

Dengue Virus Infections in Viet Nam: Tip of the Iceberg

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Abstract

Dengue is highly endemic in Binh Thuan province, southern Viet Nam. To quantify the dengue-attributable disease burden in Binh Thuan, data from different sources was compiled. In 2003, 688 220 patients consulted 112 public primary health facilities. A total of 86 449 patients had fever, of whom 7399 (8.6%, 95% CI 8.4–8.8) were booked without classifying diagnosis; this corresponds to 7.7 per 100 person years. Serological diagnosis confirmed that dengue contributed to approximately one quarter of all undifferentiated fevers presented to the public primary health facilities. The annual incidence of acute primary and secondary dengue among the total population was substantially higher and estimated to range from 5.5 to 11.1 per 100 person years. The number of notified cases of dengue in 2003 was only 527 cases, less than 1% of the total incidence of dengue.

Keywords: Acute undifferentiated fever, dengue, incidence, Viet Nam.

Introduction

Dengue is the most common arthropod-transmitted viral infection in the world.^[1,2] The geographical distribution of dengue is steadily expanding, and in many areas the epidemiology is changing stratum from epidemic to endemic.^[1,3,4] Estimations of the incidence and thus the disease burden attributable to dengue are variable. The main reason is the variability of the clinical presentation of dengue virus infections, which ranges from a mild unspecific febrile illness to dengue haemorrhagic fever (DHF) and dengue

shock syndrome (DSS).^[5,6] These complications are mainly associated with secondary dengue virus infections. Immunity against dengue virus is determined by production of neutralizing antibodies. There are four antigenically distinct dengue virus serotypes. The immune response is monotypic; it does not protect against an infection by another serotype. The immune response to secondary infections, which does not neutralize the virus, may even increase the risk of complications.^[7]

Dengue surveillance is usually based on notification of complicated cases.^[3,4] This does

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not reflect the true incidence of the disease. The majority of uncomplicated cases do not get recognition as dengue cases. This leads to substantial under-reporting of dengue in the health information systems of most developing countries, as reporting is usually based on diagnosed cases.

In this study we quantified the dengue-attributable disease burden in Binh Thuan, a dengue-endemic province in the south of Viet Nam, by comparing different data sources, and analysed these data by a pyramid-shaped presentation, similar to the Piot model that is in use for modelling tuberculosis.

Methodology

Study site and population

The study was carried out in 2003, in Binh Thuan province in southern Viet Nam. Binh Thuan had a population of approximately 1.12 million, divided over 122 administrative units including 97 communities in semi-rural areas, 14 wards (in Phan Thiet city – the capital of Binh Thuan province), and 11 small towns (nine of which are recognized as district centres). Phu Quy – an island off the coast and governed as a separate district (22 594 inhabitants), was not included in this study.^[8]

The climate in Binh Thuan is a tropical monsoon climate, with the rainy season lasting from May until approximately October. In 2003, the total rainfall was 1135 mm; the mean temperature was 26.9 °C and the relative humidity 80%. (Source: Statistical Yearbook 2003 – Binh Thuan Statistics Office, Phan Thiet).

Public health care in Binh Thuan is provided by a provincial hospital in Phan Thiet and nine district hospitals. Primary health care is provided by 103 commune and 13 regional health

facilities (further called health posts). (Source: Statistical Yearbook 2003 – Binh Thuan Statistics Office, Phan Thiet).

Data sources

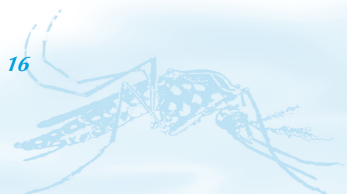
Total burden of disease and fever

The total disease burden was extracted from the routine health information system (HIS). The HIS of the public health services in Viet Nam reports at three levels: community, district and province. At community level, health data are recorded in a Health Examination Notebook (HEN) in which all patient consultations are being recorded, including patient identifiers, occupation and ethnic group.

Diarrhoea and acute respiratory tract infections are recorded in a separate column; all other diagnoses are grouped under “other”. Treatment is specified by the given medication and by whether the patient was ambulatory, had to be admitted to the health posts, or was referred to a district or provincial hospital. Malaria is recorded in a separate file. For this study an extra column was added to the HEN to identify patients who presented with fever (an axillary temperature ≥ 38.0 °C). The presumptive diagnosis of febrile patients was recorded. When no classifying diagnosis was made, this was recorded as “acute undifferentiated fever” (AUF).

