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Management guidelines for dengue patients at Tan Tock Seng Hospital and the Communicable Diseases Centre, Singapore, 2005

Notified cases of dengue infections numbered 5285 in 1998 and 1355 in 1999 in Singapore ¹. However, a historical high of 9459 cases were notified in 2004. Hitherto, as of 3 September 2005, 8850 cases have been reported ².

We have undertaken a literature review to examine the clinical features and complications of dengue virus infections, evaluate expert guidelines on clinical management of dengue, and appraise the relationship between thrombocytopenia and bleeding and whether or not there is any benefit in prophylactic platelet transfusion. In addition, a retrospective study of dengue virus infections at Tan Tock Seng Hospital and the Communicable Diseases Centre, Singapore has commenced, with preliminary results from the first 341 patients.

Definitions of dengue fever, dengue haemorrhagic fever and dengue shock syndrome

The 1997 World Health Organization (WHO)'s guide to diagnosis, treatment, prevention and control of dengue haemorrhagic fever (DHF) provides useful clinical definitions ³. In a Cuban series, these have been validated with 90% of cases diagnosed with WHO criteria confirmed by laboratory testing ⁴.

A probable case of dengue fever (DF) is defined as an **acute febrile illness with two or more of:**

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- headache,
- eye pain,
- myalgia,
- arthralgia,
- rash,
- haemorrhagic manifestations, and
- leukopenia.

It is important to recognize the many manifestations of dengue infections. A large series from Puerto Rico reported fever in 90%; headache, eye pain, myalgia, and arthralgia between 63% and 78%; rash, 50%; nausea and vomiting, 50%; diarrhoea, 30%; and cough, coryza and sore throat were present in 33% each ⁵. Likewise, in a series of 149 adult patients with DHF in Malaysia, fever was reported in 100%; headache, 81%; myalgia, 67%; arthralgia, 74%; eye pain, 34%; rash, 73%; vomiting, 63%; and sore throat, 25% ⁶.

However, the classic symptoms of headache, eye pain and myalgia were all present in only 15%-60% in four other series which involved travellers and military personnel.

The WHO clinical definition emphasizes the need to obtain laboratory confirmation of DF.

DHF is defined as the presence of:

- **fever**,
- **bleeding tendency** (the minimum of which is a positive tourniquet's test or petechiae),
- **thrombocytopenia** less than 100,000 cells/mm³, and
- evidence of plasma leakage (the earliest sign of which is a **rise in haematocrit** of more than 20% for age, gender and population).

All four must be present. However, a majority of patients admitted to hospital will have the first three signs. Some patients may not fulfil the criterion for an initial rise in haematocrit of more than 20% but may have a greater than 20% drop in haematocrit (in the absence of bleeding) after rehydration. In addition, daily clinical evaluation for pleural effusion and ascites is important.

The importance of recognising DHF earlier is its greater risk of mortality and progression to dengue shock syndrome (DSS). Over 18 years in Malaysia, DF is associated with a mortality of 0.21-0.71% in comparison with DHF with a mortality of 1.29-10.43% ⁷. In contrast, DSS has a case fatality rate of 12.9% ⁸.

DSS is defined as DHF with evidence of early circulatory failure (rapid pulse, narrow pulse pressure <20mmHg) or hypotension associated with peripheral signs of cold clammy skin and restlessness.

A **drop in platelet count** together with a **rapid rise in haematocrit** is an important and **critical early sign of DHF**, both usually occurring before fever subsides and the onset of shock. Hepatomegaly (>90% Thai children and 67% Cuban children) is observed more frequently in DHF associated with shock and acute abdominal pain is a frequent symptom before the onset of shock.

Admission criteria for dengue fever

All patients with suspected DHF should be admitted to hospital for careful monitoring and intravenous fluid replacement to prevent progression to DSS. However, while DF causes a lot of morbidity as well as incapacitates young working adults, it has a low mortality. As such not everyone needs to be admitted to hospital.



Any patients with suspected DF who are clinically unwell as defined below warrant hospitalization:

- (1) severe vomiting not relieved with oral anti-emetic preventing oral intake of fluids and severe diarrhoea not relieved with oral anti-diarrhoeal medication;
- (2) severe abdominal pain as that may herald the onset of DHF or be due to acute severe hepatitis;
- (3) dehydration as evidenced by electrolyte abnormalities or postural hypotension (more than 20 mm Hg drop in systolic blood pressure and 10 mm Hg drop in diastolic blood pressure);
- (4) elderly patients with medical co-morbidities as they are more susceptible to the effects of dehydration and studies on outpatient management of DF generally comprised young healthy adults only;
- (5) haemodynamic instability (blood pressure <90/60 mm Hg and/or pulse rate >100 beats/minute) as such patients are likely to have more severe DF;
- (6) significant bleeding manifestations as defined by persistent nose or gum bleeding, menorrhagia, haemetemesis, melaena, haemoptysis or haematuria
- (7) In addition, a patient with DF with a rising haematocrit or a haematocrit >50% is at increased risk of developing DHF and should be admitted to hospital (*Table 1*).

At the moment many doctors will admit a patient with suspected DF if the platelet count is less than 100,000 cells/mm³. The platelet count alone should not determine the need for hospitalization as discussed above. In deciding what is the appropriate threshold of platelet count for admission, we need to know the danger associated with a low platelet count, and available evidence on thrombocytopenia and the risk of bleeding in dengue infections.

There is an increased risk of bleeding when the bleeding time exceeds 10 minutes. This is detectable when the platelet count falls below 10,000 cells/mm³. The risk of bleeding is said not to be great until bleeding time exceeds 15-20 minutes, which occurs below platelet count of 5,000 cells/mm³⁹. In addition, in idiopathic thrombocytopenic purpura, spontaneous bleeding began at platelet count below 40,000 cells/mm³ and severe spontaneous bleeding was only seen at platelet count below 10,000 cells/mm³¹⁰.

Two studies (one in Kuala Lumpur, Malaysia and another in Bangkok, Thailand) have found the platelet

Table 1
Admission criteria for patients with DF (excludes DHF)

Objective criteria	Subjective criteria
(1) significant bleeding	(1) severe vomiting or diarrhoea that require i/v infusion
(2) blood pressure <90/60 mm Hg and/or pulse >100 beats/minute	(2) severe abdominal pain
(3) dehydration with electrolyte abnormalities and/or postural hypotension	(3) elderly patients with medical co-morbidities who are unwell
(4) haematocrit >50%	
(5) platelet count <80,000 cells/mm ³	



count in dengue infections did not predict bleeding^{15,16}. A retrospective study at Tan Tock Seng Hospital in 1992 reported 14.6% of patients (84.6% had DF and 14.6% had DHF) had non-life threatening bleeding (mainly gum and nose bleeding, and menorrhagia)¹¹. A prospective study in Kuala Lumpur, Malaysia (82.7% DF and 13% DHF), reported 7.1% of patients had bleeding, none of which was serious¹². The risk of bleeding appears to be greater in DHF: half the adults and children with DHF in Cuba had spontaneous petechiae; haemetemesis, 15%-30%; melaena, 5%-10%; menorrhagia, 40%; and epistaxis, 10%.

Therefore, it appears that provided a patient with DF (not DHF) is clinically well, as previously defined, admission to hospital on platelet criterion need not occur until the platelet count falls below 50,000 cells/mm³. This has been validated in a prospective study in Malaysia where 162 young adults were followed daily in outpatient and the admission criteria were bleeding (except petechiae), blood pressure <90/60, haematocrit >50% and platelet count <50,000 cells/mm³. All patients with DSS and 90% of DHF were admitted. Sixty six percent of DF was treated as outpatients. There was no death. The admission rate was reduced to 43.8% from 72% if the platelet threshold was 100,000 cells/mm³¹².

In summary, in addition to the above criteria of admission based on a clinically unwell patient, and a rising haematocrit or a haematocrit >50%, taking into consideration of logistic issues, patients should also be admitted to hospital if their platelet count falls below 80,000 cells/mm³ in the local setting.

Guide to management of DF and DHF

When DSS develops, a patient will need high dependency and intensive care management for blood

pressure support, monitoring of volume status and renal function, correction of disseminated intravascular coagulopathy, electrolyte abnormalities and metabolic acidosis, and potentially ventilatory support. In DSS, unusual manifestations of dengue infection such as dengue encephalitis, myocarditis, acute fulminant hepatitis and acute respiratory distress syndrome may complicate a patient's clinical course. Further discussion of the management of DSS is beyond the scope of this guide, which will focus on ward management of a patient with suspected DF or DHF.

A well patient with DF who is admitted for thrombocytopenia or bleeding and who can otherwise maintain good oral intake derives no additional benefit from intravenous fluid. A clinically dehydrated patient (mild tachycardia, postural hypotension, undetectable jugular venous pressure) with DF should have intravenous fluid replacement therapy and cautious correction of any electrolyte abnormalities. In general, intravenous dextrose saline 1.5 litres a day for a 50 kg person to 2 litres a day for a 60 kg person should be adequate. Hypokalaemia should be corrected with either oral potassium supplementation or intermittent doses of intravenous potassium instead of continuous intravenous potassium infusion in the absence of severe persistent vomiting and diarrhoea.

