Changing Epidemiology of Dengue Haemorrhagic Fever in Indonesia

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Abstract

Dengue fever (DF)/dengue haemorrhagic fever (DHF) is a growing public health problem in the subtropics. Dengue was first reported in Indonesia in 1968 and since then the number of reports in the literature and the number of dengue virus (DENV)-infected cases reported by the Indonesian health authorities have increased. This review addresses the changing epidemiology of dengue in Indonesia by means of a chronological overview. Over time, the morbidity and mortality of dengue disease have increased and DHF epidemics occur throughout all the 29 provinces. The outbreak trend of DHF in the country has become irregular, with a high inter-epidemic background. All dengue serotypes are circulating, although severe disease is predominantly attributed to DENV-3. The case-fatality rate is dropping over time, probably reflecting increased awareness and improved treatment protocols. An increasing percentage of adolescents and adults develop DHF relatively earlier in the course of the disease, compared with the days when DHF was considered a primarily paediatric illness. Many inter-related factors such as environmental, biological and demographic issues influence dengue epidemiology and transmission.

Keywords: Dengue, dengue virus, outbreak, epidemiology, Indonesia.

Introduction

Dengue fever (DF)/dengue haemorrhagic fever (DHF) is a growing public health problem in the subtropics. In South-East Asia, with a total population of 1.5 billion, approximately 1.3 billion people live at risk of acquiring DF or DHF. Currently, DHF is the leading cause of hospital admissions and death among children in this region. Major dengue epidemics date back to the late 17th century. However, the start of epidemics of severe dengue began in the South-East Asia region following World War II, when conditions for mosquito-borne diseases were favourable. DENV infections during these latter epidemics were accompanied by severe haemorrhage, shock and vascular leakage. The first recorded DHF epidemic occurred in Manila, the Philippines, in 1953. Thereafter the epidemic spread quickly throughout South-East Asia and further west via India, Sri Lanka, Maldives and Pakistan, and in the east to China. Many factors are thought to be responsible for the global re-emergence of DF and DHF. These include major global demographic changes and worsening of health care systems and mosquito control programmes.
Indonesia is the largest country in the region with a population of 245 million. Almost sixty per cent of the people live on the island of Java, which is most severely afflicted by periodic outbreaks of dengue disease. However, the disease is endemic in many large cities and small towns throughout the country and has also spread to certain smaller villages, where population movement and density are high. Epidemic DF has been reported in all 27 Indonesian provinces, whereas in 1968 only two provinces had reported dengue cases. This article addresses the epidemiology of dengue in Indonesia by means of a chronological overview.

Methods

Literature search and data sources

A systematic review was performed to identify eligible articles. The MEDLINE database from 1966 through 2005 was searched by two reviewers (JFPW and MDK). This was done, by combining the Medical Subject Headings (MeSH terms) and text words dengue, dengue virus, outbreak, epidemiology and Indonesia. In addition, the Indonesian Ministry of Health, WHO and experts in the field were contacted for data on epidemics occurring from 1966 through 2005. This exercise was undertaken by two different reviewers (TES and AS).

Study selection and data extraction

All identified epidemiological studies were selected. The inclusion was restricted to studies in which primary data describing morbidity or mortality could be extracted. The selection of studies and data extraction were independently performed by two of the authors (ATAM and JFPW). Any disagreement was resolved by discussion and if necessary by adjudication of a third reviewer (ECMG). A formal meta-analysis was not deemed appropriate, because the selected studies were highly heterogeneous in terms of selection and numbers of cases, classification of cases, and description of data.

Results

The computer search yielded 116 references. Forty-four articles were excluded after we had read the title and the abstract that did not address the topic under investigation (a list of these excluded articles is available with the authors). For the remaining 72 potentially relevant references, we read the full report to decide whether to select the study for this review. Several articles reported on the same study and results; therefore, in order to avoid inclusion of duplicate reports, the most detailed version of each was selected. Some articles reported on the same study, although different results were presented. All these papers were therefore included. One study investigated the total incidence rates in Indonesia from 1968 to 1985, and these data were combined with the data derived from WHO and the Ministry of Health.

The Table summarizes some of the characteristics of the selected studies, with clinical outcome and data on virology if available. The majority of the studies describe the results of outbreaks with an in-depth survey of a selected group of patients. The number of cases enrolled ranged from 72 to more than 2000.

