Dengue in French Polynesia: Major Features, Surveillance, Molecular Epidemiology and Current Situation

By

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Abstract

The emergence of dengue epidemics worldwide has paralleled the expansion of the mosquito vector Aedes aegypti, along with jet air travel and increased urbanization. All the four dengue virus serotypes (DEN-1, 2, 3 and 4) have occurred in epidemic form during the past 50 years in French Polynesia. The first epidemic with a known serotype was due to DEN-1 which occurred in 1944 during World War II. The disease disappeared from the Eastern Pacific after a Pacific-wide pandemic, but a series of epidemics occurred at short intervals during two decades: DEN-3 in 1964–1965, DEN-2 in 1971, DEN-1 in 1975–1976, and DEN-4 in 1979. From 1980 to 1988, the transmission of DEN-4 continued at a very low level until the resurgence of DEN-1 and DEN-3 in back-to-back epidemics in 1989. In 1996, DEN–2 reappeared in Tahiti and spread further into New Caledonia, the Cook Islands, Tonga, Samoa and Fiji.

As in most Pacific countries, epidemics with only one serotype have occurred in French Polynesia. Each time, the genetic analysis of the causative viruses showed that the current epidemic

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was due to the introduction of a genotype which was different from the viruses recovered from the past epidemics. These observations emphasize the need for an active system of clinical and virological surveillance for the prevention and control of epidemics, together with molecular characterization of the viruses as part of the investigation of a dengue epidemic. As of now, a new genotype of DEN-2, different from the one involved in the 1970s, is disseminating throughout the Pacific region.

Keywords: DF/DHF, DEN-1,2,3,4, epidemic, molecular epidemiology, French Polynesia.
Introduction

French Polynesia, situated in the South Pacific Ocean, consists of five archipelagos (Society, Tuamotu, Gambier, Austral and Marquesas islands) comprising 120 islands, of which only 66 are inhabited. Most of the population is concentrated in the Society archipelago which encompasses the Windward and the Leeward islands. Tahiti, the largest island of French Polynesia in the Windward group, contains the Capital, Papeete. During the past 40 years the population of French Polynesia has undergone a dramatic increase. Since 1946, it has trebled in 30 years, and it has doubled between 1966 and 1988. The last census (1996) recorded a population total of 219,521 which is unequally distributed: 74% of it is concentrated in the Windward Islands, especially on Tahiti, of which 77% live in the urbanized Papeete. In all areas the climate is hot and tropical. A hot rainy season from November to April alternates with a cooler, drier season from May to October. The annual average temperature and rainfall in Tahiti is 25.7°C and 2 m, respectively. These climatic conditions are consistent with the year-round mosquito breeding.

Epidemiological features

Epidemic pattern

Dengue fever has been known clinically in French Polynesia since the nineteenth century, with documented epidemics in 1852, 1870, 1885 and 1902\(^{(1,2,3)}\). The first outbreak of dengue in Tahiti of a known serotype occurred in 1944 as part of the Pacific-wide spread of the disease caused by DEN-1 during World War II\(^{(4)}\). The disease disappeared from the Eastern Pacific after the pandemic and, as far as is known, did not reappear until 1964 and 1969, when DEN-3 was involved\(^{(5,6)}\). From that time on, epidemics have occurred at shorter intervals: DEN-2 in 1971, DEN-1 in 1975 and DEN-4 in 1979 were successively epidemic\(^{(7,8,9)}\). With the exception of the DEN-2 outbreak, during which severe haemorrhagic cases and three deaths were observed on Tahiti in 1971, mildness of the disease characterized these past epidemics. A recent succession of epidemics took place after nine years of continued transmission of DEN-4. Back-to-back epidemics involving
DEN-1 and DEN-3 occurred in 1988–1989. It is noteworthy that dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) occurred in the latter epidemic (11 fatalities) while mildness characterized the former. These viruses were spread throughout the Pacific region with varying degrees of disease severity\textsuperscript{(10)}.

