Dear Readers,

We are happy to send you this 6th issue of Occasional Papers. You will note that we have a new name "Dengue Vaccine Initiative" but that is only a small aspect of our changed program. The creation of DVI benefited from the work of the PDVI, but the DVI is a substantially different program. It is a consortium of four organizations - International Vaccine Access Center of the Johns Hopkins University, International Vaccine Institute, Sabin Vaccine Institute, and the Initiative for Vaccine Research of WHO. We plan to continue the Occasional Papers series because it provides important information related to both DVI programs and to the eventual successful introduction of dengue vaccines in developing countries. We hope you will find these Papers valuable.

Editors

DVI is a consortium of organizations working to lay the groundwork for dengue vaccine introduction in endemic areas so that once licensed, vaccines to prevent dengue will be swiftly introduced by countries most in need.

In depth examination of important issues for the development and introduction of dengue vaccines

Clinical Dengue, Opportunities and Challenges

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Dengue is the most rapidly spreading arboviral disease in the tropics and subtropics. The global burden of dengue has increased at least four-fold over the last three decades. An estimated 50 million dengue infections now occur annually in over 100 countries, and an estimated 616,000 DALYs/year particularly in South-East Asia, the Americas, and the Western Pacific islands. About 500,000 severe dengue cases occur annually and approximately 19,000 dengue-related deaths were reported in 2002. Despite the fact that dengue is accepted as a major public health problem in some parts of the world and the World Health Assembly highlighted its importance as an emerging disease in 2006, the prevention, clinical management and outcome of patients with dengue still varies from country to country. This is particularly true as dengue emerges in new areas of the world where the public health systems are not experienced in the prevention of the disease, or the surge capacity in clinics and hospitals is not available to deal with an often sudden increase in the number of patients, and the clinical experience is limited. In these settings mortality and morbidity is often higher than in other regions where dengue has been endemic for decades.
With the massive increase in trade between Asia and Africa, increasing urbanization and travel, dengue is spreading to new regions with major outbreaks in East, West and South Africa and the Middle East in recent years. Dengue is now truly a pandemic with limited current ability to control the vector and no proven drug or vaccine.

Dengue encompasses a spectrum of clinical syndromes from dengue fever, a non-specific febrile illness through to severe dengue (Dengue Shock Syndrome, Severe Bleeding, and other severe manifestations including encephalitis, and organ dysfunction). The major differentiating feature of the latter two, being increased capillary permeability and evidence of vascular leak, leading to reduced intravascular volume which can progress to shock and death\(^1\). Dengue can progress rapidly to a life threatening condition and it is extremely important to implement clear clinical strategies with the aim of preventing the deterioration from developing further and thereby reduce morbidity and mortality. Such strategies rely on understanding the different clinical presentations, the evolution of the disease and the underlying pathogenesis. The risk of developing severe dengue is related to secondary infection with a different dengue virus serotype and therefore most commonly occurs in areas of the world where several serotypes are co-circulating. Classic dengue fever is a self-limiting febrile illness, which usually requires no more than symptomatic treatment of fever, headache and myalgia\(^2\).

### Key Messages:
- Dengue is now a major public health and clinical problem in Asia, Africa and Central and South America.
- Increasing trade, travel and urbanization will lead to the continued spread of the vector and hence the disease.
- There have been major advances in epidemiology, clinical, diagnostics, therapeutics, vector control and vaccinology in the last five years. In the next five years we need to ensure this dramatic progress is implemented to control the disease and improve the outcome of patients with disease.
- Clinical care requires very careful planning and organisation with judicious fluid replacement, dedicated staff and availability of critical tests (blood pressure, haematocrit) available to the medical and nursing staff on the wards where the patients are looked after.

##### Background

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Severe dengue with the commonest manifestation being Dengue Shock Syndrome requires prompt recognition and early treatment\(^3\). Case fatality from severe dengue varies in the hands of experienced nursing and medical staff and should be less than 1%, but can be as high as 5% and mortality rates of 13% have been reported\(^4,5,6\).