AUF was defined as any febrile illness of duration less than 14 days, confirmed by an axillary temperature ≥ 38.0 °C, without indication of either severe systemic or organ-specific disease. Malaria was excluded by microscopic examination of a thick blood smear.

The data in the HEN were aggregated in monthly reports and then sent to the district health services where they were collected by the research team.



Dengue as a cause of undifferentiated fever

The contribution of dengue as a cause of undifferentiated fever was extracted from a separate study. The details of that study have also been explained previously.^[8] In brief, in twelve non-adjacent commune health posts and the clinic of the provincial malaria station, we determined the diagnosis of patients who presented with AUF by performing serological tests on “acute” and “convalescence” serum samples. An “acute” serum sample was collected at first presentation; a second, “convalescence”, serum sample was collected three weeks later. Serum samples were stored at -20°C at the study sites until monthly transfer to Cho Ray hospital, where they were stored at -70°C . Complete pairs of acute and convalescence serum samples were tested for dengue with IgG and IgM-capture ELISA (Focus Technologies Inc., Cypress, CA, USA), as described previously.^[9] ELISA was performed at the Department of Microbiology, Cho Ray Hospital, Ho Chi Minh City, Viet Nam. The results of ELISA were classified as “acute primary dengue”, “acute secondary dengue”, “past (not acute) dengue” and “no dengue”.

Incidence of first dengue virus infections

The annual incidence of primary dengue in the general population was assessed by measuring the seroprevalence of IgG dengue antibodies among primary-school children, as described previously.^[10] The age-dependent increase of the IgG seroprevalence was used to calculate the annual incidence of primary dengue virus infections. In a second survey two years later among the same population, we calculated the incidence of primary dengue as the proportion of children who experienced seroconversion between January 2003 and April 2005, while excluding cross-reactions with Japanese encephalitis virus infections. (Khoa T. D. Thai, unpublished data)

Notification of dengue

The 2003 routine dengue notification data were used to compare with the other data. Routine surveillance of dengue is based on an algorithm supplied by the National Dengue Control Program that basically follows the guidelines of WHO, but does not require haematology support (haematocrit and/or platelets count). By using this algorithm, in principle only dengue haemorrhagic fever and dengue shock syndrome are notified and uncomplicated dengue fever is not recognized. The Department of Preventive Medicine of Binh Thuan province collects monthly cumulative reports of dengue cases from all health posts, follows trends in notification and warns for outbreaks in the province; in addition, the department also applies preventive measures. Serological confirmation is only done in some complicated cases that need referral to the provincial hospital. Sometimes serum samples are transferred to Institute Pasteur, Ho Chi Minh City, for isolation of dengue virus, but not on a routine basis.

Ethical considerations

The study was approved by the Review Board of the Cho Ray Hospital, Ho Chi Minh City. The study was explained and discussed in meetings with provincial authorities and staff of the health posts. All patients, or, for children, the parents or guardians, gave their written informed consent.

Statistical analysis

Statistical analysis was performed using statistical software (SPSS 11.5, SPSS Inc., Chicago, IL, USA). Binary regression was applied to calculate the annual incidence of DENV infection as described previously.^[10] Descriptive statistics were used to describe the distribution of the demographic and incidence data. A univariate generalized linear model was used to find the association between climate factors and monthly incidence.



Results

Total burden of disease and fever

In 2003, 688 220 patients consulted the 112 public primary health facilities which is, on average, 17 consultations per health post per day. A total of 86 449 patients had fever, of whom 7399 (8.6%, 95% CI 8.4–8.8) were booked without classifying diagnosis and were thus classified as AUF. The mean of the number of fever and AUF cases, divided by the total population of the respective communities, is presented in Figure 1. Overall, the number of consultations for fever, divided by the population, was 7.7%. The data did not specify the number of patients, only the number of consultations. Thus, if patients would present their fevers not more than one time per year to the health posts, the average

incidence of AUF would be 7.7 per 100 person years.

