Dengue surveillance in the Pacific Islands

ROB CONDON*
GEORGE TALEO**
TONY STEWART***
TONY SWEENEY****
TOM KIEDRZYNSKI*****

Abstract

Adequate monitoring of dengue activity can be achieved using a combination of mosquito vector surveillance, fever surveillance, sentinel clinicians and laboratory screening. An apparent increase in fever cases or clinically suspected DF should prompt a careful clinical and laboratory investigation. If an outbreak of dengue is confirmed, health authorities will need to implement emergency community-wide control strategies. Laboratories will quickly feel the burden of clinical monitoring of cases admitted with DHF/DSS. Surveillance can change to clinical case definitions as health workers become familiar with the presenting features of DF and DHF/DSS. Criteria for hospital referral and admission must be well understood. Routine laboratory and sentinel surveillance may resume as the epidemic wanes, and should then continue indefinitely to monitor any resurgence of dengue activity.

Introduction[1,2,3,4,8]

Globally, Dengue fever (DF) is one of the most important emerging infectious diseases. At least 20 million cases of dengue occur throughout the world each year, with an estimated 25,000 deaths. Approximately 3,000 million individuals are at risk of infection. There are four different serotypes of dengue virus (DEN-1, DEN-2, DEN-3 and DEN-4). Infection with one serotype confers life-long immunity against reinfection with that serotype, but only temporary and partial immunity against other serotypes. Secondary infection with another serotype carries a higher risk of dengue haemorrhagic fever / dengue shock syndrome, a more severe form of the disease.

This more severe form of the disease, known as dengue haemorrhagic fever / dengue shock syndrome (DHF/DSS), first appeared in the Philippines in 1953 and has since spread in association with DF.

In the Pacific, dengue was endemic in New Caledonia and, in recent years, has been responsible for epidemics in French Polynesia, Fiji, Queensland (Australia), Samoa, the Cook Islands, Vanuatu, Tonga, Kiribati, Federated States of Micronesia, Wallis and Futuna.

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The virus is transmitted by the bite of an infected female *Aedes* mosquito. In most regions of the world, including the Pacific, the most important mosquito vector is *Aedes aegypti*. This highly domesticated urban mosquito lives in close association with human populations, often indoors, and bites during the daytime. Water trapped in domestic containers (drums, trays, flower vases and bases, blocked guttering) and rubbish (tyres, tin cans, old car bodies) provides an ideal breeding site for *Aedes* larvae.

Clinical features [1,4]

Dengue infections may be asymptomatic, or may cause undifferentiated fever, classical DF, or DHF/DSS.

After an incubation period ranging from 3–14 days, classical DF begins with a high fever, severe headache and a flushed or mottled rash. Within 24 hours, retro-orbital pain, anorexia, nausea and vomiting, backache, myalgia and joint pains occur. Pain may be severe, giving rise to

*Visiting Public Health Consultant. **Coordinator, Department of Health, Vanuatu. ***Team Leader, Medical Epidemiologist, Pacific Regional Vector Borne Diseases project. ****Dr Tony Sweeney, Medical Entomologist, Pacific Regional Vector Borne Diseases project. *****Dr Tom Kiedrzynski, Notifiable Disease Specialist, SPC.

the colloquial term for this disease: "Breakbone Fever". Convalescence is usually short, but may occasionally be prolonged with weakness and depression.

If the illness takes the form of DHF/DSS, two additional pathophysiological mechanisms occur:

- increased permeability of blood vessels, resulting in plasma leakage into the tissues and leading clinically to hypovolaemia and shock;
- a haemorrhagic state, due to increased capillary fragility, low platelet count and disordered coagulation.

DHF/DSS begins abruptly and, in its early stages, resembles classical DF. The critical stage is reached when fever subsides, usually at day 5-7 but sometimes as early as day 3. The patient quickly becomes shocked with sweating, restlessness, pallor and coolness of the extremities. Without treatment, sudden collapse occurs and death may follow within 24 hours.

Active surveillance involves more care being taken to seek out cases of the disease, often with the help of key clinical staff and laboratories (e.g. the search of acute paralysis cases to survey poliomyelitis).

