Original Article

Epidemiological Characteristics of Japanese Encephalitis in Guizhou Province, China, 1971-2009*

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Abstract

Objective The aim of the study was to establish the contemporary epidemiological characteristics of Japanese encephalitis (JE) in Guizhou Province.

Methods A retrospective study of National Notifiable Disease Reporting System (NNDRS) data from 1971 through 2009, was conducted to ascertain the geographical, seasonal, and age distributions of JE incidence in Guizhou Province, China.

Results A total of 68 425 JE cases were reported in Guizhou from 1971-2009. The JE cases occurred sporadically in all 9 prefectures of Guizhou, mostly among residents of rural areas. Seasonal distribution of JE remained consistent over the period from 1971-2009 with the main transmission season starting from June to September and peaking in August. JE occurred mainly in children under the age of 15 years with peak incidence in the 0-6-year age group. Pearson's correlation analysis showed that JE vaccine distribution had a negative correlation with JE incidence rates during 1971-2009 (coefficient of correlation=-0.475, $P<0.01$).

Conclusion Over the period of 1971-2009, the JE incidence rate had declined dramatically in terms of geographical and age distributions due to JE vaccination to children at risk.

Key words: Japanese encephalitis; Epidemiology; Japanese encephalitis vaccine catch-up campaign

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INTRODUCTION

Japanese encephalitis (JE) is a mosquito-borne disease caused by a neurotropic flavivirus, named Japanese encephalitis virus (JEV). JE is one of the leading causes of viral encephalitis in Asia with 30 000 - 50 000 cases reported annually. Case-fatality rates can be as high as 60% among those with disease symptoms, and approximately 50% of JE patients can develop permanent neurologic and psychiatric sequelae[1-3].

JE has been historically endemic in China, with nationwide periodic epidemics documented since the early 1950s, notably, 5.45/100 000 in 1957, 13.36/100 000 in 1965, and 20.92/100 000 in 1971[4] (Figure 1). Prior to 1996, there were 8 000 to 10 000 JE cases reported annually in China, and these cases accounted for 80% of cases reported globally[5].

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Following the use of inactivated JE vaccines since 1968, and later by a live attenuated JE vaccine (SA14-14-2) developed and produced locally in 1988, the national JE prevalence began to decline and the JE incidence rate has remained relatively stable, at less than 1/100 000 since 1998[6]. Despite the considerable success of the vaccine in controlling JE, the high mortality rate and severe sequelae of this disease have made it a continuing public health problem in China[4,7-12].

JE is highly endemic in Guizhou Province and the annual incidence rates since 1952 are shown in Figure 1. Since 1978 the JE incidence rates in Guizou have been greater than the national average and the province accounts for 19.47%-22.29% of the national reported cases. Between 1999 and 2003 the incidence rates were 6-9 times higher than the national average.

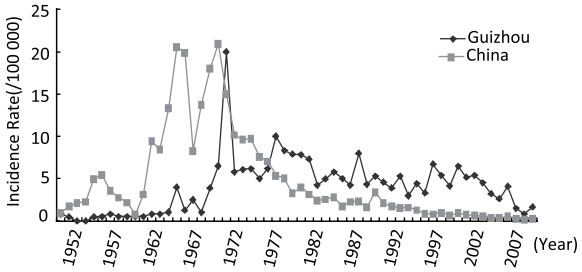

Figure 1. JE incidence in Guizhou province and the whole of China, 1952-2009.

Epidemiological analysis of JE cases in Guizhou has, however, never been studied detail[6-7,11-13], and evaluation of the effectiveness of JE vaccine catch-up campaigns has not been analyzed. In order to gain a better understanding of the distribution of JE cases in Guizhou Province, to evaluate changes in JE epidemiologic characteristics, and to recommend effective strategies for prevention and control of the disease, we undertook a thorough retrospective study of JE incidence in Guizhou over a 39-year period from 1971 to 2009. We also reviewed the epidemiological data of JE vaccine catch-up campaigns in Guizhou Province during 2004-2008.

