Type 1 Dengue fever epidemic in French Polynesia - 2001

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I. Abstract

French Polynesia was affected by a type 1 dengue fever (DEN-1) epidemic in 2001. This epidemic lasted for some 10 months, i.e. from February to November 2001, with a peak in the third week of July. It was responsible for some 33,000 cases of dengue fever recorded by general practitioners in the Society Islands group (i.e. an incidence of 16 cases per 100 inhabitants) and at least 800 cases in the other three island groups. This incidence is comparable to that estimated during the DEN-1 outbreak in 1989 (17%). The only serotype isolated at any time during this outbreak was serotype 1. The epidemic mainly affected children under the age of 13, i.e. those born after the last DEN-1 outbreak and who were, therefore, not immunised against this serotype.

The outbreak gradually spread from the Leeward Islands to the Windward Islands. The Tuamotu and Marquesas Islands were affected later, i.e. beginning in June-July. In the Austral Islands, transmission was very low and stopped completely in July during the cool season. The school holidays played a significant role in transmission of the virus between island groups. The incidence rates were lower in rural areas than in the Tahiti urban area.

Nearly 1,400 cases were hospitalised in the Territory's public and private facilities. This broad use of hospitalisation was motivated by the frequency of severe forms (called dengue haemorrhagic fever by WHO, even though their gravity is mainly linked to plasma leakage). Of those hospitalised, 633 (45%) had severe forms, 278 of which (20%) displayed shock symptoms at the time of admission. A total of eight deaths were recorded, all involving children under the age of 13.

The severe form rate was 2.7 per 1000 inhabitants. Of the 20,000 children aged 4 to 14 who had clinical dengue symptoms, 1 child out of every 20 was hospitalised and 1 out of every 37 developed a severe form. During this outbreak, previous exposure to the DEN-2 epidemic in 1996-97 appeared to have been a major risk factor for developing a severe form. The particular virulence of this strain probably played a role but this still needs to be demonstrated.

In spite of the fact that general practitioners followed hospitalisation guidelines, the hospitalisation capacities of Tahiti's paediatric services were overwhelmed, particularly during the three peak months of the epidemic in the urban area.
Vector control probably helped space the number of cases out initially, but it was not able to reduce the overall intensity of the outbreak.

The experience acquired during this epidemic has made it possible to outline response improvements for future outbreaks in the areas of both prevention and patient care.

In February 2001, the Louis Malardé Institute informed the Health Department that it had confirmed three cases of type 1 dengue fever on Bora-Bora and 2 cases in Faa'a on the island of Tahiti. That was the beginning of one of the worst dengue fever outbreaks in French Polynesia in the past 60 years.

During this 11-month period, the data collected allowed us to keep both the community and health professionals informed and to better target prevention activities. This report, which is primarily intended for French Polynesian health professionals, provides a detailed analysis of this information so as to draw lessons from the experience acquired during this outbreak.

II. Short review of dengue fever

There are four types of dengue fever virus (DEN-1 to DEN-4) which differ serologically and induce immunity specific to each serotype, which implies that an individual could sustain infections by the virus four times over the space of his/her lifetime.
Dengue fever outbreaks have been described for more than 200 years (Asia, Africa, America) ; however, the appearance of severe forms of the disease [dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)] about 50 years ago has profoundly changed the consequences of this disease. The gravity of outbreaks has increased over the past 25 years and dengue fever has become a major cause of hospitalisation and death among children.
The World Health Organisation estimated that in 1998, of the 2 billion people exposed to dengue fever, there were 50 million actual cases per year including 500,000 severe forms and 24,000 deaths.

The term 'dengue haemorrhagic fever' is inaccurate as the severity of this disease is very rarely linked to haemorrhaging but rather to the consequences of the plasma leakage which characterises severe forms. This is, moreover, the reason why we use the term 'severe dengue' (while keeping the abbreviations DHF and DSS).

There are two competing theories about the physiopathology of severe forms, i.e. :

- ⇨ On the one hand, the immuno-pathological theory, i.e. antibody-dependent enhancement (ADE), proposed by Halstead more than 30 years ago : severe forms could come about from prior sensitisation to a different serotype (Halstead 1970). The heterologous (and non-neutralising) antibodies acquired previously are thought to facilitate penetration of the virus into the monocytes, increasing viral replication in the cells and inducing production of vasoactive mediators (particularly TNF), responsible for an increase in vascular permeability. However, while this ADE phenomenon has been demonstrated *in vitro* but it has never been proven *in vivo*.
- ⇨ On the other hand, the theory of a difference in virulence between strains of the virus. In particular, certain genetic variants of a single serotype seem to be more virulent and to have a greater potential for causing epidemics.

The debate is still heated but several authors have agreed that the reality probably reflects a combination of these theories (Gubler 1998).

III. Previous dengue fever outbreaks in French Polynesia

Dengue fever outbreaks have been recorded in French Polynesia since the 19th century (1852, 1870, 1885, 1902).
Since 1944, French Polynesia has been subject to 10 dengue fever outbreaks interspersed by periods of low-level transmission.

E. Chungue has estimated incidence rates for the past outbreaks in the Windward Islands (Table 1). Over the past 25 years, these rates have varied from 17 to 25% of the population depending on the epidemic (Table 1).

Table 1 : Serotypes involved in the 10 dengue fever outbreaks identified over the past 60 years and incidence rates per 100 inhabitants residing in the Windward Islands (source : Chungue, 1998)

Year	1944	1964	1969	1971	1975	1979	1989	1990	1997	2001
Serotype	1	3	3	2	1	4	1	3	2	1
Incidence (%)	62	20	?	50	25	25	17	25	19	16

Most of these outbreaks were not considered severe (except for the 1971 and 1990 epidemics).

- ⇨ No severe forms were reported during the **outbreaks in 1975 and 1989 (DEN-1)**
- ⇨ **In 1971, the DEN-2 epidemic** produced 33 severe forms and 3 deaths (Moreau 1973).
- ⇨ **The 1990 epidemic (DEN-3)** was considered severe due to the 72 DSS and the 11 deaths recorded among the 263 confirmed cases hospitalised in the CHT paediatrics ward. DSS was observed in 72% of cases involving children

under the age of 4, most particularly in those under the age of 1 (44% of cases). In all, this epidemic led to 530 hospitalisations throughout the Territory. The cost of the epidemic was estimated at XPF 830 million.

⇨ For **the 1996-97 (DEN-2) outbreak**, very little information is available on the severity of the cases, except that there was one death involving a 22-year old man. During this outbreak, 474 hospitalisations were recorded in all public and private facilities. A retrospective study of 140 confirmed cases hospitalised in the CHT paediatrics ward showed a DHF/DSS frequency of 14%. The medical cost of this outbreak was assessed by the Malardé Institute at some XPF 440 million (3.7 million euros).
Following this outbreak, transmission of the dengue fever virus was extremely low and limited to Serotype 2.

IV. Surveillance objectives

At the beginning of the outbreak, it was decided to gather the information required to:

⇨ ensure an on-going information flow to the community and health professionals ;
⇨ help direct vector control activities ;
⇨ measure the frequency of severe forms so as to optimise patient care ;
⇨ get a detailed description of the outbreak in order to better prepare for future ones ;
⇨ evaluate the cost of the epidemic;
⇨ and, finally, formulate research theories.

V. Surveillance methods

Several surveillance systems were used to meet the various objectives.

Sentinel Surveillance Network for Febrile Syndromes

Given the high frequency of dengue fever, surveillance of the disease through use of a mandatory reporting system is not appropriate as reactivity is too low and comprehensiveness difficult to assess. Estimates made from cases diagnosed by a sample of doctors is simpler and more effective.
The Sentinel Surveillance Network for Febrile Syndromes, whose current version was put into place in 1999, is based on weekly reporting (by fax or e-mail) of all fever cases seen during the visits to the offices of the, on average, 15 public or private general practitioners in the Society Islands (Windward and Leeward Islands).
A succinct description of the clinical symptoms (pain symptoms [myalgia, arthralgia], respiratory symptoms, ENT, diarrhoea, skin rashes) is provided for every patient who consults a doctor for a fever. Automatic (computerised) grouping of these symptoms makes it possible to identify possible outbreaks (e.g. influenza syndromes, dengue-like syndromes, diarrhoea, possible case of measles). An influenza syndrome is defined by the combination of pain and respiratory or ENT symptoms and a dengue-like syndrome by isolated pain symptoms, i.e. without respiratory or ENT symptoms, possibly associated with skin or digestive symptoms.

The weekly estimate of the number of clinical cases of dengue fever was extrapolated from the number of dengue-like syndrome cases in proportion to the number of sentinel physicians who sent in their forms that week. In order to take into account gaps in the geographic presence of sentinel doctors, estimates were stratified into three zones (Leeward Islands, Tahiti urban area [Faa'a to Arue], and the rest of the Windward Islands) and adjusted to the doctors' types of practices, i.e. private practices or public clinics. This adjustment was justified by the fact that doctors in private practices see twice as many cases of febrile syndromes as doctors at public clinics (of the 15,000 fever cases described since the network began in 1999).

For the Austral, Marquesas and Tuamotu-Gambier island groups, the information provided was supplemented by a weekly report on the number of suspected cases of dengue fever seen at medical centres (Taiohae, Ua-Pou, Atuona, Rangiroa, Hao, Rikitea, Tubuai, Rurutu). This made it possible to monitor the geographic spread of the virus in these island groups.

Dengue fever hospitalisations

Surveillance procedures

⇨ A specific questionnaire was distributed to the medical, paediatrics and intensive care services of the Territory's public and private facilities so as to obtain a on-going information about such cases. The forms were sent to the Health Department by fax when the patient was released from hospital
⇨ Form validation and data entry were carried out by the GITE (Field Epidemiology Task Force) at the Health Department.
⇨ The information on laboratory confirmations was later supplemented by the results of tests conducted at the CHT laboratory (Claire Hirschauer) or the Louis Malardé Institute (Manola Laille).

- ⇨ The missing haematocrit figures for patients hospitalised at the CHT were later supplemented by the CHT's biological laboratory (Thomas Guéguen).
- ⇨ Validation of the comprehensiveness of the data on cases hospitalised at the CHT was carried out from the PMSI (Hospital discharge Information System) (Annick Valence and Pascal Jarno). This made it possible to complete data collection, particularly in services dealing with adult patients.