Symptomatic relief for various clinical symptoms of DF is important for the patient's well being. Anti-emetic and anti-diarrhoeal drugs should be prescribed for symptomatic patients as needed. Anti-histamine can help alleviate the pruritic rash of DF. An antacid or a type 2 histamine receptor blocker may ease symptoms of gastritis.

Progesterone can reduce menorrhagia aggravated by thrombocytopenia. Persistent epistaxis needs



review by an ear nose and throat surgeon as it may need nasal packing.

Paracetamol can alleviate fever $>39^{\circ}\text{C}$ although it should be avoided if there is severe transaminitis. Sponging to help reduce high fever is indicated in that context. Salicylates such as aspirin and non-steroidal inflammatory drugs should be avoided for analgesia or anti-pyrexia as they may cause gastro-intestinal bleeding (*Table 2*).

Intramuscular injections should not be administered to patients with dengue infections and thrombocytopenia.

A patient admitted for DF should be carefully evaluated clinically for the development of DHF, as evidenced by a rapidly falling platelet count concurrent with a rapid rise in haematocrit, development of a pleural effusion or ascites. This tends to occur 24 hours before and after defervescence.

Intravenous fluid replacement is the main potentially life-saving modality of therapy for a patient with DHF. In practice, 2 to 3 litres a day of intravenous dextrose saline is adequate with careful moni-

toring of volume status (jugular venous pressure, auscultation of lung bases, presence of ankle oedema) and daily haematocrit assessment. (WHO recommends an initial intravenous fluid infusion rate of 6 ml/kg/hour, reducing to 3 ml/kg/hour with clinical response or increasing to 15 ml/kg/hour with clinical worsening³. This equates to 4.3 litres a day to 21 litres a day in a 60 kg person. This is clearly not pragmatic in an adult without intensive monitoring of volume status). Intravenous fluid therapy can be reduced if haematocrit is decreasing in a clinically improving patient and often can be stopped when the patient has return of appetite and can maintain good oral intake. In general, intravenous fluid therapy need not continue for more than 48 hours in a patient who has normal vital signs, good oral intake and urine output, and normal haematocrit.

A patient admitted for DHF should be carefully evaluated clinically for the development of DSS, which may manifest as tachycardia or narrow pulse pressure before the onset of shock.

Monitoring for bleeding tendency is important in DF and DHF. Management of mild bleeding has

Table 2
Symptomatic treatment of patients with dengue infections

Symptom	Recommended treatment
Nausea or vomiting	Anti-emetic (e.g. metoclopramide 10mg four times daily as needed)
Diarrhoea	Anti-diarrhoeal (e.g. loperamide one tablet four times daily as needed)
Itchy rash	Anti-histamine
Gastritis	Antacid or type 2 histamine receptor blocker
Menorrhagia	Progesterone (e.g. norethisterone 5mg three times daily)
Nose bleed	May need nasal packing if persistent
Fever $>39^{\circ}\text{C}$	Paracetamol (avoid if severe hepatitis), sponging (avoid salicylates and nonsteroidal anti-inflammatory drugs)



already been alluded to (epistaxis and menorrhagia). Gum bleeding is usually minor and patients should be advised to avoid brushing teeth. The patient should be asked daily about other bleeding tendency especially haemetemesis and melaena. Upper gastro-intestinal bleeding should be managed by prescribing a proton pump inhibitor, correcting any coagulopathy and thrombocytopenia, and referring to an endoscopist if active bleeding continues or haemodynamic instability occurs. Bleeding appears to be more frequent and more severe in DHF compared with DF, as previously discussed.

Platelet transfusion

Prospective study in the setting of acute leukaemia and post-chemotherapy has shown no increased risk of significant bleeding and requirement for red cell transfusion if prophylactic platelet transfusion occurred at a trigger of 10,000 platelets per mm^3 compared with 20,000 platelets per mm^3 ¹³. Previously discussed evidence in idiopathic thrombocytopenic purpura adds further support to the low risk of severe bleeding with platelet count $>10,000$ cells/ mm^3 .

The following recommendation is made for platelet transfusion^{1,14}:

- (1) In a well patient with no fever and clinical bleeding, platelet transfusion is indicated if less than 10,000 platelets per mm^3 .
- (2) If there is fever or mild self-resolving bleeding, platelet transfusion is indicated if less than 20,000 platelets per mm^3 .
- (3) With significant bleeding (e.g. haemetemesis, melaena, persistent epistaxis, haemoptysis or haematuria), platelet transfusion is indicated.

Preliminary results from an ongoing retrospective study at Tan Tock Seng Hospital showed no difference in clinical bleeding among patients with platelet count less than 20,000 cells/ mm^3 irrespective of whether they were transfused (20%) or not transfused (17.8%). Transfusion of platelet did not correlate with speed of recovery.

Criteria for discharge from hospital

Even in patients with DHF, clinical recovery is rapid once fever settles, appetite returns, and platelet count begins to rise. The 1992 Tan Tock Seng Hospital study has shown no secondary fall in platelet count once it rises on two consecutive days¹¹. Previously discussed evidence suggests little risk of bleeding once platelet count is above 50,000 cells/ mm^3 . Our ongoing local retrospective study showed no influence of platelet transfusion on the upward trend of the platelet count during the convalescent phase.

The most recent 1997 WHO guideline on the management of DHF and DSS recommends discharge from hospital when:

- (1) there is no fever for 24 hours without anti-pyretic medication;
- (2) return of appetite and good urine output;
- (3) visible clinical improvement and no respiratory distress from pleural effusion or ascites;
- (4) stable haematocrit;
- (5) at least 2 days after recovery from shock; and
- (6) platelet count above 50000 cells/ mm^3 .

We recommend that DF patients can be discharged from hospital once they have no fever for 24 hours without anti-pyretic medication, have good oral



intake, normal vital signs and stable haematocrit, and rising platelet count with the last above 50,000 cells/mm³. DHF patients should not have respiratory symptoms secondary to resolving pleural effusion or ascites.

Outpatient management of young adult patients with dengue fever

Patients who are initially not admitted for dengue fever (all DHF patients should be admitted) should

be assessed daily by their general practitioner or at the polyclinics. The clinical assessment includes checking blood pressure, pulse rate and temperature daily and daily full blood count to monitor the platelet count and haematocrit. All patients should have a dengue confirmation test (preferably dengue serology, to be repeated if the first sample is negative). Patients will be admitted if blood pressure <90/60 mm Hg, bleeding (except petechiae), platelet count <80,000 cells/mm³ or haematocrit >50%.

(Reported by Dr David Lye, Associate Consultant, Dept of Infectious Diseases, Tan Tock Seng Hospital, with input from Department staff).

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Epidemiology of childhood infectious gastroenteritis in Singapore: how effectively can we control it?

Introduction

Acute infectious gastroenteritis remains an important cause of morbidity among children in Singapore. It represented 1.5% and 2.4% of paediatric admissions under 15 years of age in 2003 and 2004, respectively.

A better understanding of the aetiologies, temporal changes in their distribution, and availability of effective prevention and control measures will assist in implementing effective interventions.

This study explored temporal changes in the trend of acute childhood diarrhoeal illnesses in Singapore, as well as the distribution of implicated bacterial and viral aetiological agents.

Method

Hospital admissions at the Kandang Kerbau Women's and Children's Hospital (KKH) due to in-

fectious intestinal diseases in children under 15 years of age in the past 2 years were studied.

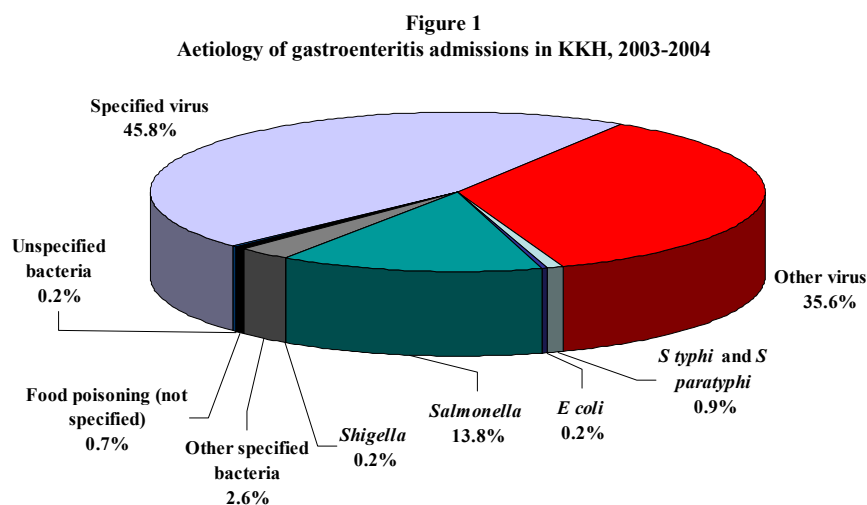
Morbidity statistics obtained from the hospital inpatient wards were analysed and interpreted together with concurrent laboratory-based surveillance information.

Temporal and demographic differences in incidence and aetiological distribution of patients were compared.

Results

A total of 1226 cases of acute gastroenteritis (<15 years) were admitted to KKH in 2003 and 2004. A breakdown of the causative agents is shown in *Fig 1*.

Bacterial agents accounted for 17.9% of the cases and *Salmonella* was the major cause (76.8%) of bacterial diarrhoea in children.



