Epidemic situation of dengue fever in Guangdong province, China, 1990-2005

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Abstract
During the period 1990 to 2005, a total of 11 844 cases of dengue fever (DF), with 3 deaths, were reported in Guangdong province. The average attack rate was 1.27/100 000 pop. The disease affected 17 out of 21 cities in the province. DF occurred throughout the year and the epidemic phase extended from July to December. DENV-1, that affected all age groups, appeared to be the predominant circulating virus, although DENV-2, -3 and -4 were also involved. *Aedes albopictus* was the only vector species responsible for the DF outbreaks.

The results of molecular epidemiological studies showed that dengue fever epidemics in Guangdong province were initiated by imported cases from South-east Asia. Control measures comprised of insecticidal fogging and elimination of man-made breeding places of *Ae. albopictus*.

Keywords: Dengue fever; Epidemiological surveillance; Guangdong; China.

Introduction
Dengue fever (DF), an acute febrile viral disease characterized by sudden onset of fever for 2–7 days (sometimes biphasic), intense headache, myalgia, arthralgia, retro-orbital pain, anorexia, nausea, vomiting and rash, is one of the most common and widespread vector-borne arboviral infections in the world. The viruses of dengue fever belong to the family *Flaviridae* and include four serotypes (DENV-1, -2, -3, -4), all of which can classically cause undifferentiated fever, dengue fever and its severe form, dengue haemorrhagic fever (DHF). The global prevalence of dengue has increased dramatically in recent decades. As per WHO estimates, DF/DHF is now prevalent in over 100 countries, posing a threat to more than 2.5 billion people in the tropics and subtropics.[1,2]

In China, in the 1980s, *Aedes aegypti* was reported in Hainan island and Leizhou peninsula, and caused an epidemic affecting one million people. However, *Aedes albopictus*, another common species of mosquito, is known to be the principal vector of DF in Guangdong province since 1990.[3-5] Guangdong
Dengue in Guangdong Province, China

has been a major province in China affected by dengue fever outbreaks in addition to Fujian, Zhejiang and Jiangsu provinces since 1990.\[6\]

Guangdong province had a population of 85 million (in 2000).\[7\] It is located in southern China in the subtropical zone, which is suitable for mosquito breeding. The first confirmed outbreak of dengue in the province was reported in 1978.\[8-9\] Since then, dengue fever has become a major public health concern. The present study focuses on the epidemiological features and molecular characterization of dengue viruses during 1990–2005.

**Materials and methods**

**Data sources**

In China, DF is a notifiable disease. Hence, all health care facilities like hospitals and clinics in the country are required to report clinical and confirmed cases of dengue to the Centers for Disease Control and Prevention (CDC) system: first to the county CDC, which then reports to the provincial CDC. Once these notifications are received, the CDC performs laboratory verification, then conducts further epidemiological investigation, and searches for other dengue cases or clusters.

Based on mandatory notification, we collected and analysed all notified cases of dengue in Guangdong province from 1990 to 2005. However, it is required by law to classify these notifications of dengue into different clinical manifestations {DF, DHF, dengue shock syndrome (DSS)}. Both clinical cases and confirmed cases are reported.\[10\]

**Case definitions**

A clinical case of dengue is defined as follows:

- Clinical symptoms, such as abrupt onset of fever, severe headache, myalgia, arthralgia, nausea, vomiting, rash, etc.
- When only sporadic cases are found or no local cases have been reported: clinical manifestations of dengue (DF, DHF or DSS) with positive IgG or IgM in a single serum specimen.
- When local cases have been reported: clinical manifestations of dengue (DF, DHF or DSS) with decreased white cell count (<4×10^9/l) and lower thrombocytopenia count (<100×10^9/l).
- The isolation of DENV, by cell culture and virus antigen preparation from culture supernatants of DENV-1, DENV-2, DENV-3 and DENV-4-infected C6/36 cells.\[11\] The culture supernatants were used as the source of E/M and NS1 antigens for ELISA. The control antigen was prepared by the same procedure from vero cells culture without viral infection.
- Positive test of real-time one-step RT-PCR: The nucleotide sequence of DENV-1 E/NS1 gene segment was isolated. Viral RNA was extracted for use in one-step reverse transcriptase polymerase chain reaction (RT-PCR). Following amplification by RT-PCR, the partial nucleotide fragments of the E/NS1 gene junction were then cloned into the plasmid pBlueScript II SK for sequencing. The following primers were used for sequencing:

  Forward primer: 5’–GTCGACACATACCAAGAAGGAG–3’
  Reverse primer: 5’–TGGATGTAACCGAGACGGAGTGCTGA–3’

The sequence results were analysed using the DNASTAR software.
• Positive seroconversion or four-fold increase in dengue-specific IgM or IgG antibody from appropriately timed paired serum (with acute-phase sera collected during day 1–7 after the onset of symptoms, and early and late convalescent sera collected during day 8–13 and day 14–30, respectively).
• High-titre dengue-specific IgM and IgG antibody in a single serum specimen where cross-reaction to Japanese encephalitis (JE) had been excluded.