Severe form definitions

The WHO has produced a definition of haemorrhagic dengue fever with or without shock syndrome (DHF/DSS) using the following criteria :

- **Severe dengue (DHF) :** occurrence of each of the four criteria below:
- ⇨ Fever or recent episode of acute fever
- ⇨ Thrombocytopaenia (platelets ≤ 100 000/mm^3)
- ⇨ Haemorrhagic manifestations evidenced by at least one of the following symptoms: positive tourniquet test (Rumpel-Leede phenomenon), mucocutaneous or visceral haemorrhaging .
- ⇨ Plasma leakage shown by at least one of the following criteria:
  - A rise in the haematocrit of at least 20% over the recuperation value (after volume-replacement therapy) or a haematocrit level higher than normal for age (>45% for children under the age of 18; for adults, >50% for men and >47% for women)
  - Serous effusion (pleural or abdominal)
  - Hypoalbuminaemia (< 25 g/l before the age of 2 and < 30 g/l after the age of 2). In the absence of an albuminaemia assay, hypoproteinaemia (≤ 50 g/l).
- **Severe dengue with shock syndrome (DSS) :** DHF criteria and the existence of at least one of the following criteria:
- ⇨ Pulse rate disproportionately high in comparison to the level of hyperthermia and narrowed pulse pressure (≤ 20mm Hg)
- ⇨ or hypotension for age (SP ≤ 80 mm Hg if age < 5 years old or SP < 90 mm Hg if age ≥ 5 years old)
- **Confirmed cases :**

Identification of the dengue virus by culture or RT-PCR or isolation of specific IgM (MAC-ELISA)

WHO guidelines for grading the severity of dengue fever cases

In cases involving thrombocytopaenia and other indications of plasma leakage:

- Grade I : positive tourniquet test
- Grade II : spontaneous bleeding
- Grade III : circulatory failure
- Grade IV :profound shock (undetectable pulse and blood pressure)

NB : due to the infrequent use of the tourniquet test, cases of severe dengue without signs of spontaneous bleeding or shock were classified in Grade I (the tourniquet test is not a required symptom in the definition of dengue fever with shock).

Definitions used in this document

- ➢ "**Dengue-like" syndrome** (sentinel network) : fever and isolated pain symptoms (without respiratory or ENT symptoms), possibly associated with skin or digestive symptoms.
- ➢ **Severe Dengue without shock (DHF)** : association of a recent episode of fever with plasma leakage symptoms and thrombocytopaenia, possibly accompanied by haemorrhagic manifestations.
- ➢ **Severe Dengue with shock (DSS)** : association of DHF symptoms with signs of shock.
- ➢ **Classical Dengue (DF)** : term used to designate cases of dengue fever without DHF or DSS.

Serology or viral isolation requests

Constant virological surveillance is conducted by the Louis Malardé Institute; this made it possible to detect the outbreak early and to continually monitor the serotype responsible. Laboratory confirmations were particularly important to confirm the epidemic's spread to those districts or islands which had not yet been affected.

The doctors participating in the sentinel network were also asked to contribute to virological surveillance efforts. They were requested to send a blood sample for each suspected case of dengue fever to the Louis Malardé Institute for viral or serological isolation, together with a clinical information sheet.

Additional studies

Several studies were conducted to supplement the information provided by surveillance:

- ➢ Study involving 200 general practitioners (3/5 of whom were in private practice) and the Territory's 15 paediatricians designed to find out their perceptions of the epidemic and to describe the attitudes they took with regard to cases of dengue fever.
- ➢ Study on case management at the CHT's emergency room (Nelly Lavillunière's medical thesis).

- Detailed study of the clinical characteristics and case management of the 74 cases of dengue fever hospitalised in the CHT's paediatrics ward (Charlotte Renaudat's medical thesis).

VI. Epidemiological characteristics

The outbreak extended over a period of 10 months, i.e. from February to November 2001 with a peak in the third week of July.
This epidemic was responsible for some 33,000 cases of dengue-like syndrome seen by general practitioners in the Society Islands and at least 800 other cases in the other three island groups.
Nearly 1400 cases were hospitalised in the Territory's public and private facilities. Of the patients hospitalised, some 633 (45%) suffered from severe forms, including 278 (20%) with shock symptoms.
A total of eight deaths were recorded, all involving children under the age of 13.
About 2400 cases were confirmed by viral isolation, PCR or serology by the Louis Malardé or CHT laboratories. The only serotype isolated during this outbreak was serotype 1.

Incidence

Dengue-like syndromes

In the Society Islands, 33 000 cases of "dengue-like" syndromes were seen by general practitioners during patient visits, i.e. an incidence rate of 16% of the population. In the Windward Islands, the incidence rate was higher in the Tahiti urban area (20%) than in rural zones (13%) (Table 2). The number of cases in the other island groups represent a minimum since they were reported only by the medical centres (excluding nursing and first aid stations). However, the Austral Islands were very little affected.

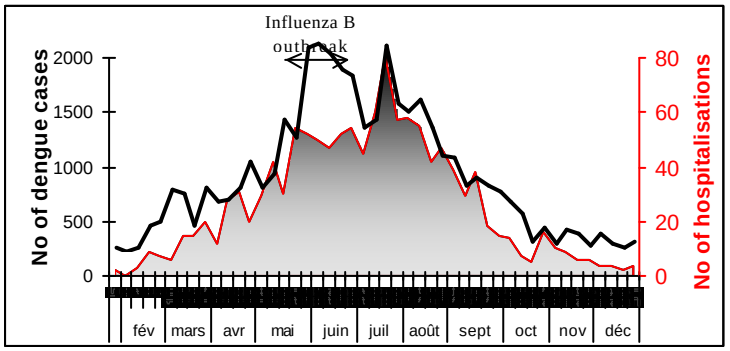
Table 2 : Incidence rates for "dengue-like" syndromes by island group

	Estimated number of cases *	**Incidence rate**
Windward Islands	28 450	17%
*urban zone ***	*15 870*	*20%*
*rural zone ****	*12 580*	*13%*
Leeward Islands	4 450	16%
Marquesas	375	> 4%
Tuamotu-Gambier	472	> 3%
Austral	42	> 0,6%
Total	**33 789**	

* using data from the sentinel network for the Society Islands group (Windward, Leeward)
** from Faa'a to Arue
*** rest of Tahiti and Moorea

Surveillance of "dengue-like" syndromes was disturbed by an influenza outbreak detected in June and confirmed in two patients by identification of the B virus through indirect immunofluorescence (Louis Malardé Institute).
The influence of this flu outbreak on dengue fever surveillance has been shown by superimposing the incidence curve of cases of dengue-like syndrome over that of cases hospitalised in the Society Islands group : it can be seen that, between 28 May and 30 June (weeks 22 to 26), there was an excess number of cases as compared to hospitalisations (Figure 1).

Figure 1 : Weekly evolution in the number of dengue-like syndromes and hospitalisations for dengue fever in the Society Islands group – February to December 2001.



Hospitalisations and severe forms by municipal district (commune)

- ⇨ The incidence rate for severe forms was 3/1000 in the Windward Islands, 2.2 in the Leeward Islands and 2.3 in the Marquesas. The Tuamotu and Austral Islands had lower rates due to the outbreak's more limited spread.
- ⇨ On the island of Tahiti, the incidence of severe forms was higher in the urban zone (Papeete and Faa'a) than in the rural municipal districts.
- ⇨ Hospitalisation rates averaged some 5.9 per 1000 inhabitants (Table 3); the highest rates were recorded in the Marquesas (9/1000 inhabitants) and on Bora Bora (8.5/1000).
- ⇨ The percentage of severe forms in hospitalised cases decreased with the geographic distance from a hospital facility, indicating a stronger tendency to hospitalise patients in the isolated islands. This percentage varied from 50% on the island of Tahiti to 35% in the Windward Islands and 26% in the Marquesas.

Table 3 : Dengue fever hospitalisation and severe forms rates per 1000 inhabitants by municipal district– February to December 2001

Municipal district	Population	Number of hospitalisations	Number of severe forms	Hospitalisation rate /1000	Severe form rate /1000	Proportion of severe forms /hospitalised
Papeete	27 500	187	96	6.8	3.5	51%
Faa'a	27 900	192	108	6.9	3.9	56%
Punaauia	21 000	100	59	4.8	2.8	59%
Paea	11 000	68	28	6.2	2.5	41%
Papara	8 500	69	36	8.1	4.2	52%
Teva I Uta	6 700	31	11	4.6	1.6	35%
Pirae	14 900	86	42	5.8	2.8	49%
Arue	9 500	57	23	6.0	2.4	40%
Mahina	12 600	75	37	6.0	2.9	49%
Hitiaa o Tera	7 500	43	20	5.7	2.7	47%
East Taiarapu	9 400	57	25	6.1	2.7	44%
West Taiarapu	5 400	32	15	5.9	2.8	47%
Total Tahiti	***161 900***	***997***	***500***	***6.2***	***3.1***	***50%***
Moorea	13 000	75	30	5.8	2.3	40%
Windward Islands	**174 900**	**1 072**	**530**	**6.1**	**3.0**	**49%**
Bora	6 200	53	20	8.5	3.2	38%
Raiatea	10 800	75	26	6.9	2.4	35%
Tahaa	4 800	31	10	6.5	2.1	32%
Huahine	5 800	18	6	3.1	1.0	33%
Maupiti	1 200	0	0	0.0	0.0	-
Leeward Islands	**28 800**	**177**	**62**	**6.1**	**2.2**	**35%**
Marquesas	**8 600**	**77**	**20**	**9.0**	**2.3**	**26%**
Tuamotu Gambier	**16 500**	**51**	**20**	**3.1**	**1.2**	**39%**
Australs	**6 800**	**2**	**1**	**0.3**	**0.1**	**50%**
French Polynesia	**235 600**	**1 379**	**633**	**5.9**	**2.7**	**46%**

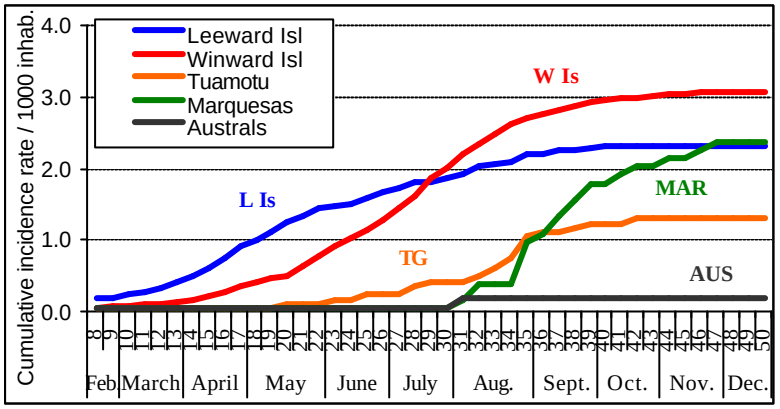
Course of the disease in time and space

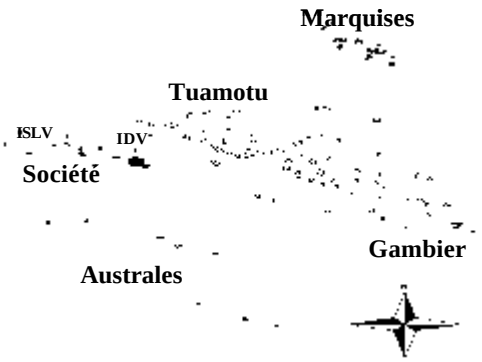
The sentinel network was not representative enough to conduct any in-depth geographic analysis of the epidemic. Hospitalisations, which depended on geographic distance, were not representative of overall cases either. The incidence of severe forms (an average of 2.7 per 1000 inhabitants) was deemed to be more reliable for assessing the outbreak's dynamics on each island and in each municipal district (with a few reservations that will be discussed in the remarks).

Graphic display of the cumulative incidence rates for severe forms in relation to the population made it possible to compare the islands and follow the chronology of the outbreak's spread (Figure 2). In addition, the shape of the curve is an indicator which makes it possible to measure the intensity of transmission.