The mean number of consultations for fever per month, for children and adults, is shown in the table, together with monthly rainfall and temperature. The mean monthly number of malaria cases (due to *P. falciparum* and *P. vivax*) is also shown for comparison. Malaria contributed to 2.8% of all fevers (including adults and children). Over the year, fever was the reason for 11.1% (range 9.1–15.0%) of consultations by adults and 15.0% (range: 6.7–24.3%) of children's consultations. The diagnosis was classified as AUF in 9.2% (range: 7.5–14.8%) of the consultations by adults and 7.8% (range: 6.3–9.6%) by children. There was no correlation between the total number of consultations and rainfall or temperature.

Figure 1: *The monthly distribution of fever and other conditions presented at primary health facilities in Binh Thuan*

Mean of the total number of consultations in all public commune health facilities in 2003, for fever (white columns) or other conditions (grey columns), divided by the total population of these communities. The error bars indicate the 95% confidence interval of the proportion of fever and other conditions, separately.

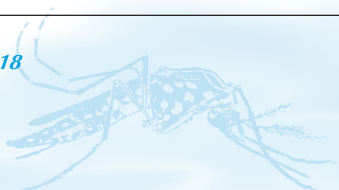
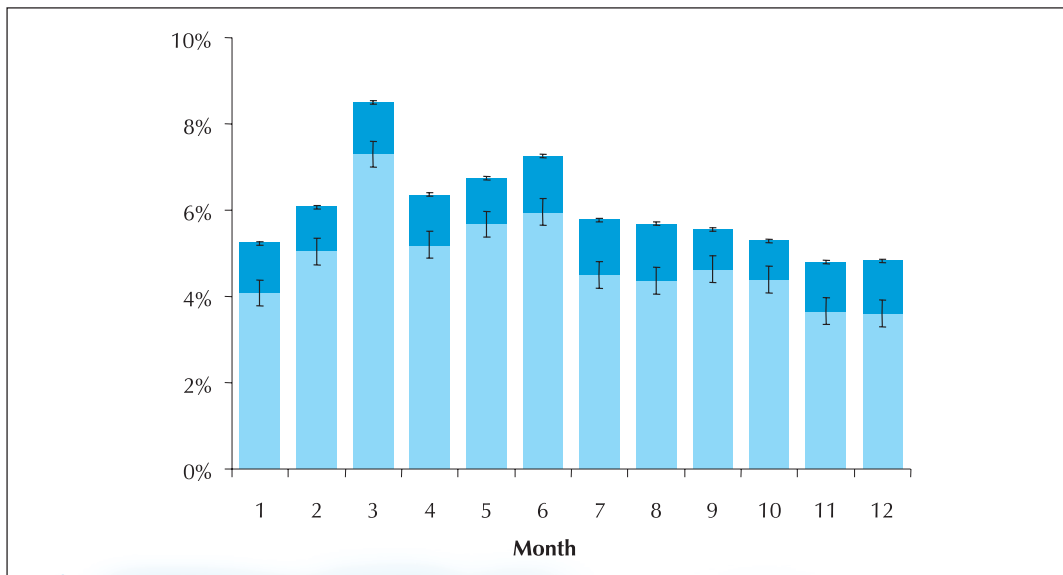


Table: Mean monthly number of consultations for fever and acute undifferentiated fever at all public primary health facilities of Binh Thuan together with climatic factors*