Early recognition and judicious fluid resuscitation is the mainstay of treatment for the circulatory compromise that is the hallmark of severe dengue, with delays being associated with worse outcomes\(^7,8\). Early and adequate fluid resuscitation in patients with signs of shock, followed by careful monitoring, have been shown to reduce mortality in severe dengue\(^9\).

Dengue can also cause other complications including gastrointestinal bleeding (particularly in adults), hepatitis, clotting abnormalities which are associated, cardiomyopathy and encephalitis\(^10,11,12,13\). Apart from clotting abnormalities which is associated with more severe degrees of prolonged shock\(^14\), these unusual complications can occur without other severe manifestations of the disease and are associated with poor outcomes. They are more common in adults and associated with other underlying diseases. Management of these particular complications requires recognition with specific diagnostic tests, careful monitoring and supportive management of the particular organ involved. For example, it can be useful to undertake lumbar puncture and cerebrospinal fluid (CSF) analysis for patients with symptoms of encephalitis with appropriate use of anti-convulsants for those associated with seizures\(^11\). Electrocardiograms and echocardiograms for dengue induced myocarditis and cardiomyopathy, with cardiac support and careful fluid balance for those with associated myocardial dysfunction can be important\(^15\).

In 2009 the World Health Organization released Dengue Guidelines for Diagnosis, Treatment, Prevention and Control (http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf). These updated the previous World Health Organization guideline released in 1997. In the WHO 1997 classification scheme for dengue hemorrhagic fever (DHF), all four criteria were required; 1) fever 2) bleeding tendencies 3) thrombocytopenia (platelet count <100,000 ml) and 4) evidence of vascular leakage, which can manifest as haematocrit rise 20% above the average for the age matched population, drop in haematocrit greater than 20% of admission following volume replacement or evidence of pleural effusion or ascites. Dengue shock syndrome was defined as meeting the 4 criteria for DHF plus evidence of circulatory failure. This classification scheme proved complicated and difficult to implement with overlap between the characteristics of DF, DHF and non-dengue febrile illnesses and there have been several proposals in the literature for refinement of this scheme\(^16,17,18\). The tourniquet test is an important parameter under bleeding tendencies in the definition of DHF but been shown to differentiate poorly between DHF and DF\(^19\). A study in Vietnamese children showed 2 of the 4 criteria for DHF (bleeding and thrombocytopenia)
occurred almost as frequently in DF as DHF, and was also a common finding in other febrile illnesses. And 18% of patients with DSS failed to meet all the 4 criteria required for DHF. Similar findings were demonstrated in a study in Nicaragua which showed infants with dengue admitted with shock, more than half did not fit into the WHO classification of DHF/DSS and more than 2/3 of adults with severe manifestations did not fit the classification. Many experienced clinicians became increasingly clear that the most important feature of the disease is the increase in capillary permeability that can lead to dengue shock syndrome. This is also the critical clinical feature that needs to be very carefully managed. By focusing the name on the haemorrhagic component (which is usually relatively minor) attention can be distracted from the key clinical manifestation i.e. the capillary permeability leading to shock. Dengue is not a haemorrhagic disease in the same category as Ebola or Marburg Disease.

Using the strict WHO classification many severe cases particularly in older age groups will be misclassified as ‘mild’ dengue fever with the potential for inappropriate management of these patients and an underestimate of the true burden of severe dengue. The 1997 WHO scheme makes epidemiological and burden of disease comparative studies difficult with many patients not fitting into the strict scheme making international comparison of studies difficult.

