Dengue is the most rapidly spreading mosquito-borne viral disease in the world. An estimated 50 million dengue infections occur annually and approximately 2.5 billion people live in dengue endemic countries. Some 1.8 billion (more than 70%) of the population at risk of dengue worldwide live in the World Health Organisation (WHO) South-East Asia Region and Western Pacific Region. Case fatality rates of more than 1% have been reported in countries within the Southeast Asia region. Dengue has become a major public health issue in this region. In response, 15th June has been designated as the Association of Southeast Asian Nations (ASEAN) Dengue Day to raise awareness and commitment at all levels to reduce dengue incidence and burden.

Despite a widely hailed vector control programme, Singapore continues to see epidemics of dengue fever (DF). The largest dengue epidemics were seen in 2004 and 2005 with a total of 9459 and 14,209 cases notified to the Ministry of Health (MOH) respectively, including 168 and 393 cases of dengue haemorrhagic fever (DHF). Aggressive vector control programmes over the years have reduced the “force of infection” that is the per capita rate at which susceptible individuals become infected. This, in turn, resulted in an epidemiological transition of dengue in Singapore from a childhood disease to an adult one. The most recent sero-prevalence study by Yew et al reported that only 17.2% of young adults in Singapore were dengue IgG positive. The age shift to older adults has become more apparent in recent years. In 2007 and 2009, incidence rates per 100,000 for 55 years and older age group were the highest among reported dengue cases.

In 2009, the incidence of DF/DHF was above 90 per 100,000 population in most age groups above 15 years of age compared to 43 per 100,000 and 23 per 100,000 population in the 5 to 14 years and under 5 years age groups respectively.

Research Programme

Recognising the disease burden and a different epidemiological profile in Singapore compared to most other countries, a signature translational clinical research grant was awarded to study dengue in December 2008. This study was given the acronym STOP Dengue (Scientific exploration of disease pathogenesis, Translational research for improved clinical management, Operational evaluation for introduction of intelligent, vector control measures and Preventive measures through innovative treatment strategies for Dengue). The ultimate aim is to translate research into clinical management that results in zero dengue fatality in Singapore. STOP Dengue focuses on the main themes of finding innovative and cost-effective ways of early dengue diagnosis, early detection of severe illness, early intervention and prevention of infection and death.

Dengue Diagnosis and Classification

Prior to STOP Dengue, a dengue consortium was formed by a comprehensive group of researchers including clinicians and basic scientists immediately after severe acute respiratory syndrome (SARS) in 2003. This consortium launched the Early DENgue Infection Outcome study (EDEN) during the 2004 to 2005 dengue epidemics. EDEN has yielded many significant findings guiding the management of dengue infection. A simple decision algorithm on EDEN demonstrated an accuracy of 84.7% using clinical, haematological and virological data in differentiating dengue from non-dengue febrile illness within 72 hours of illness.

To enhance early detection, we studied the commercially available non-structural 1 protein (NS1) test kit (BioRad Laboratories) as a rapid test in the EDEN study and found an overall sensitivity and specificity of 80.5% and 100% respectively. Another local study found it to be the most sensitive test (82%) in the primary health care setting.

Moving forward, STOP Dengue will validate these findings before promoting its widespread use in clinical settings. The Environmental Health Institute (EHI) has recently developed a saliva based test using an antigen capture anti-DENV IgA (ACA) enzyme-linked
immunosorbent assay (ELISA) technique. This has been
tested on saliva samples from an EDEN cohort presenting
within 72 hours of illness. The sensitivity was 70% in the
first 3 days of fever and 93% from days 3 to 5. The overall
specificity of the ACA-ELISA test was 97%. Saliva
testing presents an attractive non-invasive testing modality
particularly for children.