- ⇨ The outbreak began in the Leeward Islands in early February and ended in late September.
- ⇨ Transmission to the Windward Islands was delayed and only began to be significant in April (after the school holidays) with a very rapid acceleration during the month of July.
- ⇨ The Tuamotu Islands were affected beginning in June, at the time when the incidence rate in the Windward Islands was at its maximum level.
- ⇨ The Marquesas were affected at the end of July with a rapid outbreak (less than 4 months). It is noteworthy that, as in the Tuamotu Islands, the epidemic spread rapidly after the new school year began (second half of August).
- ⇨ In the Austral Islands, transmission was very low and stopped completely as from July.

Figure 2 : Cumulative weekly incidence rates for severe forms of dengue fever by island group (per 1000 inhabitants)– French Polynesia - 2001





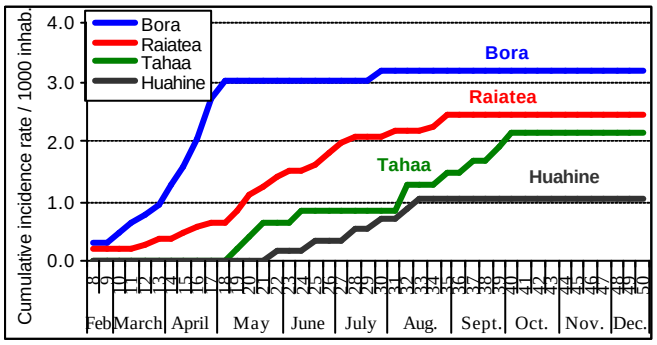
A more detailed examination reveals notable differences between the islands within each island group:

In the Leeward Islands, the outbreak was identified at the end of January on the island of Bora Bora where it lasted less than two months, followed by very low residual transmission. The school holidays in March facilitated its transmission to Raiatea where the outbreak was fairly spread out over a period of five months. The island of Tahaa was affected in early May during acceleration of the epidemic on Raiatea. The outbreak on Huahine began in late May but its scope was more limited. No cases were recorded on Maupiti, even though it is very close to Bora Bora.

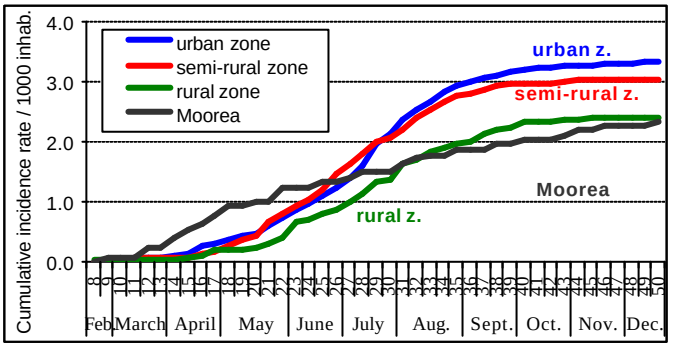
In the Windward Islands, Moorea was the first island affected, with a transmission pattern which was both slow and long. In Tahiti, in spite of the two cases identified in Faa'a in early February, the outbreak did not really begin until March in the eastern municipal districts of the urban area (particularly in Arue). The urban zone and the west coast had similar progress patterns with rapid acceleration in July ; in contrast, the rural zone experienced slower transmission and remained at a lower incidence rate than the urban zone

Figure 3 : Cumulative weekly incidence rate for severe forms of dengue fever by island group (per 1000 inhabitants)– Leeward and Windward Islands – 2001

Leeward Islands



Windward Islands



Urban zone: Faa'a to Arue
Semi-rural zone: Punaauia, Paea, Papara
Rural zone: Hitiia O Tera, East and West Taiarapu, Teva I Uta

In the Tuamotu-Gambier Islands, the first islands affected, particularly Rangiroa, were those which had frequent and direct air links with Papeete. The western and central atolls were affected much later. Of the 18 atolls which had hospitalised cases, only six had at least one severe form. The island of Mangareva in the Gambier Islands experienced a significant outbreak but no severe forms were observed (it is interesting to note that this island had not been affected by the DEN-2 outbreak in 1997).

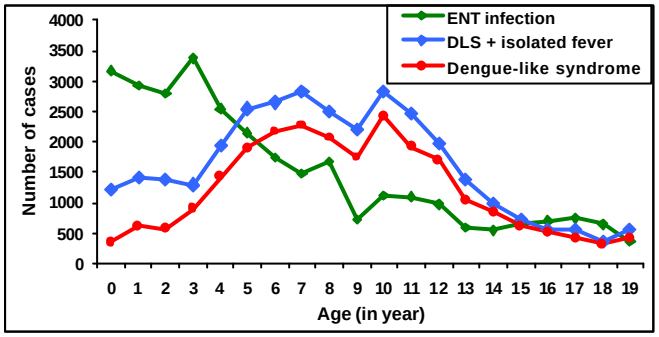
In the Marquesas, the outbreak began on the two main islands of Nuku Hiva and Hiva Oa, followed by Ua Pou, Tahuata and Fatu Hiva. No cases were observed in Ua Huka.

In the Austral Islands, transmission was very limited with a few suspected cases reported in April-May and only two hospitalisations including one severe form on Rurutu in July.

Incidence by age

⇨ **Dengue-like syndromes (Society Islands group)** : two-thirds of the cases of dengue-like syndrome occurred in children under the age of 15. The incidence rate decreased with age: from 33% for children under the age of 15 to 10% for those aged 15-34, 7% for people aged 35-44 and 4% for people aged 55 and over.
The incidence of dengue-like syndromes (diagnosed by a physician) gradually increased from 0 to 5 years of age and decreased starting from the age of 11. However, Figure 4 shows the high frequency of isolated fevers (without pain symptoms) in children under the age of 3 and the major proportion of ENT infections in visits to the doctor for fever in children under the age of 5.

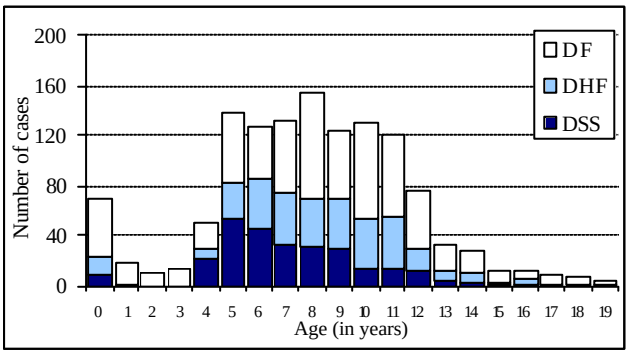
Figure 4 : Distribution by age of dengue-like syndromes, isolated fevers and ENT infections in patients under the age of 20 – French Polynesia. February to December 2001.



⇨ **Hospitalisations and severe forms**: The hospitalisation rate was 15/1000 for children under the age of 15 and 1/1000 in patients 15 years old and over. In all, 94% of the severe forms and 98% of the DSS were under the age of 15.

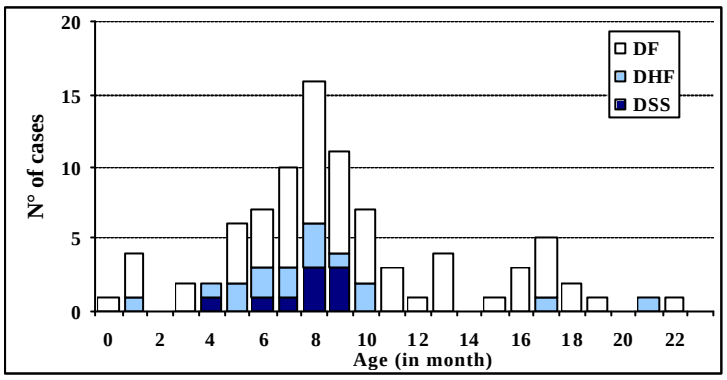
The age distribution of hospitalised patients 20 years old or less shows a bimodal curve with frequency peaks in children under the age of 1 and between the ages of 4 and 13. (Figure 5).

Figure 5 : Distribution by age and clinical form of patients under the age of 20 hospitalised for dengue fever- French Polynesia - 2001



⇨ In **children under the age of 2**, 70% of the hospitalised cases and 88% of the severe forms (rather than the expected 33%) were between the ages of 4 and 11 months with a frequency peak at the age of 8 months (Figure 6). In children aged 12 to 24 months, there were just two cases of severe forms, both without shock (17 and 21 months).

Figure 6 : Distribution by age in months and by clinical form of patients under the age of 24 months hospitalised for dengue fever – French Polynesia – 2001

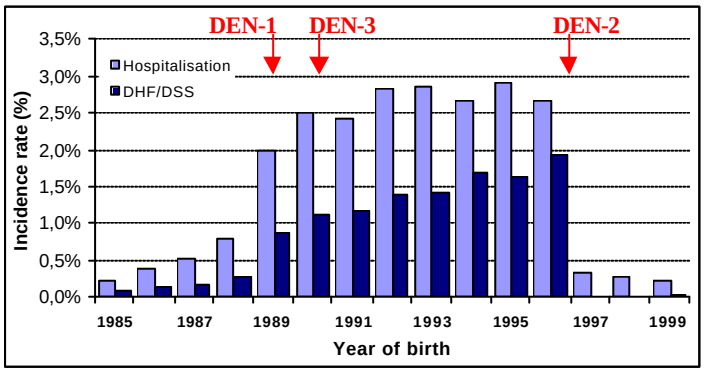


⇨ When **children over the age of one** are considered in terms of their year of birth (Figure 7), it can be noted that :

- hospitalisations and severe form rates were lower in children born before the DEN-1 outbreak in 1989;
- there is a steadily increasing trend in the severe form incidence from 1.1% for children born in 1990 to 1.9% for children born in 1996.
- Of the children born between 1997 and 1999 (i.e. after the DEN-2 outbreak), only one had a severe form of the disease.

The risk of developing a severe form was 186 (CI 95% : 26 – 1324) times higher in children born between 1990 and 1996 than in children born between 1997 and 1999.

Figure 7 : Hospitalisation and severe form rates (per 100 children) according to the year of birth (the dates of previous dengue fever outbreaks have been superimposed).



Frequency of hospitalisations and severe forms in relation to the number of dengue-like syndrome cases

In spite of significant under-estimation of the number of dengue-like syndromes in young children, the frequency with which severe forms occurred was 29 (CI 95% : 7.2 – 116) times higher in children with DF aged 4-14 than in those aged 1-3 (Table 4). Of the 20,000 children aged 4 to 14 who suffered from dengue fever, 1 child of every 20 was hospitalised and 1 out of every 37 developed a severe form.

