Aedes aegypti, Dengue and Re-urbanization of Yellow Fever in Brazil and other South American Countries - Past and Present Situation and Future Perspectives

By


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ABSTRACT

Dengue (DEN) and yellow fever (YF) viruses are two important arboviruses causing human disease. Dengue fever and dengue haemorrhagic fever (DF/DHF) reemerged in the Americas after Aedes aegypti had reinfested most tropical and subtropical regions in the hemisphere. The number of DF/DHF cases being reported are increasing each year; and in South America only Chile and Uruguay have not reported any cases. Sylvan YF has increased in the last two decades because of increasing human contact with forest areas, and the risk of its re-urbanization has increased dangerously due to the presence of Aedes aegypti proximally to areas with sylvatic YF, particularly in Bolivia, Brazil, Colombia and Peru, where YF is transmitted by Haemagogus mosquitoes. This paper gives an overview of the main epidemiological findings of YF and DEN viruses in the recent past and discusses the future perspectives of the dissemination of DF/DHF and re-urbanization of YF in South America. Current situation demands the adoption of a massive YF vaccination programme in the region in conjunction with a powerful regional plan of Aedes aegypti control to avoid deaths attributed to these two viruses in South America.

Key words: Dengue/Dengue haemorrhagic fever, Yellow Fever, Brazil, South America, Aedes aegypti

Introduction

For many decades, a programme for the eradication of Aedes aegypti was carried out in countries of the continental America. The programme was planned and initiated by the Pan American Health Organization (PAHO) in 1946. Initially the principal aim was the prevention of urban epidemics of yellow fever (YF) virus and of dengue epidemics. During the first 30 years, substantial progress was made and several countries were able to eradicate this mosquito. Unfortunately, some countries, which included Argentina, French Guyana, the
United States, Venezuela and several Caribbean countries, failed to achieve eradication. Some countries abandoned the programme, as in the case of Venezuela where transmission of dengue virus was still occurring when the government terminated its efforts in this direction\(^1\). Several Latin American countries stayed *Aedes aegypti*-free from 1961 to 1974, but slowly and gradually these countries were re-infested from the ones where the problem had remained unresolved. The resurgence of this mosquito was soon accompanied by the occurrence of dengue fever (DF) and dengue haemorrhagic fever (DHF) epidemics. It also resulted in an increased risk of the re-urbanization of the YF virus, an important viral agent responsible for large epidemics in the region in the past with high case-fatality rates. This article reviews the past and present situation of these two important arboviruses causing human disease and their vectors, and analyses the future perspectives.

**Past situation**

**DF/DHF**

In the Americas, the first documented DF epidemic occurred in 1779-80 in the city of Philadelphia, U.S.A., which was clinically characterized as "breakbone fever"\(^2\). The incidences of DF epidemics in the continent America were reported in the Caribbean region, affecting several countries, as well as in southern United States during the 18\(^{th}\) century, at least on four occasions\(^3\).

During the first half of that century, more DF epidemics occurred in the same countries, as also in Cuba, Mexico, Panama and several other Caribbean islands. The number of people that got affected was virtually unknown, but have been estimated to be in thousands. The clinical signs and symptoms observed included fever, headache, muscle and small-joint pains\(^3,4\).

In South America, the occurrence of DF epidemic was registered in Brazil during 1846-1848 and 1851-1853, and in this century in 1916 and 1923\(^5,6\). Neutralizing antibodies to DEN-1 and DEN-2 were found in inhabitants more than 50 years of age in several municipalities of the Amazon Valley, which suggested the circulation of these serotypes in that region of Brazil in the first years of the twentieth century\(^7\). Following these episodes, a new DF epidemic was reported in 1981-1982, in Boa Vista, state of Roraima, in the Amazon region at the border of Guyana and Venezuela, the countries that were suffering DF epidemics. This was the first time that dengue have been diagnosed using specific laboratory tests, and was isolated from human beings and mosquito vectors in Brazil\(^8\).

Other South American countries that experienced DF epidemics in this century were Peru during the 1950s and Venezuela between 1941-1946\(^9\).

Venezuela reported DF epidemics during the 1960s, the period when almost all South American countries had eradicated *Aedes aegypti*. DEN-2 and DEN-3 were responsible for the transmission\(^4,10\).

During the 1970s DEN-2 and DEN-3 were responsible for DF epidemics in Colombia, a country that has achieved eradication of the vector during the PAHO programme. Transmission also occurred in Guyana, French Guyana, Surinam and Venezuela\(^9\).