MATERIALS AND METHODS

Surveillance & Reporting for JE Case

It was proposed in 1952 that JE be designated a notifiable disease in China[8,14-15]. County-based monthly paper reporting using a mailing system was implemented during 1952-1985, and county-based monthly electronic reporting was implemented in 1986-2006. Prior to 2007, health authorities had monitored JE cases by following up physicians' passive reports. Thereafter, an active case-based surveillance system for JE was established in China, and detailed information on suspected clinical and laboratory-confirmed cases has been reported in real-time online under the National Notifiable Disease Reporting System of the Chinese CDC (NNDRS). This has allowed daily data sharing between central and local authorities since 2007[16-17]. The system stipulates that county Center for Disease Control and Prevention (CDC) staff visit local hospitals and clinics before and during each JE epidemic season. The system also requires local physicians to report suspected JE cases to the CDC. Thus CDC staffs are able to conduct case investigations using a standard form and collect serum and cerebrospinal fluid (CSF) specimens from each case to assess the situation in a timely manner. The review of patient records of all hospitals at the county and/or local level occurs every 10 days for suspected JE cases.

JE Case Definitions

Prior to 2006, the diagnosis of JE cases in China relied mainly on clinical symptoms of the disease and there was no systematic surveillance system. JE case definitions were adopted by the Chinese Ministry of Health when an epidemic monitoring information management system for JE cases was set up in 2006[4]. Diagnosis is based on the JE case definition published in the surveillance manual distributed to all health workers[17]. Thus, a report falls into one of three categories: (1) A suspected JE case is defined as a hospitalized patient with fever who was sick during the defined JE epidemic season (from June to October) and who had three or more of the following symptoms: headache, vomiting, focalized or generalized seizure, coma, lethargy, motor deficiency, and neck stiffness; (2) A Clinically confirmed case is defined as a patient who met the suspected JE cases definition and who had clinical laboratory results of CSF pleocytosis (>10 white blood cells/mm^3), an elevated protein concentration (>40 mg/dL), and a normal glucose concentration. (3) A Laboratory confirmed case is defined from a suspected or clinically confirmed case by meeting one of the following criteria: the presence of JEV-specific IgM in a single CSF or serum sample; the presence of JEV-specific IgG in the convalescent serum; detection of JEV neutralizing antibody titer

that had at least a 4-fold rise in the acute phase serum; detection of JEV-specific IgM/IgG that was negative in the acute phase serum, but was positive in the convalescence serum; detection of JEV RNA in CSF by a heminested reverse transcriptase PCR (hnRT-PCR); or isolation of JEV from CSF, brain tissue, or serum sample.

JE Vaccine Catch-up Campaign

Guizhou Province conducted JE vaccine catch-up campaigns from 2004-2008. The province is geographically divided into 9 prefectures, namely Zunyi (ZY), Bijie (BJ), Guiyang (GY), Tongren (TR), Liupanshui (LPS), Anshun (AS), Qiannan (QN), Qiandongnan (QDN), and Qianxinan (QXN). Counties with high incidence rates were chosen for JE vaccine catch-up campaigns. The selected counties were listed as follows: 10 counties in TR prefecture in 2004; 7 counties in QDN prefecture, 1 county in QXN prefecture, and 1 county in TR prefecture in 2005; 6 counties in ZY prefecture, 2 counties in QXN prefecture, 2 counties in LPS prefecture, and 2 counties in TR prefecture in 2006.

The JE vaccine was administered to children aged from 8 months to 10 years in 2004 to 2006. In 2007, the catch-up campaign was conducted in all 9 prefectures (i.e., 88 counties) targeting children from 8 months to 6 years old. In 2008, another catch-up campaign was carried out in 31 counties from 8 prefectures. In the 31 counties, JE vaccine was given to children from 8 months to 10 years in 5 counties, to children from 8 months to 6 years in 8 counties and from 7 to 10 years old in another 18 counties. Children who did not receive an immunization certificate or children who received a certificate but had no JE vaccine immunization history, were given a dose of live attenuated JE vaccine during 2004-2008.

