Review

Japanese Encephalitis in Mainland China

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SUMMARY: Japanese encephalitis (JE) is a seasonal epidemic disease with a 50-year recorded history in China. Its characteristics can be summarized as follows: (i) it is a seasonal epidemic disease; approximately 90% of cases are recorded in July, August, and September each year. The peak of JE onset is 1 month earlier in South China than in the north of the country; (ii) the disease is highly sporadic. It is rare for more than two cases to appear simultaneously in one family; (iii) most affected children are under 15 years old; (iv) the disease is widely distributed in all areas of the nation except Qinghai Province, Xinjiang Uygur Autonomous, and Tibet. Due to widespread application of the JE vaccine, the number of JE cases has decreased significantly nationwide, from 174,932 cases of morbidity in 1971 to 5,097 cases in 2005.

1. Introduction

Japanese encephalitis (JE) is an acute epidemic disease of the central nervous system (CNS) caused by infection with the Japanese encephalitis virus (JEV). JE mainly affects children and adolescents. According to the World Health Organization (WHO) statistics, approximately 35,000 cases of JE are reported each year, causing approximately 5,000 deaths—a mortality rate of 5 - 40%. Approximately 50% of JE patients present neurological and mental sequelae (1). JEV is transmitted by mosquitoes and the genus Culex, which is major vector. It is a perennial disease in tropical areas, but is clearly seasonal in temperate zones, with a peak incidence period between June and October each year. At present, JE is endemic in over 20 countries and areas, including the Pacific coastal areas of Far East Russia, Japan, China, North and South Korea, India, Vietnam, Laos, Myanmar, Thailand, Cambodia, the Philippines, Malaysia, Singapore, Bhutan, Indonesia, Nepal, Sri Lanka, Guam, Papua New Guinea, and Australia (2,3). The traditional endemic areas of JE are mainly located in China, where the disease is highly endemic. For example, an outbreak of JE in India in 2005 involved 5,737 reported cases and resulted in 1,344 deaths (4). At present, the areas of JE endemism are tending to expand. For instance, in 1995, an outbreak of JE occurred in Papua New Guinea and among the original inhabitants of the northern islands of Australia, and even appeared in the northern areas of Australian mainland (5,6).

Japan is the main region of JE endemism. Our data reveal the occurrence of JE cases in each province except Xinjiang Uygur Autonomous, Tibet, and Qinghai. JE is one of the four arbovirus diseases currently prevalent in Japan (7). In this paper, we summarize the epidemics of JE in mainland China in recent years and the prevention measures taken there.

2. Incidence and mortality

JE case reporting is currently mandated by law in China. Since the establishment of a case reporting system in 1951, the incidence of JE has been recorded annually in China. Further, since 2004, each JE case has been electronically recorded and the data collected at the national level by the Chinese Center for Disease Control and Prevention (China CDC); the case reporting system has thus become both more sensitive and more efficient.

Historically, there have been two major JE epidemics. The first, in 1966, had an annual incidence of >15/100,000 nationwide, whereas the second, in 1971, was associated with 174,932 cases of morbidity and an incidence of 20.92/100,000 (8-10). Since the 1980s, JE vaccination has been widely used in our country and, as a consequence, the number of morbidities has declined gradually year by year. Prior to the 1990s, the annual morbidities numbered between 20,000 and 40,000.
However, the number of JE morbidities decreased from 11,779 to 5,097 between 2000 and 2005, the annual incidence declined from 0.9489/100,000 to 0.3898/100,000, the number of mortalities declined from 375 to 214, and the mortality rate also decreased from 0.0302/100,000 to 0.0164/100,000. Over this 6-year period, the annual mortality rate ranged from 2.51 to 4.66% (11,12). The trends in the incidence and mortality of JE in mainland China in recent years are illustrated in Figure 1 and Table 1.