Table 4 : Hospitalisation and severe form rates in comparison to estimated number of cases by age – Society Islands

Age	Number of dengue-like syndromes * (1)	Number of hospitalisations (2)	Number of severe forms (3)	Dengue-like syndromes incidence rates (%)	Hospitalisation rate (2/1)	Severe form rate (3/1)
< 1 year	350	62	21	8%	17.7%	6.0%
1-3 years	2 115	40	2	17%	1.8%	0.1%
4-14 years	19 600	937	535	44%	4.8%	2.7%
≥ 15 years	10 500	121	32	7%	1.2%	0.3%
Total	**32 700**	**1160**	**590**	**15%**	**3.5%**	**1.8%**

* estimated from the Fever Surveillance Sentinel Network

VII. Clinical characteristics of hospitalised cases

Laboratory confirmation

Of the 1379 hospitalised cases, 869 (63%) involved a request for laboratory confirmation of dengue fever. Of these cases, 688 (79%) were confirmed by culture or PCR (256 cases) and/or the presence of IgM (420 cases). In 181 cases (26%), the diagnosis of dengue fever was not confirmed due to the negative results of the analyses ; as, in most of these cases, no second sample was taken, the dengue fever diagnosis cannot be disproved.
For that reason, our analysis covered all the hospitalised cases.

Clinical forms

Of the 1379 hospitalised cases, 633 (46%) involved severe forms (DHF/DSS) including 278 cases (20%) with shock symptoms (DSS) (Table 5). In the WHO grade ranking, 157 cases (25% of the severe forms) were classified in Grade I, 198 (31% of the severe forms) in Grade II and 278 (44%) in Grades III or IV.

Table 5 : Frequency of severe forms observed in patients hospitalised for dengue fever

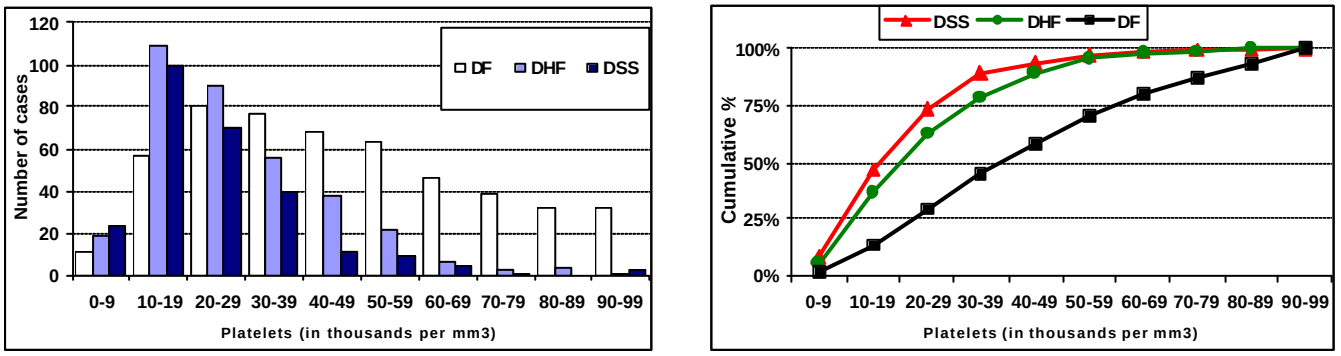
Clinical form	Number	%
Classical dengue (DF)	746	54%
Severe dengue (DHF)	355	26%
Severe dengue with shock (DSS)	278	20%
Total	**1379**	**100%**

Of the 746 cases of DF, 48 (6%) were not classified as severe forms due to the absence of one of the defining criteria (plasma leakage or thrombocytopaenia) : 24 cases with symptoms of plasma leakage but no thrombocytopaenia; 24 cases with shock symptoms but without any evidence of plasma leakage.

Thrombocytopaenia, haemorrhagic manifestations and plasma leakage

Thrombocytopaenia
Only the lowest platelet count value recorded during hospitalisation was taken into consideration for each hospitalised patient.
Thrombocytopaenia (<100 000 pl/mm³) was observed in 84% of hospitalised cases. The lowest rate was 2 900 pl/mm³. The median of the lowest platelet rates differed significantly between the cases with DSS (20 000 pl/mm³), DHF (24 000 pl/mm³) and DF with thrombocytopaenia (43 000 pl/mm³) (Figure 8).

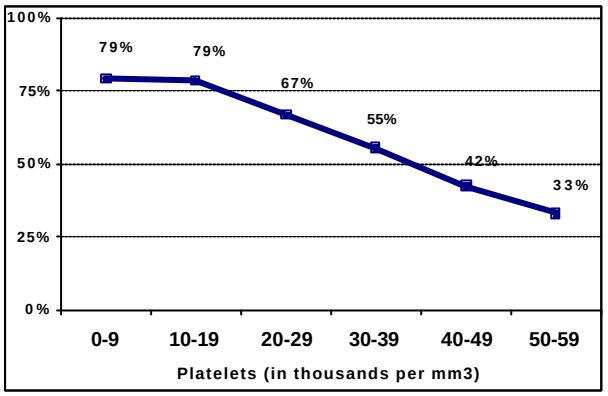
Figure 8 : Cumulative distribution of the lowest platelet counts by clinical form (in cases of dengue fever with thrombocytopaenia < 100 000 pl/mm³)



DF : Classical dengue, DHF : Severe dengue, DSS : Severe dengue with shock .

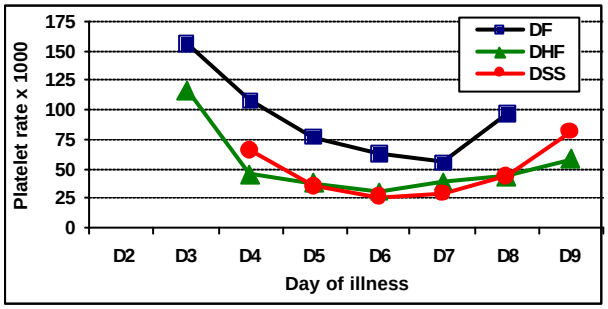
If we consider that most of the cases of dengue fever with thrombocytopaenia < 50,000 platelets were hospitalised (according to the recommendations issued at the beginning of the outbreak), it can be estimated that the probability of observing a severe form (DHF/DSS) when the platelet count was less than 20,000 was 79% and that this probability decreased to 42% with a platelet count of between 40 and 49 000 platelets (Figure 9).

Figure 9 : Probability of observing a severe form on the basis of the lowest platelet count (hospitalised cases of dengue fever).



C. Renaudat's study of 74 cases of confirmed dengue fever hospitalised in the CHT's paediatrics ward showed that the mean platelet count in cases involving DHF/DSS was half that of cases of DF fever, but that kinetics was identical with a minimum observed on the 6th or 7th day of the illness (Figure 10).

Figure 10 : Evolution, by day of illness; of the mean platelet count in 65 cases of dengue fever confirmed by PCR – CHT paediatrics ward



Source : Charlotte Renaudat (thesis in progress)

Haemorrhagic manifestations

Haemorrhagic manifestations were observed in 49% of the hospitalised cases. Their frequency increased with the occurrence of thrombocytopaenia and plasma leakage (Table 6). In severe forms, they were not more frequent when there were haemodynamic problems.

Haemorrhagic manifestations were as follows: petechiae or common purpura (29%), epistaxis or gingival bleeding (24%), extensive purpura (2%), visceral haemorrhaging (2,4%). Extensive purpura and visceral haemorrhaging predominated in cases of severe dengue fever. Some small cerebral haemorrhages without any lasting effects were diagnosed (by scanner) in one adult.

Table 6 : Frequency of haemorrhagic manifestations by clinical form in hospitalised patients.

Clinical form	N	Haemorrhagic manifestations
DF without thrombocytopaenia	225	66 (29%)
DF with thrombocytopaenia	521	234 (45%)
DHF	355	198 (56%)
DSS	273	156 (57%)
Total	**1379**	**655 (49%)**

Plasma leakage symptoms

Of the 633 cases of severe dengue fever, all displayed, by definition, at least one sign of plasma leakage. An elevated haematocrit was the most frequent symptom (Table 7). Isolated hypoalbuminaemia, without haemoconcentration or effusion, only accounted for 6% of the cases.

Table 7 : Frequency of plasma leakage symptoms in hospitalised severe forms.

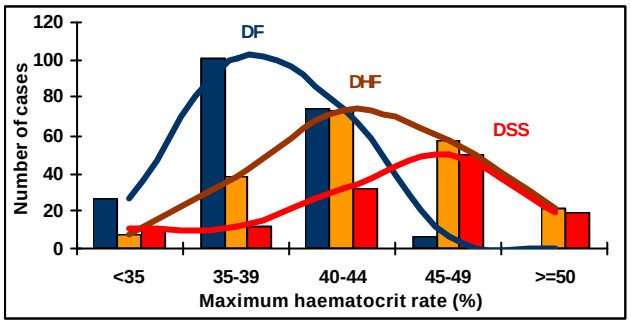
Plasma leakage symptoms		Number	%
Increased haematocrit		448	71%
Effusion (pleural or abdominal)		392	62%
Hypoalbuminaemia	or	292	46%
Hypoproteinaemia			

The frequency of plasma leakage symptoms varied according to the clincial form:

⇨ **Serous effusion** was more frequent in cases of DSS (77%) than in DHF (50%).

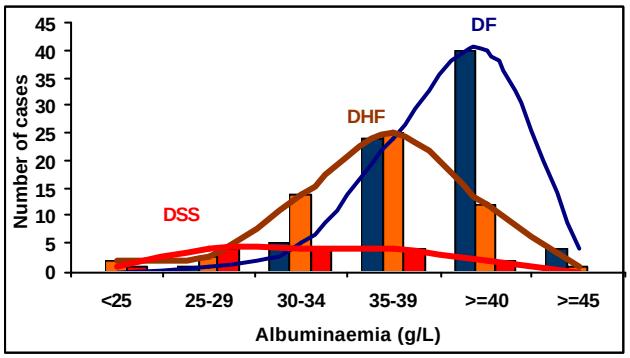
⇨ The median value of the maximum **haematocrit** (most often at the time of admission) was 38% in cases of DF fever, 44% in DHF and 45% in DSS (Figure 11).

Figure 11 : Distribution of the maximum haematocrit rate in children hospitalised in the CHT's paediatrics ward.



⇨ The median value of the **albumin** rates for cases of dengue fever seen at the CHT's emergency room (during admission or at the outpatient clinic) was 40 g/l in cases of DF, 36 g/l in DHF and 33 g/l in DSS (Figure 12). As with thrombocytopaenia, the minimum albuminaemia value was observed around the 6th day of the illness.

Figure 12 : Distribution of albumin rates in dengue fever cases treated at the CHT's emergency room.



Liver damage and blood sodium deficiency

⇨ A marked increase in ASAT (more than 10 times higher than the normal value) was observed in 106 cases (5% of the DF, 8% of the DHF and 17% of the DSS).

⇨ Blood sodium deficiency in hospitalised patients was one of the key observations during this outbreak. As natraemia is not part of the information that was systematically recorded on the reporting form, it was needed to measure it during two additional studies carried out in the CHT's emergency room and paediatrics ward.
In a similar way with both studies, the median natraemia values at admission decreased with the degree of severity of the dengue fever (Table 8).