Month	Temp. (°C)	Rainfall (mm)	Number of consultations (× 1000)						
			Adult			Children ≤15 years old			For malaria [§] (%)
			Total	For fever [‡] (%)	Classified as AUF [¶] (%)	Total	For fever [‡] (%)	Classified as AUF [¶] (%)	
1	24.9	–	33.91	3.79 (11.2)	0.56 (14.8)	15.19	2.87 (18.9)	0.28 (9.6)	0.35 (5.5)
2	25.8	–	34.02	4.06 (11.9)	0.40 (10.0)	24.56	2.87 (11.7)	0.22 (7.6)	0.28 (4.2)
3	27.1	–	39.06	4.29 (11.0)	0.32 (7.5)	47.18	3.14 (6.7)	0.28 (8.7)	0.22 (3.0)
4	28.6	15	41.11	4.33 (10.5)	0.34 (7.7)	25.55	3.62 (14.2)	0.28 (7.7)	0.19 (2.4)
5	28.1	249	38.84	3.58 (9.2)	0.31 (8.8)	27.31	3.80 (13.9)	0.25 (6.7)	0.17 (2.3)
6	28.0	102	46.58	4.26 (9.1)	0.37 (8.7)	27.0	4.36 (16.1)	0.31 (7.2)	0.17 (1.9)
7	27.2	281	41.03	4.24 (10.3)	0.34 (8.1)	14.99	3.64 (24.3)	0.28 (7.7)	0.19 (2.4)
8	27.4	97	39.01	4.00 (10.3)	0.38 (9.4)	14.38	3.21 (22.3)	0.30 (9.3)	0.19 (2.7)
9	27.2	168	31.41	3.51 (11.2)	0.40 (11.4)	21.11	2.90 (13.7)	0.28 (9.6)	0.18 (2.8)
10	27.1	106	31.85	4.16 (13.1)	0.33 (8.0)	15.62	2.50 (16.0)	0.16 (6.3)	0.14 (2.1)
11	26.7	108	27.39	3.65 (13.3)	0.32 (8.9)	11.91	2.88 (24.2)	0.20 (6.8)	0.18 (2.9)
12	25.1	9	25.71	3.86 (15.0)	0.30 (7.6)	13.51	2.94 (21.8)	0.20 (6.8)	0.16 (2.4)
	26.9	1135	429.92	47.72 (11.1)	4.38 (9.2)	258.30	38.73 (15.0)	3.02 (7.8)	2.41 (2.8)

[‡] (%) percentage of fever among all consultations

[¶] percentage of AUF among all consultations for fever

[§] percentage of malaria (*P. falciparum* and *P. vivax*) among total of fever consultations (adults and children)

* Source: Statistical Yearbook 2003 – Binh Thuan Statistics Office, Phan Thiet

Dengue as a cause of undifferentiated fever

In 2003, paired serum samples were collected from 1636 patients with AUF who attended the 13 study sites. Of these, two cases per health post and per month were randomly selected totalling 275 (16.8%) paired serum samples. These samples were tested for

dengue virus IgM- and IgG-specific antibodies with ELISA. Acute dengue was found in 70 (25.5%) cases, including 23 (8.4%) cases of acute primary dengue [21 (7.7%) children < 15 years; 2 (0.7%) ≥ 15 years] and 47 (17.1%) cases of acute secondary dengue [19 (18.4%) and 28 (16.3%) respectively]. A past dengue virus infection was detected in 161 (58.5%) cases [36 (35.0%) < 15 years and 125 (72.7%)