Haemorrhagic manifestations are often also present in DHF/DSS, and range from a fine petechial rash to copious, constant bleeding from diverse sites around the body. With early diagnosis and vigorous treatment, most patients with DHF/DSS will recover.

Confirmation of dengue diagnosis

1,5,6,7

Definitive diagnosis can only be made using specific laboratory tests. Serological laboratory tests can be difficult to interpret, due to the relatively slow rise in antibody titre in flavivirus infections and the presence of cross-reacting antibodies. During an epidemic, however, after the initial laboratory confirmation, it is possible to make a presumptive diagnosis on clinical and epidemiological grounds, without the need for laboratory confirmation.

The definitive laboratory tests for dengue confirmation are virus culture and isolation, and properly done PCR (*polymerase chain reaction*)–as well as viral antigen detection in fixed tissues (dead patient). Virus culture and isolation can be used within the first 5-6 days after the onset of fever, with a decreasing sensitivity over time. PCR is now more frequently used in routine by some laboratories. It requires proper protocols and precautions in order to avoid false positives due to contamination. PCR can detect dengue viral RNA at any stage of the disease, even during the convalescence phase.

The most commonly used serological tests are ELISA (*enzyme-linked immunosorbent assay*) and IHA (*indirect hemagglutination*). Although they are less specific, these tests are much easier and cheaper to perform. Their sensitivity increases as the sensitivity of virus culture and isolation decreases. Two successive samples are needed to confirm a case. If a high titre of antibodies is detected in one sample, it can be enough for a suspected case to become presumptive.

A rapid immunochromatographic screening test (*Dengue Fever RAPID*; PanBio Pty Ltd, Brisbane, Australia) has been introduced a couple of years ago to laboratories in the western Pacific. This is a "card" test which detects both IgM and IgG simultaneously, using a single application of serum. Cut-off points are set so that any positive result suggests acute or recent dengue infection. PanBio Pty Ltd quotes a specificity of 93% for their rapid test, which means there is a 7% false positive rate. This limits its clinical usefulness as a diagnostic test in individual patients. However, it is still specific enough to be a very useful surveillance tool in dengue-prone populations.

Types of surveillance

Government regulations in most countries require health workers to report cases of certain important and serious communicable diseases to the health authorities. This type of surveillance is called **passive surveillance**; although it often misses a proportion of cases, it is still very useful in monitoring overall trends in disease incidence. Examples of diseases subject to passive surveillance include malaria, sexually transmitted diseases, tuberculosis and cholera.

To gain a more accurate impression of the number of cases of a disease occurring in the community, another type of surveillance, called **active surveillance**, may be used. Active surveillance involves more care being taken to seek out cases of the disease, often with the help of key clinical staff and laboratories (e.g. the search of acute paralysis cases to survey poliomyelitis).

A special type of active surveillance, called **sentinel surveillance**, is based on reports from a small number of specially trained and motivated practitioners working in key positions. Sentinel surveillance provides less complete information about the total incidence of disease in the community. It can, however, provide early warning of the arrival of a rare or serious disease in key or high-risk locations.

Figure 1. The outpatient screening criteria fFor clinically suspected dengue fever in an adult

Sustained fever (eg >38°C) for >2 days
plus any TWO of the following clinical pointers:

- bone or joint pain
- severe headache or retro-orbital pain
- persistent vomiting
- rash (maculopapular or petechial) or flushing
- spontaneous bleeding (includes epistaxis, bleeding gums, haematemesis, melaena, fresh blood in stools, menorrhagia, purpuric rash or a positive tourniquet test)
- low blood pressure (<100/60) or reduced pulse pressure (<20 mm Hg)
- dizziness

or

- unexplained death (with or without haemorrhage) within 1 week of onset of a febrile illness

Whatever form of surveillance is used, it should be designed to integrate with surveillance of other diseases with similar clinical symptoms (e.g. surveillance of measles, influenza, Fever of Unknown Origin).

Dengue surveillance for Pacific Island nations

Our dengue surveillance systems should help us to:

- monitor the performance of environmental management programmes;
- provide early warning of the arrival or resurgence of dengue in a country or community;
- monitor the total number of cases, when they occur, and where, thereby guiding the activities of vector control teams and health educators;
- monitor the severity of disease in each case (classical DF or DHF/DSS);
- monitor the adequacy of patient management; and
- define the serotypes of dengue virus which are circulating in the country.