Routine laboratory tests identified *Campylobacter* in 4.7% and 2.9% of stool cultures in 2003 and 2004, respectively.

Viral pathogens accounted for 81.4% of episodes of acute infectious diarrhoea in children.

Routine diagnostic laboratory data identified rotavirus in 12.2% and 19.5% of stool specimens tested for the viral antigen in 2003 and 2004, respectively.

The weekly rotavirus antigen-positive rates closely followed the trend of total gastroenteritis admissions in both years (Fig 2).

No seasonal pattern was observed and there was a 57.6% increase in admissions due to acute gastroenteritis from 2003 to 2004. Rotavirus antigen-positive rates rose by 59.7% in 2004 as well.

The average length of hospitalization among patients was 4 days, ranging from 1 day to 47 days.

The proportion of Indian and Malay children admitted for gastroenteritis was relatively high (Fig 3), as compared to the general population.

More than half (56.9%) of patients under 15 years old were aged between 1 year and 4 years (Fig 4).

Figure 2
Comparison of rotavirus antigen-positive samples with gastroenteritis admissions, KKH, 2003-2004

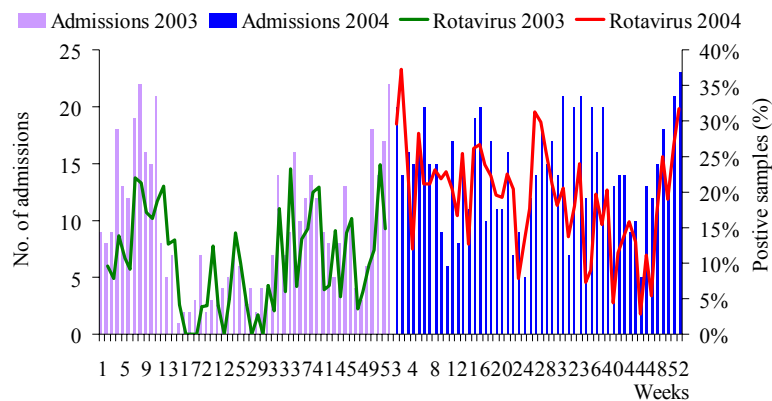


Figure 3
Ethnic distribution of gastroenteritis admissions, KKH, 2003-2004

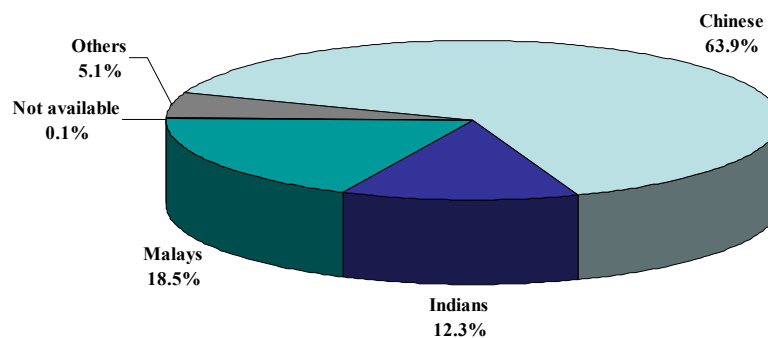
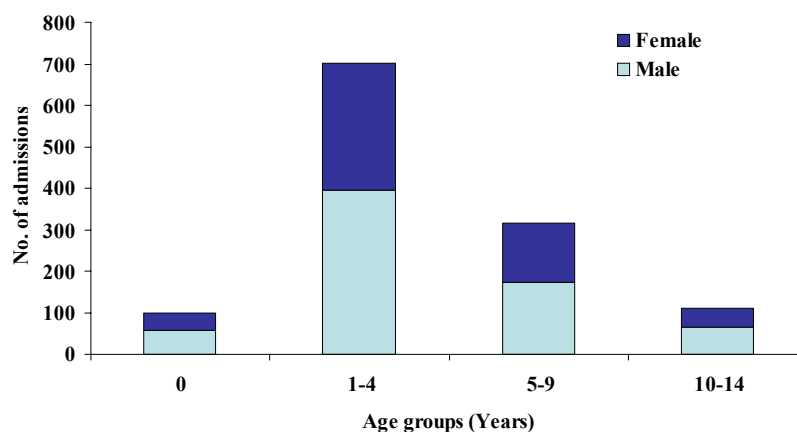


Figure 4
Age and gender distribution of gastroenteritis admissions, KKH, 2003-2004



Comments

Childhood diarrhoea of infectious origin contributes approximately 1–2 % of inpatient morbidity in Singapore, and viral infections remain the most common cause. Unlike in temperate countries, no seasonal pattern was observed¹. Enteritis due to a specified virus, which was the major aetiology of gastroenteritis, includes rotavirus, adenovirus and Norwalk viruses. Further analysis of the various viral pathogens should be conducted. Ethnic-related differences in diet and methods of food preparation could be examined to determine the cause of higher morbidity in certain ethnic groups.

Only supportive therapy is available for viral gastroenteritis² although some viral vaccines, such as rotavirus vaccines, would be useful to reduce the burden of disease in some settings.

Public education on proper food handling and good hygiene practices should be maintained throughout the year. As children aged between 1 and 4 years constituted the majority of patients, education activities should be extended to the childcare centre.

A multi-pronged approach to the prevention and control of gastroenteritis in the community is essential.

(Reported by Lum MY, Ye T, Ang LW and Chow A, Communicable Diseases Surveillance, Ministry of Health)

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Acknowledgements

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An update on the dengue situation in Singapore

Dengue is endemic in Singapore, with year-round transmission observed. In the past two decades, a surge in cases has been observed in 1992, 1998 and 2004.

In 2005, the number of dengue fever (DF)/dengue haemorrhagic fever (DHF) cases has increased since May, following a decline from January to April. In the first half of the year, a weekly average of 204 dengue cases was reported. A surge in the weekly number of cases to 546 was observed in the last week of August. As of 17 September 2005, 10,237 cases have been notified to the Ministry of Health (MOH) (Fig 5). Thus far, there have been 8 dengue-related deaths reported this year.

The majority (99%) of cases were acquired locally. In previous years, HDB dwellers represented 46% to 65% of reported dengue cases annually. This

proportion has increased to about 75% in 2004 and 2005 (Fig 6).

Geographically, dengue has established itself in previously classified low-endemic areas in the western part of the island since 2004 (Figs 7-9).

A higher proportion of males have been affected, with a male-to-female ratio of 1.4:1 in 2005. Majority of the infected were aged 15 years and above. The highest incidence occurred in young adults aged 15–24 years. Children under the age of 5 years had the lowest incidence. However, the age-specific incidence for the age group 5–14 years has increased significantly from 2003 to 2004 (Figs 10 & 11). In 2005, this age group represented 13% of the reported cases (Fig 12). Overall, adults aged 15–44 years represented 68% and 65% of dengue cases in 2004 and 2005, respectively.