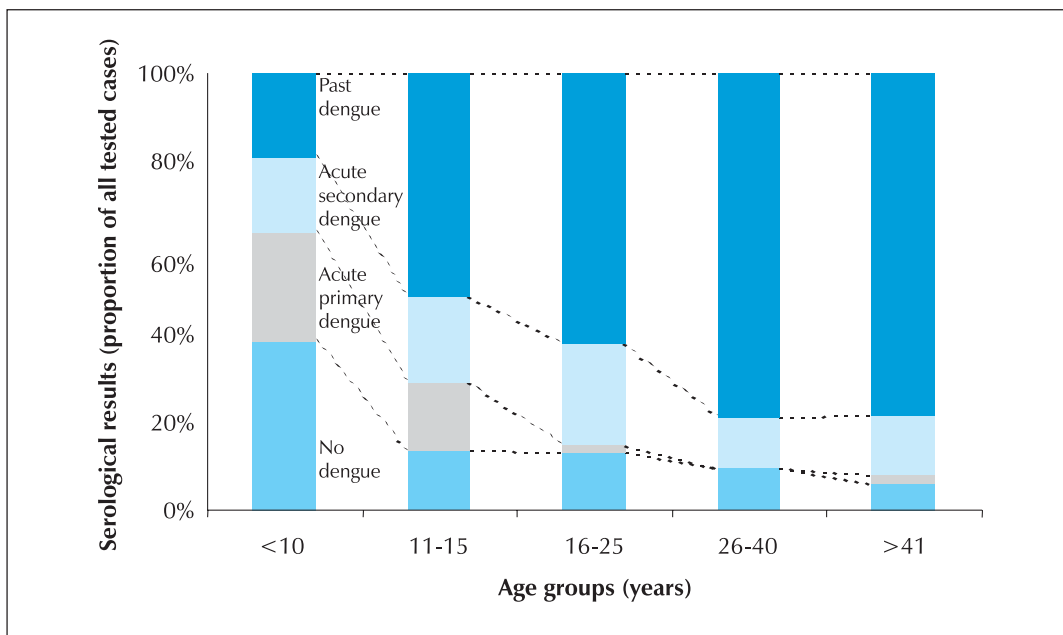


≥ 15 years]. In 44 (16.0%) patients [27 (26.2%) < 15 years and 17 (9.9%) ≥ 15 years] the tests were negative (Chi-square on two age groups and four diagnoses: 55.043 (df = 3); *P* value < 0.001). Figure 2 shows the serological diagnoses per age group.

Figure 3 shows the monthly distribution of the proportion of acute dengue cases among the total of cases with AUF. The number of cases with dengue was higher in the rainy season than in the dry season [49 (31.0%) vs. 21 (17.9%); chi-square 6.046, df 1, *P* value = 0.014].

Figure 2: *The serological diagnoses of dengue per age group*

The serological diagnosis, confirmed by ELISA on paired serum samples, in 275 patients with acute undifferentiated fever, who presented at primary health facilities in Binh Thuan



Incidence of first dengue virus infections

The annual incidence of acute primary dengue was calculated by binary regression with a log-log link function, thus applying a model of loglinear decrease of the proportion of dengue IgG-naïve children among primary-school children.^[10] The overall annual incidence of primary infections (seroconversion) was 11.7 per 100 person years. In the serum bank of

patients with AUF, we observed similar patterns. The dengue IgG prevalence in convalescent samples increased by age from 60% among children younger than 10 years to 94% in adults older than 41 years.

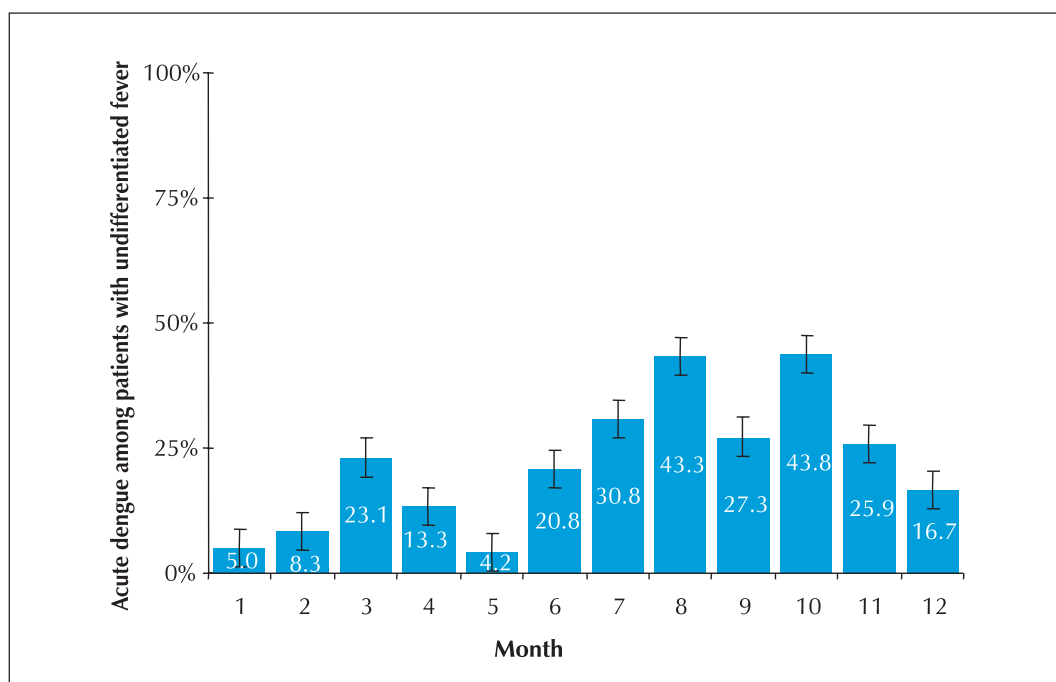
Dengue notification

In 2003, a total of 527 dengue cases was notified. This was not further specified or broken down into age groups.