We can use our knowledge of the natural history of dengue infection, and experience from previous outbreaks, to guide our surveillance activities. We need good vector surveillance, combined with astute clinical surveillance for cases of DF and DHF/DSS.

In most cases, the arrival of dengue will be noticed first in periurban communities with poor environmental hygiene, ie areas with conditions conducive to the breeding of *Aedes* mosquitoes. Areas where sporadic cases of dengue already occur should be monitored very closely. In countries with no current dengue activity, the risk will be greatest in international sea- and airports with connections to dengue-endemic regions.

We will now look at mosquito vector surveillance, and three types of clinical surveillance for dengue:

1. Fever surveillance.
2. Sentinel clinicians.
3. Active laboratory surveillance.

Mosquito vector surveillance

In order to monitor the risk of outbreaks it is important to survey mosquito populations in places likely to be affected. This involves collection of larvae and adults inside houses and in the immediate vicinity outside houses in urban localities. It is important that representative samples are collected so that the data are meaningful and can be associated with changes in mosquito density.

Standard methods for larval surveys have been developed for this purpose in which the numbers of containers positive for *Aedes* mosquito larvae are related to the total number of containers and the total number of premises surveyed. Surveys of adult mosquitoes are more difficult to carry out as the efficiency of this method will vary according to the abundance of mosquitoes present at the time of the survey as well as the skill of the collectors. Nevertheless, information collected on adult mosquitoes is important and directly relevant to the risk of epidemics.

As a general rule vector surveys should be carried out at monthly intervals. It is particularly important that vector monitoring activities should be increased at the onset of the wet season to give early warning of increases in mosquito numbers. Such indications should alert the authorities to implement vector control and source reduction activities to minimise the risk of dengue transmission should the virus be introduced into the community.

Fever surveillance

The first indication of an outbreak of dengue in a community will often be an increase in the number of patients presenting with a febrile illness to local health facilities.

In countries where malaria is prevalent, primary health care protocols generally require all patients with a fever

Figure 2. Screening criteria for hospital admission for suspected severe dengue

Admit anyone with Dengue Haemorrhagic Fever / Dengue Shock Syndrome or any one of the Danger Signs.

Dengue Haemorrhagic Fever (DHF/DSS)

- **Fever** >38°C lasting at least 2 days
  plus
- **Bleeding**
  or
- **Platelet count <100,000/ml**
  or
- **Plasma leakage** - at least ONE of haematocrit >50% *OR* pleural effusion and/or ascites and/or hypoproteinaemia

Important: Look out for **Dengue Shock Syndrome = DHF + signs of circulatory failure**
(rapid, weak pulse, systolic BP<90 in adults or <80 in children, cold, clammy skin, restlessness). **This needs more aggressive fluid therapy**.

to have a blood slide examined for malaria parasites. An outbreak of non-malaria febrile illness will therefore result in an overall increase in the number of malaria-slide requests, coupled with an increase in malaria-slide negativity rates. These figures can be easily monitored in most laboratories.

An increase in the number of non-malaria fever cases in an at-risk community should trigger a prompt clinical and laboratory investigation to determine the cause of the outbreak. Dengue and other febrile illnesses of major public health importance, like influenza and measles, must be excluded.

In non-malarious countries, fever surveillance is a little more difficult as there are generally no routine tests or data collections to reflect the number of patients presenting with fever. Because of the 35% overlap in symptoms between dengue and measles, an apparent increase in measles notifications needs a careful confirmation of the presumed diagnosis, and exclusion of dengue. An increase in hospital admissions for fever of unknown origin (FUO) may highlight the beginning of a dengue outbreak, but this method is unlikely to be timely enough to allow quick recognition of the problem and the commencement of necessary control activities.