Data Collection and Analysis

We collected the data of JE cases and deaths from the NNDRS between 1971 and 2009; we reviewed the JE vaccine coverage rates from routine immunizations and we analyzed the vaccination records of catch-up campaigns from district health authorities. Population denominators for calculation of JE incidence and mortality rates were determined on the basis of data reported by the Guizhou provincial Bureau of Statistics. The JE vaccine distribution figures cited in this study were provided by the Health Bureau of Guizhou Province between 1971 and 2009. The vaccination history of each JE case was traced through the NNDRS during 2007-2009. The seasonal, geographic, and age distributions of JE cases in Guizhou were analyzed by descriptive epidemiology. Epidemiologic data were analyzed using Microsoft Excel and Epi Map. Pearson's correlation analysis was used to examine relationships between JE incidence rates and the doses of JE vaccine distributed. *P* values of <0.01 were considered statistical significant. All statistical evaluations were carried out in the SPSS Version 13.0 for Windows.

RESULTS

Incidence and Mortality of JE

A total of 68 425 JE cases were reported in Guizhou Province during 1971-2009. The epidemic status of JE over the years can be divided roughly into 5 stages (Figure 1). (I) During 1952-1970, the annual JE incidence rates were below the annual national average levels. (II) During 1971-1980, the annual average reported JE cases were 2 037, and the incidence rate of JE was reduced from 18.96/100 000 in 1971 to 5.66/100 000 in 1980. Notably, the highest historically recorded JE epidemic, involving 4 344 reported cases and 816 deaths, occurred in 1972. (III) During 1981-1990, the average annual reported JE cases were 1 676, and the annual incidence rates of JE were higher than the annual national average levels. (IV) From 1991 to 2003, the average reported JE cases were 1 591 per year. The average incidence rate was 4.6/100 000; the highest JE incidence rate was 6.36 in 2000 (V). During 2004-2009 the JE incidence rate changed from 4.53/100 000 in 2003 to 3.18/100 000 in 2004 (a 29.58 % reduction) after initiation of JE vaccine catch-up campaigns in 2004. The JE incidence rate dropped to 2.66/100 000 after catch-up campaigns in 2005 (a 16.35% reduction compared to incidence rate reported in 2004). Figure 1 shows that the JE incidence rate decreased from 4.07/100 000 in 2006 to 1.5/100 000 in 2007, which was a 62.16% reduction from 2006 after a provincial-wide JE vaccine catch-up campaign. Following a continued JE vaccine catch-up campaign, there were only 320 JE cases reported in 2008, and the incidence rate fell to 0.845/100 000, (a 45.45% reduction compared to that of 2007). In 2009, there were 633 reported JE cases, and the JE incidence was 1.67/100 000.

There were 7 460 deaths from JE from 1971-2009. The average number of deaths each year decreased from 434 to 188, and average mortality rates decreased from 0.99-3.56/100 000 to

0.32-1.16/100 000 between 1971-1980 and 1981-1990. An average of 75 deaths from JE occurred each year, and the mortality rates ranged from 0.14/100 000 to 0.28/100 000 from 1991 to 2003. The average number of deaths declined to 45 cases per year, and the mortality rates ranged between 0.06/100 000 and 0.22/100 000 from 2004 to 2009. In 1972, the mortality rate of 3.56/100 000 was the highest ever recorded in history. The mortality rate of 0.06/100 000 in 2008 was the lowest ever recorded.

Geographical Distribution of JE Cases

Figure 2 shows the geographical distribution of JE cases and the incidence rates of JE in different epidemic stages in 9 prefectures of Guizhou Province. Prior to the JE vaccine catch-up campaigns (i.e., 1971-2003), the prefectures of AS, TR, QDN, ZY had higher incidence rates than other parts of the province. JE incidence rates were 10.95-12.18/100 000 during 1971-1980 in AS, TR, QDN, and GY prefectures, 6.32-7.96/100 000 during 1981-1990 in AS, TR, QDN, and ZY prefectures and 5.75-7.05/100 000 during 1991-2003 in AS, TR, and ZY prefectures.