Figure 3: *Acute dengue among acute undifferentiated fever*

The monthly distribution of the proportion of patients with acute undifferentiated fever at 13 primary health facilities in Binh Thuan, who were diagnosed with acute dengue by ELISA. The error bars indicate the 95% confidence interval of the proportion of acute dengue



Discussion

This study showed that dengue was a very common disease in the area, and that routine notification data grossly underestimated its true incidence.

In this study, we applied ELISA for the serological confirmation of dengue. ELISA, though not recognized as a gold standard, has sufficient sensitivity and specificity for both serodiagnosis in patients as well as for epidemiological studies, in comparison to the plaque reduction neutralization test (PRNT) and haemagglutination inhibition assay (HI).^[6,11-14] Previous studies indicated that dengue is highly endemic in southern Viet Nam and can

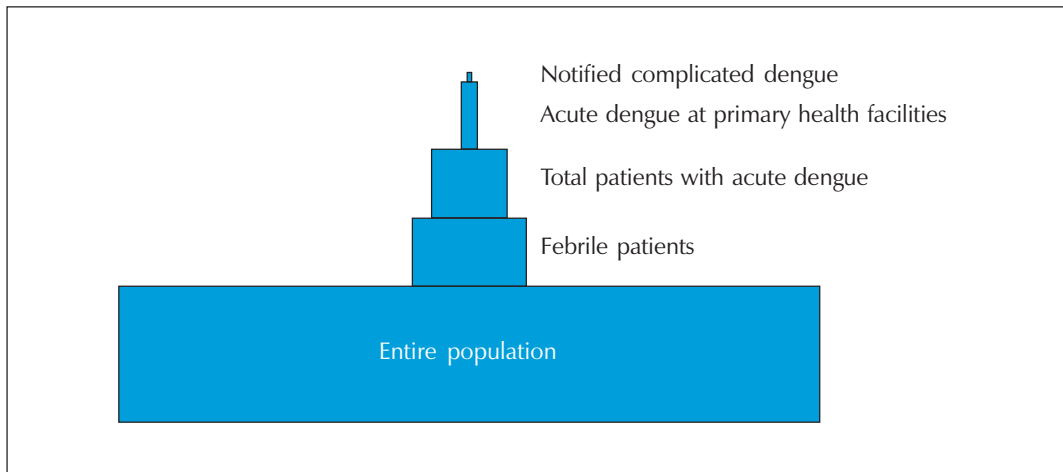
therefore be considered a disease of childhood.^[15,16] In Binh Thuan province, dengue is the most frequent cause of all fevers presented to the public primary health services.^[17]

Based on the findings in this study, we constructed a model that quantifies and illustrates several echelons at which dengue can present to the public health services, analogous to the Piot model that was developed for tuberculosis control and other diseases^[18] (Figure 4). The base of this pyramidal model depicts the total population. Superposed on that are four levels that refer to disease and health consumption: the total number of patients in Binh Thuan with AUF,



Figure 4: *The pyramid of dengue*

The total number of patients with acute undifferentiated fever who seek help at public primary health facilities, the estimated total number of acute dengue virus infections among the total population, the number of persons with acute dengue who seek help at primary health facilities and the number of dengue cases notified by the routine surveillance system. The square areas of the blocks are proportional to that of the total population of Binh Thuan province



the total number of cases with acute dengue, the number of patients with dengue that present to the public primary health services, and the number that actually becomes notified as dengue.

In order to calculate these totals, we needed to make some assumptions and approximations. The total population of Binh Thuan was 1.12 million in 2003, but the age distribution was not known. At the next layer of the pyramid, we observed that 86 449 consultations were booked for fever. This corresponds to 7.7 per 100 person years among the general population if we assume that no patient consults the health posts for fever more than once a year and that no patient goes to other health providers.