Figure 5
Dengue notifications and incidence rate, 1984 - 17 Sep 2005

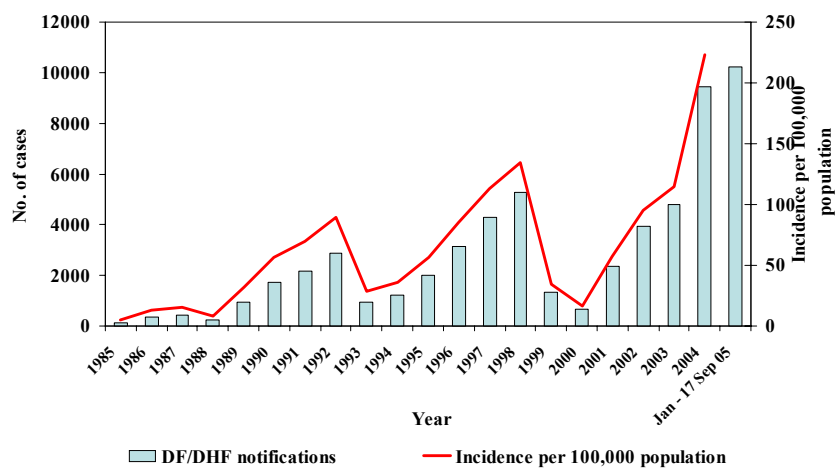


Figure 6
Distribution (%) of dengue cases by housing type, 1991 - 17 Sep 2005

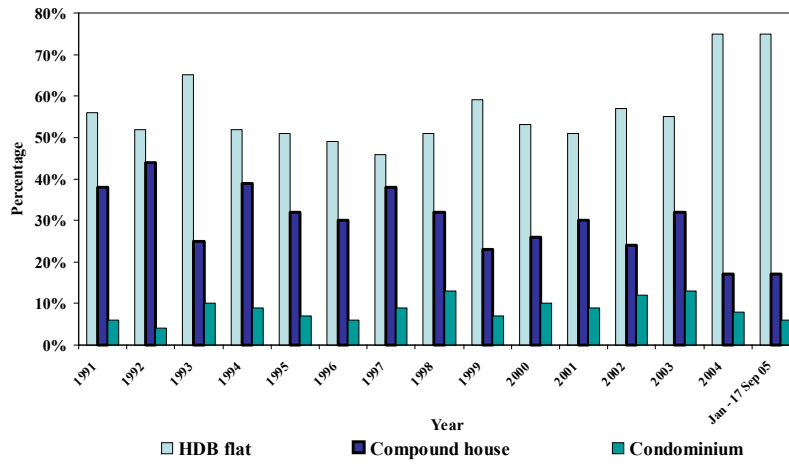


Figure 7
Distribution (%) of dengue cases by Development Guide Plan zone, 2003

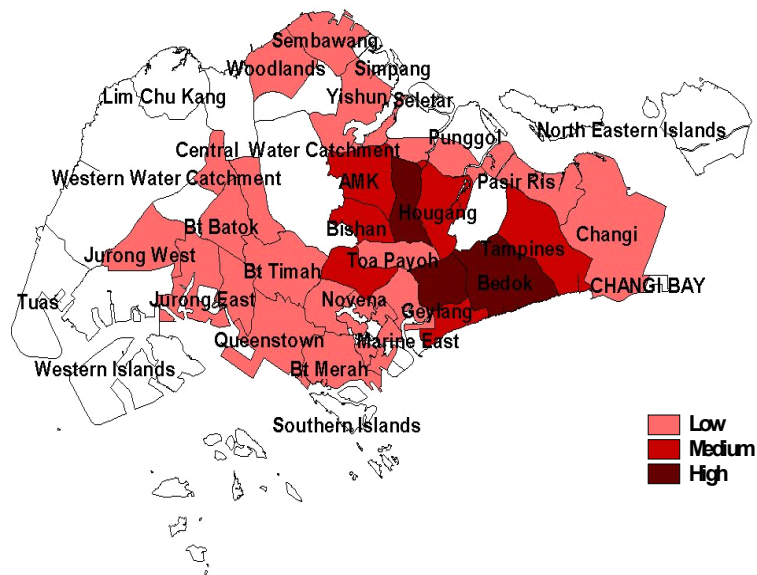


Figure 8
Distribution (%) of dengue cases by Development Guide Plan zone, 2004

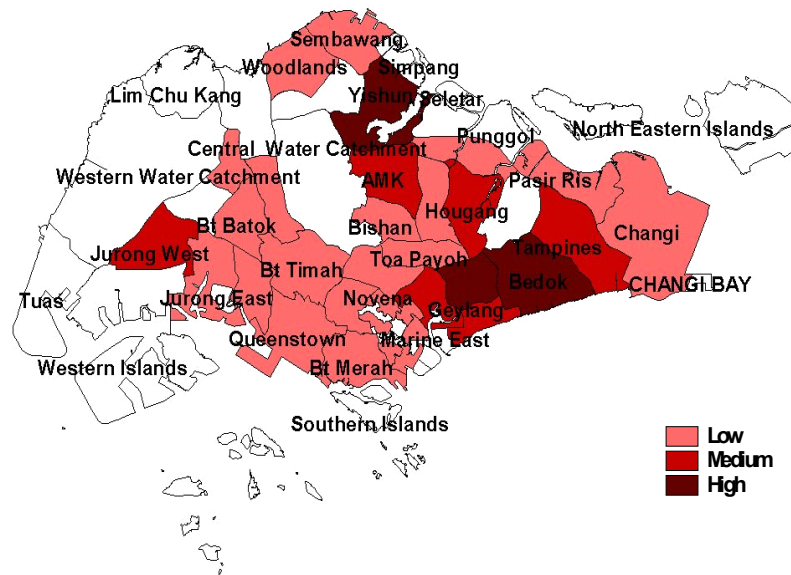


Figure 9
Distribution (%) of dengue cases by Development Guide Plan zone, Jan – 17 Sep 2005

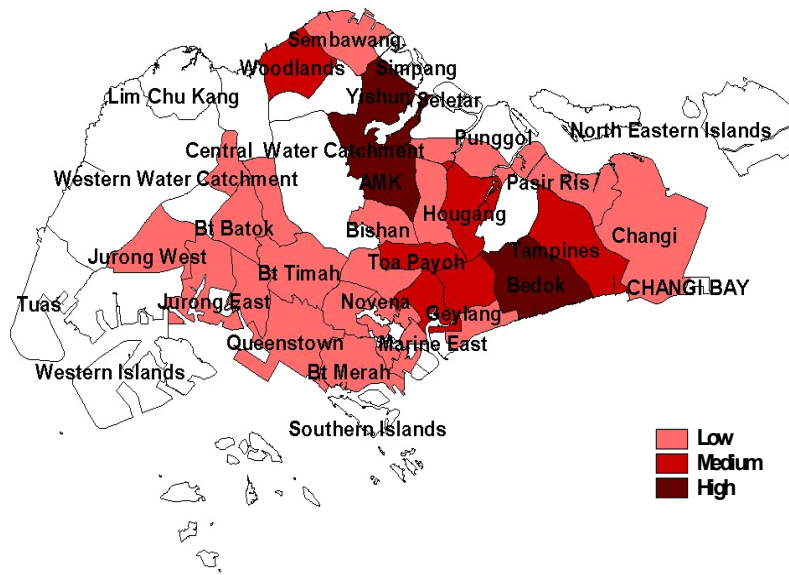


Figure 10
Age-specific dengue incidence in males, 1999-2004

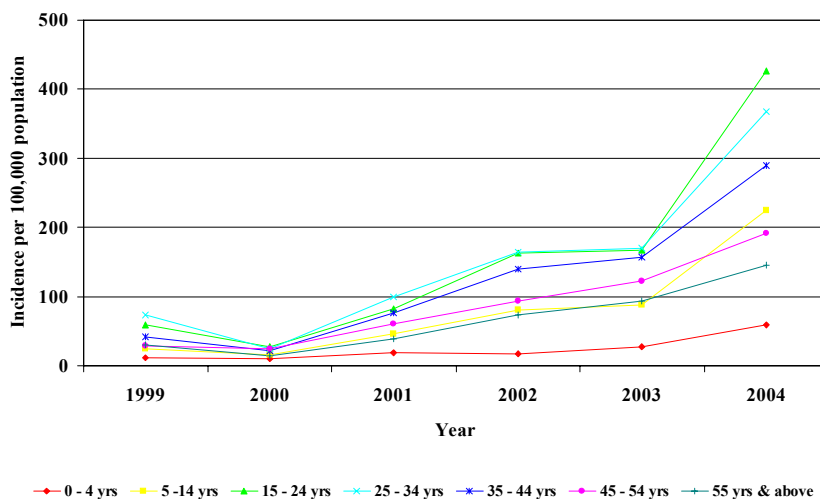


Figure 11
Age-specific dengue incidence in females, 1999-2004

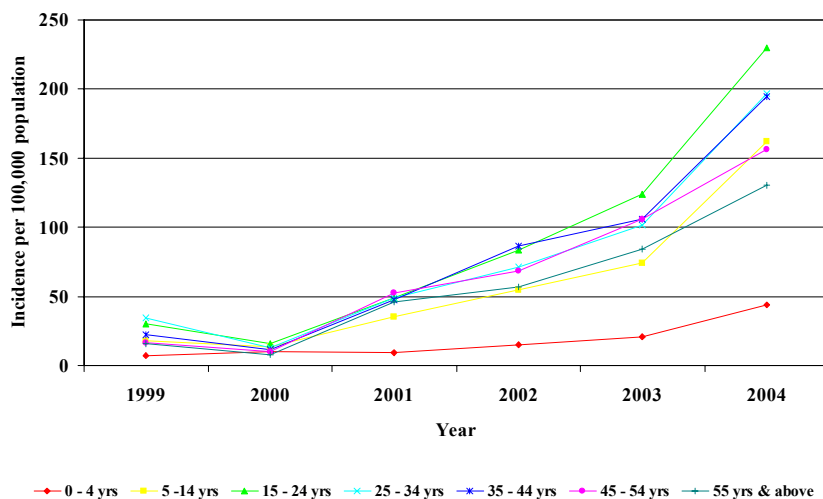
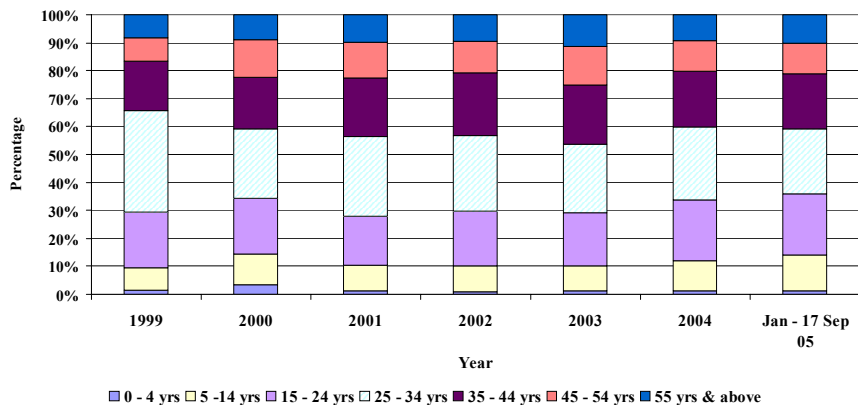


Figure 12
Age distribution (%) of dengue cases, 1999 - 17 Sep 2005



In terms of circulating virus strain, DEN-1 remains as the predominant strain even though DEN-3 has become more prevalent in recent months (*Fig 13*). The predominant circulating dengue virus serotype had shifted from DEN-2 in 2001-2003 to DEN-1 in 2004-2005 (*Fig 14*).

