

The 2005 Dengue Epidemic in Singapore: Epidemiology, Prevention and Control

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Abstract

Introduction: We investigated the 2005 outbreak of dengue fever (DF)/dengue haemorrhagic fever (DHF) to determine its epidemiological, virological and entomological features to further understand the unprecedented resurgence. **Materials and Methods:** All physician-diagnosed, laboratory-confirmed cases of DF/DHF notified to the Ministry of Health, Singapore during the outbreak as well as entomological and virological data were analysed retrospectively. **Results:** A total of 14,006 cases of DF/DHF comprising 13,625 cases of DF and 381 cases of DHF, including 27 deaths were reported, giving an incidence rate of 322.6 per 100,000 and a case-fatality rate of 0.19%. The median age of the cases and deaths were 32 and 59.5 years, respectively. The incidence rate of those living in compound houses was more than twice that of residents living in public and private apartments. The distribution of DF/DHF cases was more closely associated with *Aedes aegypti* compared to *Aedes albopictus* breeding sites and the overall *Aedes* premises index was 1.15% (2.28% in compound houses and 0.33% to 0.8% in public and private apartments). The predominant dengue serotype was DEN-1. A significant correlation between weekly mean temperature and cases was noted. The correlation was strongest when the increase in temperature preceded rise in cases by a period of 18 weeks. **Conclusion:** The resurgence occurred in a highly densely populated city-state in the presence of low *Aedes* mosquito population. Factors contributing to this resurgence included lower herd immunity and change in dominant dengue serotype from DEN-2 to DEN-1. There was no evidence from gene sequencing of the dengue viruses that the epidemic was precipitated by the introduction of a new virulent strain. The current epidemiological situation is highly conducive to periodic dengue resurgences. A high degree of vigilance and active community participation in source reduction should be maintained.

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Introduction

Dengue is the most important human viral disease transmitted by arthropod vectors.¹ Some 2500 million people – two-fifths of the world's population – are now at risk from dengue.² WHO currently estimates that there may be 50 million cases of dengue worldwide every year.³

Dengue viruses, members of the *Flaviviridae* family, occur as 4 distinct serotypes that are transmitted from infected to susceptible humans principally by *Aedes aegypti* mosquitoes.⁴ Infection with one dengue serotype provides lifelong immunity to that specific virus, but there is no long-term cross-protective immunity to the other serotypes.⁵

Dengue virus infections may be asymptomatic or may lead to undifferentiated fever, dengue fever (DF), dengue haemorrhagic fever (DHF) or Dengue Shock Syndrome (DSS).⁶ The risk of DHF/DSS could increase in persons with pre-existing dengue antibody, either actively or passively acquired, although fatal DHF/DSS does occur in primary dengue infection.⁷ A minority of patients will still progress into fatal DHF/DSS with intractable coagulopathy despite receipt of prompt supportive measures.⁸

Despite its well-established integrated nationwide *Aedes* mosquito control programme, Singapore has not been spared from the regional resurgence of dengue.⁹ Dengue

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illness, though relatively benign, has a high morbidity and places a great burden on hospital beds,¹⁰ accounting for 1.4%, 2.0% and 3.2% of all hospital discharges in 2003, 2004 and 2005 (when it was the fourth commonest cause), respectively.¹¹

An epidemic of DF was first reported in Singapore in 1901.¹² The first reported outbreak of DHF in Singapore in 1960 involved 70 hospitalisation cases.¹³ All 4 dengue viruses are endemic in Singapore with cases of DF and DHF reported year round. Since 1960, large epidemics occurred almost annually from 1961 to 1964 and 1966 to 1968.¹⁴ Following the implementation of a national *Aedes* control programme incorporating source reduction, health education and law enforcement in 1969, the disease incidence rate decreased from 42.2 per 100,000 in 1969 to between 3 and 10 per 100,000 for the period 1969 to 1972.¹⁵ A large epidemic occurred in 1973¹⁶ and despite further intensification of *Aedes* control which had resulted in sustained suppression of the *Aedes* mosquitoes as reflected by the low *Aedes* Premises Index (percentage of premises found breeding *Aedes* mosquitoes) over the years, successive epidemics occurred in 1986,¹⁴ 1989,¹⁷ 1992,¹⁸ 1998¹⁹ and 2004²⁰ with the dengue incidence increasing more than 10-fold from 16.7 per 100,000 in 1987 to 223.1 per 100,000 in 2004²¹ (Fig. 1). The incidence of DF/DHF appeared to follow a 6-year cycle of increasing incidence with peaks in 1992, 1998 and 2004.