The 2009 WHO Classification scheme builds on the previous schemes and is not a major change. It places less emphasis on categorical disease groups but represents the illness as a syndrome ranging from mild to severe illness, with a focus on recognizing clinical danger signs and identifying patients early who are more likely to progress to severe disease. The emphasis is on the capillary permeability, the plasma leak, and prevention and management of the ensuing shock. In the WHO 2009 scheme there is Dengue and Severe Dengue with the Severe Dengue cluster including patients with Dengue Shock Syndrome, Haemorrhage and Organ dysfunction (including encephalitis, hepatitis, myocarditis etc). The crucial element of any classification system is to highlight the important features of severity and identify patients at greatest risk of progression to severe disease. This sort of re-evaluation requires prospective evidence and further testing to ensure its utility. It is important that there remains a single classification system that is endorsed by the World Health Organization. Over recent years a large number of schemes have been suggested. This fragmentation of the classification system for what is a global disease would be damaging to the clinical management of the disease. The 2009 World Health Organization Guidelines are not perfect and should evolve as more evidence becomes available. But they do help clarify some of the complexity and ambiguity of earlier schemes.
Progress in the last decade

There have been several advances in the case management of dengue in the past decade with large randomized trials addressing the optimum fluid management for severe dengue. There has also been progress in improving case classifications and clinical algorithms to help and guide treatment, plus some answers regarding adjunctive and antiviral treatments.

In 1999 a randomized trial looking at the immediate effects of four intravenous fluids (colloids and crystalloids) in 50 Vietnamese children with DSS, showed that colloid dextran 70 normalized haemotcrit and Cardiac index the fastest after the initial resuscitation. This led on to a larger study in 2001 using similar fluids in 230 Vietnamese children with DSS, and looked at sustained effects as well as immediate. No clear difference was demonstrated between the four fluids in time to recovery except in the subgroup of patients presenting with severe shock (defined as pulse pressure of 10 mmHg or less), where colloids improved haemodynamic parameters more rapidly.

In 2005 the largest fluid trial for DSS was published, 512 children with moderate to severe DSS were fluid resuscitated with either ringers lactate or 2 different colloids (dextran or starch). Ringers lactate at a dose of 25 mls/kg over 2 hours, as the initial resuscitation fluid was found to be as efficacious as either colloid in moderate DSS. Of the two colloids tested in severe DSS starch was preferable due to less adverse reactions over dextran 70. Further randomized and preferably blinded trials are needed in severe dengue shock syndrome to determine which fluid and at what dose to use in the initial resuscitation of these patients.

Progress has been made in the last decade in highlighting the changing epidemiology of the disease and its clinical characteristics which are essential in recognition and effective case management. For example what was generally thought of as a paediatric disease, reports in the last decade from Singapore, Viet Nam, Thailand, India, Indonesia and Central and South America show a broadening age distribution with an increasing burden of disease in adults. This carries implications for clinical care and also for public health and vaccine strategies as the focus has traditionally been on dengue as primarily a disease of children. The clinical and public health implications of dengue in adults needs further research. This patient population often present with dengue infection complicated by co-morbidities including gastric ulcers, obesity, asthma, diabetes and cardiovascular disease. The complications of dengue in pregnancy both for the mother and the unborn baby is also a special consideration. A study published in 2008 attempted to address this issue for all age groups and to improve on the WHO classification, constructing a decision algorithm able to distinguish early dengue from non-dengue illness with an accuracy of 84.7%, and using haematological and viral parameters, it was able to predict those who will go on to get severe disease with a sensitivity and specificity of 78.2% and 80.2%. Decision algorithms and guidelines aimed at improving on the early recognition and treatment of warning sign
of impending shock may prove useful in new global guidelines on dengue management.

There has been no major breakthrough in specific treatment for dengue with no antiviral or immune modulatory drugs reaching Phase III trials yet. Research into antiviral agents against dengue has not received the same attention as vaccine development over the last thirty years, but with greater understanding of the virus molecular biology, this will hopefully act as a stimulus for the development of novel therapeutics and antivirals. Steroids trials were undertaken in the 1970 and 1980s but applying contemporary methodologies for randomized controlled trials it is really not possible to be sure from these studies whether there is a beneficial effect of steroids in dengue. Over the last 30 years there has been no development of further adjunctive therapy in for this disease. A small study recently showed no benefit of IVIG on recovery of severe thrombocytopenia in DHF. Dengue is perhaps unique among the common infectious diseases in having such a poorly developed research program into potential therapeutic interventions aimed at either the pathogen or the immune response.