Epidemiological overview

The first cases of DENV infection in Indonesia were reported in 1968 in the cities of Jakarta (West Java) and Surabaya (East Java). These
### Table: Characteristics of selected studies

<table>
<thead>
<tr>
<th>Year and location of study</th>
<th>Study population</th>
<th>Clinical outcome</th>
<th>Mortality</th>
<th>Virus serotypes</th>
<th>Ref</th>
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</thead>
<tbody>
<tr>
<td>1968–1970, Jakarta</td>
<td>A total of 96 cases with fever of unknown origin were studied. Of these, 56 had a confirmed or presumptive diagnosis of dengue</td>
<td>Patients were not classified</td>
<td>16 patients died (17%)</td>
<td>–</td>
<td>[9]</td>
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<tr>
<td>1969–1970, Bandung</td>
<td>Out of 268 cases with acute fever, 65 proved to have a dengue virus infection</td>
<td>Six patients had haemorrhagic manifestations (9.2%). There were no patients with circulatory failure</td>
<td>There were no deaths</td>
<td>No virus could be typed</td>
<td>[12]</td>
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<td>1973–1974, Jakarta</td>
<td>Of 104 suspected dengue, 81 patients were included</td>
<td>There were 32 cases with DSS (39.5%)</td>
<td>Eight patients died (10%)</td>
<td>Virus could be isolated in only 5 patients (one DENV-1, one DENV-2, two DENV-3, and one DENV-4)</td>
<td>[28]</td>
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<td>1974, Manado</td>
<td>A total of 195 patients were included, of whom 131 were confirmed</td>
<td>There were 125 DHF cases and 70 DSS cases (only 6 out of 8 DSS cases tested were confirmed to have dengue)</td>
<td>There were 37 deaths among 70 DSS patients</td>
<td>Most patients were infected with serotype 1</td>
<td>[14]</td>
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<tr>
<td>1975–1983, Jakarta</td>
<td>1451 serologically confirmed cases were studied. In 142 cases, a virus could be isolated</td>
<td>–</td>
<td>34 fatal cases were reported. Unknown if these were all fatal cases</td>
<td>All four serotypes were circulating, although DENV-3 predominated (22 DENV-1, 50 DENV-2, 67 DENV-3 and 3 DENV-4)</td>
<td>[18]</td>
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<td>1976–1977, Bantul</td>
<td>A total of 1260 clinically diagnosed cases were reported to the Indonesian Health Authority. Only 126 were studied in detail, of which 69 had confirmed dengue and 28 had a presumptive diagnosis of dengue</td>
<td>Of 45 virologically confirmed cases 18 had DF (40%), 8 had DHF II (18%), 16 had DHF III (36%) and 3 had DHF IV (7%)</td>
<td>32 deaths among 1260 clinically diagnosed cases (2.5%)</td>
<td>Virus could be isolated in 45 of the 69 confirmed dengue cases (65%): 18% DENV-1, 60% DENV-3 and 22% DENV-4</td>
<td>[15,16]</td>
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<td>1978, Sleman</td>
<td>A total of 114 patients with a clinical diagnosis of dengue were included. Of 68 patients from whom blood samples were available, 35 had confirmed dengue and 19 had a presumptive diagnosis of dengue</td>
<td>Of 39 cases from whom adequate clinical information was available, only 5 (13%) had overt haemorrhagic manifestations. Two patients (5%) suffered from dengue shock syndrome</td>
<td>–</td>
<td>Eight out of 25 cases tested positive for DENV-3</td>
<td>[17]</td>
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<td>1991–1993, Bandung</td>
<td>A total of 306 clinically diagnosed dengue patients were studied. Of these patients, 128 were confirmed dengue cases</td>
<td>Of the confirmed cases, 33 developed shock (19%).</td>
<td>There were 4 deaths among the confirmed cases</td>
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<td>[37]</td>
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<td>1988, Jakarta</td>
<td>98 cases clinically diagnosed of having DHF were included</td>
<td>Six patients were classified as DHF I (6%), 44 patients as DHF II (45%), 32 as DHF III (33%) and 16 as DHF IV (16%)</td>
<td>–</td>
<td>Virus could be isolated in 17 of the 98 cases (17%)</td>
<td>[38]</td>
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<td>1993–1994, Jayapura</td>
<td>A total of 72 patients with fever of unknown origin were included. Forty-four patients had a clinical diagnosis of dengue, 20 were laboratory confirmed</td>
<td>Of the patients with a clinical diagnosis of dengue, 8 were classified as DF, 9 as DHF I, 23 as DHF II, and 4 were classified as DHF IV</td>
<td>–</td>
<td>Virus could be isolated from 9 patients: 2 DENV-1, 1 DENV-2 and 6 DENV-3</td>
<td>[7]</td>
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<td>1995, Yogyakarta</td>
<td>A total of 1837 patients were followed up over time. At inclusion 1032 patients (56%) proved to have had a dengue infection in the past</td>
<td>During follow-up 96 patients were diagnosed with fever of unknown origin. Eleven of these patients had serologically or virologically confirmed dengue. Six patients were classified as DHF (1 DHF I, 2 DHF II, 2 DHF III and 1 DHF IV)</td>
<td>–</td>
<td>All four serotypes were isolated from 11 confirmed acute dengue cases (1 DENV-1, 1 DENV-2, 4 DENV-3 and 1 DENV-4).</td>
<td>[19]</td>
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</table>
reports were followed by reports from Bandung (West Java) and Yogyakarta (Central Java).\textsuperscript{11,12} Since then, suspected dengue cases were recorded by the Ministry of Health. Initially, the reported incidence rates were recorded in Java only and these were relatively low.\textsuperscript{6,8-10} In the early 1980s, these rates increased from 10,000 to 30,000 each year,
and since the last 10 years, the reported incidence rates have further increased to approximately 30,000 to 60,000 cases each year. Significant peaks were reported in 1973 and 1988, but during 1998 and 2004, a record number of 72,133 and 78,690 cases were documented (Figure 1).[13] Today, dengue has spread over all 29 Indonesian provinces (Figure 2A), with an inter-epidemic background between 10,000 and 25,000 cases annually.