Sentinel clinicians in health facilities in at-risk locations can be asked to document the number of cases of fever they see each week. This technique of fever surveillance can be as simple as placing a tick mark for each case of fever on a list of names of communities/villages served by health facility, with simple stratification by age (eg child/adolescent/adult). Weekly totals will help staff to confirm a clinically suspected outbreak of febrile illness, and determine the main communities and predominant age groups affected.[8]

Outpatient surveillance by sentinel clinicians

In the urban tropics, a low level of dengue virus activity may be maintained in a silent transmission cycle; asymptomatic cases go unrecognised, while symptomatic cases may experience only a non-specific viral illness.

The sentinel clinician network relies on a small group of experienced primary health care providers (doctors, nurse practitioners) working in selected high-risk locations. Their aim is to detect cases of non-specific viral syndrome with features suggestive of classical DF and arrange for dengue serology or a rapid screening test.

It is helpful if sentinel clinicians have a set of well-defined clinical guidelines to ensure consistency in their referrals for testing. The guidelines need to be sensitive enough to detect cases presenting as mild viral syndrome, but specific enough not to over-burden the laboratory service. In some situations, staff may be taught to perform rapid dengue screening tests in the outpatient department or clinic.

An example of screening criteria for clinically suspected dengue in adults is shown in Figure 1. Symptoms in children are often more variable and less specific making accurate clinical diagnosis difficult. In addition to the case definition in Figure 1, cases with symptoms of shock or dehydration must be admitted and a diagnosis of DHF/DSS considered. Figure 2 shows the criteria for hospital admission for suspected severe dengue (DHF and DSS). Early detection of severe cases, and appropriate case management is a priority during a dengue outbreak.

Sentinel clinicians on hospital wards

One case of DHF/DSS occurs for every 100 to 200 cases of classical DF. Hospital clinicians can assist surveillance efforts by monitoring inpatient admissions in identified risk centres. Their aim is to detect severe

disease, suspicious of DHF/DSS which, because of severity, atypical presentation or arrival of the patient during the night, may have by-passed the outpatient surveillance system.

They will ensure that any of the following categories of patient have dengue serology in addition to other relevant indicative tests:

- admission diagnosis of viral encephalitis, aseptic meningitis or meningococcal septicaemia
- fever with petechiae and/or haemorrhagic manifestations
- fever of 2–7 days' duration, and not responding to treatment for the presumed cause of the fever
- fever, with deterioration in overall condition when temperature falls, especially if peripheral perfusion is poor
- presumed measles, influenza or rubella, but with an atypical presentation
- an unexplained death (with or without haemorrhage) within 1 week of onset of a febrile illness

Diagnosis must rely more on clinical judgement and less on laboratory confirmation.

Active laboratory surveillance

The aim of active laboratory surveillance is to monitor dengue serology in specimens from patients who live in identified dengue risk areas and who present with undifferentiated fever.

In countries where malaria is prevalent, laboratories should regularly screen a sample of malaria-negative fever patients for dengue using a rapid screening test. The actual sampling method will depend on the number of patients coming through the health facility and the resources available in the laboratory. At times when workloads are low, dengue screening may be done on all malaria-negative patients; at busier times, screening may only be necessary on a proportion of malaria-negative cases (eg every 5th specimen, or all specimens on a given day each week).

In countries without malaria, physicians and laboratories in dengue risk areas should ensure that the diagnostic work-up for FUO includes dengue serology (or at least a rapid screening test).

The regional reference laboratory should confirm any positive results and attempt to identify the specific serotype of dengue virus.

Modified surveillance in the event of an outbreak

If an outbreak becomes established, clinicians will quickly become familiar with the symptoms and signs of dengue. Refresher training at the first sign of resurgence of dengue activity will enhance their effectiveness.

During an outbreak, laboratory services can quickly become swamped. Diagnosis must rely more on clinical judgement and less on laboratory confirmation. Health authorities may formally advise a change-over from laboratory to clinical case definitions for surveillance.

At the same time, criteria for hospital admission and guidelines for outpatient management must be available to clinical staff. Classical DF can be managed symptomatically at home and the patient advised to return if signs of progression to DHF/DSS occur. All patients with suspected DHF/DSS (ie those with an elevated haematocrit, circulatory insufficiency or signs of bleeding) should be admitted to hospital. Patients with less severe illness, but who live far away and have nowhere local to stay, may also be admitted for observation.

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