3. Seasonal distribution of cases

JE cases are reported from January to December each year nationwide and reveal a low incidence in the periods from November to May. However, the number of morbidities in June is typically double that occurring in May. The number of morbidities occurring in July and August each year are generally pooled. The number of morbidities in August accounts for 41.14% of the total annual morbidities. The relatively high morbidity level is maintained in September, declines in October, and then decreases significantly in November. The number of morbidities between June and October accounts for 97.42% of the total annual morbidity. Over this 6-year period, the annual mortality rate ranged from 2.51 to 4.66% (11,12). The trends in the incidence and mortality of JE in mainland China in recent years are illustrated in Figure 1 and Table 1.

4. Geographic distribution of cases

A total of 31 provinces in mainland China have reported JE cases; the exceptions including Qinghai Province, Xinjiang Uygur Autonomous, and Tibet. The cases are scattered in various endemic localities with no obvious aggregation of the disease. Based on the average annual incidence of JE between 1996 and 2005, the regions of endemism in mainland China can be classified into the following four groups (Figure 3).

4-1. Highly endemic areas

The average incidence in these areas is considered to be approximately >1/100,000. The areas include Sichuan Province, Guizhou Province, Chongqing City, Shaanxi Province, and Yunnan Province. Annually, the number of morbidities in these five provinces accounts for 50% of the total cases nationwide, comprised as much as 74.1% of the total cases in 2002. The combined population of these areas, however, represents only 26% of the national population (10,11,13-16).

4-2. Moderately endemic areas

The average incidence in these areas is considered to be between 0.5/100,000 and 1/100,000. The areas include the

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of JE cases</th>
<th>Incidence (1/100,000)</th>
<th>No. of death cases</th>
<th>Mortality (1/100,000)</th>
<th>Case fatality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
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<td>0.8660</td>
<td>379</td>
<td>0.0318</td>
<td>3.677</td>
</tr>
<tr>
<td>1997</td>
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<td>0.8343</td>
<td>370</td>
<td>0.0307</td>
<td>3.678</td>
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<tr>
<td>1998</td>
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<td>0.9977</td>
<td>510</td>
<td>0.0407</td>
<td>4.083</td>
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<tr>
<td>1999</td>
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<td>0.6889</td>
<td>348</td>
<td>0.0280</td>
<td>4.067</td>
</tr>
<tr>
<td>2000</td>
<td>11,779</td>
<td>0.9489</td>
<td>375</td>
<td>0.0302</td>
<td>3.184</td>
</tr>
<tr>
<td>2001</td>
<td>9,795</td>
<td>0.7707</td>
<td>246</td>
<td>0.0194</td>
<td>2.511</td>
</tr>
<tr>
<td>2002</td>
<td>8,769</td>
<td>0.6548</td>
<td>229</td>
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<tr>
<td>2003</td>
<td>7,860</td>
<td>0.5829</td>
<td>366</td>
<td>0.0271</td>
<td>4.6565</td>
</tr>
<tr>
<td>2004</td>
<td>5,422</td>
<td>0.4171</td>
<td>200</td>
<td>0.0154</td>
<td>3.6887</td>
</tr>
<tr>
<td>2005</td>
<td>5,097</td>
<td>0.3898</td>
<td>214</td>
<td>0.0164</td>
<td>4.1985</td>
</tr>
<tr>
<td>Total</td>
<td>90,136</td>
<td>–</td>
<td>3,237</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
following seven provinces: Shanxi Province, Henan Province, Anhui Province, Hubei Province, Hunan Province, Jiangxi Province, and Guangxi Province. Between 2000 and 2002, the number of morbidities accounted for 20% of the cases nationwide (10,11,17-19).

