was also no statistical difference between JE-L and JE-I in the reporting rates of serious AEFI in all 2010–2013. However in 2012, the reporting rates of serious AEFI following JE-L were lower than JE-I. The increasing trend in the reporting rates of AEFI following the immunization of JE-L and JE-I may be related to the improved reporting to CNAEFIS during 2008–2013. The increased trends were similar to the reporting rates of all AEFIs during the same period; the reporting rates of all AEFIs in CNAEFIS of China continuously increased from 2010 to 2013 [22–25].

In previous CNAEFIS data analysis, only JE vaccines were included in the study [20–23]. However, in our study, at least one third of AEFIs had other concurrently administered vaccines. In addition, in the ≤1-year group, which was the target group of EPI, an in AEFI for JE-L, more than half the cases were related to JE-L in combination with other vaccines. In these situations, it is difficult to determine the responsible vaccine for some adverse events, such as allergic reactions. Since concurrent vaccination could not be avoided, we included all AEFIs related to JE in the CNAEFIS database.

The gender distribution of JE-L and JE-I AEFIs cases was similar to all other vaccines [22–24], as there were more male than female cases. Most reported cases were ≤1 year old, consistent with the China Immunization schedule for EPI vaccines. Most reported AEFIs were relatively mild and self-limiting, with a diagnosis of common and minor adverse reactions, including fever, local redness and swelling, and local induration. Besides the mild and self-limiting adverse reactions, nearly 97% of cases recovered, and only 22 death cases were reported during the study period.

Currently, there are several JE vaccines used in China. About 8 domestic manufacturers in China produce JE-L and JE-I. In the mainland of China, since 1968, JE-I vaccines (Hamster kidney cell inactivated vaccine) were manufactured domestically. The mass vaccination period of JE was after 1989, the year JE-L was developed and manufactured by Chengdu institute of biological products company, and until 2001, the yield of JE-L was more than 200 million doses in all. Following the positive assessment by the WHO of China's vaccine National Regulatory Authority in 2011 [25] and with the development of a vaccine manufactory in China [26], JE-L was the first vaccine in China to be prequalified by the WHO [27]. Different JE vaccines have been used in other countries. For example, the United States (US) used an inactivated mouse brain-derived JE vaccine (JE-I) for travelers (most of them were adults) from 1992 to 2009. Japan used JE-I for children. Takahashi [4] reviewed the post-marketing surveillance of JE-I from Japan and the US. The total adverse events rate was 2.8 per 100,000 doses in Japan and 15.0 per 100,000 doses in the US.

JE-L was widely used in countries in the Western Pacific region and Asia (China, Korea, and India), but very limited data are available on the adverse effects of JE-L in these countries. An analysis of the post-marketing surveillance of JE-L from 2009 to 2012 by the Chinese National Center for Adverse Drug Reaction (ADR) Monitoring [2] showed that in 6024 AEFIs, only 70 were considered severe. The Global Advisory Committee on Vaccine Safety (GACVS) of the WHO reviewed these data and noted that although there was no evidence of a safety signal, the number of events recorded in the AEFI reporting system was low, given that >70 million doses of the vaccine have been administered [25].

Table 1
Characteristics of AEFIs after JE-L and JE-I vaccination, China, 2008–2013.

		JE-L				JE-I			
		As most suspected* N = 23627 (%)		Others N = 9559 (%)		As most suspected N = 1357 (%)		Others N = 336 (%)	
Serious	Serious	244	1.03	66	0.69	51	3.76	0	0.00
	Non-serious	23,383	98.97	9493	99.31	1306	96.24	336	100.00
Gender	Female	13,444	56.90	5358	56.05	768	56.60	190	56.55
	Male	10,183	43.10	4201	43.95	589	43.40	146	43.45
Age group	≤1 yr	13,306	56.32	8712	91.14	710	52.32	320	95.24
	2–6 yrs	10,036	42.48	825	8.63	511	37.66	14	4.17
	≥7 yrs	285	1.21	22	0.23	136	10.02	2	0.60

* There were at most three suspected vaccines were reported in one AEFI cases, the reporters will put one vaccine as the most suspected vaccines. JE as most suspected means JE was most suspected related to adverse events in the reports.

Table 2
Number and estimated AEFI reporting rates of after JE-L and JE-I by severity* of AEFI, China, 2010–2013.

AEFI	JE-L				JE-I				Rate ratios	
	Non-serious		Serious		Non-serious		Serious		Non-serious	Serious
	No. of cases	Reporting rates**	No. of cases	Reporting rates	No. of cases	Reporting rates	No. of cases	Reporting rates	(95% CI)	
2010	2428	75.97	43	1.35	96	33.99	5	1.77	2.23 (1.83–2.76)	0.74 (0.32–2.17)
2011	5816	168.51	41	1.19	102	124.86	1	1.22	1.35 (1.12–1.65)	0.85 (0.19–19.85)
2012	8495	240.25	69	1.95	756	294.80	13	5.07	0.82 (0.76–0.88)	0.38 (0.22–0.72)
2013	12908	343.11	98	2.60	308	295.79	1	0.96	1.16 (1.04–1.30)	2.37 (0.54–54.72)
2010–2013	29647	212.60	251	1.80	1262	174.15	20	2.76	1.22 (1.15–1.29)	0.65 (0.42–1.05)

* The severity of AEFI were classified according to national AEFI guidelines. Serious AEFIs 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.
** Reporting rates: per million vaccination doses given

Table 3
Clinical Diagnosis of serious AEFI after the immunization of JE-L and JE-I, China, 2008–2013.