The incidence of DF/DHF continued to increase unabated from 2004 into 2005. We investigated the 2005 outbreak to determine its epidemiological, virological and entomological features to further understand the unprecedented resurgence.

Materials and Methods

In Singapore, the National Environment Agency (NEA) is responsible for regular vector and viral surveillance, vector control, cluster or outbreak response and research. The Ministry of Health (MOH) is responsible for dengue case surveillance and clinical management, and works closely with NEA to ensure that the public health authorities have access to up-to-date information on the dengue situation and are able to promptly implement vector control measures. To facilitate case surveillance, the Infectious Diseases Act requires medical practitioners to notify all cases of and deaths from DF and DHF to the MOH within 24 hours. This can be done through fax or via a dedicated website. The information required for each notification includes demographic data such as name, unique identification number, date of birth, ethnic group, gender, residential and school or workplace addresses, dates of diagnosis and onset of illness and whether the diagnosis was clinical or confirmed by laboratory tests. MOH provides clinical

criteria for diagnosis of DF and DHF, and recommended laboratory tests and clinical management in a guidebook that is made available to all medical practitioners.²² Data on deaths from DF/DHF were also obtained from the Singapore Registry of Births and Deaths.

Medical practitioners are also required to re-notify dengue cases to the MOH through the same process if they had initially diagnosed the patient as DF and who subsequently fulfilled the clinical criteria for DHF.²² In addition, laboratories are also required to notify MOH of all patients whose blood samples tested positive for acute dengue infection. Serotyping was performed by the NEA's Environmental Health Institute (which also carried out gene sequencing), the National University Hospital and the Singapore General Hospital.

Upon receipt of notification, clinically suspect and laboratory confirmed cases of dengue were investigated and interviews were conducted where necessary to complete the collection of epidemiological data. Details of cases were sent promptly to NEA where officers determined the clustering of cases and conducted site visits for further investigations. A cluster is defined as 2 or more cases epidemiologically linked by place of residence or work/school (within 150 m) and time (onset of illness within 14 days). NEA officers also carried out *Aedes* surveillance, and "search and destroy" operations. Clustering and analysis of entomological data were performed with a geographical information system (GIS). Entomological surveillance was supplemented by 5000 ovitraps placed around Singapore.

Only physician-diagnosed, laboratory-confirmed cases of DF/DHF notified to the MOH were included in this study. All duplicate notifications were removed prior to analysis. The reference populations for the computation of various incidence rates were based on the 2005 estimated mid-year population²³ and the 2000 population census in Singapore.²⁴ For the analysis of demographic data, we further restricted the cases to those who were Singapore residents. For comparison between the ethnic groups, only the Chinese, Malay and Indian populations were considered.

Statistical analysis was performed using Microsoft Office Excel 2003 and SPSS 15.0. Age and gender adjustments for each of the major ethnic groups were done using the direct method with the 2005 mid-year Singapore population as the base population. Differences between the age-gender-standardised incidence rates of the 3 ethnic groups were computed and tested for statistical significance using the Z-test.²⁵ Statistical significance was taken as $P < 0.05$ level.

Results

The year began with a high incidence which had continued from 2004 before a decline was observed in late February.

It remained relatively low in March and April. A sharp increase was noted in May 2005 and this continued to reach a peak in September 2005. After a nationwide vector-control campaign, the number of cases reported weekly decreased steadily, reaching a low in December 2005 (Fig. 2).

A total number of 14,006 laboratory-confirmed cases comprising 13,625 cases of DF (97.3%) and 381 cases of DHF (2.7%) whose date of onset of illness was between 1 January 2005 and 31 December 2005 were reported. The overall incidence rate was 322.6 per 100,000. Of these, 13,818 (98.7%) were indigenous cases with no travel history to a dengue endemic area outside Singapore within the 7 days prior to the onset of illness. There were 27 deaths (median age, 59.5 years; range, 9 to 89 years) directly attributed to dengue infection giving a case-fatality rate of 0.19% for all dengue cases and 7.1% for DHF cases. The incidence rate for indigenous cases among non-Singapore residents (409.3 per 100,000) was 1.4 times higher than for residents (297.8 per 100,000).