During the 1980s the expansion of dengue accompanied the distribution of the vector, *Aedes aegypti*, and during these years, a second potential vector, the Asian mosquito, *Aedes albopictus*, was introduced in the region\(^11\). New countries reported DF epidemics, which included Bolivia, Ecuador, Paraguay, Peru and Brazil. These countries
had not experienced DF epidemics before or dengue viruses were absent from there for many years or decades. The extended new circulation of dengue viruses, the susceptibility of almost all inhabitants and the high rates of vector mosquito indices, resulted in large-scale dengue transmission with explosive epidemics.

In Brazil that had more than 130 million inhabitants and had serious problems related to water supplies and waste management in urban areas, the spread of dengue viruses was quick. In 1986, when Rio de Janeiro state, south-eastern region, was infected with DEN-1\(^{(12)}\), in the same year this serotype was responsible for the epidemics in Ceara and Alagoas states in the north-eastern region. Three years later, eight states in three geographical regions reported DF epidemics (Table 1). Tens of thousands of cases were notified, but a survey carried out among schoolchildren in the metropolitan area of Rio de Janeiro city estimated the occurrence of about one million infections during 1986-1987\(^{(13)}\).

During these DF epidemics in Brazil and other Latin American countries, a few cases of DHF were also reported. Except the 1981 Cuban DHF epidemic, no other DHF epidemic was reported in the continental America\(^{(10, 14, 15, 16, 17)}\).

In the years 1989-1990 an epidemic of DHF was reported throughout Venezuela, which was the second major DHF epidemic in the Americas. It reported over 6,000 cases and 73 deaths. DEN-1, DEN-2 and DEN-4 were isolated during the episode, but only DEN-2 was recovered from four fatal cases\(^{(4, 9)}\).

**Yellow fever (YF)**

The YF virus was one of the most important human infectious diseases in the past, and a model in epidemiology and public health. YF was first suspected to be associated with *Aedes aegypti* by the Cuban scientist, Carlos Finlay, and its transmission was established by the US Major, Walter Reed. Before and after the works of Finlay and Reed, the virus was responsible for devastating epidemics in urban centres of Africa and America\(^{(18-20)}\). Fortunately, the discovery of the YF vaccine by Theiler & Smith\(^{(21)}\), a milestone in medical history, was responsible for the prevention of the YF urban epidemics. Effectiveness of the vaccine was so high that

<table>
<thead>
<tr>
<th>Year</th>
<th>Countrywide</th>
<th>North</th>
<th>Northern</th>
<th>C. West</th>
<th>Southeast</th>
<th>South</th>
</tr>
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<td>12,000</td>
<td>12,000</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>1986</td>
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<td>13,802</td>
<td>-</td>
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<td>1987</td>
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<td>190</td>
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<td>1989</td>
<td>5,334</td>
<td>-</td>
<td>4,213</td>
<td>-</td>
<td>1,121</td>
<td>-</td>
</tr>
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<td>1990</td>
<td>40,642</td>
<td>-</td>
<td>15,950</td>
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<td>1991</td>
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<td>396</td>
<td>1,671</td>
<td>1,148</td>
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<td>7,086</td>
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<td>788</td>
<td>1,462</td>
<td>4,836</td>
<td>-</td>
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<tr>
<td>1994</td>
<td>56,621</td>
<td>18</td>
<td>49,828</td>
<td>5,864</td>
<td>911</td>
<td>-</td>
</tr>
<tr>
<td>1995</td>
<td>132,180</td>
<td>3,221</td>
<td>57,974</td>
<td>32,819</td>
<td>35,111</td>
<td>3,055</td>
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<td>1996</td>
<td>179,780</td>
<td>2,788</td>
<td>125,400</td>
<td>14,839</td>
<td>32,230</td>
<td>4,523</td>
</tr>
</tbody>
</table>

Table 1. Dengue cases reported to Ministry of Health, Brazil, by geographical region, 1982-1998
in continental South America the last cases of urban YF were reported in 1942 \(^5,\,17,\,19\). Inspite of the existence of the jungle maintenance cycle of the virus \(^22\), the vaccine could reduce the impact of YF sylvatic outbreaks, and contributed decisively to the arrest of its re-urbanization. On the other hand, the vector eradication programme developed under PAHO leadership also maintained the *Aedes aegypti*-free status of many countries that had been free from YF epidemics.