The first large recorded outbreak occurred in 1973 (Figure 1). A total of 10,189 cases was reported, of which 6,225 cases were diagnosed in Semarang, the capital of central Java.[6] No specific data were reported about the severity of the disease. In the next year, another outbreak was reported outside the island of Java, in Manado, North Sulawesi.[14]

An epidemic of DHF characterized by severe disease and high viraemia occurred in Bantul, a rural area in Central Java, during the latter part of 1976 and early 1977.[15,16] If all shock cases were considered, no relationship between dengue serotype and disease severity were found; however, all three fatal cases were associated with DENV-3. A year later, a DENV-3 outbreak occurred in Sleman, 40 km north of Bantul, characterized by mild disease.[17] The age distribution was similar to that of the Bantul outbreak; however, less severe cases were reported in this outbreak (DSS cases: Bantul 37% vs. Sleman 13%).

From 1975 to 1983, a total of 1,451 serologically-confirmed (haemagglutination inhibition test) DHF patients from Jakarta were followed during their hospital stay.[18] Of these

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**Figure 1: DHF morbidity and mortality in Indonesia from 1968-2005**

The solid line represents the total number of DHF cases officially reported during the years 1968–2005. The dashed line represents the total number of deaths from DHF per year during the years 1968 till 2005.
(Source: WHO, Sumarmo 1987)
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Figure 2: The incidence rate and case-fatality rate of DHF in Indonesia in 2005

This figure shows: (A) the number of DHF cases among 100,000 civilians [the incidence rate (IR)] throughout the 29 Indonesian provinces in 2005 and (B) the percentage of deaths among reported DHF cases [case-fatality rate (CFR)] throughout the 29 Indonesian provinces in 2005.
(Source: Ministry of Health, Indonesia, 2006)

cases, 142 were virologically confirmed. Fatal disease occurred in 34 virologically-confirmed infections; in 75 cases shock was present (77% of fatal cases). DENV-3 was most frequently associated with severe and fatal infections.

A five-month-long outbreak emerged in September 1993 through February 1994 in the city of Jayapura, the provincial capital of Papua, easternmost Indonesia. Although the first case of DHF was reported in 1979, the disease had
shown transient disappearance from this region. A total of 217 cases were reported and 72 suspected DHF cases were enrolled during an outbreak investigation. The majority (68.7%) of the included individuals did not have significant levels of specific IgM at the time of their admission, 11.4% had a primary infection, 17.1% a secondary infection, and the remaining cases had an indeterminate test result. Nine cultures became positive from 63 whole-blood and 68 serum samples inoculated in mosquitoes.