Epidemics with only one serotype have occurred. Each epidemic serotype replaced the previous serotype that had been transmitted during the inter–epidemic period. Simultaneous transmission of both serotypes was only observed for a short period of time (2–4 months) when the epidemic serotype was taking place. During these periods, co–circulations were demonstrated for DEN–2/DEN–1 in 1975, DEN–1/DEN–4 in 1979, DEN–1/DEN–3 in 1989, and DEN–3/DEN–2 in 1996. The endemic virus was generally swept out 7 weeks to 4 months after the recognition of the new epidemic. This is illustrated by Fig.1a and Fig.1b.
**Figure 1a.** DEN–1 and DEN–3 epidemics (1988–1990): Monthly distribution of dengue virus serotypes

**Figure 1b.** DEN–2 epidemic (1996–1997): Monthly distribution of dengue virus serotypes
Morbidity and mortality

Although accurate data regarding morbidity are not available, a review of published and unpublished literature allowed us to obtain estimates of dengue infection in the Windward Islands during the major epidemics which occurred between 1944 and 1997 (Table 1). Estimated morbidity rates were calculated by using the data obtained by serological and/or epidemiological surveys. The estimation of the attack rates involved antibody prevalence in cohorts of susceptible populations and measurements of absenteeism in schools and government and business offices. The serological attack rate was generally around 50% as determined immediately after the epidemic transmission. According to clinical and serological surveys, the proportion of asymptomatic infections was estimated to be 30%\(^8,11,12\). During an outbreak the mortality rate is usually low (see Table 1). The morbidity trend of the epidemics is also illustrated by the number of (i) clinical cases reported by physicians (reported cases), (ii) cases for which a request for laboratory confirmation is made (suspected cases), and (iii) virologically and/or serologically confirmed cases (Table 2). The annual incidence rate during the inter-epidemic periods (endemic transmission) is unknown.

One study that concerned the long inter-epidemic period between 1980 and 1987 showed an acquisition rate of dengue antibodies of 3% per year in a cohort of susceptible children\(^13\).

<table>
<thead>
<tr>
<th>Year of epidemic</th>
<th>Serotype</th>
<th>Population Windward Is. (1000's)</th>
<th>Estimated morbidity rate(%)</th>
<th>No. of fatal cases</th>
<th>No.of infected persons (1000's)</th>
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</thead>
<tbody>
<tr>
<td>1944</td>
<td>DEN-1</td>
<td>29.8</td>
<td>62</td>
<td>-</td>
<td>26</td>
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<tr>
<td>1964–65</td>
<td>DEN-3</td>
<td>55.2</td>
<td>20</td>
<td>-</td>
<td>ND*</td>
</tr>
<tr>
<td>1969</td>
<td>DEN-3</td>
<td>79.1</td>
<td>ND*</td>
<td>-</td>
<td>ND*</td>
</tr>
<tr>
<td>Year of epidemic</td>
<td>Serotype</td>
<td>Reported cases*</td>
<td>Suspected cases</td>
<td>Confirmed cases</td>
<td></td>
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<tr>
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<td>DEN-3</td>
<td>72</td>
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<tr>
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<td>DEN-2</td>
<td>12943</td>
<td>-</td>
<td>-</td>
<td></td>
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<tr>
<td>1975–76</td>
<td>DEN-1</td>
<td>2032</td>
<td>2018</td>
<td>694</td>
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</tr>
<tr>
<td>1979</td>
<td>DEN-4</td>
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<td>1783</td>
<td>630</td>
<td></td>
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<tr>
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<td>6034</td>
<td>4836</td>
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<td>5583</td>
<td>1357</td>
<td></td>
</tr>
<tr>
<td>1996-97</td>
<td>DEN-2</td>
<td>7230</td>
<td>4424</td>
<td>2027</td>
<td></td>
</tr>
</tbody>
</table>

*ND: not determined.

Table 2. Dengue cases reported during the epidemics in French Polynesia, 1964–1997

Transportation and spread of virus
In addition to the lack of effective mosquito control, the origin of the Pacific-wide pandemic of DEN-1 (1941–1945) was very likely related to intensive movements of human populations among and into areas that were permissive to dengue transmission during World War II. Hence, in 1944, an extensive epidemic of dengue occurred in the Society archipelago, French Polynesia.
Together with entomological surveys in other Pacific islands\(^{(14,15,16)}\), the evidence of experimental transmission of dengue virus between monkeys suggested that *Aedes polynesiensis* served as a natural vector in the past epidemics in French Polynesia\(^{(14)}\). Conversely, the geographical distribution of the disease and the entomological surveys carried out during the post-war epidemics (1964–1996) were more consistent with the role of *Ae. aegypti* as a vector. For instance, while *Ae. aegypti* was reported in 1953 in Tahiti, its presence had expanded progressively throughout French Polynesia, which was coincidental with the advent of inter–island air connections: in the 1970s in the Tuamotu, in 1982–1986 in the Marquesas Islands, and in 1979–1986 in the Austral Islands\(^{(17)}\).