With specific diagnostics now available early in the disease and a plethora of drugs in late stage development for other flaviviruses (mostly from the pharmaceutical industry aimed at hepatitis C and to a lesser extent West Nile Virus) it is to be hoped that this area will develop in the coming years. Clinical trials are currently underway or recently published assessing a range of therapeutic interventions for dengue including chloroquine, steroids, and novel anti-viral agents. The design of such trials is complex and requires very careful consideration of the key clinical, virological, pharmacological and immunological end-points. There is a need to refine these endpoints and develop a consistent approach to the assessment of therapeutics for dengue. There is a growing global consensus on the need to harmonize these trials and ensure that studies are designed using common methodologies to facilitate the development of drugs for dengue. It is hoped that such a consensus document will be published in 2011.

There has been increasing research in the last decade into the pathogenesis of dengue. A study published 2008 identified a molecule, CLEC5A (C-type lectin domain family 5, member A) that interacts with the dengue virus to stimulate the release of proinflammatory cytokines. Anti-CLEC5A monoclonal antibodies reduced the dengue virus induced plasma leakage and halved the mortality in mice models. This and further studies into the mechanism of vascular leakage and endothelial dysfunction may also lead to better targeted treatment options in the future. There are major research effort now underway including very large host and viral genetic studies, birth cohorts followed for the long term, community participation and case control studies and studies of viral diversity, molecular epidemiology, vector control, clinical management and Phase III vaccine intervention trials. It is likely that by 2020 there will be major advances in dengue with progress that actually has a clinical and public health benefit in all of these areas. But major challenges remain and need to be addressed if this research is to have a real impact on individuals and communities.
Major clinical challenges in the next 5 years

1. Clinical management

a. Early identification of patients at most risk of progression to severe disease and learning how to intervene to prevent that progression.

b. Development of specific therapeutic interventions aimed either at the virus or at the immune response. Anti-viral drugs that reduced viral load in infected individuals might also reduce transmission and hence play a role in reducing epidemics.

c. Evidence based clinical interventions derived from prospective randomized controlled trials aimed to reduce morbidity and mortality.

d. Implementation of existing knowledge on clinical care and dissemination of this knowledge from centers with extensive experience to clinicians seeing dengue for the first time (much of this is relatively simple but labor intensive including careful monitoring, nursing care, access to regular haematocrits on the wards where patients are cared for and judicious fluid replacement).

e. Clinical management guidelines are required for patients of all ages. The management of infants, children and adults is different. Until recently most work has focused on the treatment of children with the disease but further research is needed on how to manage infants and adults.

2. Diagnostic tests

As dengue presents with non-specific symptoms, and current diagnostics are either slow, expensive or have low sensitivity, improved diagnostics are urgently needed to facilitate early identification allowing for appropriate management of cases but also on a larger scale for public health purposes, in surveillance and early recognition of outbreaks. To help in triage of patients it would also be useful to develop bedside tests for specific biomarkers to identify prognostic markers for severe disease.