After the catch-up campaigns (i.e. 2004-2009), the overall incidence rates of JE decreased remarkably and 8 of 9 prefectures had an incidence rate of less than 3 per 100 000. The only prefecture that showed an incidence rate greater than 3/100 000 was BJ. The JE case-based surveillance system showed that JE cases took place sporadically all over the prefectures. 570 JE cases came from 78 separate counties (88.63%) in 2007, 320 cases from 82 counties (93.18%) in 2008, and 633 cases from 88 counties in 2009.

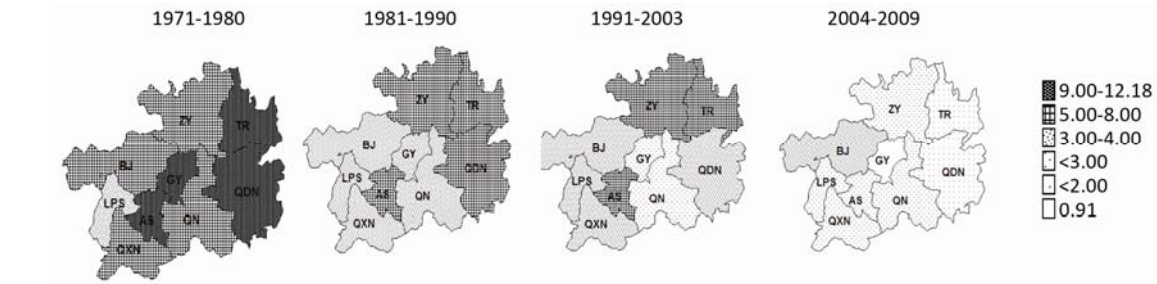

Figure 2. Geographical distribution maps of JE cases in Guizhou province, China, 1971-2009. Figures denote number of JE cases per 100 000 total population.

Seasonal Distribution of JE cases

Figure 3 reveals the monthly distribution of JE cases in four epidemic periods between 1971 and 2009. JE cases were reported throughout the year from January to December, but with higher incidence occurring from June to September, when 92.12% JE cases were recorded during the years 1971-2009. The monthly distribution data showed that the number of JE cases started to increase in June, reaching its peak in August, and then started to decline from September. November to May had the lowest number of cases reported in the year. July and August together accounted for over 70% of reported JE cases. For example, 72.59% of JE cases occurred in July and August during 1991-2003 and 88.43% occurred during 2004-2009. Despite significantly reduced JE cases during and after the catch-up JE vaccine campaigns, Figure 3 clearly demonstrates that seasonal distribution patterns of JE cases remained the same over the four epidemic periods from 1971-2009.

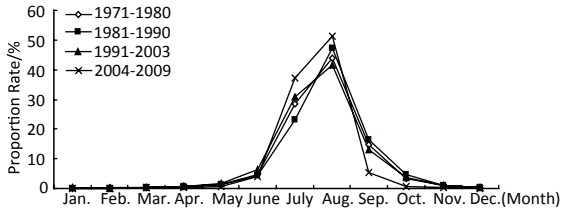

Figure 3. Monthly distribution of JE cases proportion rate in Guizhou, China, 1971-2009.

Age Distribution of JE Cases

The order of incidence rates from high to low was 0-6 years, 7-14 years, and 15 years or more in the years 1990-2009 (Figure 4). The highest incidence rate of 29.3/100 000 was observed in children aged 0-6 years in 2006. Strikingly, a huge drop in incidence rate from 29.3/100 000 in 2006 to 8.14/100 000 in 2007 (a 72.7% reduction) in this age group was probably a result of a provincial-wide vaccine catch-up campaign in 2007. The lowest incidence rate of 0.05/100 000 was seen in the ≥ 15 age group in 2008. This age group showed a steady

JE incidence rate over the 20-year period. The tapering off of age-specific attack rates after the age of 14 is probably due to increased prevalence of neutralizing antibody from natural exposure and sub-clinical infections.