The size and frequency of dengue epidemics are related directly to social and economic development, especially urbanization\(^{(18,19)}\). For instance, the first urbanized locale, Papeete, became so in 1850 during the European colonization. Coincidentally, the first occurrence of dengue on Tahiti was reported in 1852. The disease was limited to Papeete which had been recently urbanized with an increased seaport activity. In the 1960s, important changes in the ecology of dengue in French Polynesia occurred after the construction of the international airport in 1960–1961. This event suddenly brought French Polynesia into the modern era, with accelerated urbanization that paralleled an increasing number of dengue outbreaks. The increase of population in Papeete and its surrounding localities comprised of workers recruited from the rural part of Tahiti and from neighbouring islands. Between 1956 and 1988 the population of Tahiti rose from 50% to 76% of the total population of French Polynesia; of these, 79% resided in urban areas. The expansion of Papeete led to the growth of adjacent suburbs. At this time, the metropolitan Papeete lied along a 40 km coastal border only a half kilometre wide.

The first re-introduction of dengue viruses was related to multiple factors: increased jet air travel, high density of susceptible population in urban areas, and lack of mosquito control. Papeete was hit by a DEN–3 epidemic in 1964, as was Makatea island, a nearby island of the Tuamotu archipelago whose urban areas were subjected to exploitation of
phosphates. Regular exchanges existed between these two sites, in both of which Ae. aegypti were abundant. The limited transmission within these areas was apparently related to the sparse distribution of Ae. aegypti in most islands of French Polynesia\(^5\). A flare-up of DEN-3 was reported in 1969 in Papeete\(^6\).

The speed and frequency of human exchanges by jet air travel make possible the introduction of dengue viruses by a dengue-infected traveller from hyperendemic areas. A parallel has been observed between the spread of dengue viruses and the route and frequency of air travel between the infected and the permissive areas within the Pacific region\(^20\). This was exemplified by the epidemics which occurred in the Pacific islands in the 1970s, which always emerged from countries/areas which had intensive international traffic. The disease has spread secondarily from these points to neighbouring island countries. For instance, in 1979 the first occurrence of DEN-4 outside Asia was observed on Tahiti. Three years later, DEN-4 had spread to many islands of the Pacific. At the country level, in French Polynesia, the geographical diffusion of the epidemics may be seen in the dynamics of the recent epidemics. Fig. 2 shows clearly that the DEN-1 epidemic in 1988–1989 moved from the Windward Islands to the Leeward Islands and on to the Marquesas and Austral Islands\(^21\). Furthermore, DEN-3 was first detected in the tourist island of Bora Bora in the Leeward Islands, and spread subsequently to Tahiti, then to the remote archipelagoes\(^21\). These situations were consistent with the fact that inter–island air travel was more intense between Tahiti and the Leeward Islands than with the Marquesas and Austral Islands.

**Clinical features**

The disease has been generally mild. However, dengue illness caused by all four serotypes is naturally accompanied by haemorrhagic manifestations\(^22\). In most epidemics, a proportion of cases presented with minor haemorrhagic signs: 15% in 1964 (DEN-3), 4% in 1969 (DEN-3), 3% in 1971 (DEN-2), 15% in 1975–1976 (DEN-1), 5% in 1989 for epidemic DEN-1, 14% for epidemic DEN-3, and 18% in 1996–1997 for DEN-2. The two occurrences of severe
manifestations requiring hospitalization were in 1971 (33 cases, 3 fatalities) and 1989–1990 (401 cases, 11 fatalities). The 1971 epidemic involved mostly adults (63%) while children represented 69% of the cases in 1989–1990, an outbreak in which haemorrhagic manifestations were observed among 59% of the hospitalized children. In 1996, among the 232 hospitalized children, the number of severe forms was low (19 cases), and the proportion of children presenting with haemorrhagic manifestations was 36%. Only one death (adult) was reported\(^5,6,7,8,10,23\).