3. Prediction and ability to respond to outbreaks

Dengue is rapidly spreading globally with major outbreaks in new regions and is now truly a pandemic (New Delhi 1998, Rio de Janeiro 2008, Cape Verde 2009) with continued endemic disease in its historical hot spot in South East Asia. The public health and clinical response to these major expected or unexpected outbreaks can put an enormous strain on already over-stretched public health systems and hospitals. Dengue endemic areas are often located in resource poor countries with health centers lacking basic equipment and limited nursing and medical staff available for assessing and monitoring patients with dengue. In epidemics even well-equipped health centers may be overwhelmed.
The ability to predict epidemics and to put in place the public health and clinical needs to deal with the often massive surges in demand would be a major advance. In many ways dengue serves as a very important model for emerging infectious diseases and how to respond to huge increases in demand for medical services. This requires careful planning, triage and coordination of medical services throughout the system, from education of the public, primary level health care up to tertiary level hospitals. Few countries have organized systems to deal with such sudden increases in the number of patients. As nursing and medical care of more severe dengue patients can be very labor intensive organization of triage and concentration of resources on those most in need (those in whom it is possible to prevent progression to severe disease and those with established severe disease) is an essential component of the ability of any system to cope. Which patients to send home with advice and which patients to admit is one of the hardest things in medicine, and is a particular problem in dengue. Further research to identify early warning signs to aid triage, and studies to assess the benefit of early interventions with simple measures (i.e. oral rehydration) are important. Sensitive bedside diagnostic tests of dengue that can identify early infection (potentially based on a combination of NS1, IgM and IgG) could make a major contribution to this. To have an impact clearly these need to be widely available and affordable.

Work needed to overcome the challenges

The 2009 WHO classification scheme should continue to incorporate data from large multicenter descriptive studies from different dengue endemic areas, and all age groups to help define clinical and laboratory parameters for early identification of patients at risk of developing severe disease. Special groups of patients should be addressed separately including pregnant women and patients with co-morbidities. Clear guidelines should address admission criteria and clinical management, including monitoring of cases, fluid replacement therapy, management of complications and discharge criteria. We urgently need to map the global distribution of dengue and work out the true burden of disease and its economic costs. We cannot expect policy makers and governments to prepare and respond to dengue in these financially challenging times unless we produce the evidence of the true burden to their communities and what they might gain from implementing control and management strategies. New diagnostics for dengue should have the following specifications: positive
early in the infection, rapid and easy to use in resource limited settings, and be affordable. In an ideal world they would be able to distinguish between primary and secondary infection and dengue serotype. Although there are number of commercially available rapid diagnostic tests for dengue, there is often a discrepancy between the accuracy of what the manufacturer’s claim and those reported form clinical trials\textsuperscript{31}. Therefore large trials are needed to ensure validated diagnostics tests are developed for dengue.

The development of models to help predict epidemics and allocate resources to deal with this surge demand would be a major advance. These could be developed using simple notifications of suspected dengue cases (as in Singapore) and epidemic tracking, or more sophisticated using climate changes, entomological indices integrated using GIS mapping with patient data. Resources could then be allocated to areas of need. Equipping community and district health centers with basic monitoring systems, e.g. blood pressure monitors plus laboratory equipment, with minimum tests including equipment for haemotocrit, white blood count and platelet measurements.

Standardized training programs for nursing and medical staff in both dengue endemic and epidemic areas, plus community education for recognition of early warning signs, appropriate management and timely referral are needed. Dissemination of information through all levels of health care system with regular updates as new guideline information becomes available. To ensure the presence of adequate staffing at all levels, education & training of doctors, nurses, ancillary health care workers, and laboratory staff must be priority. Countries like Thailand, Vietnam, Cuba, Nicaragua and areas of Brazil that have committed time and resources in education and training of health personnel in dengue case management have the lowest case fatality of severe dengue in the world. Educational programmes customized for different levels of health care to reflect the scope of setting-specific capacity should be supported and implemented widely.

These four countries have focused on ensuring this education process is disseminated throughout the countries including in rural provinces. This requires time and energy of the individuals involved and dedicated teams who travel extensively throughout the country. Their programmes have changed dengue and the models should be looked at and developed by other countries.