During the ‘60s, ‘70s and ‘80s, YF cases or outbreaks were reported almost exclusively in Bolivia, Brazil, Colombia and Peru. The vectors responsible for the transmission were mosquitoes of the forest canopy, chiefly *Haemagogus* spp. and to lesser extent *Sabethes chloropterus*, and possibly *Aedes fulvus* in Brazil \(^19,\,23,\,24,\,25\).

In Brazil, excepting the three epidemics which occurred in Goiás, Pará and Maranhão states \(^17,\,26,\,27\), sporadic cases or small outbreaks were documented.

**Present situation**

**DF/DHF**

Epidemics of DF have exploded in the American region. To date, except Chile and Uruguay, all countries have reported DF epidemics and at least five of them - Brazil, Colombia, Ecuador, French Guyana and Venezuela - have suffered major or minor DHF epidemics \(^4,\,10\). In 1998, Argentina reported for the first time in its history an epidemic of DF after 82 years \(^28\), and Uruguay became infested with *Aedes aegypti*, after more than 30 years of freedom from it. Therefore, presently, only Chile is *Aedes aegypti*-free \(^10\).

In Brazil, *Aedes aegypti* has quickly spread over the whole country during the current decade. To date, all the 27 states are infested by the vector, and transmission has been reported in at least 23 states in all the five regions (Table 1 and Figure 1). In 1990, DEN-2 invaded Rio de Janeiro \(^29\), and an epidemic during 1990-1991 resulted in the reporting of 99,707 DF and 462 DHF cases and eight deaths \(^30\). In 1991, this serotype was responsible for the first epidemic of DF in Tocantins state \(^31\) in the Amazon region, about 2,000 km away from Rio de Janeiro. And, in 1994, a large epidemic of DF, with 24 cases of DHF with 11 deaths, was reported in Ceará state \(^16\). This serotype, to date, has been found in at least 16 states, while DEN-1 has been recognized in 20 states, and co-circulation of both serotypes reported in at least 12 states. The number of DF cases has increased dramatically in Brazil in all its geographical regions since 1994, especially in the north-east and south-east \(^30\). These two regions reported more than 1,100,000 cases, representing 87.5% of all notified dengue cases in the country (Table 1, and Figure 1).

<table>
<thead>
<tr>
<th>Country</th>
<th>DHF cases</th>
<th>Deaths</th>
<th>Case-fatality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venezuela</td>
<td>34,193</td>
<td>284</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Source: FUNASA, Ministry of Health (Brazil).
Venezuela has reported annually hundreds of DHF cases, with dozens of fatalities. From 1990 till 1998, this country reported to PAHO 34,193 cases of DHF and 284 deaths, and since then has been the leading country reporting DHF in the region and in all Americas (Table 2). Next to Venezuela, so far, DHF cases have occurred in Colombia, which reported 13,512 cases and 60 deaths. Brazil has notified 795 DHF cases and 40 deaths, and, finally, French Guyana, with 57 DHF cases with two fatal outcomes. A comparison of the occurrence of DF/DHF among Brazil, other South American countries and North/Central American countries is given in Table 3.
Aedes aegypti, Dengue and Re-urbanization of Yellow Fever in Brazil and other South American Countries - Past and Present Situation and Future Perspectives (Contd.)

Table 3. Reported DF/DHF cases/deaths in Brazil, South America and North-Central America in 1990s. Comparison of the percentage for each region*