**Socioeconomic impacts**

In islands with limited populations, dengue fever is generally an epidemic disease. In Asia, where the occurrence of DHF/DSS is frequent, the social and economic cost is high (US $31.48 million per year in Thailand\(^2\)). However, epidemics of the classical disease are not to be overlooked. For instance, during the last epidemic of DEN–1 in French Polynesia, of the 161 subjects from whom a reply to the question about the number of days absented from work was obtained, 125 indicated a 3–5 days of absence.
Moreover, in the 1996–97 DEN–2 epidemic, the direct costs were estimated to be US $2.5 million, including laboratory costs, hospitalization, and medical care. The indirect costs, including morbidity–related absenteeism from work, the cost of lost production and prevention and control activities was around US $1.98 million. The estimated total cost worked around US $4.48 million (i.e. US $20 per inhabitant). From this study, it was evident that the estimated total cost of the 1989–90 DEN–3 epidemic, including the DHF/DSS cases, was US $40 per inhabitant, whereas the estimated cost of the 1988–89 DEN–1 epidemic was US $15 per inhabitant. Estimation of the costs for loss of tourism was not made.

**Surveillance, prevention and control**

Before 1975, the DHF epidemics did not benefit from any special control programme. They were generally explosive and ended after exhaustion of the susceptible population. In 1975, Tahiti was expected to have DEN–1 virus reintroduced from Fiji. With the efforts of both regional (South Pacific Commission) and local authorities, a network of dengue control and surveillance was set up. Subsequent funding supported the development of a community–based vector control programme. Despite the implementation of preventive measures, an epidemic occurred a short time later. Epidemic control involved adulticiding of mosquitoes using ultra low volume (ULV) spraying of insecticides. Larvicidal source reduction measures involved the destruction or treatment by insecticides of breeding sites. Educational programmes accompanied these measures®. During the 1979 DEN–4 epidemic, similar measures were implemented. After these series of epidemics, the control programme was maintained at a minimum level which comprised continued health education and limited entomological surveillance at the international airport and at a few sentinel stations.

Finally, the only constant and immediately available surveillance system is the laboratory–based system. Laboratory capabilities were reinforced, and modern and rapid viral and serological analyses were made available. Urgent diagnosis of suspected DHF/DSS was carried out by reverse transcriptase polymerase
chain reaction (RT–PCR), allowing a result within as little as one day\(^\text{25}\). Since 1988, the surveillance of dengue fever has been based on the monitoring of (i) cases reported by physicians; (ii) suspected cases; and (iii) confirmed cases. Trends of dengue activity and the virus serotype are continuously monitored.

Actually, the weekly incidence of suspected cases constitutes a valuable indicator of dengue activity\(^\text{26,27}\). Since all the diagnoses are made only in our laboratory, the data are immediately available. A sudden rise in laboratory requests precipitates an immediate telephone survey among sentinel physicians. In addition, through a small group of selected sentinel physicians, any increase in dengue–like illness is reported and investigated. Blood specimens are obtained from representative cases and processed to detect dengue infection by virus isolation or RT–PCR and/or dengue IgM antibody detection. In addition, information on dengue activity in the Pacific region is taken into account in order to stimulate awareness in the medical community or to set up timely sentinel surveillance, as happened in 1996 when DEN–4 was detected in New Caledonia\(^\text{28}\). Subsequently, DEN–2 was detected instead.

The detection of a serotype different from the one which is endemically transmitted constitutes a very important feature while considering whether further epidemic transmission might occur. A retrospective analysis of the situation in French Polynesia in recent years shows that a new epidemic followed each detection of a new serotype in a sizeable susceptible population in a country where mosquitoes were always present. In 1988, the first isolation of DEN–1 in Tahiti island intervened during a nine–year inter–epidemic period of a low–level incidence of DEN–4\(^\text{11}\). The epidemic peaked a few weeks after, and the disease spread throughout most of the islands of French Polynesia. The first isolation of DEN–3 was observed in April 1989 in Bora–Bora island, then in June 1989 in Tahiti island. The epidemic was recognized in August in Tahiti\(^\text{21}\). Furthermore, the recent DEN–2 epidemic peaked in January 1997 after the first case was detected by laboratory survey in August 1996. Thus, virological surveillance is of importance for an early warning surveillance system.
Molecular epidemiology