A prospective study initiated in 1995 showed that the incidence for one or more dengue infections among a cohort of 4–9-year-old children in Yogyakarta was 29.2% in the first year of the study. An average of 56.2% had antibodies against one or more virus types at the start of the study; of these, 34.3% had serological evidence of prior exposure to a single serotype. Among children without the serological evidence of prior exposure, 26.8% (216 of 805) sero-converted. Six of the 1837 included children were hospitalized during the follow-up; all of them appeared to have a secondary or tertiary dengue infection.

During the period November 1997 till May 1998, again, DHF outbreaks were reported throughout the Indonesian archipelago. Eleven provinces were involved, and all the outbreaks occurred in urban areas. The outbreak started during November 1997 in Jambi, South Sumatra, and Lampung (western part of Indonesia). From here the outbreak spread involving all provinces in Sulawesi and the provinces of West Nusatenggara and East Timor, continuing towards Ambon, the capital of Maluku province, and finally it arrived in Jakarta in March 1998. The average attack rate was 1.2 per 1000 population whereas the highest attack rate occurred in Palembang, a city in South Sumatra (1.6 per 1000 population).

The trend analysis of the 1998 Palembang outbreak demonstrated a 3-fold increase of dengue cases between January and April, compared to historical records. A changing trend in epidemic transmission was observed, going from a 5-year cyclic occurrence to an annual phenomenon. Concerning age distribution it has to be noted that a relatively large proportion of adolescents and young adults were infected.

In April 2001, a second outbreak occurred in Papua. In Merauke, a town located in the south-eastern corner of the province, a retrospective case control study was performed. Fifteen acute cases, 37 convalescing subjects and 32 comparable controls were enrolled. Dengue virus IgM antibodies were detected in 27% of the acute clinical cases, 30% in the convalescing cases and in only 3% of the controls. DENV-3 was the only dengue virus serotype detected by RT-PCR, all in the acute samples. By reviewing hospital records, a total number of 172 suspected cases were identified. The estimated CFR among all suspected dengue cases was 1.2%.

To study the natural history of DENV infection in West Jakarta, 785 volunteers were included using a cluster investigation method in the period from October 2001 to October 2003. All subjects were family members or neighbours of 53 index cases, which had previously been hospitalized. At enrolment, 11 subjects were viraemic (3 cases DENV-1, 8 cases DENV-2). In 5 of these cases the virus could be isolated. Seventeen new infections (2.2%) were identified post-enrolment. Ten were positive by the RT-PCR (1 case DENV-1, 7 DENV-2, 1 DENV-3 and 1 DENV-4). In 5 cases the serotype was confirmed by culture.
Nine post enrolment subjects were symptomatic, of which one case progressed to DHF. The calculated incidence rate of dengue infection was 567 cases per 1000 persons-years of follow-up, and the calculated DHF incidence rate was 33 DHF cases per 1000 persons-years of follow-up.

In 2004, another outbreak began to spread throughout Indonesia, with Jakarta being the most affected area. According to WHO, 78,690 cases and over 900 deaths were reported in Indonesia that year. Ten hospitals, all located in Jakarta, included a cohort of 272 hospitalized patients to confirm the disease etiology. Dengue infection was determined in 66.2% of all cases, 55.6%, 17.2% and 27.2% had DF, DF with haemorrhagic manifestations, and DHF respectively. Of the confirmed DHF cases, 82.5% had evidence of a secondary infection. Viral isolation was attempted on 28 acute sera from the serologically positive individuals and identified all four serotypes. There was a greater extent of infections among those aged 15 years and older.