<table>
<thead>
<tr>
<th>Year</th>
<th>Brazil N(%)</th>
<th>DHF (Deaths)</th>
<th>South America N(%)</th>
<th>DHF (Deaths)</th>
<th>North-Central America N(%)</th>
<th>DHF (Deaths)</th>
<th>Americas N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>40,642(34.4)</td>
<td>274(8)</td>
<td>38,318(32.4)</td>
<td>3,364(53)</td>
<td>39,265(33.2)</td>
<td>8(1)</td>
<td>118,225</td>
</tr>
<tr>
<td>1991</td>
<td>97,209(61.8)</td>
<td>188(0)</td>
<td>22,678(14.4)</td>
<td>2,076(26)</td>
<td>37,453(23.8)</td>
<td>45(2)</td>
<td>157,340</td>
</tr>
<tr>
<td>1992</td>
<td>3,215(5.3)</td>
<td>-</td>
<td>25,262(42.0)</td>
<td>1,142(17)</td>
<td>31,705(52.7)</td>
<td>611(9)</td>
<td>60,182</td>
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<tr>
<td>1993</td>
<td>7,086(8.8)</td>
<td>-</td>
<td>44,556(55.3)</td>
<td>3,187(20)</td>
<td>28,935(35.9)</td>
<td>1002(5)</td>
<td>80,577</td>
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<tr>
<td>1994</td>
<td>56,621(31.3)</td>
<td>24(11)</td>
<td>52,554(29.0)</td>
<td>4,175(14)</td>
<td>71,907(39.7)</td>
<td>537(34)</td>
<td>181,082</td>
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<tr>
<td>1995</td>
<td>132,180(38.6)</td>
<td>112(2)</td>
<td>92,685(27.0)</td>
<td>6,408(57)</td>
<td>118,095(35.4)</td>
<td>1,708(54)</td>
<td>342,960</td>
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<td>1996</td>
<td>179,780(60.6)</td>
<td>69(1)</td>
<td>53,971(18.2)</td>
<td>3,437(24)</td>
<td>62,820(21.2)</td>
<td>1,586(53)</td>
<td>296,571</td>
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<tr>
<td>1997</td>
<td>254,939(60.3)</td>
<td>35(5)</td>
<td>63,711(15.1)</td>
<td>10,250(71)</td>
<td>104,178(24.6)</td>
<td>1,498(77)</td>
<td>422,828</td>
</tr>
<tr>
<td>1998†</td>
<td>536,398(72.8)</td>
<td>93(13)</td>
<td>102,062(13.8)</td>
<td>10,896(64)</td>
<td>98,540(13.4)</td>
<td>1,326(14)</td>
<td>737,000</td>
</tr>
<tr>
<td>Total</td>
<td>1,308,070(54.6)</td>
<td>795(40)</td>
<td>495,797(20.7)</td>
<td>44,935(346)</td>
<td>592,898(24.7)</td>
<td>7,419(249)</td>
<td>2,396,765</td>
</tr>
</tbody>
</table>

*Source: Pan American Health Organization; # Excepting cases from Brazil; ‡ Provisional data.

Yellow fever

The major vector of YF virus is *Haemagogus janthinomys*, a species with strict sylvatic habits that it stays all the time in the forest canopy, biting only when people intrude into the forest(17, 23, 27).

The present occurrence of jungle YF in Latin America has shown widespread distribution over the last decades to four countries (Brazil, Bolivia, Colombia and Peru). In the last two years, besides these four countries, Venezuela and Ecuador have reported some cases that occurred after decades of absence of YF (Figure 2). A couple of cases have also been reported in Surinam (imported from Brazil) and French Guyana.

The number of cases and deaths reported during 1985-1998 in different periods are shown in Figure 3. The case-fatality rate for YF in South America during this period was 53.2%. Compared with DHF (with case-fatality rate of 1.3% in the Americas), the low number of YF cases is not accompanied by low lethality. It will not be surprising that in the event of an urban YF epidemic, the number of deaths would be very high as a consequence of the large number of susceptible populations in almost all countries. The situation could turn out to be more...
dramatic in countries like Argentina, Chile and Uruguay, where almost all inhabitants are non-immune for YF and, as such, susceptible to the virus. In the past, too, it was observed that any occurrence of the urban transmission of YF was followed by a dramatic increase in mortality, and the degree of risk remains the same (17,18,32) today.

Despite the availability of the YF 17D vaccine that for decades has been used with excellent response (giving protection for at least 10 years), large population groups still remain unimmunized. Many of them live in high-risk areas where transmission is closeby or re-infestation by *Aedes aegypti* has recently occurred. These areas have been identified in the YF endemic regions of Brazil, Bolivia, Colombia and Peru, the four countries that have reported more of YF cases in the Americas.

*Aedes aegypti* susceptibility to YF virus

Presently, YF cases in South America have only been transmitted by sylvatic vectors, especially *Haemagogus janthinomys* (17,23,26,27). But the susceptibility of the *Aedes aegypti* population circulating in Latin America to YF virus needs to be established in order to assess the increased risk of the re-emergence of the urban transmission (33). It is possible that the annual occurrence of several cases in Brazil and hundreds of cases in Peru and Bolivia might have been transmitted by *Aedes aegypti*. Surprisingly, urban transmission has not been reported yet excepting six limited cases in Santa Cruz, Bolivia, but denied by the health authorities of that country (34).

A warning is coming and the advice is clear: there are two complementary ways to follow; first, the vaccination of all inhabitants in South America, initially for the people living in countries where YF transmission is established through *Aedes aegypti*, later in regions of DEN focus inside of YF endemic areas, and, finally, in countries with DEN epidemics and in regions outside of YF endemic areas. It is equally essential to establish a powerful *Aedes aegypti* control programme in South America, or preferably in all Americas, to prevent DHF epidemics.