Epidemiological Findings

The median age of DF/DHF cases among Singapore residents was 32 years. The age-specific incidence rate was

lowest among those less than 5 years of age (Table 1). The incidence rate then increased with age, peaking in the 15- to 24-year-old age group and gradually declined thereafter.

Overall, males had a significantly higher incidence rate compared to females (324.7 per 100,000 and 272.0 per 100,000, respectively). However, the difference in age-specific gender incidence was mainly restricted to the 15- to 44-year-old age group (421.6 per 100,000 vs 318.4 per 100,000; $P < 0.001$). There was no statistically significant difference in the incidence of DF/DHF between males and females in those aged 14 years and below, as well as those who were above 44 years of age.

Among Singapore residents, the age-gender-adjusted incidence rate of DF/DHF was highest in the Chinese (312.8 per 100,000) followed by the Malays (288.4 per 100,000) and the Indians (173.9 per 100,000). Overall, the Chinese had a significantly higher incidence rate compared to the Malays ($P < 0.005$) and Indians ($P < 0.001$). The Malays also had a significantly higher incidence rate compared to the Indians ($P < 0.001$).

The incidence rates of those residing in compound houses (710.7 per 100,000) was more than twice that of those living in HDB (Housing and Development Board) flats (332.1 per 100,000) which are typically government-built high-rise apartments and about 2 and half times that of residents of private condominiums (298.8 per 100,000).

A total of 1190 clusters involving 5362 epidemiologically linked cases were identified. This constituted 38.3% of all reported cases. The mean number of cases in each cluster was 3 (range, 2 to 75) and the mean duration of transmission was 5 days (range, 1 to 54). The 5 largest clusters were at Yishun Street 72 (75 cases, August to October), Marsiling Crescent (54 cases; August to September), Upper Boon Keng Road (50 cases; June to July), Lorong 7/Lorong 8 Toa Payoh (47 cases; August to October) and Kang Ching Road (45 cases; October to November)

Historically, DF/DHF cases had been concentrated in the north-eastern and south-eastern parts of Singapore. In this epidemic, large numbers of cases were reported from the northern and south-western parts of Singapore.

Table 1. Age-specific Incidence of Reported DF/DHF, 2005

Age group (y)	No. of cases	Incidence rate per 100,000
0-4	158	78.4
5-14	1537	304.4
15-24	2237	486.9
25-34	1878	338.3
35-44	1987	311.7
45-54	1460	255.0
55-64	749	232.5
65-74	375	205.6
>74	184	169.7
Total	10,565	298.1

Table 2. Distribution of Dengue Serotypes, 2000-2005

Year	No. of blood samples tested	No. positive and serotype distribution (%)			
		DEN-1	DEN-2	DEN-3	DEN-4
2000	327	4 (36.4)	4 (36.4)	1 (9.1)	2 (18.2)
2001	354	1 (6.7)	12 (80.0)	0 (0.0)	2 (13.3)
2002	331	16 (30.8)	28 (53.8)	2 (3.8)	6 (11.5)
2003	525	8 (9.2)	70 (80.5)	4 (4.6)	5 (5.7)
2004	560	144 (67.0)	59 (27.6)	5 (2.5)	7 (3.0)
2005	1948	661 (71.2)	70 (9.2)	178 (19.0)	4 (0.6)