By using molecular techniques, the transmission pathways of the viruses have been suggested and seem to corroborate with the descriptive epidemiology. Analysis of genome sequence relatedness demonstrated genotype groupings among all four DEN virus serotypes (29). Thus, one to five genotypes were defined among virus strains isolated in different geographic areas and over periods ranging from 33 to 53 years. Each genotype seems to have a defined focus of endemicity. However, certain genotypes appeared to have been transported to another part of the world where they became established. Different transmission pathways of these viruses around the world are pointed out, and co-circulation of two or more genotypes in the same geographic region has been observed, especially for DEN-2 viruses. The first genetic evidence of the existence of a sylvatic cycle of dengue virus, clearly different from outbreak viruses, was demonstrated, and further confirmed by molecular analysis (30, 31). Owing to the current circulation of dengue viruses in our region, the molecular epidemiology of DEN-2 viruses is particularly worthy of emphasis.

Nucleotide sequencing of different parts of the genome as short fragments or entire genes (prM, E or NS3) allowed several authors to perform comparative analysis of a large variety of dengue virus strains. Sequence data obtained recently in our laboratory or those retrieved from published databases were compared within each serotype virus. Hence, fragments of the E protein gene of (i) 180 nucleotides (nt 82 to 261) from DEN-1 and DEN-4 viruses, (ii) 198 nucleotides (nt 85 to 282) from DEN-2 viruses, and (iii) 195 nucleotides (nt 73 to 267) from DEN-3 viruses were compared (29). A divergence of 6% within the studied region was taken as a cut-off point for virus groupings.

Three genotype groups were defined for DEN-1 viruses, and clustering of virus isolates for which linkages would be expected on epidemiological grounds was observed (32). Genetic relationships were detectable over a 50–year span (Hawaii, 1944, to the Indian Ocean, 1993). For instance, earlier epidemic strains from the Pacific (1974–1978)
clustered in genotype 1 while recent epidemics strains from French Polynesia and New Caledonia (1988–1989) and the Comoros Islands (1993), as well as from French Guiana, Guadeloupe, Puerto Rico, Brazil, Peru, Nicaragua and Cuba, fell in genotype 2 (as do the American strains). Therefore, it is likely that the recent epidemics of DEN–1 in the Pacific region are due to the strain derived from mutation through silent transmission. Furthermore, a high level of dissemination of DEN–1 genotype 2 during recent years, as shown by the clustering of the viruses recently isolated in countries that have ties with French tropical countries (French Guiana, French Pacific territories, Comoro Islands) was suggested, although the direction of the spread was not specified.

Figure 3. Molecular epidemiology of DEN–2 viruses
The maximum divergence over the E protein gene fragment was approximately 20% among DEN-2 viruses. The dendrogram shown in Fig. 3 depicted five genotypic groups and agreed generally with previously published phylogenetic trees\(^{30,31,33}\).

Two genotypes have been involved in the Caribbean. The Jamaican genotype (genotype 2) was confirmed as to be related to virus strains from South-East Asia (97.5% similarity with Vietnamese 1974 and 1996 strains). As mentioned by Guzman et al.\(^{33}\), the Cuban strain (1981) was closer (98% similarity) to the old New Guinea C strain (1944) and clustered in the same genotype 2. The Puerto Rican strain is shown to be transmitted in the Caribbean, Central America, India, and the South Pacific (Tonga 1974, Tahiti 1975) within the genotype 4. Interestingly, the recent virus isolated during the actual epidemic on Tahiti in 1996 falls into a new genotype (genotype 3) together with recent isolates from New Caledonia. Data sequence from D. Phillipps (personal communication) allowed also the classification of 1992 Queensland, 1997 Cook Islands and Samoa isolates in the same genotype. This new genotype is significantly distinct from the previous virus groups (9% divergence with genotype 4). The Tahiti 1996 strain presented a 12.5% difference with the earlier Tahitian virus (1975), and agreed with the evidence of a virus recently introduced rather than to the hypothesis of a new variant derived from earlier virus. Its closer genotype is genotype 1, in which isolates from Torres Strait (D. Phillipps, personal communication), Burkina Faso or Sri Lanka fell.