In Jul and Aug 2005, DHF contributed to 3.2% and 2.1%, respectively, of all reported cases. Over the past 20 months (Jan 04-Aug 05), the proportion of DHF in total dengue notifications remained low at 0.6-6% (*Fig 15*).

To date, there have been 8 reported dengue deaths this year, giving a case fatality rate (CFR) of 0.9 per 1,000 cases. The CFR has declined over the past 5 years. In 2004, the CFR was less than 1 per 1,000 cases (*Fig 16*).

The number of dengue hospitalizations decreased from late-2004 to April 2005. However, there

has been a sharp increase since May 2005, which corresponded with the observed increase in reported cases.

In May 2005, the utilisation of bed days for patients with dengue fever at public hospitals ranged from 0.8% at National University Hospital (NUH) to 2.7% at Tan Tock Seng Hospital (TTSH) /Communicable Disease Centre (CDC) (*Figs 17 & 18*). By August 2005, dengue has taken up 6% of available bed-days in TTSH/CDC, Alexandra Hospital (AH) and Changi General Hospital (CGH), and around 3% for NUH and Singapore General Hospital (SGH).

Data from the Centre for Transfusion Medicine show that platelet transfusions for dengue accounted for more than 10% of all such transfusions in June 2005 (423 out of 4017 units transfused). The number of platelet transfusions for dengue increased by 48% from 286 units in Jan 2005 to 423 units in June 2005.



Figure 13
Dengue virus serotypes (%), Jan 2004 - Aug 2005

(Singapore General Hospital Department of Pathology, Environmental Health Institute, Tan Tock Seng Hospital Department of Pathology and Laboratory Medicine, National University Hospital Laboratory, and Kangdang Kerbau Hospital Laboratory)

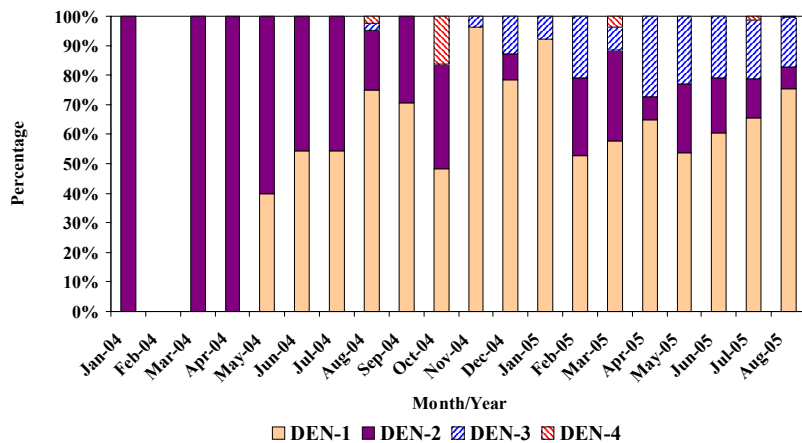


Figure 14
Dengue virus serotypes (%), May 1992 - Aug 2005

(Singapore General Hospital Department of Pathology, Environmental Health Institute, Tan Tock Seng Hospital Department of Pathology and Laboratory Medicine, National University Hospital Laboratory, and Kangdang Kerbau Hospital Laboratory)

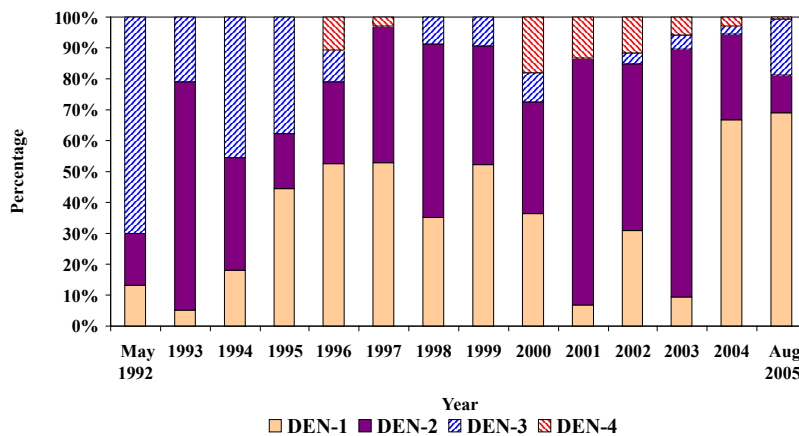


Figure 15
DF/DHF monthly notifications, Jan 2004 - Aug 2005

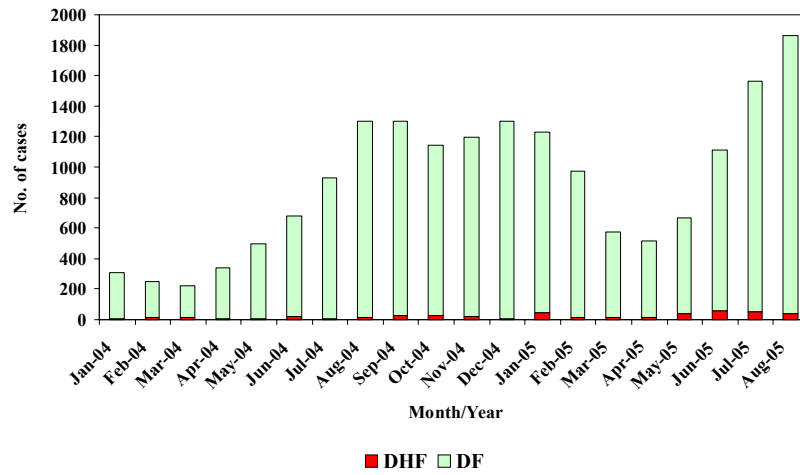


Figure 16
DF/DHF case fatality rate (per 1,000 cases), 2000 - 2004

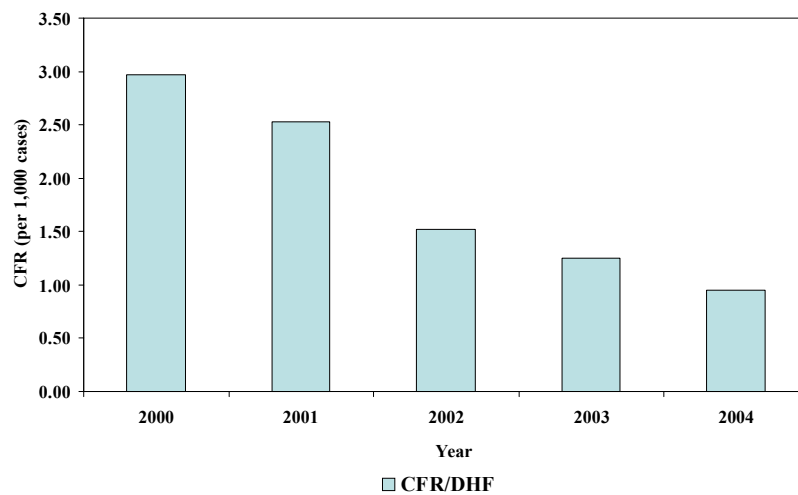


Figure 17
DF/DHF monthly hospitalisations, Jan 2004 –Jul* 2005

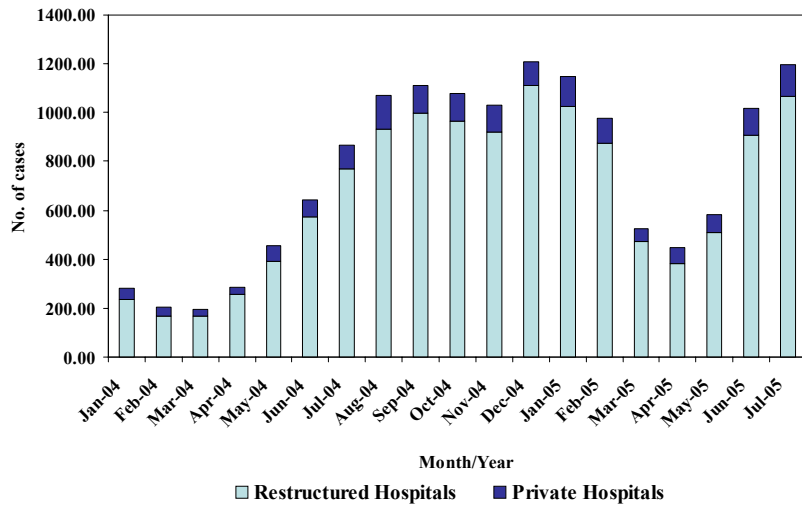
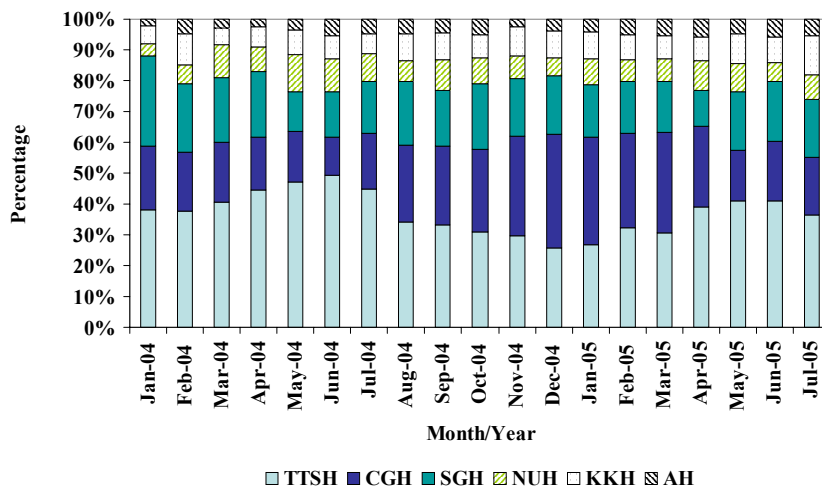


Figure 18
DF/DHF monthly hospitalisations, Jan 2004 – Jul* 2005
(restructured hospitals)



* Number for Jul 05 is preliminary.