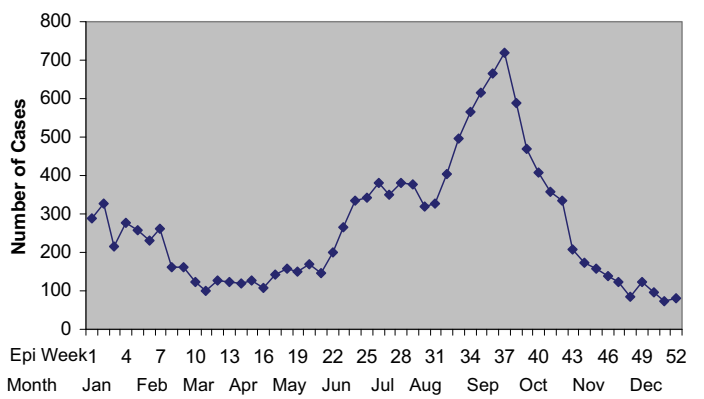
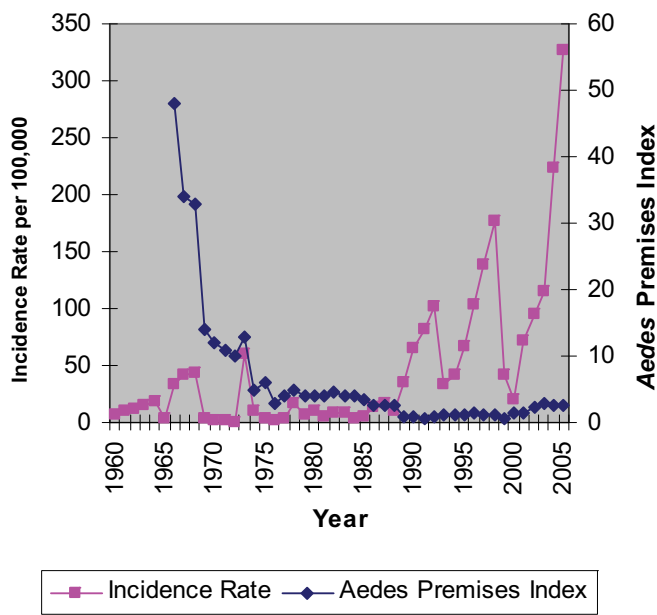


Fig. 2. Weekly distribution of reported DF/DHF cases by onset of illness, 2005.

Fig. 1. Incidence rate of reported DF/DHF and the *Aedes* Premises Index in Singapore, 1960-2005.