The five provinces with an incidence >1/100,000 are located in southwest and middle China and lie adjacent to each other. The seven provinces with incidence between 0.5/100,000 and 1/100,000 are located on the eastern periphery of the abovementioned five provinces and are closely adjacent to them. The combined JE morbidities of these 12 provinces account for 80% of the total cases nationwide, whereas their combined population constitutes only 40% of the national population. In addition, the total number of JE morbidities in mainland China has decreased significantly in recent years compared to those reported in historical records, and the 5,097 cases reported in 2005 was the lowest annual figure to date. However, despite this downward trend, the ratio of the number of morbidities in the 12 high- and moderate-incidence provinces as a percentage of the national total cases is in-

<table>
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<tbody>
<tr>
<td>JAN</td>
<td>20</td>
<td>17</td>
<td>43</td>
<td>24</td>
<td>16</td>
<td>10</td>
<td>25</td>
<td>18</td>
<td>7</td>
<td>2</td>
<td>182 (0.20)</td>
</tr>
<tr>
<td>FEB</td>
<td>9</td>
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<td>20</td>
<td>10</td>
<td>7</td>
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<td>20</td>
<td>10</td>
<td>11</td>
<td>2</td>
<td>107 (0.12)</td>
</tr>
<tr>
<td>MAR</td>
<td>21</td>
<td>37</td>
<td>40</td>
<td>18</td>
<td>15</td>
<td>21</td>
<td>45</td>
<td>30</td>
<td>27</td>
<td>12</td>
<td>266 (0.30)</td>
</tr>
<tr>
<td>APR</td>
<td>36</td>
<td>43</td>
<td>69</td>
<td>43</td>
<td>35</td>
<td>39</td>
<td>49</td>
<td>33</td>
<td>34</td>
<td>6</td>
<td>387 (0.43)</td>
</tr>
<tr>
<td>MAY</td>
<td>119</td>
<td>154</td>
<td>214</td>
<td>130</td>
<td>131</td>
<td>121</td>
<td>213</td>
<td>268</td>
<td>118</td>
<td>67</td>
<td>1,535 (1.70)</td>
</tr>
<tr>
<td>JUN</td>
<td>639</td>
<td>584</td>
<td>797</td>
<td>826</td>
<td>520</td>
<td>498</td>
<td>874</td>
<td>956</td>
<td>430</td>
<td>696</td>
<td>6,820 (7.57)</td>
</tr>
<tr>
<td>JUL</td>
<td>2,915</td>
<td>2,654</td>
<td>4,245</td>
<td>2,438</td>
<td>3,029</td>
<td>3,193</td>
<td>4,485</td>
<td>2,888</td>
<td>1,745</td>
<td>2,225</td>
<td>29,817 (33.08)</td>
</tr>
<tr>
<td>AUG</td>
<td>4,109</td>
<td>4,419</td>
<td>5,079</td>
<td>3,413</td>
<td>5,817</td>
<td>4,210</td>
<td>2,510</td>
<td>3,157</td>
<td>2,575</td>
<td>1,796</td>
<td>37,085 (41.14)</td>
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<tr>
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<td>1,818</td>
<td>1,540</td>
<td>1,469</td>
<td>1,278</td>
<td>1,723</td>
<td>1,241</td>
<td>404</td>
<td>407</td>
<td>393</td>
<td>238</td>
<td>10,511 (11.66)</td>
</tr>
<tr>
<td>OCT</td>
<td>439</td>
<td>427</td>
<td>373</td>
<td>267</td>
<td>355</td>
<td>331</td>
<td>92</td>
<td>62</td>
<td>60</td>
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<td>106</td>
<td>101</td>
<td>76</td>
<td>88</td>
<td>90</td>
<td>42</td>
<td>25</td>
<td>16</td>
<td>6</td>
<td>677 (0.75)</td>
</tr>
<tr>
<td>DEC</td>
<td>56</td>
<td>73</td>
<td>40</td>
<td>33</td>
<td>43</td>
<td>29</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>2</td>
<td>298 (0.33)</td>
</tr>
<tr>
<td>Total</td>
<td>10,308</td>
<td>10,060</td>
<td>12,490</td>
<td>8,556</td>
<td>11,779</td>
<td>9,795</td>
<td>8,769</td>
<td>7,860</td>
<td>5,422</td>
<td>5,097</td>
<td>90,136 (100.00)</td>
</tr>
</tbody>
</table>

Fig. 2. Seasonal distribution of JE case in China.