(Reported by: Chow A, Ye T, Ang LW, Foong BH, Kita Y, Communicable Diseases Surveillance Branch, MOH).



Aedes mosquito surveillance, control and research in Singapore

The *Aedes* control programme in Singapore consists of three key elements – active surveillance, public education and community involvement and enforcement.

Active surveillance

The National Environment Agency (NEA) conducts active surveillance in areas prone to dengue and/or high density of mosquitoes (e.g. construction sites, schools, compounds of landed properties). On the average, some 40,000 residential premises and 900 non-residential premises and grounds (construction sites, schools, etc.) are inspected every month.

Areas that are prone to dengue constitute about 10% of Singapore's land area, and are surveyed once in every six months. Surveillance operations are coordinated through the Situation Room located at NEA HQ, using a Geographical Information System (GIS), to monitor and analyse the distribution of *Aedes* mosquitoes and dengue cases.

Public education and community involvement

NEA carries out public education on dengue through posters at bus shelters and MRT stations, panels in MRT and LRT trains, advertisements in newspapers, and dengue messaging on radio. For private and public organisations (e.g. schools, construction sites), NEA works with them to put in place dengue control programmes; for example, the Environmen-

tal Control Officers (ECOs) programme for construction sites.

In Apr 2004, the 'Mozzie Attack' programme was launched with the aim to encourage residents to get rid of stagnant water that can potentially breed mosquitoes in their homes. The programme has successfully rolled out in all 84 constituencies in Singapore. NEA also keeps the grassroots and other agencies updated regularly, and actively engage the members of the public as well as other key strategic partners such as the Community Development Councils in the common fight against the *Aedes* mosquito. [A Community Development Council is a committee that is appointed in each of the five Districts in Singapore (each District comprising one or more electoral constituencies). Chaired by a Mayor, it functions as a local administration of its District, initiating, planning and managing community programmes to promote community bonding and social cohesion]. NEA has also assisted in the formation of Dengue Prevention Volunteer Groups to further bring the dengue prevention message to the grassroots.

Enforcement

The Control of Vectors and Pesticides Act is the main legislation dealing with propagation of conditions conducive for mosquito breeding. NEA typically enforces the law against recalcitrant persons who continually breed mosquitoes or do not remove potential mosquito breeding habitats in their premises despite having being told to do so.



Owners of residential premises found with mosquito breeding are fined \$100 for the first offence and \$200 for repeat offences. For non-domestic premises (e.g. commercial buildings and temples) found with mosquito breeding, the owner of the premises will be fined \$200. The corresponding penalties for construction sites are heavier (starting at \$2,000), given the greater propensity for breeding to be found in these premises.

NEA's key operational strategies in dengue control

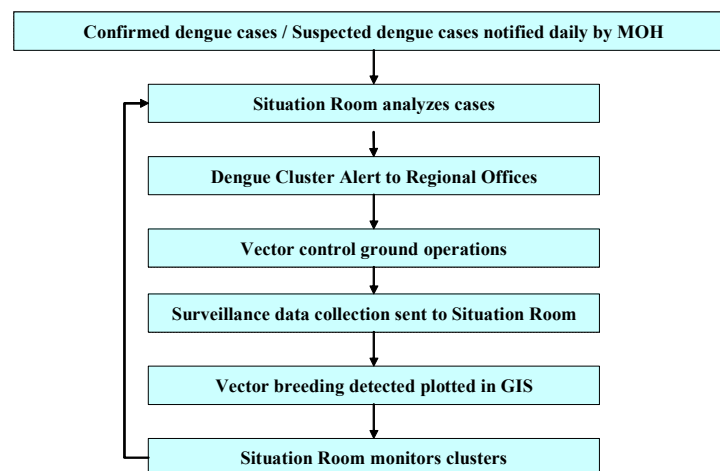
Currently, Ministry of Health (MOH) notifies NEA of suspected/confirmed dengue cases. When dengue cases are reported in an area, NEA will carry out search and destroy and fogging operations at the affected locality and the immediate neighbourhood quickly. The objective is to break the disease transmission by preventing more mosquitoes from breeding through removal of all breeding sources as well as killing the adult mosquitoes which could be carrying the dengue virus.

When a dengue cluster (i.e. 2 or more dengue fever cases within 150 metres of their respective residential/workplace addresses and within 14 days of their respective onset dates) is reported, NEA will send in an outbreak control team to thoroughly comb the area and carry out fogging and follow-up checks until the cluster is closed. NEA will also alert the residents and rope in the grassroots organisations to help in an immediate outreach programme in which residents in the affected area are advised to remove the breeding habitats in their homes. About 88% of the clusters are closed within 14 days from the onset date of the last reported case. However, clusters accounted for only about a third of the reported cases. The entire operational workflow is illustrated in *Fig. 19*.

Research

The Environmental Health Institute (EHI), established in April 2003, researches on infectious diseases of public health concern, with focus on vector-borne diseases. Staffed with 6 post graduate degree (PhD and Masters) holders that specialize in ento-

Figure 19
Operational workflow for dengue control



mology, microbiology and immunology, and 20 bachelor graduates and diploma holders, EHI works on 4 programmes: vector control, epidemiology, surveillance and diagnostics.

Vector control

The Vector Control programme seeks to understand the behaviour of mosquitoes, and develop and evaluate vector control tools and measures. Some examples of the research and the findings are described below.

Aedes flight range

Research at EHI has shown that *Aedes* mosquitoes in Singapore have a flight range of at least 560 m in urban setting, and 740 m in rural areas¹. This is in contrast to traditional belief that they do not fly more than 100m. In addition, it was also found that the *Aedes* mosquitoes could disperse through all 21 floors of an apartment block after their release from the 12th floor. Their competence in long-range flight for oviposition (laying eggs) may suggest that the successful minimisation of potential breeding sites in Singapore has forced them to go further for oviposition.

Aedes adaptation

A study conducted at EHI demonstrated the ability of *Aedes* mosquitoes to adapt². Mosquitoes bred from clean water had preference for clean water for oviposition. However, when bred in water with repellent, the new generation of *Aedes* showed no preference between clean water and water with repellent.

New vector control tools and strategies

Besides introducing environmentally friendly and effective biological agents (*Bacillus thuringiensis*

israelensis, Bti) for control, EHI has also developed the gravitrap (lethal ovitraps) for trapping both larvae and adults of *Aedes* mosquitoes. Feasibility test on such a mosquito control method will be conducted after mass production of the traps in 3 months' time. Meanwhile, a pilot study will be conducted, using conventional ovitraps for monitoring *Aedes* population, and possibly for controlled breeding. Community participation will be considered for this pilot.

Effectiveness of insecticides

Efficacy and resistance testings are regularly done to ensure that the 2 major mosquitoes (adults and larvae) in Singapore, *Culex* and *Aedes*, are susceptible to the chemicals used.

Transgenic mosquitoes for vector control

As a long-term project, EHI is working with OxiTech (UK) and Oxford University, to explore the use of dominant lethal male *Aedes* to control mosquito population to a lower level.

Epidemiological research

The research programme aims to understand the transmission dynamic of dengue in Singapore. Dengue occurs in cycle within the year, usually peaking in the hottest months of June to August, like in other countries in the region. However, last year, we were hit by an unusual cycle, which lasted till February 2005. As a result, at the lowest point in April 05, the number of human cases remains as high as the peaks of 2002 and 2003. Data from the previous years is currently under analysis to gain a better understanding of the situation.

Under the programme, transmission dynamic within a dengue cluster is analysed to support opera-



tions. Antibody tests are performed on volunteers to determine the level of immunity to dengue within a population. The project also seeks to determine the proportion of asymptomatic and undiagnosed cases.

Singapore sees regular importation of dengue cases. Nucleotide sequencing of part of the viruses has been performed on isolates of DEN 1, 2 and 3 from recent years, to understand the impact of importation. Phylogenetic analysis shows that majority of each serotype clusters tightly in a group, suggesting local transmissions. More sequencing will be performed to determine when the virus was introduced. In addition, aided by experiments in human cell line and mosquitoes, EHI seeks to determine the epidemic potential of the viruses.