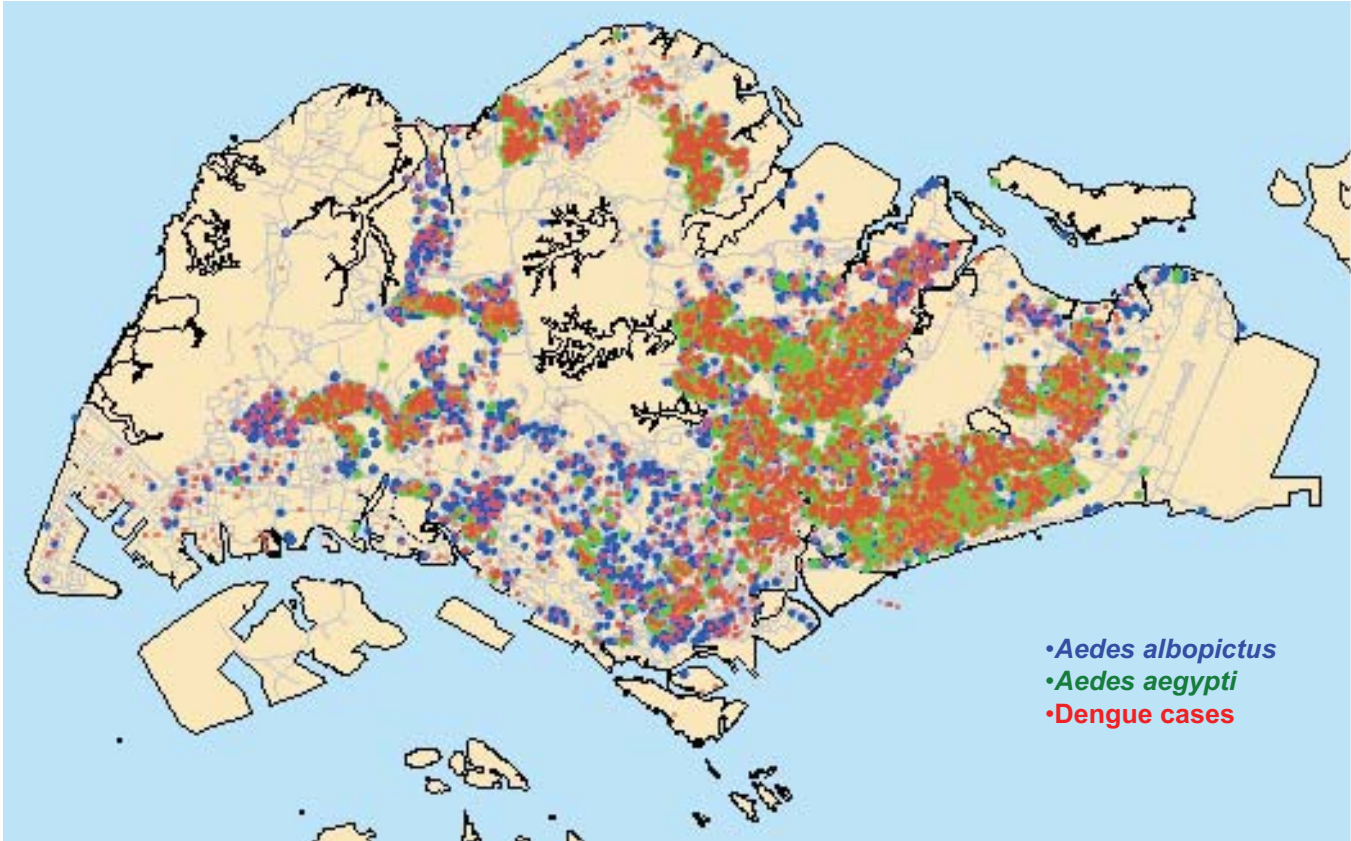


Fig. 3. Distribution of dengue cases and *Aedes* breeding sites.

A significant correlation between weekly mean temperatures and cases was noted and the correlation was strongest when increase in temperature preceded rise in cases by a period of 18 weeks ($r = 0.60$; $P < 0.001$).

Virological Findings

DEN-1 was the predominant serotype comprising 71.2% of all cases followed by DEN-3 (19.0%), DEN-2 (9.2%) and DEN-4 (0.6%) (Table 2). Gene sequencing carried out by the Environmental Health Institute showed that the same DEN-1 had been circulating in Singapore since 2002.

Entomological Findings

The distribution of dengue cases was more closely associated with *Aedes aegypti* than *Aedes albopictus* breeding sites (Fig. 3). Fifty per cent of all mosquito breeding was found outdoors. The majority of outdoor breeding habitats were discarded receptacles, broken/choked drains and physical structures such as link ways, water pump rooms and gully traps.

The overall *Aedes* premises index was around 1.15%, with the highest percentage detected in compound houses (2.28%), followed by condominiums (0.8%) and HDB flats (0.33%). There was no correlation between the week-to-week *Aedes* Premises Index and number of DF/DHF cases.

The top 5 breeding habitats for *Aedes aegypti* were domestic containers (26%), ornamental containers (24%), discarded receptacles (7%), flower pot plates (4%), and roof gutters (3%). In the case of *Aedes albopictus*, the most common breeding habitats were discarded receptacles (21%), domestic containers (10%), ornamental containers (10%), gully traps (5%), and canvas/plastic sheets (5%).

Prevention and Control

A number of additional aggressive measures were introduced to curb the rising trend. An Inter-Ministerial Committee headed by the Minister for the Environment and Water Resources was formed in September 2005 to handle the outbreak, as well as an inter-agency Dengue Coordination Committee involving the Permanent Secretaries of the Environment, Health and National Development ministries and heads of key government statutory boards. This was to ensure that various policy initiatives by the ministries were well-coordinated. A Dengue Watch Committee involving the mayors was set up to coordinate outreach to the community, and an Expert Panel comprising local and international experts to advise the Government on the prevention and control measures was appointed.

An inter-agency dengue task force was also constituted to enhance the communication and coordination on dengue

control efforts among various government agencies and private organisations. As a first step, the agencies and private organisations undertook a thorough source reduction exercise among all the infrastructures, properties and development sites under their charge. This included increased frequency of cleaning public drains and inspection of rooftops. The mosquito control programmes and audit systems by each agency also underwent a review to ensure more source reduction efforts on the ground rather than just focusing on fogging. Permanent solutions to eliminate potential sources of stagnant water, such as repairs to infrastructure, sealing up of cracks, backfilling of land and removal of roof-gutters were carried out. Each agency would also execute a tighter and more comprehensive inspection regime. With this task force in place, NEA could now liaise directly with the person-in-charge and implement measures more swiftly especially in areas with a major dengue cluster.

NEA also led an inter-agency technical committee to review the designs of drains and rooftop gutters. As a result of the review, the following improvements were made:

- a) The design of HDB block corridor drains was improved to facilitate water flow.
- b) Rooftop gutters which posed a high potential for mosquito breeding have been banned in new developments through the Building Plan approval process.
- c) Secondary rooftops, which also posed a high potential for mosquito breeding, were subject to regular checks. Where water stagnation was inevitable, repair works were either carried out or granular larvicide was regularly applied; and
- d) Approximately 10 km of defective public drains were identified and repaired to minimise water stagnation.