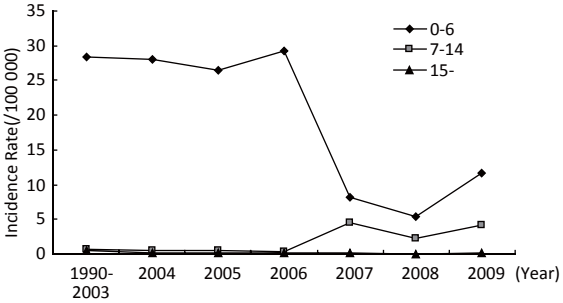

Figure 4. Age distribution of JE incidence rate in Guizhou, China, 1990-2009.

We also calculated the proportion rates of JE cases for each age group during 1990-2009. The greatest portion of JE cases occurred under the age of 15 years old and accounted for 89.88%-97.78% of total JE cases reported. Among children aged 0-6 years, the highest JE proportion rate was 76.58% in 2000 and the lowest proportion rate was 50% in 2007. The highest proportion of 44.56% in 2007 and the lowest proportion of 19.62% in 1997 were observed among age group of 7-14 years, and the highest proportion of 10.12% in 1996 and the lowest proportion of 2.22% in 2005 were seen in the ⩾15 year age group.

The Association between Vaccination and JE Incidence Rate

Figure 5 compares incidence rates of JE with the doses of vaccine distributed in Guizhou provinceduring 1971-2009. From 1971 to 2003, 650 000 doses of JE vaccine were distributed each year, while 1 610 000 doses of JE vaccine were distributed each year between 2004 and 2009. Pearson's correlation analysis was conducted between the doses of JE vaccine distributed and JE incidence rates during 1971-2009. There was a significant negative correlation between the amount of vaccine distributed, and JE incidence rates (coefficient of correlation=-0.475, $P<0.01$).

Guizhou Province conducted JE vaccine catch-up campaigns in a phased manner to target high-risk counties by using the live attenuated SA 14-14-2 JE vaccine during 2004-2008. In particular, a provincial wide catch-up vaccination campaign was conducted in 9 prefectures in 2007. During this 5-year period, more than 6.13 million children were immunized, and reported coverage rates were 67.39%, 70.39%, 91.78%, 93.57, and 96.69%, respectively (Table 1). Our data showed that lower JE incidence rates in 2007 and 2008 were correlated with immunization of susceptible children.

In 2008, the JE vaccine was integrated into the national Expanded Programme of Immunization (EPI) in Guizhou Province. Two doses of the live attenuated SA 14-14-2 JE vaccine were scheduled to be given, one at the age of 8 months and the second at 2 years old. In rural areas, village health care providers provide JE vaccine every 2 months, whereas in urban areas, JE vaccine is delivered at fixed township immunization sites at least once a month. The routine immunization surveillance system

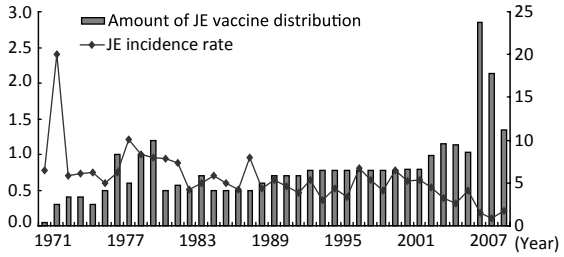

Figure 5. Age distribution of JE incidence rate in Guizhou, China, 1990-2009.

Table 1. Summary of JE Vaccine Catch-up Campaigns in Guizhou, 2004-2008

Year	Target Counties	Target Population	No. of Children Inoculated	Reported Coverage (%)	Reported JE	
					No. of Cases	Incidence Rate (/100 000)
2004	10 counties	8 m-10 y	351 045	67.39	1 230	3.18
2005	10 counties	8 m-10 y	396 958	70.39	1 037	2.66
2006	12 counties	8 m-10 y	754 608	91.78	1 519	4.07
2007	88 counties	8 m-6 y	2 201 124	93.57	570	1.54
2008	31 counties	8 m-10 y	1 503 052	96.69	320	0.84

showed that the reported JE vaccine coverage rates were above 95% in 2008-2009. The integration of JE vaccine into EPI, coupled with the vaccine catch-up campaign in 2008 resulted in the lowest incidence ever recorded in the 39 year period. However, in 2009, the JE incidence rate rose again compared with those of in 2007 and 2008 when JE vaccine catch-up campaign ceased.