**Virology**

In the 1960s, the clinical diagnosis of DHF was based on the existence of fever of unknown origin accompanied by a haemorrhagic tendency with or without symptoms of shock. This diagnosis could be supported by a positive haemagglutination inhibition test. No virus isolations were made at that time. The first isolations of dengue virus took place during the 1970s in Jakarta, Medan (North Sumatra) and Semarang. Limited data suggest that DENV-2 was the predominant virus in that time, and indeed DENV-2 was isolated most frequently from the Semarang epidemic in 1973. The 1974 Manado outbreak showed that, of the 125 serological identifications of the etiological agent, DENV-1 was the predominant virus in both non-shock and shock cases. Virological surveillance using the mosquito inoculation technique was performed during the period 1975–1979 in eight Indonesian cities. A total of 297 cases were isolated and all four serotypes were found, of which DENV-3 was dominant. In early 1976, DENV-3 was increasingly associated with fatal cases of DHF in Jakarta. Epidemics of DHF associated with DENV-3 continued occur in 1977 in Java and West Kalimantan. It was suggested that the virulence of DENV-3 had changed. During the Bantul epidemic in late-1976, virus isolation was attempted from 69 patients who had 4-fold or greater rise in HI-antibody between acute and convalescent sera. Ninety-five isolations succeeded (65%) and 3 serotypes were found: DENV-3 (60%), DENV-4 (22.2%) and DENV-1 (17.8%). From all patients classified as having a primary infection, virus was isolated (100%), in secondary infection this number decreased to 57%. An approximately 5-fold higher viraemia was found in secondary infections compared to primary infections. Virus titres were comparable between the DENV-1, 3 and 4 isolates. Data from the Sleman epidemic early-1978 showed that DENV-3 could be isolated eight times from 25 acute samples (32%); no other serotypes were found. Acute samples were defined as described above. The isolation rate in primary infections was 45%, in secondary infections 23%. Overall viraemia in Sleman patients was lower, compared to those from Bantul (Bantul 67% DENV-3 titres ≥ 10^6 MID₅₀ per ml, Sleman 37% DENV-3 titres ≥ 10^6 MID₅₀ per ml).

Between 1980 and 1983, a total of 164 isolations, using the mosquito inoculation technique, were reported from eight Indonesian cities (Medan, Ujung Pandang, Palembang, Jakarta, Yogyakarta, Surabaya, Pontianak, Manado). DENV-2 (n = 57) and DENV-3 (n = 73) were predominant. Similar findings were noticed during the period 1984–1985. Of the 51 virus isolations, DENV-4 was not found and DENV-3 (n = 24) was
predominant.[6] From 1985 till 1986, 36 successful isolates were made out of 377 serum samples. Serotypes were distributed as follows: DENV-2 (18), DENV-3 (12), DENV-1 (4) and DENV-4 two isolates.

From the 1995-1996 Yogyakarta prospective cohort study, all serotypes were prevalent at the start of the study.[19] DENV-2 slightly predominated and was also most frequently transmitted (among all 4 serotypes) during the first year of the study. Of the children seen in the hospital because of fever, 11 out of 107 had serological or virological evidence of a recent dengue infection. DENV-3 accounted for most of the cases. Of the 6 hospitalized children (DHF=3, DSS=3) the infection sequence was recognized in 5 patients: DENV-2 DENV-1 (n=3), DENV-2 DENV-4 (n=1), DENV-1 DENV-3 (n=1). Of all seroconversions to a second dengue infection, the sequence DENV-2 DENV-1 and DENV-1 DENV-2 were predominant.

During the prospective Bandung cohort study, all four serotypes were detected, with DENV-2 predominating. Three of the four DHF cases were due to DENV-3 virus. The DSS case was recognized as a secondary infection of the sequence DENV-2 DENV-1.

During the outbreak investigation of Suwandono et al., from 28 acute sera dengue serotype was confirmed by either RT-PCR or culture.[5] DENV-3 was found in most cases (n=18; 64.3%) followed by DENV-4 (n=4; 14.3%), DENV-2 (n=4; 14.3%) and DENV-1 (n=2; 7.1%). The DENV-3 isolates showed similarities to previous viruses isolated in Indonesia during an outbreak in 1998.

Morbidity and case-fatality rates (CFR)

During the first year of recognition, a total of 58 cases (including 24 deaths) were recorded.[6] In 1970, a total of 34 dengue cases were identified among 48 suspected paediatric patients in Yogyakarta.[11] Subsequently, eight were classified as DHF and two cases progressed to dengue shock syndrome (DSS).

The Indonesian health care authorities reported a dengue morbidity rate of 15.28 per 100 000 persons, 30 per 100 000 persons and 13.7 per 100 000 persons in the years 1997, 2004 and 2005 respectively (unpublished data, Ministry of Health).