The majority of drains found breeding *Aedes* mosquitoes were scupper drains at common corridors of HDB flats and the sides of multi-storey car parks. Town councils had to undertake regular cleaning and repairs including increasing the number and size of openings for easy cleaning and maintenance; and increasing the gradient of the drains to prevent water stagnation. Weekly inspection of the scupper drains was also undertaken to prevent water stagnation. NEA also increased the cleaning frequency of the open roadside drains from once every week to once every alternate day. For closed drains, *Bacillus thuringiensis israelensis* (Bti) or chemical larvicides were used, using the misting method to spread to hard-to-reach areas. Anti-malarial oil was discouraged because of clumping and its low rate of spreading.

To raise community awareness and increase the participation of the community in preventing mosquito breeding, the 'Campaign Against Dengue' was launched

on 18 September 2005 in all 84 electoral constituencies. NEA stepped up its outreach to the community with an emphasis of the importance of source reduction and prevention of secondary transmission from infected dengue patients in the overall strategy to control the outbreak. To do this, a '10-minute Mozzie Wipeout' pamphlet was distributed to all households to educate the public to check and remove stagnant water in homes. During the campaign, some 10,000 grassroots members and Dengue Prevention Volunteers were mobilised to conduct door-to-door house visits to all HDB homes and private residences island-wide to help with the distribution of the pamphlets and educate residents on dengue prevention. Educational materials were also distributed to construction workers, factory workers in industrial estates, shipyard workers as well as foreign domestic workers to increase their awareness on dengue prevention. Advisory letters and dengue prevention guidebooks were also distributed to some 14,000 tenants in the industrial estates by the relevant agencies.

In order to implement an effective preventive surveillance programme and to overcome the challenges faced in prioritising indoor and outdoor inspections, it was crucial to address the issue of manpower. NEA increased its field deployment of officers from 110 to 510, which was a 363% increase in manpower. With an enhanced field deployment, sufficient checks could be carried out to address both outdoor and indoor breeding. NEA inspected over 934,000 premises in 2005 (an increase of 50% compared to 2004) and carried out more than 52,000 surveys on non-residential premises and public and private areas (an increase of 60%). Dengue hotlines were also set up by NEA and more than 16,000 calls on mosquito breeding and dengue fever were received. All calls were investigated within 24 hours and any breeding sites found were destroyed.

In addition, a 'carpet combing' exercise was carried out on the weekends during the period from 17 September to 22 October 2005. NEA mobilised additional manpower with the help of government agencies, volunteers and town councils to thoroughly search and destroy mosquito breeding grounds in public and private residential housing estates and their surroundings. Some 6000 volunteers were involved in the entire exercise. Around 1000 mosquito breeding habitats were found and destroyed and another 8400 potential breeding sites were removed.

Discussion

The 2005 outbreak was unprecedented in both the size of the outbreak and the geographical distribution of cases. Mathematical modelling suggested that the aggressive control measures implemented seemed effective in reducing the number of dengue cases in the first week after the start of the outdoor 'carpet combing' and indoor '10-minute Mozzie Wipeout' vector control measures.²⁶ It was also

shown that the first 'carpet combing' exercise in the electoral constituencies with the highest incidence provided a great impact in reducing the number of dengue notifications with a decreasing rate of return for subsequent exercises.²⁷

Possible Factors Contributing to the Outbreak

There were several factors which could have contributed to the 2005 outbreak and the general increase in the incidence rates of DF/DHF in Singapore.

Firstly, it appears that the successful vector control programme over the last 2 decades has brought about a paradoxical situation in that outbreaks tend to occur more frequently and with even greater intensity because of the low herd immunity of the population.^{9,28} This is reflected in the decreasing seroprevalence of dengue virus infection among the population from 47% in 1990-1991 to 39.6% in 1993 and to 29.4% in 1998.²⁹

Secondly, Singapore's rising population density (3538/km² in 1970 to 6369/km² in 2006³⁰) provided increasing opportunities for interactions between humans and the mosquito vector. In addition, the *Aedes aegypti* mosquito exploits hard-to-find habitats in the urban environment. With the intensive vector control and source reduction programme, the *Aedes* mosquito has exploited new areas to breed and survive.