Table 8 : Median natraemia value (in mmol/L) during admission by clinical form

		Natraemia value (mmol/L)		
	Number of cases	Classical dengue (DF)	Severe dengue without shock (DHF)	Severe dengue with shock (DSS)
CHT paediatrics study	67	132	130	128
CHT emergency room study	150	135	131	128

Deaths

A total of eight deaths occurred during the epidemic. Six of the deceased patients had been living on the island of Tahiti, one on Tahaa (Leeward Islands) and one on Takaroa Atoll (Tuamotu).
Three children died at home (Tahaa Island and Takaroa Atoll) or upon arrival at the hospital (Tahiti).
The children who died were between the ages of 18 months and 12 years.

The causes of death were as follows:

⇨ Seven children aged 5 to 12 initially displayed a state of shock associated with plasma leakage symptoms (DSS).

⇨ One child, 18 months old, died without any symptoms of plasma leakage or hypovolemic shock or thrombocytopaenia. The dengue fever diagnosis was confirmed by RT-PCR. This child probably had acute encephalitis.

The case fatality rate for severe forms was 1.1 %.

Specific clinical forms

- One case of acute encephalitis in one of the deceased children had a neurological pattern of epileptic seizures and a tendency to curl up in a foetal position. The scanner revealed hypodensity in the cerebral trunk and the basal ganglia, which favours an ischemic origin. The presence of the DEN-1 virus in this child's CSF was confirmed by RT-PCR.
- One 58-year-old adult displayed typical Guillain-Barré syndrome on the 8th day of the illness with complete recovery within two weeks.
- Several cases of ocular involvement were observed, mainly in adults. These problems were characterised by a central scotoma with oedema and retinal haemorrhaging. At least one case suffered longer-term effects with a permanent reduction in visual acuity.
- At least three cases of perinatal transmission were recorded in newborns six days after birth when their mothers displayed clinical dengue symptoms at the time of birth. All recovered spontaneously.

Reasons for and length of hospitalisation

The **reasons for hospitalisation** were mentioned in 922 cases (67% of hospitalised cases).
Several categories of reasons for hospitalisation can be identified (Table 9) :

⇨ DF before the 4h day of the illness (15% of hospitalisations) with a predominance of digestive symptoms (diarrhoea and/or vomiting) or a poor reactions to fever (hyperpyretic convulsions) or on the basis of other diagnoses (e.g. gastro-enteritis, leptospirosis, suspected meningitis)

⇨ DF from the 4th day on (39% of hospitalisations) with a predominance of thrombocytopaenia and haemorrhagic manifestations

⇨ severe dengue without shock (DHF) (26% of hospitalisations) in which abdominal pain (probably ascites) and thrombocytopaenia predominated

⇨ severe dengue with shock (DSS) (20% of hospitalisations) for which shock symptoms had been identified before admission in 37% of cases. The concept of thrombocytopaenia or haemorrhagic manifestations appeared less frequently in the reasons for hospitalisation.

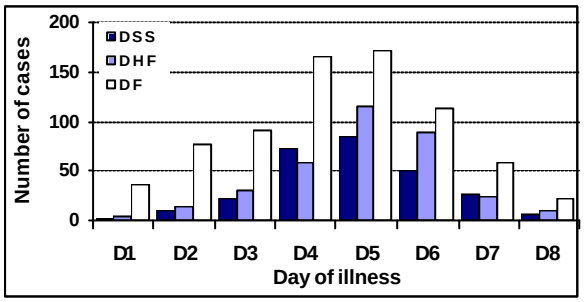
Table 9 : Frequency of reasons for hospitalisation by clinical form and day of hospitalisation

	Dengue fever < D4	Dengue fever ≥ D4	Severe dengue without shock (DHF)	Severe dengue with shock (DSS)
Number	100	360	257	205
Alteration of overall state of health	21%	26%	27%	27%
Signs of shock	1%	1%	2%	**37%**
Thrombocytopaenia	11%	**30%**	**39%**	17%
Haemorrhaging	27%	**33%**	26%	15%
Abdominal pain	24%	22%	**32%**	23%
Vomiting	**33%**	14%	13%	11%
Diarrhoea	12%	4%	4%	4%

Hospitalisations in the intensive care unit were relatively infrequent (25) and were mainly justified by three types of symptoms : profound shock, the need for respiratory assistance (particularly due to large-scale effusion) or the occurrence of poorly controlled visceral haemorrhaging.

Period of hospitalisation after the onset of disease:
Although it was sometimes difficult to pinpoint the exact date symptoms first appeared, it was possible to calculate the period of hospitalisation after the onset of disease. Some 4/5 of the cases were hospitalised on or after the 4th day of the illness (Figure 13) ; 12% of the cases of shock occurred on the 4th day.

Figure 13 : Distribution by clinical form of dates of hospitalisation after the appearance of clinical symptoms



D1 : first day of the illness

VIII. Treatment of dengue fever

Private practice doctors

General practitioners and paediatricians, both public and private, treated more than 33 000 cases of dengue fever. It is likely that nearly 3/4 of the cases were monitored by private physicians. It should be possible to estimate the number of visits to the doctor generated by this outbreak using the information provided by *Caisse de Prévoyance Sociale* (Social Welfare Scheme). At the very least, this number was higher than two visits per patient.

A survey of general practitioners, paediatricians and hospital doctors (excluding surgeons) conducted in September 2001 gathered 96 responses (i.e. 42% from general practitioners, 43% from public health doctors in the medical clinics and 15% from doctors working in public or private hospitals) from the 220 doctors involved.

Prescriptions

⇨ Most of the additional tests were prescribed on the 4th day of the illness with a FBC-platelets for all non-hospital physicians, a CRP and aminotransferase assay for half of them and an ionogram and an albuminaemia test for at least one doctor out of every 5 (Table 10).

Table 10 : Percentage of non-hospital doctors who normally prescribed additional tests.

Tests	Percentage of doctors
FBC - platelets	96%
Aminotransferase	50%
CRP	43%
Ionogram	16%
Albuminaemia	16%
Coagulation test	9%

⇨ The average length of sick leave prescribed for adults was 7 days.

⇨ Half of the non-hospital physicians said that they had occasionally prescribed antibiotics, most often on the 4th or 5th day due to symptoms or out of fear of surinfection linked to neutropaenia, and less frequently, as of the 1st day when there was doubt about the diagnosis.

Clinical surveillance of cases and difficulties with hospitalisation

⇨ The key factor in surveillance of dengue fever cases was clinical symptoms (85% of the hospital physicians and 70% of the city doctors) rather than thrombocytopaenia.

⇨ Difficulties linked to hospitalisation were mentioned by 20% of the city doctors (and 1/3 of the hospital physicians) :

- The shortage of hospital beds was a problem during the peak of the epidemic.
- This was exacerbated by the fact that doctors were afraid of the possible abrupt appearance of shock ("better to over-hospitalise than under-hospitalise ").
- Excessive media coverage of the deaths brought about an upsurge in concern among parents.
- In addition there were difficulties with patient monitoring, particularly laboratory, during the weekends, which led to proposing hospitalisation or visits to the CHT's emergency room at the weekend.
- Although clinical symptoms were deemed decisive in surveillance, a drop in the platelet count, seen as a forewarning of a severe form, generated a great deal of hesitation on the part of general practitioners.

- The somewhat deceptive clinical picture at the beginning of the illness (e.g. diarrhoea, ENT infections) frequently led to hesitation about diagnoses in children.

Information

⇨ The clinical guide distributed was read by 95% of the doctors who responded to the survey ; 17% of them would have liked more information on detailed clinical symptoms (particularly atypical forms at the beginning of the disease), an explanation of shock symptoms, essential additional tests and details on the evolution of biological symptoms.

Hospital facilities

Of the 1379 hospitalised cases, 82% were in Papeete, at either the Territorial Hospital or in private clinics (Table 11). At least 46 cases were transferred to the CHT after being hospitalised in a clinic or in one of the 'outlying' hospitals (Taiohae, Moorea, Taravao ou Uturoa) ; these cases were counted in the figures for the facility to which they were transferred.

Table 11 : Facilities for hospitalising dengue fever patients – French Polynesia -2001

Facility	Number	%	Facility	Number	%
CHT including :	751	55%	Uturoa Hospital incl :	121	9%
Paediatrics	*647*		*Paediatrics*	*99*	
Medical	*76*		*Medical*	*22*	
General intensive care	*25*		Moorea Hospital	38	3%
Neonatal intensive care	*3*		Taravao Hospital	24	2%
Cardella Clinic	193	14%	Taiohae Hospital	67	5%
Paofai Clinic	181	13%			

Analysis of **hospitalisation sites by the patient's island or island group** of residence provided information on how medical care facilities were used by doctors (Table 12) :

⇨ In Tahiti Nui, 2/3 of hospitalisations took place at the CHT and 1/3 at private clinics;
⇨ In Tahiti Iti, only 1/4 of the patients were hospitalised in Taravao Hospital;
⇨ Nearly half the cases residing on Moorea were hospitalised in Afareaitu Hospital;
⇨ In the Leeward Islands, 94% of the cases from Raiatea and Tahaa and only 28% of the cases from Bora and Huahine were hospitalised in Uturoa Hospital;
⇨ 95% of the cases in the northern Marquesas and 65% of the cases in the southern Marquesas were hospitalised in Taiohae Hospital.

Table 12 : Hospitalisation facility by patient's island or island group of residence – French Polynesia - 2001

		Distribution of hospitalisation sites		
Island or island group of residence	**Number of hospitalised cases**	**Private Clinics**	**CHT**	**Local hospital ***
Raiatea	75	0%	5%	**95%**
Tahaa	30	3%	0%	**97%**
Bora	53	**25%**	**49%**	26%
Huahine	18	**22%**	**50%**	28%
Tahiti Nui	906	**36%**	**63%**	1%
Tahiti Iti	89	15%	**61%**	**24%**
Moorea	75	12%	**40%**	**48%**
Northern Marquesas	61	2%	6%	**92%**
Southern Marquesas	16	0%	**38%**	**63%**
Tuamotu	50	14%	**86%**	0%
Total	**1373**	**27%**	**55%**	**18%**

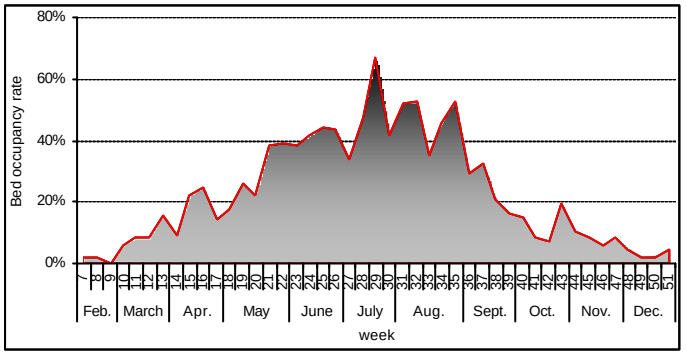
* Uturoa Hospital for the Leeward Islands, Taiohae Hospital for the Marquesas, Afareaitu Hospital for Moorea and Taravao Hospital for Tahiti Iti.

Hospital bed occupancy rates in paediatrics wards were calculated using the ward's theoretical capacity: CHT (39 beds), Uturoa Hospital (11 beds), Cardella Clinic (13 beds up until August and then 6 beds) and Paofai Clinic (13 beds).