Surveillance

Surveillance at EHI seeks to monitor the re-emergence of new serotypes and emergence of new strains of dengue virus. Spatial and temporal distribution of the four serotypes of dengue is analysed. EHI has developed a PCR serotyping technique, which has increased the throughput of serotype surveillance. Ongoing surveillance and research projects have shown a non-uniform distribution of serotypes in Singapore. As a result, a collaborative project has been initiated among MOH, NEA and Tan Tock Seng Hospital to understand the distribution of the 4 serotypes, and possibly understand the impact of the emergence of new serotype in a region.

(Reported by Tan H K, Environmental Health Department and Ng L C, Environmental Health Institute, National Environment Agency).

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Working with the Dengue Consortium, which comprises the Genome Institute of Singapore and Novartis Institute of Tropical Disease, EHI has commenced on whole genome sequencing to detect emergence of new strains, and mutations that may have altered the properties of the virus.

Besides viruses from humans, EHI has initiated a project on isolation of viruses from *Aedes* larvae. Adult female *Aedes* is known to be able to transmit dengue virus to its eggs, which subsequently develops into infected larvae. Though the rate of transmission is reportedly less than 3%, EHI will test the feasibility of using its in-house developed PCR for such purpose.

Diagnostic and pathogenicity

Laboratory diagnosis of dengue fever serves a number of functions: management and treatment of patients; outbreak control; and epidemiological surveillance. Working very closely with various hospitals like Tan Tock Seng Hospital, National University Hospital and Kandang Kerbau Hospital, EHI has developed diagnostic tools to target the various stages of the disease.

In addition, EHI supports various research projects conducted at Tan Tock Seng Hospital, which seeks to understand the clinical aspects of dengue; eg, to determine any predictors of dengue haemorrhagic fever, and the pathogenicity of ocular manifestation among some dengue patients.



A cluster of imported falciparum malaria, Sept 2005

In Sep 2005, the Ministry of Health (MOH) identified a cluster of falciparum malaria cases involving Nigerian students who had recently arrived in Singapore. The first case was a 23-year-old female student who arrived on 5 Sept 2005 and developed fever the following day. She was treated at East Shore Hospital (ESH) and notified to MOH as a malaria case on 7 Sep 05. Subsequently, another seven students, all males, aged 20-25 years, developed fever between 13 and 16 Sept 05. They were notified by Singapore General Hospital (SGH) on 18 and 19 Sept 05.

Epidemiological investigations showed that the cases were part of a cohort of 72 young Nigerians (age range 17-27 years) who had been selected by a local informatics company for training in Singapore under a 2-year study programme run by the company's school of business. They were drawn from various parts of Jigawa State in Nigeria through a rigorous process conducted by the company. Prior to their arrival, they had lodged at a hostel in Kazaure for about 2 weeks before moving to Lagos. From there, they flew in batches via Dubai to Singapore from 5-8 Sept 05.

In Singapore, the Nigerian students stayed at a private hostel in Tanjong Katong. Health officers immediately carried out fever surveys and active case finding among the students of the hostel and residents in the vicinity. The hostel could house a maximum capacity of 800 residents and had some 680 other foreigner students from various countries. None of them were found to be symptomatic. The management of

the hostel was further instructed to monitor their residents and seek medical consultation to exclude malaria for any of the students developing symptoms.

Blood screening of the Nigerian students for malarial parasites was also conducted. A total of 181 blood films were taken on 21, 22, 26 and 29 Sept 05, and 13 students tested positive for *Plasmodium falciparum*. Twelve of them were asymptomatic while one developed fever on 25 Sept 05. They were referred to hospital for treatment and isolation. All the cases recovered.

While Tanjong Katong is not a malaria receptive area, the National Environment Agency was alerted on 19 Sep 05. The housekeeping of the premises was found to be satisfactory. There were no habitats within the premises that were conducive for the breeding of *Anopheles* mosquitoes although the drains were subjected to tidal influence. There was also no major construction activity or foreign workers' quarters in the vicinity. Nonetheless, as a precautionary measure, the hostel management activated their pest control operators to carry out night thermal fogging.

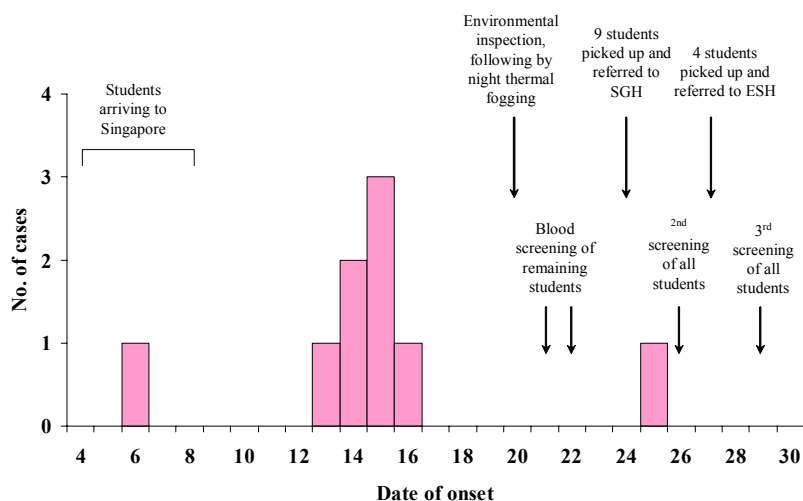
The epidemic curve of the imported cases and actions taken are depicted in *Fig 20*.

Comments

Falciparum malaria is an infectious disease of major public health importance. The incubation period for *P. falciparum* is 9-14 days¹, while the extrinsic incubation period (time needed for the malarial



Figure 20
Time distribution of 9 malaria cases involving Nigerian students in Singapore, Sep 2005



parasites to undergo development within the mosquito vector before they are infectious to humans) is 10-21 days². Working backwards on the likely source of infection based on the dates of onset of the patients from 6-16 Sept 05 and the known incubation period of 9-14 days, a common source exposure to infective mosquitoes would have likely occurred between 28 Aug and 2 Sep 05. This strongly implicated Kazaure in Nigeria as the place where transmission occurred. Further investigation revealed that there was an outbreak of malaria occurring in Kazaure at the time when the students were staying there.

Singapore has been certified by the World Health Organization to be free of indigenous malaria since Nov 1982³. Despite this achievement, the country remains both vulnerable and receptive to the re-introduction of malaria; vulnerable, because of the constant influx of travellers and receptive, because of the presence of *Anopheles* vectors. This cluster of imported falciparum malaria cases was picked up by the comprehensive and well-established system of epidemiological surveillance. Vigilance in detecting cases remains the key to prevention and control of malaria in Singapore.

(Reported by Han HK, Lim J, Abdul Rahman, Png CK, Lim S, Ooi PL, Disease Control Branch, MOH).

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Epidemiology of food poisoning outbreaks in Singapore, 2001-05

Introduction

Food poisoning is a term applied to illness acquired by consumption of contaminated food. These illnesses are caused by microbes, toxins, or foreign agents and chemicals not normally found in food. An outbreak occurs when two or more cases experience similar illness resulting from ingestion of a common food. In the surveillance of food poisoning outbreaks in Singapore, the Ministry of Health (MOH) receives notifications through a number of channels and conducts epidemiological investigations into substantiated incidents. These notifications may come directly through the MOH_Info email line, or direct calls to the Disease Control Branch and/or Corporate Communications Division. In addition, members of the public can lodge a complaint through the National Environment Agency (NEA) at their NEA_Contact email line, which is then forwarded to MOH.

Prior to 2005, a substantiated food poisoning outbreak was one in which more than one case exhibited gastrointestinal symptoms. In January 2005, after setting a benchmark against surveillance systems of the US and UK, a revised definition of a substantiated food poisoning notification was introduced, and it was defined as one involving two or more cases who had consumed food from the same source on the same day, and with epidemiological details (incubation period, symptoms) provided. A new set of triggers for field investigation of food poisoning outbreaks was also introduced.

Epidemiological investigations into food poisoning outbreaks serve three purposes: to describe and analyse the burden of food poisoning in the local population, to develop knowledge of disease causation as well as emerging agents, and to prevent future outbreaks. By analyzing the yearly outbreak data, trends can be monitored and the prevalence of outbreaks caused by specific agents, practices, or food vehicles quantified to develop strategies in the prevention and control of food-borne diseases.

The objective of this report is to review the epidemiological features of food poisoning outbreaks in the period between Jan 2001 and Jun 2005.

Epidemiological findings

In Singapore, a case of food poisoning is defined as an individual who, after consumption of a specific meal, develops either: (1) two or more of the symptoms: nausea, vomiting, diarrhoea, abdominal pain, or fever; or (2) several bouts of vomiting or diarrhoea alone. The diagnosis must be verified by a medical practitioner and the case must be able to provide epidemiological details. From 2001- June 2005, a total of 1,054 notifications involving 7,345 cases of food poisoning were substantiated with full epidemiological as well as contact details of the informant (*Table 3*). Among these notifications, there were 719 established outbreaks.

A review of 265 outbreaks in 2004-05 showed that the clinical features reported by the cases, in de-



scending order of frequency, were: diarrhoea (32%), abdominal cramps (26%), vomiting (23%), fever (10%), nausea (7%), headache (2%), bloatedness (0.5%), muscle ache (0.5%), flushing/trembling (0.5%), cold sweat (0.2%), and lethargy (0.2%). The mean and median incubation periods were ascertained and many outbreaks had incubation periods in the range of 1-7 hours (Table 4).