The total number of dengue cases was derived from the annual incidence. The school

surveys showed that the true annual incidence of first infections was approximately 11 per 100 person years among subjects who were never infected before. The total number of primary dengue infections can be calculated from the total population of sero-naïve subjects if we make a few assumptions. Here, we assumed that (i) half of the population of Binh Thuan was 25 years of age or younger and (ii) that in this age group the loglinear decrease of sero-naïve subjects was constant over the years, similar to what we found in primary-school children. By doing so, we easily calculated that approximately 21 600 (3.7%) persons younger than 25 years suffered from primary dengue every year. This number had to be increased by the number of cases of acute primary dengue among persons older than 25 years, but since the incidence of dengue was lower in older age groups, the proportion decreased, but not lower than its half, 1.8%. Thus, every



year, approximately 1.8% to 3.7% of the total population suffered from acute primary dengue.

In the study on the causes of fever, we observed that acute secondary dengue was approximately twice as common as acute primary dengue, so that the total number of cases with acute primary or secondary dengue should range from 5.5% to 11.0% of the total population of Binh Thuan. In absolute terms, this is approximately 60 000 to 120 000 cases.

This number would increase if two dengue virus types circulate simultaneously. In 2003, the blood of 15 cases of dengue was sent to Institute Pasteur in Ho Chi Minh City for virus isolation. In three cases DENV-2 was isolated. In 2001, six cases of DENV-2 and three cases of DENV-3 infections were identified by virus isolation in 61 blood samples (Institute Pasteur Ho Chi Minh City, unpublished data). For drawing the pyramidal figure, we assumed the circulation of only one serotype.

The third level was the total number of dengue-infected patients who sought help at public primary health services. From the serological studies on the causes of acute undifferentiated fever, we know that one quarter of the patients with acute undifferentiated fever actually had dengue, which corresponds to 1.9 per 100 person years among the total population. This is a 2.9 to 5.8-fold difference with the total number of cases of acute dengue (5.5% to 11.1% of the total population). These subjects also suffered from dengue but apparently did not seek help or did so from other health providers. Furthermore, if this also applies to all other causes of fever, then the total number of cases of AUF could also be 2.9 to 5.8-fold higher.

Lastly, only 527 cases of complicated dengue were notified, which corresponds to

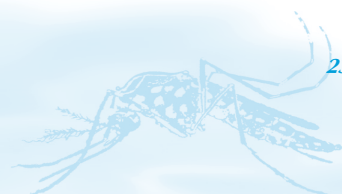
0.4% to 0.9% of the total number of cases with dengue.

Figure 4 shows that the burden of disease attributable to dengue was much greater than what was being notified as such, even if our assumptions contain large deviations from the reality.

Dengue has been reported in over 100 countries, mainly in the tropics and subtropics, but the true extent of the incidence is not known.^[1,3] In South-East Asia, despite the increase in the reported cases of dengue haemorrhagic fever, it is generally accepted that the incidence of the infection is largely under-reported.^[3] The poor surveillance system of dengue is considered to be the reason for the underestimation of the infection.^[4] Our findings, however, suggest that the unspecific clinical presentation is the main reason why the notified data represent a very small fraction of the total number of dengue infections in the world.

Our findings reflect the recent estimations of the global incidence of dengue.^[4,19,20] It is estimated that, annually, between 50 and 100 million cases of DF occur among the more than 2.5 billion people at risk. The annual total number of DHF cases is estimated at 250 000, approximately 2% of the total of dengue virus infection.

The consequences for surveillance are two fold. First, notifications based on the case definitions of complicated dengue grossly underestimate the total burden of the disease. Secondly, the complication rate of dengue is very low in highly endemic regions as long as the number of secondary infections is low. The latter could lead to the conclusion that the main focus of surveillance should be the detection of new serotypes entering an endemic area, for example, by using molecular tools at some



sentinel sites, so that a sudden increase in the incidence of acute secondary dengue can be anticipated.

In conclusion, dengue is highly endemic in southern Viet Nam and leads to much health consumption. The routine notification system, however, grossly underestimates the true incidence. This study underscores the need for effective dengue control measures that would limit the transmission of the virus till a vaccine becomes available, and makes a case for other methods of surveillance that would anticipate outbreaks of secondary infections.

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Acknowledgement

This study was carried out with the support of the Netherlands Foundation for the Advancement of Tropical Research (WOTRO).

We thank our colleagues in the Department of Virology, Cho Ray Hospital, Ho Chi Minh City, for their contribution with laboratory analysis. We are very grateful to the doctors and other personnel of the Binh Thuan Provincial Malaria Centre, Phan Thiet, and health posts for their cooperation.



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