Saturation of the paediatrics wards on the island of Tahiti was high with at least 40% of the theoretical beds in paediatrics occupied by dengue fever patients from June to August with a peak during the 3rd week of July (65 children hospitalised, i.e. 70% of the theoretical bed capacity) (Figure 14).

The median hospital stay was 3 days (average : 3.8 days and extremes 0 to 94 days). In all, dengue fever cases caused 5280 days of hospitalisation (including 4200 in paediatrics wards).

Figure 14 : Dengue fever occupancy rates of theoretical paediatric beds in Tahiti (CHT, Cardella, Paofai)

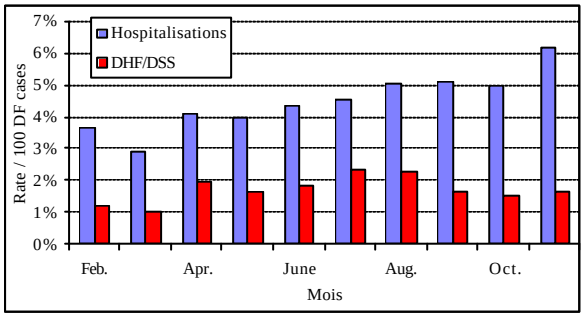


Evolution of severe forms and hospitalised cases over time

Except for the very beginning of the outbreak (February, March), a period during which the number of cases was low, it can be seen that the frequency of severe forms relative to the number of dengue-like syndromes varied very little over time (Figure 15). The percentage of DSS from among all the severe forms fluctuated between 40 and 50% during the epidemic.

The percentage of hospitalised cases increased slightly from 4% of all the cases before May to 5% between August and October to more than 6% in November (due to hospitalisations in the Marquesas).

Figure 15 : Monthly evolution of hospitalisation rates and severe forms relative to the number of dengue-like syndromes – Society Islands



IX. Prevention activities

Two types of measures were taken during the outbreak : vector control and information

- A programme to eliminate mosquitoes was carried out by the Public Health and Hygiene Service, and was focused on those neighbourhoods with high population densities, while fully realising the limited and transitory effectiveness of simply destroying adult mosquitoes. The main objective was to slow down the outbreak's spread in order to limit saturation at health care facilities.
- These measures were accompanied by appeals to the population at large to destroy larval breeding areas, the only really effective action.
- In order to optimise care for severe forms, particularly in children, information was conveyed to health professionals and the population on a regular basis.

Vector control

Vector control activities were conducted by the Public Health and Hygiene Service's vector control unit, comprising eight people and headed by an entomologist. The number of team members only increased at the end of August with the addition of four extra staff.

Perifocal control

- ⇨ On Bora Bora, the Leeward Islands Hygiene Service agent introduced larval breeding area control measures in collaboration with the local municipality. However, the impact of these activities was limited due to the already significant spread of the outbreak before its identification.
- ⇨ Perifocal control measures were taken in February as soon as the first case was identified in Faa'a on the island of Tahiti. This consisted of spraying for adult mosquitoes and destroying larval breeding areas around the patient's home and at nearby schools. This action seems to have been effective as no other cases were diagnosed in this geographic area for several months.

Spraying insecticides to kill adult mosquitoes

- ⇨ A systematic mosquito elimination campaign was implemented in the most urbanised areas of Tahiti between February and mid-July in three successive rounds. It consisted of treatments using ULV (ultra-low volume) insecticide spray against adult mosquitoes twice over the entire area, with a change in insecticide's chemical base during the second treatment so as to limit the risk of the appearance of resistance in the mosquitoes. The products used were, in order, permethrin (synthetic pyrethroid) and unscented malathion (organophosphate).
- ⇨ The treatments were repeated from 22 August to October, no longer in a systematic manner but selectively in the most affected neighbourhoods (based on the frequency of hospitalisations during the preceding week).

Systematic visits to centres frequented by children

- At the beginning of the outbreak, all such facilities in the urban area were visited (treatment against adult mosquitoes and destruction of larval breeding areas).
- Systematic visits were made to Tahiti's crèches, child care centres and holiday centres from 16 July to 10 August in order to destroy larval breeding areas. These visits were accompanied by the distribution of educational video cassettes ("*Voleurs de sang*" (blood burglars) kits already shown in schools).
- During the week before the children went back to school in August 2001, all the kindergartens and primary schools in the urban area and its periphery underwent treatment against adult mosquitoes.

Information activities

Population

- ⇨ Some 400 TV ads about eliminating larval breeding areas and the need for personal protection were shown on the two local television stations (TNTV et RFO) during the outbreak.
- ⇨ Reports on the TV news and the five radio stations were carried in French and Tahitian on a regular basis.
- ⇨ An "Outbreak Trend Chart" was sent to the media on a regular basis by the Health Department and the Malarde Institute. As the epidemic evolved, the frequency of the publication of the chart changed, i.e. from weekly to bi-monthly and then to monthly.

Health professionals

The following information tools were sent out:

- ⇨ A "Clinical Guide for Practitioners" (see annexe) in March and then in April 2001.
- ⇨ A report on the first 150 hospitalisations describing the characteristics of severe forms in May 2001.
- ⇨ A "Weekly Outbreak Trend Chart" which went out to some 150 recipients by e-mail throughout the epidemic (doctors, health services, WHO, South Pacific Commission (sic) for transmittal to the other countries in the Pacific).

X. Comments

Thoughts on surveillance

Outbreak detection:

Detection of this outbreak was delayed since the first case diagnosed was a severe form in a patient living on Bora-Bora, who was hospitalised on 2 February with clinical symptoms dating from 30 January ; yet it seems quite unlikely that the epidemic could have started with a severe form. In addition, the initial rise in the curve showing the outbreak's transmission on Bora Bora (Figure 3) appears to be too abrupt when you consider that the time needed to transmit the illness from one person to another is about 15 days. It seems more likely that the virus was introduced in late 2000.

There was a number of reasons behind this delay in detection :

- As there had not been any outbreaks for four years, doctors' vigilance with regards to dengue fever was at the lowest possible level and so there were very few requests for dengue serology tests (267 prescriptions and 36 positive tests in 2000).
- No external warning notices had been received from other South Pacific countries, except for the small island of Palau (Belau) (north of Papua New Guinea) with which French Polynesia has no special ties.
- The outbreak began on Bora Bora during a period, i.e. between late November 2000 and February 2001, when the only sentinel physician on that island was unable to transmit his fever reports (technical difficulties with his fax machine).
- The same detection delay was observed in Hawaii (but their last outbreak occurred some 50 years ago) where a DEN-1 epidemic was identified in September 2001, whereas the first cases, confirmed retrospectively, had occurred as early as late May 2001.

Definitions

- Dengue-like syndromes: the sensitivity and specificity of the definitions used by the sentinel network are far from ideal; in fact, flu-like syndromes if detected early may not show any respiratory or ENT symptoms and so may be classified as dengue-like syndromes. Conversely, real cases of dengue accompanied by respiratory or ENT symptoms may have been classified as influenza. In addition, very young children have few if any pain symptoms, in which case, dengue fever may be diagnosed as an isolated fever. However, it is difficult to improve these definitions. Requests for virological or serological confirmation are too infrequent (about 10% of the cases, normally with a single blood sample taken at the beginning of the illness) to be reasonably included in the definition.

- Hospitalised cases of dengue fever: due to the lack of systematic requests for serology in 37% of the hospitalised cases, it was not possible to classify such cases using laboratory confirmation criteria. Moreover, the dates of hospitalisation fell in the worst period, i.e. between D4 and D8 when the probability of viral or serological isolation was at its lowest level. Of the 181 cases with negative blood tests or viral cultures, 82% of these cases showed, with a background of recent fever, either a thrombocytopaenia <100 000 platelets, or haemorrhagic manifestations, which was sufficient to consider them as probable cases of dengue fever in the context of this epidemic.

- Severe forms (DHF/DSS): use of the definition criteria proposed by the WHO is always difficult. These criteria are criticized on a regular basis for various reasons, either because they do not explain all the deaths or because they require information that is not collected systematically (biological markers of plasma leakage or the tourniquet testing). As the tourniquet test, a non-specific indicator of capillary weakness, is not used on a regular basis, we considered that the disease's gravity was linked to haemodynamic problems brought about by plasma leakage and not systematically associated with spontaneous bleeding. Strict use of the WHO definitions would have led to a 25% underestimation of the number of severe cases.

Estimating the number of cases of dengue fever

The sentinel network's estimate of the number of cases is approximate and we are aware that this system is not perfect. However, these estimates had fewer drawbacks than mandatory reporting (which has problems with comprehensiveness and would be difficult to manage with some 1000 to 2000 cases per week over a period of several months) or a simple count of confirmed cases, since we know that, in general, there are too few requests for serological confirmation, due to its limited benefit for the patient. The incidence rates obtained were much more consistent than the mandatory reporting rates published in many countries, which considerably underestimate the reality of the situation.

Hospitalisations for dengue fever

Hospitalisation surveillance was a key element in this outbreak. This demanded a great deal of work, both in terms of the doctors and interns who filled out the forms and for data validation and entry. Missing information was systematically supplemented, in particular the haematocrit figures on children hospitalised in the CHT's paediatrics ward, where the figures were obtained from the laboratory.

Constant information feedback was essential for maintaining motivation within the various services.

A comparison was made with the CHT's information system's hospital stay summaries. This made it possible to complete those reports that had not been made, mainly at the beginning of the outbreak. A second comparison conducted in October showed that most of the non-reported cases were non-severe cases.

However, there was a slight under-reporting of cases in adults, particularly at private clinics and in a few hospital wards.

Scope of the outbreak

In the Society Islands group at the beginning of 2001, the number of people at risk of being infected by serotype 1 was estimated at 88,000, including:

- the 60,000 children under the age of 13, born after the DEN-1 outbreak in 1989 ;
- and about 20% of the population over the age of 13 (28,000 people), i.e. those who had not been affected by the 1989 outbreak and those who had arrived in the Territory after that time. E. Chungue estimated that, at the end of 1990, at least 70% of the population had been immunized against the serotype 1 virus (Chungue 1992). Residual transmission of the virus after the epidemic usually does contribute to increasing (theoretically by some 3% annually) the percentage of people immunized. However, residual transmission of DEN-1 after the 1989 outbreak was very limited due to the appearance of DEN-3 in 1990.

The sentinel network made it possible us to estimate the number of cases of infection clinically diagnosed by general practitioners at about 33,000 cases (16% of the population). However, these cases only represented some 70% of infected individuals as about 30% of the infections are asymptomatic or paucisymptomatic forms so are not identified as dengue fever by doctors (this percentage is probably higher in young children).

Given this information, it can be estimated that the number of people infected by the type 1 virus in 2001 was 47,000 individuals in the Society Islands, i.e. 53% of the people at risk before the outbreak (this corresponds to the disease rate normally found in serological surveys in past epidemics). At the end of 2001, it can be estimated that about 80% of the entire population had been immunized against Serotype 1 (Table 13). This is consistent with Reiter's models which show that an outbreak ends once 80% of the population has been immunized against the serotype involved ('herd immunity', also described for other infectious diseases).