DISCUSSION

With the introduction of an inactivated JE vaccine (P-3 strain) in Guizhou province in 1968, and a live attenuated vaccine (SA14-14-2) developed in the early 1990s, JE incidence has been steadily decreasing in Guizhou province. However, due to limited to access the financial resources, the JE vaccine has only been used in the selected high-risk counties prior to the JE epidemic season each year. Hence, JE vaccine has only provided partial coverage to the susceptible population[15,18].

Nevertheless, statistical analyses in this study indicated a significant negative correlation between the doses of JE vaccine distributed and JE incidence rates. Along with increasing the usage of JE vaccine in Guizhou, with 574 000 to approximately 1 220 000 doses distributed each year from the early 1970s to the late 2000s, the incidence of JE was significantly reduced. The JE vaccine catch-up campaigns conducted in Guizhou between 2004 and 2008 also contributed greatly to the control of the disease. In particular, the provincial-wide catch-up campaign in 2007 with approximately 2.20 million children immunized at one time, led to a huge decrease of JE cases from 1 752 cases in 2003 to 320 cases in 2008. Accordingly, JE incidence rate decreased from 4.66/100 000 in 2003 to 0.85/100 000 in 2008. Our data showed that a 1-dose massive JE vaccine catch-up campaign had proved to be effective and rapid in controlling JE.

Geographic distribution analyses of JE incidence in Guizhou showed that none of prefectures was free of JE cases between 1971 and 2009. But the severity of the epidemics in all prefectures was reduced 2-10 fold during JE vaccine catch-up campaigns and/or after implementation of a routine JE vaccine immunization program to children under the age of 2 years. This further proved the effectiveness of mass JE vaccination of susceptible populations for disease control. Similarly, integration of JE vaccine into the EPI in the beginning of 2007 has resulted in obvious changes with regard to epidemic risk and the geographical distribution of JE for many provinces in China. For example, Shanghai, Jiangsu, Zhejiang, Fujian, and Guangdong provinces in southeastern of China, which were previously high endemic areas of JE, have now become low endemic areas[6,19].

This retrospective study revealed that the JE seasonal pattern in Guizhou showed a significant increase in July with a single epidemic peak in August between 1971 and 2009. This seasonality was the same before and after the JE vaccine catch-up campaigns. Guizhou Province is an underdeveloped rural area with a hilly terrain located in southwestern China. It has a subtropical climate with the rainy season extending from May through August. People were living in rural areas breeding pigs and growing rice all year round. These conditions provide the necessary ecological components required for transmission of JEV, i.e. high-density breeding of *Culex tritaeniorhynchus* mosquitoes and pig breeding during and just after the rainy season from June to September[8,20-25].

From 1990-2009 in Guizhou, 50%-77% of the JE patients were preschool children under the age of 7 years; 20%-45% of JE cases were among children aged between 7 and 14 years, and adults comprised less than 10% of total reported cases. In recent years, with the JE vaccine being widely administered to those under the age of 10, the age composition of JE cases has begun to change. In Japan since the 1980s, and in Korea since the 1990s, over 60% of JE cases occurred among older adults[26-29]. Similarly, shifting of age prevalence towards adults was also observed in Taiwan after initiation of JE vaccination programs[30], as well as in Shanxi, Shandong and Gansu provinces in China. Current data shows age shifts between 30.8%-78.2% of JE cases occurring at 40 years or older[7,14,31]. In an outbreak of viral encephalitis which occurred in Yuncheng prefecture, Shanxi Province of China between July and August in 2006, more than 86% of the patients were older than 30 years of age, with only 10% younger than 7 years[32]. However, our study demonstrated that age shifting of JE toward adults had not yet occurred in Guizhou between 1990 and 2009. This was due largely to the lower JE vaccination coverage among young children.