Fig. 3. Geographic distribution of JE in China.
creasing—from 82.7% in 1998 to 91.4% in 2002, and to 88.85% in 2005—demonstrating that the onset of JE is becoming more prevalent in these areas.

4.3. Slightly endemic areas

The average incidence in the slightly endemic areas is considered to be between 0.1/100,000 and 0.5/100,000. The areas include the following seven provinces: Shanxi Province, Gansu Province, Jiangsu Province, Shandong Province, Fujian Province, Guangdong Province, and Zhejiang Province. In addition, there are a further 10 provinces and areas with an incidence <0.1/100,000: Hebei Province, Ningxia Province, Shanghai City, Liaoning Province, Inner Mongolia Province, Hainan Province, Tianjin Province, Beijing City, Jilin Province, and Heilongjiang Province (10,11,20-22).

4-4. Non-endemic areas

There have been no JE cases reported from three provinces: Qinghai Province, Xinjiang Uygur Autonomous, and Tibet. Although individual imported cases might be recorded from these areas, they can still be regarded as non-endemic (10,11,23).

According to the analysis of the annual incidence of JE cases in each province, before the 1970s, the JE cases mainly appeared in localities in the north of China, including Beijing City, Tianjin City, Shandong Province, Shanghai City, Zhejiang Province, Jiangxi Province, Fujian Province, and Guangdong Province, and also from coastal areas in the east (10). However, the incidence in these areas has undergone a significant recent decline, and at present the average incidence is approximately 0.1/100,000. This reveals that the endemic areas of JE have shifted from the eastern coastal areas to the southwest and middle provinces. The current low incidence of JE in the eastern coastal areas is mainly attributed to the rapidly developing economy of this region that has resulted in a relatively high coverage of JE vaccination (10).

5. Age and gender distribution

In terms of the age distribution of JE morbidity, JE cases have been recorded in subjects in infancy to those over 75 years old (Figure 4). The proportion of 2-, 3-, and 4-year-olds is relatively high, accounting for 10.88, 12.88, and 12.33% of all cases, respectively. Young patients under 6 years of age accounted for 68.10% of the total cases. In the years between 2000 and 2005, young patients under 15 years of age accounted for 91.19, 91.26, 91.06, 90.14, 89.80, and 90.6% of the total cases nationwide, respectively (11).

The age distribution of JE deaths is similar to that of morbidities. Death cases have been recorded in all age groups, with the highest proportion in 2-, 3-, and 4-year-olds, accounting for 10.69, 11.95, and 10.84% of total JE death cases, respectively. JE deaths in patients under 15 years of age account for 83.7% of total deaths, and among these, deaths in patients under 6 years of age account for 65.22% of JE fatalities.

The number of males among JE patients has exceeded that of females, with a ratio of 1.3:1 in recent years (11).

6. Occupational distribution

The data on the occupational distribution of JE cases between 1996 and 2005 reveals that diaspora children account for 54.51% of total morbidities and 54.72% of total mortalities. According to reports in 2005, the occupation of morbidity patients is mainly diaspora children, students, and kindergarten children, accounting for 88.5% of the total morbidities. Among these, diaspora children accounted for 53.6%, students for 23.4%, and kindergarten children for 11.5%, while farmers accounted for 8.3% of all morbidity patients. Mortalities occurred mainly in diaspora children (50.3%), followed by students (21.1%), farmers (15.8%), and kindergarten children (7.0%) (11).

7. Prevalence of JEV isolates

JEV, a Flavivirus belonging to the family Flaviviridae, was first isolated in Japan. JEV was first isolated in China in the 1940s (24-27). An inactivated form of the P-3 strain has been used to develop a JE vaccine. Since its first discovery in China, multiple strains of JEV have been isolated in the country. Strain SA14 was isolated from mosquitoes in China and has been used to develop a live attenuated JE vaccine.