The disease manifestations and outcomes of dengue
infection differ between children and adults. Two local
studies demonstrated that fewer adult infections fulfilled
the classification of DHF or dengue shock syndrome (DSS)
as defined by the second edition of the WHO dengue
guidelines, which was published in 1997 using the data
mostly from children. The disease severity was classified
during clinical pictures in adults and increasing reports
on cases with severe outcomes not fulfilling the 1997 WHO
disease severity classification led to the review of the WHO
guidelines. The third edition of guidelines for dengue
was published in 2009. Several distinct differences from
the previous guidelines include the introduction of gastro-
inestinal symptoms and warning signs as additional criteria
to probable dengue diagnosis, the use of warning signs for
triage to determine the level of care and a complete change
of disease severity classification. The latest guideline
classifies disease severity into dengue infection, dengue with
warning signs and severe dengue. The criteria for severe
dengue include severe plasma leakage, severe bleeding and/
or severe organ involvement. This has become an area of
intense study comparing the applicability of the two sets
of the WHO guidelines in each geographic area that might
differ in demographic and disease patterns. Local studies
comparing the 2 sets of WHO guidelines found discrepancies
in assigning disease severity outcomes. A proportion of
subjects fulfilling the 2009 guidelines of severe disease
did not fall into the more severe form of dengue disease
using the 1997 guidelines. These findings concur with an
international multi-centre study.

Hospital Admission and Treatment

High hospital admission rates that overwhelmed
healthcare delivery were reported during the 2004 to 2005
dengue epidemics. STOP Dengue utilises a two-pronged
approach based on retrospective and prospective cohorts
to study who should be hospitalised for dengue treatment.
The retrospective cohort based on cases managed in Tan
Tock Seng Hospital (TTSH) cases in 2004 applied the WHO
1997 severity classification to yield 2 predictive models (a
probability equation and a simple decision tree) for disease
progression. The models were able to assist the primary
care physicians in predicting whether the patients will
subsequently develop DHF: parameters predicting disease
progression were clinical bleeding, high serum urea, low
serum protein with or without low lymphocyte proportion.
Applying the models on a 2007 TTSH cohort showed a
comparable sensitivity and specificity. Of note, the
predominant serotype in the year 2004 was dengue serotype
1 compared to the predominant serotype 2 in the year 2007.
Research using similar models to predict progression to
severe disease using the WHO 2009 classification will be
done next. The Prospective Adult Dengue Study (PADS)
follows subjects on a daily basis during acute illness to
examine the applicability of warning signs in triaging care
and to identify predictive markers of disease severity
for hospitalisation. This prospective cohort will be used
to validate the predictive models developed from our
retrospective cohorts. The findings of these studies will
contribute greatly to evidence-based treatment approaches
for dengue.

It is of concern that clinical data on dengue in the elderly
is extremely lacking. A few recent reports suggested that
older patients had fewer symptoms including fever that
may contribute to missed or late diagnosis. A local
study showed similar findings in other reports indicating a
higher mortality among older patients. Such disconcerting
findings emphasise the need for further research to improve
clinical care in this vulnerable population.

The mechanisms underlying dengue-associated vascular
leakage has yet to be fully elucidated. The lack of relevant
animal models has greatly hampered the understanding of
the pathogenesis of dengue infection. In this edition of the
Annals, Tan et al describe a mouse model in which systemic
manifestations of dengue resembling human disease can be
elicited by subcutaneous administration of a non-mouse-
adapted DEN2 virus strain (D2Y89P-PP1) into AG 129
mice. This offers an opportunity to identify the molecular
players involved in the pathogenesis of dengue infection
and provides a platform to test novel prophylactic and
therapeutic agents. There are currently no licensed antiviral
available for the treatment of dengue infection. Treatment
doing is largely supportive, i.e. rest and appropriate
fluid management. Thrombocytopenia, a hallmark of dengue
infection and bleeding is also eloquently discussed by
Kurukularatne et al in this edition. Platelet transfusion, a
common practice that lacks supporting scientific evidence
is up against STOP Dengue’s prospective study which
assesses the risks and benefits of platelet transfusion for
dengue infection.

The long and winding journey of dengue vaccine
development appears more positive in recent years.
However, dengue vaccines need to be inexpensive as the
majority of countries experiencing dengue epidemics are
developing countries. It will take considerable time for

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dengue vaccines to be administered widely to populations at risk. There is thus an urgent need for dengue research to develop low cost, simple, accurate, and acceptable tools to enable early diagnosis, early prognosis and appropriate treatment so as to achieve the best possible outcomes.

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REFERENCES