According to the 5th population census data, Guizhou province accounted for 20% of the 40 million children in China under 10 years of age. This means that more than 8 million children are exposed to high risk of JEV every year. Although 650 000 doses of JE vaccine were used each year, the

estimated JE vaccine coverage rate under 10 years old was less than 10% during 1991-2003.

We surveyed 2 201 124 children aged between 8 months and 6 years old regarding their JE immunization history in 2007 and found that more than 65% of children had not received the vaccine. This could result in a great portion of young children being infected by JEV during the epidemic season. Older children and adults are at lower risk for JEV as the majority of them have already been infected at least once and developed neutralizing antibodies against JEV.

With regard to the success of the JE control strategy carried out in Guizhou, we have seen continuously declining JE incidence by promoting JE vaccination. In addition, with massive vaccination campaigns conducted between 2004 and 2008, the strategy has been improved by integrating the JE immunization into the EPI in Guizhou province. Since 2008, the reported routine JE immunization coverage rate has surpassed 95% with a two-dose program. However, we have to be aware of certain disadvantages. The routine immunization program only targets children of 8 months and 2 years of age. We still face a large population of young children aged over 2 years who are at risk for JEV due to lower JE vaccine coverage in the past. In fact, we observed an increase of JE cases in 2009 to almost double that reported in 2008 (where the number of cases was the lowest reported for 39 years in Guizhou). The possible reasons for this increase in 2009 are the following. First, cessation of the JE vaccine catch-up campaign in 2009 may have resulted in previously unimmunized preschool and young school-age children becoming infected during the JE epidemic season. Second, accuracy of the data is clouded by the fact that the current JE case reporting system records the total number of encephalitis cases and only limited numbers of JE cases have a specific etiologic diagnosis. Ye *et al* investigated 1 382 JE patients from case reporting system in 2006 in Guizhou, and JE was etiologically confirmed in 1 210 (87.6%) patients while 67 encephalitis patients (5%) had various other viral pathogens including echovirus, mumps virus, herpes simplex virus, and cytomegalovirus[13]. They also reported that only 9.2% of acute meningitis and encephalitis syndrome (AMES) patients in their study were laboratory-confirmed JE cases in 2006-2008[33]. Consequently, the reported number of JE cases is not always accurate.

We are aware of the data limitations in this study, including lack of consecutive JE vaccine coverage rates for analysis of the relation between JE incidence and vaccine coverage rate and lack of a solid surveillance system to discriminate JE cases caused by JEV from other AMES pathogens. However, it is clear that the JE virus is still circulating in the environment, particularly in the rural areas of Guizhou Province, where pig rearing is common. As a result of this study, JE endemic regions in Guizhou can be categorized into 4 groups according to their prevalence. The endemic regions ordered from high prevalence to low prevalence are (1) Bijie prefecture; (2) Zunyi, Liupanshui, Anshun, Qiannan, and Qianxinan prefectures; (3) Tongren and Qiandongnan prefectures; and (4) Guiyang prefecture. With a combination of the following control strategies, JE could theoretically be prevented : (I) Educating the population to be aware of the occurrence of the disease; (II) Controlling the mosquito vector by using pesticides; (III) Promoting personal protection: keeping residents away from mosquitoes by increasing distance between houses and rice fields and pigsties, as well as using mosquito nets and insect repellents to avoid mosquito bites; (IV) Immunization of domestic pigs; (V)Immunization of the population at risk.

This study demonstrates that human JE vaccination had proven to be the single most effective control measure. Thus, to ultimately control JE in Guizhou Province, there is a need for better definition of the areas containing high-risk populations, and re-enforcement of JE surveillance measures to include immediate case reporting with laboratory confirmation. The JE vaccine catch-up campaigns are still necessary but ideally should focus on all previously uncovered preschool and young school-aged children before the outbreak season. Epidemiological data should be reviewed frequently to evaluate the control measures and implement required modifications.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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