Clinical diagnosis	JE-L				JE-I*	
	First suspected, N = 244 (%)		Not first suspected, N = 66 (%)		First suspected, N = 51 (%)	
Febrile convulsion	83	34.02	16	24.24	33	64.71
Thrombocytopenic purpura	22	9.02	15	22.73	2	3.92
Encephalitis and meningitis	23	9.43	5	7.58	1	1.96
Henoch-Schönlein purpura	18	7.38	6	9.09	4	7.84
Anaphylactic shock	21	8.61	1	1.52	3	5.88
Apsychia	11	4.51	4	6.06	5	9.80
Seizure	16	6.56	1	1.52	1	1.96
Laryngeal edema	4	1.64	1	1.52	1	1.96
Acute Disseminated Encephalomyelitis (ADEM)	5	2.05	0	0.00	0	0.00
Arthus reaction	3	1.23	1	1.52	0	0.00
Guillain Barre Syndrome (GBS)	1	0.41	1	1.52	0	0.00
Others	37	15.16	15	22.73	1	1.96

* For JE-I, There was no cases coded as serious AEFIs when administered in combination with other vaccines.

Table 4
Suspected SDR of JE using 3 DPA methods, China, 2008–2013.

Methods (criteria)	Results
PRR (lower limit of 95% CI of PRR > 1 & n > 3)	JE-I - febrile convulsion PRR = 7.44, Lower limit of 95% CI = 1.59
EB (EB05 > 2 & n > 3)	JE-I - febrile convulsion EB05 = 3.27
BCPNN (lower limit of 95% CI of IC > 1 & n > 3)	JE-I - febrile convulsion Lower limit of 95% CI of IC = 1.64

One of the primary goals of AEFI passive surveillance is to detect vaccine safety signals and generate hypotheses for further studies. Using vaccination doses as a denominator, AEFI incidence rates are calculated. Through a comparison with historic data and published studies, emerging vaccine safety signals are detected. However, since serious AEFIs are very rare, and it is difficult to determine the background incidence rate, in recent decades, researchers on pharmacovigilance have applied data mining methods in the detection of drug adverse events' signals on vaccines [28]. One of the main analysis methods is disproportionality analysis. In the US, PRR [15,16], which was also used in the UK Yellow Card Scheme (YCS) (the spontaneous reporting system in the UK), and the Gamma Poisson Shrinkage model (GPS), which was also noted as EB data mining, has been used to screen Vaccine Adverse Events Reporting System (VAERS) data and generate signals, including signals from seasonal influenza vaccines and from newly licensed vaccines [18–20]. The WHO Uppsala Monitoring Center (UMC) has used a similar data mining method, BCPNN, to detect safety signals [17,29]. These methods were not used as routine SDR screening in CNAEFIS, but we applied the methods to compare the SDR between JE-L and JE-I as supplementary analysis to evaluate the safety of JE in China. Febrile convulsions are the commonest type of seizure in children occurring in 2–5% of all children, 2–5% of young children in North America and Europe, and 6–9% in Japan [30,31]. It usually occurs between 3 months and 5 years, with a peak incidence at 18 months [32], which was also the target age of vaccinations, especially for JE-L and JE-I. Generally, at least 50% of children who present with febrile convulsion will have no identified risk factors [33]. As elevated body temperature is frequently observed following immunization, and febrile seizures are the most common seizure disorder in infants and children, they are the most common type of non-epileptic seizure observed following immunization [33]. The signal of febrile convulsion has been found after measles-mumps-rubella combined vaccine (MMR), diphtheria-tetanus-pertussis combined vaccine (DTP), and seasonal influenza vaccine in some countries, such as the US and Australia [34–37]. However, an increased risk of febrile convulsion after JE has rarely been reported. In a randomized trial with 26,239 subjects, within 30 days follow-up, the incidence proportion of seizure was 0.1%, and fever lasting more than 3 days was 2.7% in the group vaccinated with JE-L. There was no statistically significant difference between vaccinated and unvaccinated groups for seizure or fever lasting more than 3 days [38]. In our study, using the 3 data-mining methods, an SDR: JE-I and febrile convulsion was detected compare with JE-L. This indicated that there was a disproportionality in reports of febrile convulsion after JE-I compared to JE-L. However, when comparing the overall estimated reporting rates of febrile convulsion after both vaccines, there was no significant difference. In addition, febrile seizures after JE were less common than after measles-contained vaccines and varicella vaccines [36]. Therefore, the SDR of JE-I and febrile convulsion should be interpreted with caution.

CNAEFIS, as a national passive surveillance system, has its strengths and limitations. Even if it serves as a useful source for vaccination safety evaluation in China, the findings in CNAEFIS should be interpreted with caution. The natural limitations of passive surveillance include over- and under-reporting, biased reporting, and inconsistency in the quality and completeness of reports among others [37]. Meanwhile, the clinical diagnosis of AEFI cases varied in provinces of China, as we did not have a standard procedure or definition of AEFI diagnosis, and we did not use the standard definitions created by the Brighton Collaboration [39]. In our analysis, since CNAEFIS were case-based reporting system, and vaccination doses were collected based on summarized tables from vaccination clinics, these 2 data resources were not exact matched. There were no information on whether the vaccine used as NIP vaccine or voluntary vaccines in CNAEFIS, and no gender and age information on vaccination doses, all those related incidence could not be estimated using current data.

In conclusion, during the study period of 2008–2013, the majority of AEFIs following JE vaccines were minor and common adverse reactions, and there was no significant difference between the estimated reporting rates of serious AEFI following JE-I and JE-L. For serious AEFIs, more than 97% of cases recovered. We recommend consider further study to discern effects of concurrent vaccination with JE vaccines and take more sensitive methods to detect signals.

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