Future perspectives

Large epidemics of DF/DHF

It is possible that in a few years, South America will become an endemic region where massive epidemics of DF/DHF will occur affecting millions of people. The number of DF/DHF cases are already on the increase (Table 3). It is known that several factors play a role in DEN transmissibility, but the three most important factors are the following:

*The growth of population:* The population growth in urban centres in South America has not been accompanied by an improved level of environment. This growth has facilitated the re-establishment of *Aedes aegypti* and favoured the perpetual breeding of the disease vector. This has been further facilitated by increased migration of people to urban areas which suffer from unplanned and haphazard growth without any civic facilities. Accumulation of solid wastes becomes a difficult proposition to handle. Civic authorities are unable to provide enough drinking water, which results in large-scale storage practices.

*Lack of public health services:* Because of financial constraints, the governments of the countries have not been able to develop enough public health services which could cope with the problem. There is also a paucity of trained personnel who could manage vector control activities.

*Change in human life style:* The globalization of world economies has brought in a sea-change in the lifestyle of people. The facilities for fast long-distance travel have facilitated the transportation of viruses in incubation anc
viremia periods from Africa and Asia to Europe and America and vice versa. This, probably, was the major mechanism which facilitated the spread of dengue viruses in the world. Another factor is the disposable receptacles. These receptacles, in many countries, have been the source of collecting clean water, especially rain water, which not only promoted extensive breeding of the vector species but also resulted in its geographical spread.

**Urban transmission of YF**

From 1985 to the first half of 1998, PAHO reported 2,603 cases and 1,385 deaths due to sylvatic YF in Latin America (Figure 3), giving a case-fatality rate of 53.2%. These numbers, from our point of view, do not represent the reality of the disease because these figures are hospital-based and do not represent the total infections. It is known that severe forms of YF represent no more than 10% of all infections, and also that the inapparent and mild forms are not diagnosed, except in ongoing studies during epidemics. Under-notification is the rule and it is possible that many cases, including severe cases, are not correctly diagnosed. Consequently, these cases are neither notified to government authorities nor to PAHO/WHO, hence no control measures are adopted.

On the other hand, we do not believe that the YF virus has no contact with *Aedes aegypti*, since the countries reporting YF cases have also reported DF/DHF cases. As in the case of Brazil, high indices of *Aedes aegypti* have been reported from all over the country. Secondly, in Brazil the vector is also present in the endemic areas of YF and many states have reported DF as well as YF cases too.

Therefore, the risk of YF’s re-urbanization is increasing, especially outside the endemic areas where the vaccine coverage is very low. To illustrate, in the first half of 1999 (data not shown), Brazil reported 46 YF cases and some patients moved during incubation and viremia periods to areas reporting DF cases (Vasconcelos PFC personal information). Logically, a contact of *Aedes aegypti* with these patients facilitated the transmission. Fortunately, urban YF cycle was not established, although an increased risk will be felt for a long time.

**Conclusion**

The occurrence of DF/DHF epidemics and the increased risk of re-urbanization of YF need a prompt response from the health authorities in the region in order to prevent in the new millennium a picture similar to what was observed in the first decades of the twentieth century, when thousands of lives were lost especially due to urban YF epidemics.

Consequently, a continental initiative to control the spread of DF/DHF and to prevent the re-urbanization of YF in South American countries is essential. International organizations such as PAHO/WHO, in our view, may take this initiative and urge the countries of the region to strengthen public health services to meet these heightened challenges. It should be possible to train manpower for the professional management of solid waste disposal, improve drinking water supplies to prevent storages, and develop surveillance mechanisms both for disease vectors and cases with well-equipped hospital services for better management of severe cases.

There is a strong case for establishing linkages between various government departments to promote intersectoral coordination and to develop information, education and communication (IEC) programmes and to involve communities, NGOs and other voluntary agencies in a spirit of partnership.

YF vaccination is yet another area which requires attention. We know 17D vaccine provides protection for 10 years or more but reports are also available which show protection up to 35 years. PAHO/WHO may support more research into this aspect and also help the countries financially for indigenous production of this vaccine for mass vaccination.
Networking of information (possibly through the Internet) is equally important for the dissemination of updates on cases/deaths and other risk factors.

These initiatives, taken collectively by the governments of the countries, and actively supported and facilitated by PAHO/WHO, will go a long way in preventing/controlling DF/DHF and YF epidemics in the continent.

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