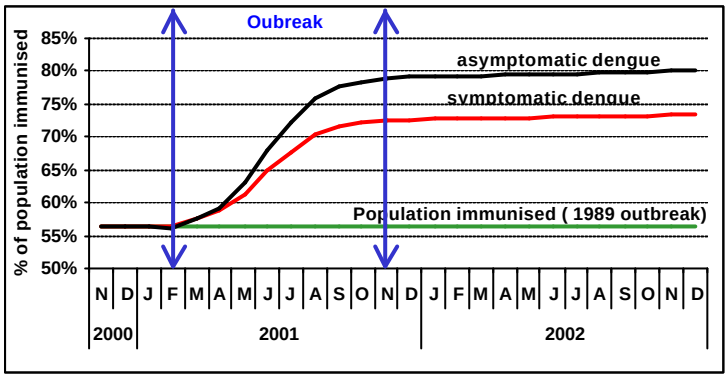
Table 13 : Estimates of the number and incidence of at-risk and infected individuals during the 2001 dengue fever epidemic in the Society Islands group.

	Number	Incidence /100 inhabitants
People immunized (at the beginning of the outbreak)	113 600	56%
"Dengue-like" syndromes	33 200	16%
Asymptomatic infections	14 200	7%
People immunized (at the end of the outbreak)	161 000	80%

The rates estimated by E. Chungue (Chungue 1998) for the outbreaks that occurred over the past 25 years in the Windward Islands vary from 17 to 25% of the population depending on the epidemic; these variations linked to the percentage of people at risk and therefore to the time elapsed since the last outbreak of the same serotype. (Table 1). The 16% incidence rate observed in 2001 in the Windward Islands is comparable to the estimated rate of 17% for the DEN-1 outbreak in 1989 (which itself occurred 14 years after a DEN-1 epidemic in 1975). The 2001 outbreak did not, therefore, differ in scope from previous epidemics. As with the others, it came to an end when the percentage of the population at risk of being infected by DEN-1 decreased.

Figure 16 shows the outbreak's dynamics, in particular, the changeover from an epidemic to an endemic situation. The fact that an outbreak is considered to have ended does not mean that transmission comes to a halt. It persists as a residual endemic disease for several years, with a mean infection rate estimated by E. Chungue at 3% annually for the population at risk. This period of endemic disease is dangerous since, due to decreased vigilance, severe forms are likely to be monitored less closely. In theory, residual cases should be observed in the form of small foci in the less affected geographic zones.

Figure 16 : Evolution over time of the percentage of the population immunized against DEN-1 (Winward Islands 2001)



Children under the age of 13-14 were those most affected by the outbreak, as could be expected since they were born after the last DEN-1 outbreak in 1989-89 and so were not immunized against this serotype.
However, the incidence rate for dengue-like syndromes in children under the age of 4 seems surprisingly low. Although they are less likely to be at school, it is doubtful that these children were less exposed to mosquitoes and so to the virus. This was confirmed by several previous studies, in particular the one conducted by the Malardé Institute in 1997 after a 10-month DEN-2 outbreak. This study showed that DEN-2 antibody prevalence was the same for children aged 0-4 (58%) as it was for children aged 5-9 (52%) (Deparis 1998).

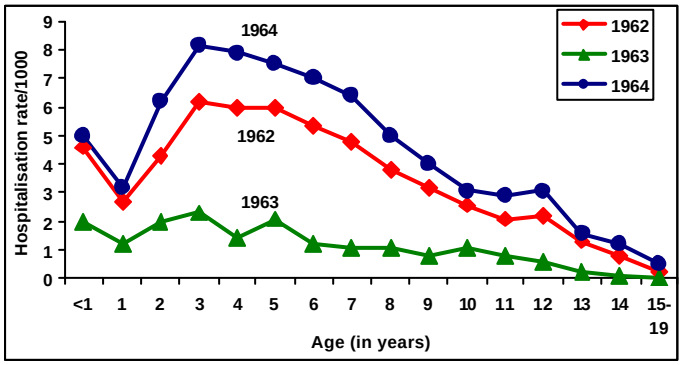
It is more likely that these children more often had asymptomatic or unclear forms:
- young children have more difficulty expressing their pain syndromes and, as we have seen, the frequency of isolated fevers is high in children under the age of 3. The frequency of ENT infections is also a reason for under-diagnosis (or inaccurate classification in the sentinel network data).
- asymptomatic forms or those with few symptoms may also be more frequent in cases of primary dengue than in secondary dengue.

Severe forms

As we pointed out in the introduction, there are two opposing - or perhaps complementary - theories with regard to the pathogenesis of severe forms, i.e. Halstead's "facilitating antibodies" theory and the theory of differences in virulence between strains of the virus.

The bimodal nature of age distribution in severe forms or hospitalisations has already been described (in particular in Thailand in 1962-1964 [Figure 17] and in Cuba in 1981). This feature, which is unusual in comparison to other infectious diseases, was the basis for the development of Halstead's theory in the early 1960s.
These two peaks have been explained in infants by the influence of passively acquired maternal antibodies and in children by a previous exposure to a different serotype.

Figure 17 : Hospitalisation rates by age for DHF/DSS in Bangkok and Thonburi (Thailand) in 1962-64 (according to Halstead, 1970)

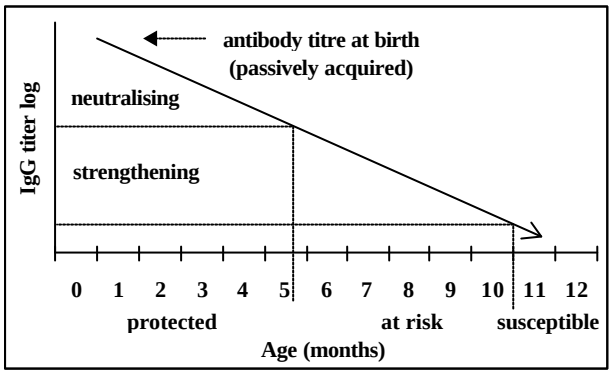


Severe forms in infants

Halstead had already shown in Thailand in 1962-64 that there was an increase in hospitalisation rates for infants over the age of 4 months, reaching a peak at 7 months, and then decreasing up to the age of 11 months. In 1988, Klicks measures the maternal antibody titres of infants with severe forms of dengue fever. This author showed that these titres, which corresponded to antibody titres at birth, had a strong correlation to the child's age in months at

the time he got the illness, with the highest risk of developing a severe form occurring, on average, at 8.2 months in Thailand.
These observations were attributed to the steady decrease in maternal antibodies which brings about three successive phases: a protection phase between the ages of 0 and 5 months, followed by a period where the antibodies no longer neutralise but rather 'facilitate' severe infections, and finally the complete disappearance of these antibodies at about the age of 11 months leaving the child open to a 'normal' infection (Figure 18).
Age distribution of hospitalisations and of severe forms in infants during the 2001 outbreak in French Polynesia was completely consistent with these observations.

Figure 18 : Breakdown of the IgG acquired passively during pregnancy and the risk of infants acquiring an infection or severe form of dengue fever (according to Klicks 1988)



Severe forms in children
In comparison to Southeast Asian countries where there is simultaneous transmission of several different serotypes on an on-going basis, the epidemiological characteristics of dengue fever outbreaks in French Polynesia provide a unique opportunity to study the influence of a previous exposure, fairly limited in time (i.e. a few months), to another serotype.
As dengue fever outbreaks always spread out over a period of a few months, the normal portrayal of severe forms by age group does not allow the timing of exposure to be correctly taken into account. For that reason, study of the frequency of severe forms by birth cohorts sheds new light.
This analysis demonstrated the major influence of being born before 1997 (and therefore before the DEN-2 epidemic) had on the occurrence of severe forms. The risk of developing a severe form was 186 times higher for children born between 1990 and 1996 than for those born between 1997 and 1999.
This observation does not exclude a specific virulence for the strain responsible for this outbreak or possible interaction between the 2001 and 1997 viruses.

Inter-epidemic interval and severe forms:
Halstead showed that the risk of seeing severe cases of dengue fever was higher when an outbreak occurred within six months to five years of the preceding one (Halstead 1970). This does not exclude the occurrence of severe forms at a later date as was the case in Cuba in 1997 where the inter-epidemic interval was 16 years.
Study of the 10 outbreaks which have occurred since 1994 showed that:
- of the 5 outbreaks which occurred less than 5 years after the preceding one, 3 of them were considered as severe (2 year interval for the 1971 outbreak, six months for the one in 1990 and 4 years for the one in 2001).
- The other 5 outbreaks were described as not severe.

Year	1944	1964	1969	1971	1975	1979	1989	1990	1997	2001
Serotype	1	3	3	2	1	4	1	3	2	1

However, the concept of a severe outbreak is subjective and it is frequently evaluated by the number of deaths observed. It is possible that all outbreaks will have some severe forms but that their frequency and degree of clinical expression vary due to either the virulence of the strain or the specific serotype sequences. Identifying and quantifying the severity of an outbreak is also linked to the quality of surveillance.
Even so, the 2001 epidemic in French Polynesia was distinctive in that it had a mean DHF/DSS incidence rate of 2.7/1000 inhabitants (reaching some 3.9/1000 in Faa'a), which is comparable to the 3.2/1000 rate observed during a major outbreak in Thailand in 1987.

Treating dengue fever patients

Hospitalisation criteria

The clinical practice guide, distributed to doctors in March 2001 (see appendix), included hospitalisation criteria (occurrence as from the 4th day of the illness of: thrombocytopaenia < 50 000 pl/mm^3, clinical or laboratory signs of plasma leakage or shock, visceral or extensive cutaneous haemorrhaging).

These hospitalisation criteria proved to be useful in limiting the overloading of hospital services. The only criticism given involved isolated cases of thrombocytopaenia which cannot be considered an adequate reason for hospitalisation. This is even more true as the minimum platelet count is reached on the 7th day, by which time the probability of observing shock has become very low. In practice, indications of plasma leakage (clinical or laboratory: persistent abdominal pain, hypoalbuminaemia, high haematocrit) or shock as from the third day of the illness should be adequate.

More than ever, the term 'haemorrhagic dengue fever' seems inappropriate as minor bleeding (petechiae, epistaxis, gingival bleeding) is a poor indicator of severe forms of dengue fever. The tourniquet test, which takes a long time to carry out, has still not been adopted by doctors, so its practical interest is difficult to assess.

Blood sodium deficiencies, which appeared more frequently than in other outbreaks, did not seem to have been related to anorexia or digestive problems during the first few day of the illness. The usefulness of an ionogram as part of the systematic surveillance of dengue fever and the early use of oral rehydration solutions will have to be debated.

For the next outbreak, it will be important to emphasise:

- ⇨ the existence of rather deceptive symptoms at the start of the illness, with, in particular, diarrhoea in 20 to 30% of the cases.
- ⇨ haematocrit surveillance, a simple criterion, recommended by the WHO, as an elevated haematocrit is a warning sign of haemodynamic problems;
- ⇨ the kinetics of thrombocytopaenia, as a low platelet count does not have the same prognostic value on D4 as on D8 ;
- ⇨ the fact that some 12% of the cases of shock may take place before the 4th day of the illness and that the start of clinical symptoms is not always easy to identify ;
- ⇨ detailed explanations of shock symptoms, in particular those which are poorly known by general practitioners, e.g. the concepts of tachycardia that is disproportionate to the temperature and narrowed pulse pressure (e.g. 110/95 mm Hg).