Four genotypes were defined among 30 isolates of DEN-3 viruses with the entire gene or restriction analysis\(^{34}\). The first group contained isolates from the South Pacific (1988 to 1995), Singapore (1973) and Indonesia (1973 to 1991). The second group comprised the viruses from Asia (1956 to 1995) including the reference strain H-87 and the Vietnamese strains (1974 and 1995). The third was composed of one isolate from Thailand (1971). The fourth genotype included the early strains from French Polynesia (1964 to 1969) and from Puerto Rico (1963).
Maximum divergence over the studied region was approximately 12% and corresponded to the distance between the early (1964 and 1969) and recent (1989 to 1995) Polynesian/New Caledonian DEN-3 strains. Hence, it is unlikely that the recent isolates result from a genetic mutation of the remaining endemic virus, since no DEN-3 virus has been isolated within a 20-year period. Therefore, as for DEN-1, these data suggest that the recent epidemics in the Pacific are due to the introduction of a new variant virus rather than the re-emergence of a strain derived from mutation through silent transmission. Moreover, there is a sequence similarity between a New Caledonian strain (1988) recovered four months before the recognition of the epidemic. This favours the hypothesis of the emergence of DEN-3 epidemics in the Pacific from Indonesia via New Caledonia after several months of latency.

DEN-4 viruses seem to occur as a single genotype around the world. The sequence variation in the same region of the E protein gene among DEN-4 viruses was lower (4.9%) than among the three other serotypes since the maximum divergence was 20% for DEN-2 viruses, 12% for DEN-3 viruses, and 6.9% for DEN-1 viruses. However, microheterogeneity was observed within DEN-4 geographic strains that clustered in two subgroups. Interestingly, the recent isolate from New Caledonia (1996) appears to be more closely related to the viruses from Indonesia. This variant was present for only a few weeks in early 1996. Whether its failure to be transmitted intensively is related to a weak adaptation of the virus to its vector and/or host or to unfavourable climatic conditions, combined with an active vector control programme, is difficult to state (M. Laille, unpublished data). Moreover, transportation of virus from one continent to another is illustrated by the isolation of the Haiti 1981 strain in Senegal from a patient who had just arrived from Haiti[31].

These studies demonstrated that dengue viruses could be identified and classified in genotypic groups that may circulate concurrently in the same region. Moreover, in some instances, the origin of the newly introduced
virus has been suggested. For instance, close relationships between the Polynesian strains (1964 and 1969) and the Puerto Rican (1963) DEN–3 strain or between the Polynesian (1975) and Puerto Rican (1969) strains or Trinidad (1957) DEN–2 strains, suggest possible virus exchanges between the Caribbean and the South Pacific owing to the frequent trades from Europe via the Panama channel. The South Pacific–American connection was also suggested by the close genetic relationships between DEN–4 viruses (99 to 100% homology). In more recent years, the introduction of a new virus in the South Pacific seems to be more related to frequent air travel exchanges with Indonesia (DEN–3 in 1989, and DEN–4 in 1996). Each time, a new epidemic was due to the introduction of a new genotype. The current DEN–2 virus spreading from Tahiti to New Caledonia and the Cook Islands belongs to the same genotype. This emphasizes the efficient dissemination of viruses among these island countries through intra–regional travel. Furthermore, certain genotypes of the viruses have been associated with severe disease potential. However, it is still unclear whether any particular molecular change is involved in the pathogenicity of DHF/DSS.

Current situation

Fig. 4 illustrates the yearly distribution of the suspected and confirmed dengue cases from 1988 to 1997. Since its recent introduction, DEN–2 has been continuously transmitted. In view of the risk of epidemic dengue, when considering the time elapsed since the last epidemic of a given serotype and the size of the population born subsequently, French Polynesia is at high risk for the reintroduction of DEN–4, and to a lesser extent, of DEN–1. Retrospective observations concerning the epidemiology and control of the recent epidemics showed that emergency adulticiding and larvicidal control have to be applied immediately after the detection of the first emergence of either virus. Advantage may be taken of the usual one–to– several months of the time lag before the recognition of an epidemic.

In conclusion, improved laboratory–based surveillance, genetic investigation of circulating viruses, disease surveillance (specific and
febrile diseases), health education programmes, and vector control programmes must be promoted for the better prevention and control of epidemics.

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