The focus of the educational programs is to develop capacities for:

- Applying effective triage
- Improving recognition of dengue cases
- Improving clinical and laboratory diagnosis of dengue
- Improved clinical management of dengue

National committees need to monitor and evaluate clinical management and outcomes. Review committee at different levels (e.g. national, state, district, hospital) should review dengue deaths, evaluate the
care delivery system, and feedback to the doctors on how to improve care. There should also be education of the population about dengue in order to: include patients and their families in their own care, being prepared to ask for medical care at the right time, avoid self medication, identify skin bleedings (petechiae), consider the day of defervescence (and during 48 hours) as the time when complications more frequently occur and look for warning signs as intense and continuous abdominal pain, and frequent vomiting.

Mass media can give an important contribution if they are correctly briefed. Workshops and other meetings with journalists, editors, artists and executives can contribute to design the best strategy for health education and communication without scaring people.

During dengue epidemics, nursing and medical students together with community activists can visit homes with a double purpose: to educate on health and to actively trace dengue cases. This activity has demonstrated to be feasible, inexpensive and effective, and must be coordinated with the Primary Health Care units, having printed some messages on dengue illness and warning signs to be delivered to the community. Medical care providers as physicians and nurses must include health education actions into their daily activities considering that promotion and prevention are also an important part of the work they have to do.

Institutional and resource needs to overcome the challenges

**Laboratory services** - Minimum laboratory services should include equipment for haematocrit, white blood counts and platelet measurements. Ideally the haematocrit measurements should be performed on the wards where patients are looked after and the results immediately available to clinicians. This requires a paradigm shift in many hospitals but is essential to the careful monitoring of patients and appropriate clinical management. Sending a haematocrit test to the laboratory at 7 am, getting a result back four hours later and adjusting the fluid regimen then is a recipe for disaster. The haematocrit test is essential in guiding clinical care and the test and the clinical response to the result needs to happen simultaneously and be regularly monitored and the fluid regimen adjusted with the results. Larger referral centers should be able to provide further haematological investigations including full blood count and differential and coagulation plus basic biochemistry tests for electrolytes, renal and liver function. Rapid diagnostic tests or
point of care tests for dengue diagnosis should be available at rural health centers and further viral diagnostic tests should be available at referral centers along with appropriate facilities for the support of the vital organs including both invasive and non-invasive ventilation.

**Human resources** - The vital resource to overcome the challenge of reducing dengue morbidity and mortality is trained medical staff including doctors and nurses. Adequate staffing numbers at the triage centers and primary health clinics will help timely and correct patient management including unnecessary admissions to hospital and appropriate treatment of those needing urgent attention, particularly during epidemics. The use of mobile teams of experienced nurses and doctors who can travel to support local health care centres and hospitals during major outbreaks should be explored and on call teams based in tertiary centres who are available 24 hours a day at least on the phone to provincial and district hospitals to offer advice. In Thailand and Vietnam the health authorities have arranged frequent hands on refresher courses on clinical management of dengue to staff in provincial and district hospitals. Although time consuming for senior staff this has undoubtedly lead to a reduction in mortality and morbidity throughout the health care system.

**Consumables** - Stocks of intravenous fluids including crystalloids and colloid solutions and intravenous administration sets should be available at all levels of health services.

**Medications** - Supplies of antipyretics and oral rehydration solution for the rural health centers. In referral centers stocks of diuretics, glucose, potassium and calcium replacements, vasopressors and inotropes should be available.

### Summary

Effective case management of severe dengue can reduce mortality rates to <0.2%, yet regional case fatality rates vary between 1-13%. It is therefore extremely important in any dengue control program to include specific evidence based clinical guidelines on case management. Clinical guidelines should incorporate new evidence from descriptive and randomized trials. There is a need to standardize these studies and they must include infants, children and adults.

We need to document the true burden and the human and financial cost of the disease. With the incidence and now global spread of dengue there are major challenges in the next decade. However with new interest from scientists and clinicians working to advance our knowledge in pathophysiology, diagnostics, clinical management, vector control and vaccines we will have the tools to curb this trend. We need to be bolder in how we make use of these advances.
References


References


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