Hospitalisation capacities

The hospitalisation capacities of Tahiti's paediatric services were overwhelmed, especially during the three peak months of the epidemic in the urban zone, in spite of the fact that that outbreak was spread out over time. These difficulties were accentuated by a lack of medical personnel during the school holidays and by the closing down of six beds at the Cardella Clinic in August. The CHT and clinics coordinating their efforts well in order to optimise use of available beds.

The outlying hospitals managed the outbreak on the basis of their ability to monitor patients, especially at night. It can be seen that Uturoa Hospital was not very attractive for those living on Huahine and Bora Bora, probably due to infrequent air flights between those islands.

Taiohae Hospital was a special case as the doctors there successfully adopted a rather broad hospitalisation policy so as to offset difficulties in monitoring children in the remote valleys of the Marquesas Islands. Medical evacuations to Papeete were very limited in number. It was the only island group affected by the epidemic which did not record any deaths from dengue fever.

For that reason, we might ask ourselves if an increased capacity to care for patients on the island of Tahiti would not have made it possible to reduce the number of deaths.

Finally, a medical and economic analysis of the outbreak still has to be carried out in collaboration with the SPC and the CHT's Medical Information Service. If we base ourselves on estimates made during previous epidemics, it is very likely that the costs of the 2001 outbreak went well over XPF one billion (8.3 million euros or 7.7 million US dollars) and had a significant impact on health expenses.

Prevention

It has to be admitted that vector control activities did little to change the outbreak's intensity, as had been the case with previous outbreaks at a time when population densities were, however, lower and control resources were proportionally stronger.
At most, the epidemic was probably delayed in the urban zone. Spraying at the end of the outbreak is theoretically more efficient as it destroys a greater number of infected mosquitoes than it does at the beginning. This strategy was disappointing and did not prevent high incidence rates in the urban area. However, the lack of any means to measure vector densities did not allow us to judge the effectiveness of control measures, and particularly, to correlate them to the evolution of the incidence rate.

The only really effective action is to have those who create larval breeding areas destroy them. But little is known about the population's compliance in this regard, although it is readily said that the population is not very cooperative or motivated.
It is true that *Aedes aegypti's* effectiveness as a dengue fever vector is formidable: using models, Reiter showed that, with an immunity level of 60% of the population against the serotype being transmitted, there has to be a density of < 3 *Aedes* / person in order to avoid the emergence of a dengue fever outbreak (Reiter 1998), a goal that may seem difficult to achieve in French Polynesia's climate conditions. Only the Austral Islands have winter temperatures low enough : after a few cases in May and June, transmission halted during the cool season, and, to date, has not begun again.
This climate effect can also be found in New Caledonia where outbreaks stop during June and July. Comparison with the outbreak in Hawaii in 2001 (imported from French Polynesia) is interesting as it mainly developed in one region on the island of Maui (Hana municipal district) that has climate conditions similar to those in French Polynesia. The outbreak was more limited there as the local vector is *Aedes albopictus*, which has a rural habitat and is much less effective than *A. aegypti* in transmitting the dengue fever virus.

It is worthwhile recalling the characteristics of transmission of the outbreak between the islands :
- ⇨ The school holidays played an important role in transmitting the outbreak between the islands, showing that the movement of viremic individuals constitutes a greater risk than the transport of infected mosquitoes.
- ⇨ In each island group, the first island affected was the one where tourism activities are highest (both local and foreign visitors), i.e. Bora, Moorea and Rangiroa.
- ⇨ The rural zones experienced a more limited outbreak in terms of the number of cases and the number of severe forms than that in the urban zone, thereby confirming the fact that transmission risks are linked to population density. Geographic isolation seems to have only rarely served as a means of protection; the dengue-free islands were limited to Maupiti, Ua Huka and a few atolls in the Tuamotu Islands.

XI. Prospects

Our experience with the 2001 epidemic has made it possible to delineate the main outlines of the activities to be developed, whether this be in the framework of the Territorial Health Care Organisational Scheme or in targeting prevention activities.

Prevention
It is possible that, as in the rest of the world, future outbreaks will occur at an accelerating pace. Past experience has shown that:
- the risk of severe forms appears likely to be higher if a new serotype should spread within the next 5 years ;
- once an outbreak has begun, it becomes difficult to control.

- ⇨ The main objective must, then, be to avoid the introduction of a new serotype of this virus, something which involves:
  - on-going activities designed to reduce the number of larval breeding areas **during the period between outbreaks** with stronger involvement of municipal district governments in these actions;
  - strengthening the **outbreak warning system** (see below), particularly in those islands most visited by tourists, in order to improve the effectiveness of initial perifocal control measures.
- ⇨ Any strategy must include implementation of **vector density indicators**, which are vital for evaluating activities and motivating the people involved. In addition, surveillance for **the most common types of breeding area** should make it possible to determine the most effective messages.
- ⇨ A 'knowledge, attitudes, practices' study is vital **for assessing the impact of the messages** broadcast to the community about destroying larval breeding areas.

⇨ During a confirmed outbreak period, **strategies for spraying insecticides against adult mosquitoes** will also have to be re-evaluated in terms of cost-effectiveness.

Patient care

While the concept of severe dengue fever does not systematically involve a vital prognosis, every suspected DHF need enhanced surveillance and care. This implies appropriate solutions such as :

⇨ adapting **full hospitalisation capacities** during the outbreak itself ;

⇨ making use of the possibility of **day hospitalisation** (rehydration beds) for 'borderline' cases, as is done in cases of diarrhoea in newborns in certain hospitals in metropolitan countries.

Epidemiological surveillance

⇨ The early warning system must be strengthened by:

- an increase in the number of participants in the Febrile Syndrome Sentinel Network; however, due to the initially slow transmission of the virus, this system is likely to be slow in reacting at the beginning of the outbreak.
- encouraging doctors to write more prescriptions for **dengue fever confirmation tests** during the period between outbreaks; as serology does not allow the serotype to be identified, the use of PCR should be favoured (with funding which needs to be determined).

⇨ The system for **reporting hospitalised cases of dengue fever** proved to be particularly efficient for monitoring the epidemic. It should be maintained on an on-going basis in addition to the two surveillance systems mentioned above.

XII. References

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XIII. Appendix : Clinical Guidelines for Practitioners (2001)

Guidelines prepared in collaboration with the CHT's Intensive Care Unit, Paediatrics Ward, Neonatal Intensive Care Unit, the Malardé Institute, the Health Department (distributed in March and April 2001)

When should you suspect a case of dengue fever?

A suspected case of dengue fever is defined by the combination of, at least:

- ➔ A high fever (≥ 38°5), which began abruptly less than 10 days beforehand.
- ➔ A pain syndrome:
  - headaches (particularly retro-orbital pain).
  - arthralgia / myalgia.
- ➔ And the absence of any other major starting point for infection.

Laboratory assessment

In order to both eliminate other causes of acute fever and assess the severity of the case, it may be justifiable to request a FBC with a platelet count.

Laboratory confirmation of dengue fever:

- Outside the period of an epidemic or when the outbreak has not yet been confirmed in the patient's geographic area of origin, it is recommended that laboratory confirmation be sought for all suspected cases (dry tube blood sample).
- During an outbreak, laboratory confirmation is only useful for severe or atypical forms.

Depending on the time between the beginning of clinical symptoms and the sample date, the exam will either use serology or viral isolation techniques (PCR is reserved for patients hospitalised with severe forms).

Stage of illness	**Technique**	**Time needed for result**
between 1st and 5th day	PCR	24 hours
between 1st and 5th day	Viral isolation	1 week
after the 6th day	Serology (IgM)	24 hours

Dengue fever phases

⇨ The **incubation period** is normally 5 to 7 days.

Most patients have a **febrile phase** lasting 4 days on average (extremes : 2 to 7 days). The fever and pain syndrome may be accompanied by a generalised erythema early on or later by a maculopapular rash (normally during defervescence). Bleeding during the febrile period is a result of thrombocytopaenia but does not serve in any way as a forewarning of severe forms. The FBC frequently displays initial lymphopenia, followed by leukopenia and thrombocytopaenia (<100 000 pl/mm^3), which, at this stage, is not a sure indicator of a future severe form.

⇨ This phase is followed by a **critical period** (beginning on the 4th or 5th day of the illness) which lasts 2 to 3 days. It is during this critical period, normally afebrile, that severe forms of dengue fever may develop (so-called haemorrhagic dengue fever). These severe forms are associated with all of the symptoms below:

- ⇨ Haemorrhagic manifestations (e.g. tourniquet test *, pupura, epistaxis, gingival bleeding),
- ⇨ And thrombocytopaenia,
- ⇨ And, especially, plasma leakage due to increased vascular permeability : hypoproteinaemia, ↗ haematocrit, serous effusion (particularly abdominal which reveals itself through abdominal pain and/or persistent vomiting). It is this plasma leakage, much more than the haemorrhagic manifestations, which makes severe forms so grave.

This picture can be aggravated by shock.

** the tourniquet test consists of using a pressurised armband to maintain pressure equivalent to the patient's mean pressure (SP+DP/2)for five minutes and noting, after removal of the armband, whether or not petechial lesions have appeared.*
The test is considered positive when there are at least 10 petechiae per 2.5 cm² (1.6 x 1.6 cm) of skin surface area. Results may be negative in cases of shock.

Criteria for hospitalising dengue fever patients

Hospitalisation of patients suspected of having dengue fever is recommended when one of the following serious symptoms is observed during the critical period (i.e. beginning on the 4th day of the illness) :

⇨ The following functional symptoms:

- Neuro- psychic problems (e.g. restlessness, torpor, lethargy).
- Intense abdominal pains or significant persistent vomiting

⇨ Haemorrhagic syndrome:
- Signs of extensive visceral or cutaneous / mucous haemorrhaging.
- Severe thrombocytopaenia (≤ 50 000 pl / mm).

⇨ Symptoms of plasma leakage:
- Serous effusion (e.g. pleural, ascites).
- Hypoproteinaemia, hypoalbuminaemia.
- Haematocrit 20% higher than the normal level for age group.

⇨ Shock syndrome (e.g. thready pulse, narrowed pulse pressure, hypotension, peripherial cyanosis, oliguria)

Dengue fever treatment principles

- Classical form
- Avoid : aspirin, ibuprofen (e.g. Advil®) and any type of anti-inflammatory .
- Strict bed rest.
- Individual protection from mosquitoes, destruction of larval breeding areas around the patient's house.
- Inform patient of the 'critical period' and serious symptoms which should lead to an immediate visit to the doctor / hospital.

- These severe forms require rapid hospital care. Before transfer to the hospital:
  ⇨ Fluid replacement therapy, on the advice of a doctor, must be started early by rapidly administering 20 cc / kg of macromolecular solution (Plasmion®) while awaiting arrival at the hospital. Otherwise, saline intervention fluid (NaCl 9 g / l) may be administered. Hypo-osmolar solutions (Ringer lactate) must be avoided as they may aggravate cerebral distress.
  ⇨ Carefully monitor the patient to avoid over-hydration.