Vector surveillance

In Guangdong, surveillance of Aedes albopictus was carried out throughout the year, particularly in areas reporting active cases. The investigations included search for Aedes breeding places and determining the entomological indices, viz. Breteau index (BI) (number of positive containers for Aedes per 100 houses) and Container index (CI) (percentage of containers positive for Aedes breeding) until two weeks after the last local case was reported.

Results

Epidemiological information

During the period of 16 years (1990–2005), a total of 11,844 cases of dengue fever and 3 deaths were reported in Guangdong province (Table). The notification rates ranged from 0.003 to 9.75 per 100,000 population per year. The epidemic peak appeared in 1995. The male-to-female ratio was 1:1.02. All age groups were involved, although most of them (72.07%) were aged 15 to 50 (Figures 1, 2).

An analysis by occupation indicated that out of the 11,470 reported cases, 2,842 were workers, 3,482 farmers, 1,552 students, 749 office clerks, 711 unemployed and household persons and 294 were children. It is noteworthy that medical staff accounted for 0.92% of the cases (106 cases).

Seasonal distribution

The majority of the dengue cases (93%) were notified from August to October, although cases were reported throughout the years (primarily

Figure 1: Epidemic status of dengue fever in Guangdong, 1990–2005
### Table: Epidemiological data for dengue fever in Guangdong province, 1990-2005*

<table>
<thead>
<tr>
<th>Time</th>
<th>Cases</th>
<th>Incidence (1/100 000)</th>
<th>Outbreak place (number of cases, serotype)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>374</td>
<td>0.6</td>
<td>Guangzhou (372, DENV-1, 4)</td>
</tr>
<tr>
<td>1991</td>
<td>371</td>
<td>0.57</td>
<td>Guangzhou (258, DENV-1) Zhongshan (112, DENV-1)</td>
</tr>
<tr>
<td>1992</td>
<td>2</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>1993</td>
<td>359</td>
<td>0.53</td>
<td>Foshan (352, DENV-2)</td>
</tr>
<tr>
<td>1994</td>
<td>4</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>6812</td>
<td>9.75</td>
<td>Guangzhou (5337, DENV-1) Zhaqing (983, DENV-1) Chaozhou (349, DENV-1) Nongguang (90, DENV-1)</td>
</tr>
<tr>
<td>1996</td>
<td>2</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>632</td>
<td>0.87</td>
<td>Chaozhou (601, DENV-1) Jieyang (31, DENV-1)</td>
</tr>
<tr>
<td>1998</td>
<td>488</td>
<td>0.66</td>
<td>Foshan (464, DENV-1) Guangzhou (10, DENV-1)</td>
</tr>
<tr>
<td>1999</td>
<td>304</td>
<td>0.406</td>
<td>Zhongshan (180, DENV-1) Jieyang (90) Chaozhou (17, DENV-3)</td>
</tr>
<tr>
<td>2000</td>
<td>401</td>
<td>0.531</td>
<td>Chaozhou (265, DENV-1), Shantou (131)</td>
</tr>
<tr>
<td>2001</td>
<td>365</td>
<td>0.46</td>
<td>Yangjiang (137, DENV-1) Zhongshan (84, DENV-2) Zhuhai (68, DENV-2) Jiangmen (53)</td>
</tr>
<tr>
<td>2002</td>
<td>1576</td>
<td>1.77</td>
<td>Guangzhou (1421, DENV-1) Jieyang (65, DENV-1) Zhongshan (26)</td>
</tr>
<tr>
<td>2003</td>
<td>82</td>
<td>0.09</td>
<td>Guangzhou (78, DENV-1)</td>
</tr>
<tr>
<td>2004</td>
<td>49</td>
<td>0.06</td>
<td>Zhongshan (36, DENV-1) Chaozhou (5)</td>
</tr>
<tr>
<td>2005</td>
<td>23</td>
<td>0.03</td>
<td>Not available</td>
</tr>
</tbody>
</table>

*Only three deaths were reported in 1991 with mortality rate of 0.005.
imported cases) (Figure 3). Dengue outbreaks occurred from June to November, with peaks during August to October.

**Geographical distribution**

Approximately 63% of cases were reported from Guangzhou (the Capital city), 10% from Chaozhou, 8% from Zhaoqing, and 7% from Foshan. The outbreaks occurred in all these years with the exception of 1992, 1994, 1996 and 2005. Although multiple outbreaks occurred in Guangzhou, Zhongshan, Foshan, Chaozhou and Jieyang, there was no place where DF outbreaks occurred over two consecutive years (Figure 4).