The monthly distribution of food poisoning outbreaks in 2002-05 showed no discernible seasonal trend. Peak months occurred in Apr 2002, Dec 2003 and Jul 2004 (Table 5).

A wide variety of establishments were implicated in the outbreaks from Jan 2001-Jun 2005. Of these, non-hotel restaurants and eating houses accounted for majority of the implicated establishments (Table 6).

Table 3
Food poisoning notifications, 2001-June 2005

Year	Substantiated notifications	Established outbreaks	Cases involved
2001	235	140	1256
2002	238	169	2247
2003	199	145	1517
2004	317	202	1768
2005	65	63	557
Total	1054	719	7345

Table 4
Average incubation periods of food poisoning cases involved in outbreaks, 2004-June 2005

Year	< 1 hr	1-7 hrs	8-14 hrs	≥ 15 hrs	Unspecified
2004 (n=202)	7 (3.5%)	89 (44.1%)	56 (27.7%)	20 (9.9%)	30 (14.9%)
2005 (n=63)	1 (1.6%)	29 (46.0%)	23 (36.5%)	10 (15.9%)	0 (0%)
Total	8 (3.0%)	118 (44.5%)	79 (29.8%)	30 (11.3%)	30 (11.3%)

A total of 1,013 food handlers from implicated establishments were referred for routine stool screening. The pick-up rate for pathogens was low and ranged from 0.9-4%, with *Salmonella* being the most commonly isolated pathogen (Table 7).

Of 1,866 food samples taken in the course of epidemiological investigations in 2001-June 05, 190 (10.2%) tested positive for a number of causative agents that were bacterial in nature (Table 8). *Staphylococcus aureus* was the most frequently isolated pathogen in the food samples. An increase in the pick-up rate of pathogens was observed in the first six months of 2005 with 17 (15.3%) of 111 food samples tested positive.

Comments

Food poisoning is probably one of the most common causes of acute illness¹ but many instances are unrecognized and unreported. Notifications are not mandatory and hence, for various reasons, certain incidents (eg, at weddings and on board ships) may not be captured. Cases are also difficult to differentiate from other diarrhoeal diseases unless there is a distinctive clinical syndrome (eg, botulism). Further, outbreaks may be missed because the contaminated item is an ingredient of a vast variety of food prepared. In addition, due to the retrospective nature of food poisoning investigations, the causative agent is rarely identified. The positive isolation of an



Table 5
Monthly distribution of food poisoning outbreaks, 2002-June 2005

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
2002	11	10	5	21	17	11	17	20	16	13	13	15
2003	25	14	1	2	5	7	10	13	9	11	14	34
2004	20	14	16	17	17	13	24	18	19	12	18	14
2005	11	8	15	9	7	13	-	-	-	-	-	-

Table 6
Establishments implicated in outbreaks, 2001-2005

Implicated establishment	2001	(%)	2002	(%)	2003	(%)	2004	(%)	2005	(%)
Restaurant (hotel)	6	(6.3)	7	(4.1)	15	(10.3)	10	(5.0)	6	(9.5)
Restaurant (other)	24	(25.3)	57	(33.7)	58	(40.0)	67	(33.2)	24	(38.1)
Eating house	18	(19.0)	30	(17.8)	42	(29.0)	33	(16.3)	9	(14.3)
Hawker centre	5	(5.3)	14	(8.3)	3	(2.1)	11	(5.4)	3	(4.8)
Private food court	17	(17.9)	17	(10.1)	3	(2.1)	15	(7.4)	2	(3.2)
Fast food outlet	5	(5.3)	2	(1.2)	2	(1.4)	9	(4.5)	2	(3.2)
Other outlets (cake shop, snack bar, takeaway)	12	(12.6)	13	(7.7)	5	(3.5)	16	(7.9)	2	(3.2)
Canteen (factory)	0	(0)	2	(1.2)	2	(1.4)	2	(1.0)	4	(6.3)
Canteen (school) pri, sec, junior colleges	4	(4.2)	5	(3.0)	3	(2.1)	6	(3)	3	(4.8)
Canteen (tertiary) e.g. polytechnics, universities	0	(0)	1	(0.6)	0	(0)	0	(0)	0	(0)
Supermarket	3	(3.2)	5	(3.0)	1	(0.7)	4	(2)	1	(1.6)
Fairs (fun fairs)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Fairs (RC fairs)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Fairs (food fairs)	1	(1.1)	0	(0)	2	(1.4)	3	(1.5)	1	(1.6)
Catering (licensed)	0	(0)	8	(4.7)	4	(2.8)	12	(5.9)	3	(4.8)
Catering (unlicensed)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Food factory	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
In house (army)	0	(0)	1	(0.6)	0	(0)	0	(0)	0	(0)
In house (police)	0	(0)	1	(0.6)	1	(0.7)	0	(0)	0	(0)
In house (school)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
In House (hostel)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
In house (DRC)	0	(0)	1	(0.6)	1	(0.7)	1	(0.5)	0	(0)
In house (prison)	0	(0)	2	(1.2)	0	(0)	0	(0)	0	(0)
In house (childcare centre)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Other institutional kitchen	0	(0)	3	(1.8)	3	(2.1)	13	(6.4)	3	(4.8)
Foreign workers dormitory	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Total	95	(100)	169	(100)	145	(100)	202	(100)	63	(100)



Table 7
Screening of food handlers for pathogenic enterobacteria, 2001-June 05

Year	Food handlers screened	Food handlers positive	<i>Aeromonas</i> sp.	<i>Salmonella</i> sp.	<i>Vibrio parahaemolyticus</i>	<i>Vibrio cholerae</i> non-O1
2001	276	11 (4.0%)	4	5	1	1
2002	110	1 (0.9%)	0	1	0	0
2003	190	6 (3.2%)	0	5	1	0
2004	356	10 (2.8%)	7	2	1	0
2005	81	3 (3.7%)	0	1	2	0
Total	1013	31 (3.1%)	11	14	5	1

Table 8
No. of food samples taken and pathogen pick-up rates, 2001-05

Year	Samples + swabs taken	Samples + swabs positive (%)	<i>S. aureus</i>	<i>E. coli</i>	<i>B. cereus</i>	<i>Salmonella</i> sp.	<i>V. parahaemolyticus</i>
2001	601	54 (9.0%)	30	17	0	1	6
2002	376	41 (10.9%)	19	17	0	2	3
2003	273	24 (8.8%)	13	7	1	1	2
2004	505	54 (10.7%)	38	10	5	1	0
2005	111	17 (15.3%)	10	6	1	0	0
Total	1866	190 (10.2%)	110	57	7	5	11

enteropathogen from a food sample is purely circumstantial and reflects the prevailing situation when the sampling was performed.

Based on the notifications received, the major implicated establishments were eating houses and non-hotel restaurants. Eating houses are ubiquitous in Singapore housing estates and hence, it is not unexpected that they contribute a large proportion to the notifications. The latter also constituted a high proportion of food poisoning cases probably because restaurant diners expect a higher standard of food safety at these places and consequently are more likely to notify MOH should they develop illness.

An indication of the likely aetiological agents of the outbreak may be derived from the incubation periods²; viz. <1 hour (likely chemical agent), 1-7 hours (*Staphylococcus aureus* or *Bacillus cereus*), 8-

14 hours (other bacterial agents), and ≥ 15 hours (other agents). The most common incubation period was 1-7 hours, suggesting toxin-producing bacterial agents. This is supported by the observation that the most commonly isolated pathogen in food samples for the period 2004-June 2005 was *Staphylococcus aureus*, a bacterium found in human nasal mucosa, skin and hair follicles and associated with foods which require substantial handling³.

Our epidemiological investigations showed that many outbreaks were of uncertain aetiology. Viruses are likely to be a significant contributor to many outbreaks, as 10%-16% of the food poisoning outbreaks had incubation periods of 15 hours or more. Laboratory testing for norovirus and other viral agents was established only in 2004 and detection of these viruses has been infrequent.



While sanitary conditions have improved over the years, increased globalization and travel as well as the growing popularity of exotic foods⁴ have led to exposure to new food threats. Today, food poisoning may also be the first marker of a bioterrorism act⁵. The increased pick-up rate of enteropathogens from food samples in the first six months of 2005 could be attributed to revised criteria for field investigations which limited the number conducted to just those of likely public health concern.

The prevention and control of food poisoning and other food-borne diseases regardless of specific

cause are based on the same principles; ie, avoiding food contamination, destroying or denaturing contaminants, and preventing further spread or multiplication of these contaminants. Ultimately, these depend on educating food handlers about proper practices in cooking and storage of food and personal hygiene. It is a collaborative effort of the regulatory authorities: the Agri-Food and Veterinary Authority (AVA) provides the first line of defence and ensures that food and livestock imports meet acceptable food safety standards, while NEA is the watchdog for retail hygiene and environmental sanitation. MOH works with these agencies to manage outbreaks and safeguard public health.

(Reported by Wong C, Nur Rasidah, Yip R, Lim S, Ooi PL, Disease Control Branch, MOH)

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The data in this Bulletin are provisional, based on reports to the Communicable Diseases Division, Ministry of Health. Any comments or questions should be addressed to:

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