In the last decade, dengue disease has caused more than 400 deaths every year in the country, and in 1998, this number went to up to 1414 (Figure 1). When appropriate supportive therapy is given, the CFR in Asian countries remains approximately between 0.5% and 3.5%.[31] In Indonesia, the CFR has steadily declined over time from 41% in 1968[10] to less than 2% since 2000, and the lowest rate of 1.21% in 2004 (Figure 3).[32] In 2005, the mean CFR was 1.34%, but this number varies between different provinces (Figure 2B).

Conclusion

Epidemics of DF and DHF have become an important public health problem throughout the Indonesian archipelago since it was first recognized in 1968. The epidemiology of DHF in the country is changing alarmingly given the increasing number of infections reported from all provinces. The outbreak trends of dengue, in general characterized as a cyclic pattern, have become somewhat irregular, with a high endemic background. A higher percentage of adolescents and adults seem to develop DHF.[5] The median age of DHF patients from Jakarta was 4 years and 11 months during the period 1979–1984.[6] Recent data from the Ministry of Health show an increasing number of DHF in children aged 15 years and older (unpublished data, Ministry of Health). Other reports also show this trend.[15,21] Furthermore,
it may be stated that the reported case-fatality rate has decreased over time. Increased awareness and better diagnostics have led to prompt recognition of the infection in health care facilities. Improved treatment protocols and local guidelines have contributed to this decline. Hopefully, the case-fatality rates will decline further in the near future.

Concerning clinical outcome in terms of the rating of disease severity, it is not clear whether the ratios of DF, DHF and DSS have changed. Such information could not be clearly deduced from the reports studied. In the field, the disease severity is changing depending on outbreak severity and not following a regular pattern.

Figure 3: **Case-fatality rate among DHF patients in Indonesia during 1968–2005**

The case-fatality rates (%) are denoted on the Y axis in percentages during the years 1968-2005. (Source: WHO, Sumarmo 1987)

However, there are some drawbacks in the presented data. Besides more awareness, diagnostic tools and diagnostic facilities have improved over time, which undoubtedly have led to more reporting. Dengue outbreaks are now recognized earlier, and more sensitive and specific diagnostic tests help to confirm the disease. Case definitions of WHO, also used by the Indonesian Ministry of Health, are based on both clinical and diagnostic criteria. It is stated that any suspected or confirmed case should be reported. Because it is unlikely that many cases will have laboratory confirmation, the reported cases will not always represent the real situation. This accounts even more for a country with many epidemics and a high endemic transmission. Not surprisingly, in the presented studies, the gap between suspected and confirmed cases is substantial. Moreover, perhaps some of the referenced older studies are less convincing. This is because they sometimes lacked a detailed method of selection and the diagnostic tools used then were less accurate. However, it is the only data we have.

Multiple factors influence the occurrence of dengue epidemics, of which environmental, biological and demographic factors play a central role. The dengue incidence is associated with warmer, more humid climate.\textsuperscript{[4]} Higher temperatures have been shown to
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Enhance vector efficiency and mosquito-biting behaviour. Indeed, a marked increase in the rainfall and sustained higher temperatures compared to earlier years were the key factors during the Palembang outbreak. Furthermore, the epidemiological pattern throughout the year shows a peak incidence of DENV infections during the months of October through April, usually coinciding with the rainy season.

Endemic transmission requires, besides the mosquito vector, an immunologically susceptible population and the circulation of the dengue virus. The presence of multiple circulating strains and the introduction of new and more virulent viruses increase the incidence of DHF epidemics. Some Indonesian studies clearly showed the relevance of secondary infections. Of all the serotypes identified in Indonesia, DENV-3 was the most frequently linked to the severe disease. Important demographic factors contributing to the transmission of dengue viruses also concern unprecedented population growth accompanied by unplanned and uncontrolled urbanization, a framework in which Indonesia perfectly fits.

Dengue is on the rise in Indonesia. Hence, epidemiological surveillance must be established along with education campaigns and sustainable vector control programmes to control its transmission. To obtain good and trustworthy epidemiological data, surveillance centres should be well-equipped and should function in different provinces and report on regular basis to the Ministry of Health. The increasing number of severe, potentially fatal cases and the absence of an effective vaccine stress the need to continue all efforts in understanding the dengue epidemiology.

References