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**Figure 2: Age composition of dengue cases in Guangdong province, 1990-2005**

![Age composition of dengue cases in Guangdong province, 1990-2005](image)

**Figure 3: The seasonal dynamics of DF and Aedes albopictus in Guangzhou province**

![The seasonal dynamics of DF and Aedes albopictus in Guangzhou province](image)
Dengue virus

In Guangdong, all four serotypes, DENV-1–4, caused the dengue outbreaks. With the exception of 1990 and 1993, DENV-1 appeared to be the predominant circulating virus. In addition, DENV-2 and DENV-4 were isolated from patients in Foshan, Zhongshan and Zhuhai city. Many of the index cases of these outbreaks were imported from outside China. For example, index cases were imported from China, Macao Special Administrative Region (SAR), Singapore and Thailand during 2003. All reported cases in 2005 were imported from South-east Asia.

The phylogenic tree of the sequenced 14 strains of DENV-1

The phylogenic tree of the sequenced 14 strains of DENV-1 isolated between 1990 and 2005 has been mapped and it branches into two genotypic groups (Figure 5). The nucleotide sequences showed maximum homology of 99.2% with Indonesian strains, 100% with strains from the Philippines, and 98.8% with strains from Thailand.

Surveillance of vector

Aedes albopictus is a highly urbanized species and, in the Guangdong province, it breeds in water stored in man-made containers and natural habitats. The seasonal distribution of Aedes albopictus is correlated with a Breteau index which, in turn, is affected by temperature and rain. In Guangdong, the density of Aedes albopictus peaked from May to October, and was very low from November to February.
Discussion

We have provided the epidemiological information of dengue spanning over a period of 16 years from 1990 to 2005 in Guangdong province. Our data sources are based on mandatory notification, which have the intrinsic inadequacies such as incomplete reporting, or false positive results due to cross reaction of dengue viruses with Japanese encephalitis vaccine viruses. In addition, dengue notifications in China are not classified by clinical manifestations (DF, DHF or DSS), a majority of them are known to be presented as classical dengue fever. For example, a total of 758 cases of dengue were reported in 1995, of which 12 (1.58%) were DHF.\(^{[6]}\) Out of the 978 hospitalized dengue cases in an infectious disease hospital of Guangzhou in 2002, only two were DHF.\(^{[12]}\)

A secular trend of increased reporting of dengue outbreak was observed. The developing economy and rapid urbanization within Guangdong have contributed towards increased opportunities for the development and transmission of DF in the province, especially in the Pearl delta region. Risk factors for DF epidemic included: (i) the changing lifestyle of people; for example, more people now grow bonsai and raise fish in tanks near their homes; (ii) more construction sites with poor sanitation conditions; (iii) frequent travel to and from South-east Asia resulting in importation of viruses, especially the Chaozhou and Shantou; (iv) delayed detection and treatment of active disease due to lack of knowledge of DF among primary medical staff; and (v) high densities of vector mosquitoes. The vector control mainly covered adult *Aedes* mosquitoes control, which remains largely an ineffective intervention.
The evidences from epidemiological investigation and molecular epidemiology supported the hypothesis that the identified dengue cases were imported from other countries into Guangdong. The circulating virus strains in an area were usually different in different years, and different virus serotypes prevailed in different areas in one year. From 1979 to 1999, the circulating DENV-1 strain belonged to two geno-subtypes. It is likely that most of these strains were imported from neighbouring countries such as the Philippines, Indonesia and Thailand, where indigenous dengue epidemics have been confirmed. The results of nucleotide sequencing showed that DENV-1 was closely related to viruses identified in these regions. High mosquito density and favourable natural conditions (such as optimal temperature and rainfall) are responsible for localized outbreaks, once dengue viruses are imported into the province.\(^{[13]}\)

For building up an early response to outbreaks, it is necessary to improve diagnostic capacity and strengthen training and reporting awareness of local physicians, particularly in early detection, diagnosis, notification and isolating patients. Secondly, it is important to establish a vector monitoring system to understand population dynamics of Aedes albopictus. Thirdly, comprehensive measures of prevention and control including environmental solid waste disposal and chemical, biological and ecological control should be developed. Lastly, community health education needs to be strengthened to improve awareness of the dengue virus transmission through Aedes albopictus.

From our experience, source reduction and use of non-chemical methods supported by intersectoral and community participation are the most potential methods for control of dengue during interepidemic periods. The Breteau index is the most important indicator to predict impending dengue outbreaks in this province. Maintaining lower BI levels (below 5) is a very effective measure to prevent and control dengue outbreaks. Further studies are required to determine the BI cut-off value for mosquito control to prevent DF outbreaks.

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**References**