In recent years, multiple strains of JEV have been isolated from the cerebrospinal fluid (CSF) and blood of Chinese JE patients, as well as from mosquitoes and midges collected in areas including Shanghai City, Yunnan Province, Guizhou Province, Henan Province, Sichuan Province, Fujian Province, Liaoning Province, and Heilongjiang Province. Moreover, a molecular biological study of JEV has been launched (28-38).

By tissue culture methods, seven strains of JEV have been isolated from Culex tritaeniorhynchus collected in the suburban area of Shanghai City. All seven newly isolated strains exhibit a positive reaction with standard JEV antibodies. A molecular biological study has demonstrated that each of these strains belongs to genotype 1 of JEV (30). This is the first report of the isolation of genotype 1 JEV in China.

Genotypic analysis of 100 JE strains isolated in mainland China revealed that they possessed two JEV genotypes (genotypes 1 and 3). JEV genotype 3 strains are primary epidemic strains. JEV genotype 1 has been known since 1979 (37). Two JEV genotypes were detected in specimens from JE patients and from mosquitoes simultaneously with a JE outbreak in Yuncheng Prefecture, Shanxi Province, in 2006 (38). The genome analysis of two JEVs from bats in Yunnan, China in 1980 showed both virus isolates belong to genotype 3. The viruses have a close relationship with JEVs isolated between mosquitoes and humans in the same region over 2 decades (39).

8. Control and prevention of JE

8-1. JE vaccine

Inoculation with an inactivated vaccine (P-3 strain) was developed and has been used in China for vaccination since the beginning of the 1970s. A JE live attenuated vaccine (SA14-14-2) has been used since the beginning of the 1990s.
and its safety and efficacy have been evaluated (40,41). A total of 300,000,000 people have been vaccinated with this attenuated vaccine. Prior to 2006, a total of 16 provinces had used JE vaccination as part of their immunization program; local governments provide the population with free JE vaccination (42). Beginning in 2006, prevention and control of JE in China has advanced with the integration of JE immunization into the Expanded Programme of Immunization (EPI) in mainland China, especially in rural and underdeveloped areas.

8.2. Surveillance of JE

In recent years, the government has paid great attention to the prevention and treatment of JE. In 2004, the Ministry of Health, China (MOH, China) advocated an increase in the research on JE, and in 2006 announced a national surveillance program for JE (43). At present, 22 surveillance sites have been established in 13 provinces nationwide in order to monitor JE epidemics, generally in areas with a high incidence of JE. The surveillance includes case reports, close monitoring of the nature of transmission media, pathogen monitoring, and JE antibody monitoring among humans and swine (43).

In recent years, the international society has augmented the support to JE prevention in China. Since 2001, a program of The Japan Health Science Foundation has supported research in the “molecular epidemiological study of Japanese encephalitis virus in China”. In 2005, the Program for Appropriate Technology in Health (PATH) in America launched a JE surveillance project in the highly endemic area of Shaanxi Province, for which sera and CSF samples of local JE cases have been collected for laboratory diagnosis. The WHO, together with MOH, China, has launched an acute meningitis and encephalitis surveillance (AMES) program in four provinces (Hubei, Shandong, Guangxi, and Hebei).

9. Conclusion

The data indicate that the incidence of JE has been decreasing substantially; in 2008 for example, there were only 2,975 reported JE cases and 142 deaths in 25 provinces in mainland China. The overall incidence of JE should decrease even more due to the introduction of the JE vaccine into the EPI system; nevertheless, JE currently remains also a high-importance public health problem in China. Recently, the tendency of the age distribution in JE morbidity has swung toward teenage patients. The genotype of JEV has changed from G3 only to G1 and G3, which means two genotypes are circulating in China. Although the vaccine has been used in newborns, the vaccine strategy should be adjusted according to changes in the characteristics of the disease, especially in terms of the local outbreaks of JE. Strengthening the sensitivity of the surveillance system should also be an effective way to control the disease.

ACKNOWLEDGMENTS

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