Thirdly, the predominant dengue serotype for 2001-2003 was DEN-2. This was replaced by DEN-1 in June 2004 although this strain had been circulating in Singapore since 2002. This change in dengue serotype could have exposed a significant proportion of the population who may be immunologically naive to the new circulating serotype, although this is difficult to prove conclusively. However, a displacement in predominant serotype has been associated with outbreaks in other countries.³¹ There is no evidence from gene sequencing of the dengue viruses that the epidemic was precipitated by the introduction of a new virulent strain.

Fourthly, temperature could have played a contributory role in this epidemic as demonstrated by the significant correlation between temperature and dengue incidence. In the laboratory, the rate of dengue replication in *Aedes aegypti* mosquitoes increased directly with temperature.³² Other studies have also found a correlation between average temperature and risk of dengue infection.³³ This long lag period which we found is hard to explain although a study in Barbados revealed a similarly long time-lag of 15 weeks.³⁴

Finally, although vector control remains the key component of Singapore's dengue control strategy, it had been suggested that changes in epidemiological emphasis away from vector control to case detection could have contributed to the resurgence.³⁵

Groups with Higher Incidence Rates

We found from this study that non-residents, those living in compound houses, males, Chinese and those aged 15 to 24 years had higher incidence rates compared to their counterparts.

The observed difference in incidence between Singapore residents and non-residents could be due to large numbers of immunologically naive non-residents from non-dengue-endemic countries while the higher incidence in residents of compound houses compared with residents of HDB flats and condominiums could be explained by the differential *Aedes* premises index. It had also been suggested that transmission of dengue viruses outside the home might contribute to the higher incidence in the older age groups.³⁶

For differences in gender, ethnicity and age, a seroprevalence survey in 2004 conducted by MOH involving 4152 participants aged 18 to 74 years and representative of the Singapore population suggested some paradoxical results.³⁷

Firstly, it found no statistical difference between the genders with regard to both recent and previous dengue infection. Secondly, there was no statistical difference between the ethnic groups with regard to recent dengue infection although Indians had a significantly higher overall seroprevalence compared to the Chinese and Malays. Thirdly, those aged 18 to 24 years had the lowest rate of recent dengue infection while the risk actually increased significantly with age.

Several reasons might explain this discrepancy. Different health-seeking behaviour between the various groups could be a confounder. This might partially explain the lower incidence amongst the older age groups who might have a tendency to self-medicate or seek attention from traditional healers who are not obliged to notify the MOH of dengue infection. These cases will not be reflected in notifications to MOH. As many employers require certification of unfitness to work by a registered medical practitioner before medical leave is granted, different health seeking behaviours by the gender groups due to different labour force participation rates might also be a possible factor. The differences among the ethnic groups might similarly be due to different health-seeking behaviours. Differential severity of dengue infection might also be a confounder although further research is needed.

Limitations

Reliance on notification data was a limitation on this study. Firstly, even though medical practitioners and directors of clinical laboratories were required to notify all cases of DF/DHF to MOH, mild cases with undifferentiated fevers could lead to under-reporting. Nevertheless, the high public awareness during the outbreak would have

minimised this. Secondly, the accuracy of the data used in this study was dependent on what was submitted by the medical practitioners. Thirdly, the high estimated ratio of symptomatic to asymptomatic cases of 1:19³⁷ meant that even if notification and data collection were fully complete and accurate, the epidemiological picture would still not be complete.

Conclusion

Increase in international travel,³⁸ human density and global climate change, particularly increasing temperatures, will have a significant impact on the incidence of DF.³⁹ Singapore is likely to be affected by these. It has grown steadily as an international travel hub and in the last 50 years, has seen an average temperature increase of between 1 and 1.5°C.⁴⁰ Dengue is a resurgent problem globally; and being endemic to the region, Singapore can expect dengue to recur on a regular basis. Importation of new strains of dengue virus into Singapore might also compound the problem.

As such, DF and DHF will continue to present a major public health challenge to Singapore and we have to ensure that the public health system is able to meet them. Given the high asymptomatic to symptomatic ratio of DF/DHF, it is no surprise that only a minority of cases could be epidemiologically linked to a cluster. Continued epidemiological, serological and virological surveillance, together with a heavier emphasis on entomological surveillance as well as an aggressive vector control programme which incorporates public education on dengue prevention and community participation in source reduction remain the key to control dengue transmission in Singapore. However, the development of a safe and effective vaccine against all 4 dengue serotypes might be the only definitive long-term solution to control DF/DHF in Singapore.

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