Dengue Case Management

Report of an informal expert consultation
Colombo, Sri Lanka, 12–14 August 2013

World Health Organization
Regional Office for South-East Asia

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Annexes

Acronyms

AFRIMS	Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand
AIIMS	All India Institute of Medical Sciences, New Delhi, India
CFR	case–fatality rate
COMBI	communication for behavioural impact
DENV	dengue virus
DF	dengue fever
DHF	dengue haemorrhagic fever
DSS	dengue shock syndrome
ICD 10	International Classification of Diseases (10th revision)
IEC	information, education and communication
IgM	immunoglobulin M
IL-6	interleukin 6
IV	intravenous
IVM	integrated vector management
MoH	Ministry of Health
NS1	nonstructural protein 1
ODC	one-day care
OPD	outpatient department
TDR	UNICEF, UNDP, World Bank and WHO Special Programme for Research and Training in Tropical Diseases
TM	thrombomodulin
WR	WHO Representative

1. Background

During the past 50 years, the global incidence of dengue has risen 30-fold. Approximately 1.8 billion (more than 70%) of the population at risk for dengue worldwide live in the WHO South-East Asia and Western Pacific regions, which bear nearly 75% of the current global disease burden. Except the Democratic People's Republic of Korea, all 10 countries of the South-East Asia Region including India are endemic for dengue.

The increasing burden of dengue in the Asia–Pacific Region is a matter of serious concern. The incidence of dengue is increasing as the disease spreads, and explosive outbreaks are occurring in newer geographical areas. Mortality is the highest during the initial period of the outbreak or epidemic. Children in particular are at high risk of mortality as a result of complications and lack of access to prompt treatment.

The epidemiology of the disease and outbreaks proved that dengue-affected urban areas are experiencing a progressively worsening situation in recent years. This can be attributed to unplanned and uncontrolled urbanization and concurrent population growth, putting severe constraints on civic amenities, particularly water supply and solid waste disposal, thereby increasing the breeding potential of vector *Aedes aegypti* mosquito. High population density of the vector increases the opportunities for transmission of dengue. The spread of dengue is worsened by increasing trade and travel. Therefore, dengue cannot be controlled if efforts are limited to one country. Hence, the WHO regional offices for the Western Pacific and South-East Asia decided to adopt a bi-regional approach in the Asia– Pacific Region. The interventions that are currently available have been relatively effective for more than two decades; but clearly, there is a need for the development of new and improved diagnostic, preventive and therapeutic tools. Until then, available tools should be used wisely. Otherwise, a very high price will have to be paid.

In 1997, WHO introduced guidelines on dengue[1] with the case definition of dengue fever (DF) and dengue haemorrhagic fever (DHF) which were adapted by all WHO regions. Dengue cases were reported to WHO stratified by severity, DF and DHF accordingly. In 2009, WHO Headquarters in collaboration with the UNICEF, UNDP, World Bank and WHO Special Programme for Research and Training in Tropical Diseases (TDR) published fresh guidelines[2] for the diagnosis, classification and management of dengue, with a new classification of dengue and severe dengue. The expert group of WHO Regional Office for South-East Asia did not follow the TDR classification and brought out expanded 1997 guidelines in 2011. The case classifications of WHO (1997, extended 2011) and TDR (2009) are at Annexes 3 and 4.

Due to lack of uniform criteria, there is great confusion among the countries in reporting cases of dengue to WHO. If classification is not uniform, comparisons and aggregations between countries can be misleading. Besides, correct classification is clinically important, because death is associated with the more severe form of the disease. Moreover, cases of dengue can be misclassified at the time of diagnosis, because of the confusion over two sets, or difficulties with using the WHO classification system. The severity of dengue is also a predictor of the use of health-care services.

An informal expert consultation on case management of DF/DHF was held in Colombo, Sri Lanka, from 12 to 14 August 2013 to examine the scope of harmonizing both the case classifications to make it user-friendly and to guide the service providers in the countries of the WHO South-East Asia Region in understanding the disease. Experts in dengue clinical case management from all the 11 Member States of WHO South-East Asia Region as well as from two countries of the Western Pacific Region participated. (See Annex 1 for list of participants.)

[1] Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever, revised and expanded edition. New Delhi: World Health Organization; 2011. (SEARO Technical Publication Series No.60;ISBN 978 920 9022 387 0; [http://www.searo.who.int/entity/vector_borne_tropical_diseases/documents/SEAROTPS60/en/index.html]

[2] Dengue – Guidelines for diagnosis, treatment, prevention and control, new edition (WHO/HTM/NTD/DEN/2009.1). Geneva: World Health Organization: 2009; ISBN: 978 92 4 154787 1; [http://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf, accessed 16 January 2014]

2. Objectives

The specific objectives were as follows:

(1) to review the emerging scenario of disease and status of case management in dengue;

(2) to discuss and identify mechanisms for effective case management in dengue, especially clinical management research;

(3) to strengthen monitoring and evaluation of clinical management;

(4) to establish a network of experts on case management of dengue in the South-East Asia Region.

3. Opening session

In his opening remarks, Dr Firdosi Mehta, WHO Representative to Sri Lanka, said that the disease burden in Sri Lanka reported in 2012 was 44 456. However, a marked reduction in case–fatality rate (CFR) had been observed over the years. Later, with training on clinical management at centres of excellence (supported by WHO), it has come down to below 0.5% in 2012 from 2009. The establishment of a Presidential Taskforce with multistakeholder participation and opening of a specialized treatment centre at Negombo General Hospital demonstrate the Government's commitment to dengue prevention and control.

3.1 Inaugural speech

In his inaugural speech, the Regional Director for WHO South-East Asia Region, Dr Samlee Plianbangchang said that effective prevention and control of dengue mainly relies on environmental management and community-based multidisciplinary and multisectoral actions. Reducing dengue morbidity is not straightforward. The outbreaks need to be predicted well in advance through well-coordinated epidemiological and entomological surveillance to implement control activities.

The political will to control the epidemic is very evident in Sri Lanka. The establishment of the Presidential Taskforce with the participation of

several ministries is an important milestone in the country's efforts to control dengue, as dengue control demands a multipronged response. The Presidential Taskforce ensures interministerial coordination from the top down to the provincial, district, divisional and community levels in the implementation of prevention and control activities.

3.2 Address of Chief Guest

Mr Nihal Jayathilake, Secretary, Ministry of Health (MoH), Sri Lanka, stressed that the most efficient way to reduce mortality is early case detection and appropriate clinical management. Handling frequent outbreaks of dengue is not an easy task, especially for the countries in the South-East Asia Region, due to limited resources. Despite challenges such as unexpected surges and limited bed strength in hospitals, several measures have been taken to improve the clinical management of dengue.

National guidelines for management of adult and paediatric cases in Sri Lanka have been recently updated with inputs from leading clinical experts. Groups of consultant physicians and paediatricians have been trained in recent advances in clinical management at centres of excellence, especially in Thailand. With the help of the trained clinicians, the MoH has been conducting refresher training programmes for doctors and nurses involved in dengue clinical management. It is worthy of mention that mainly due to these measures, the clinicians have succeeded in bringing down the dengue CFR in Sri Lanka considerably in recent years.

He said that steps have been taken to improve hospital facilities with establishment of high dependency units and provision of equipment such as micro-haematocrit machines and ultrasound scanners. Recently, a new dengue treatment unit, with all advanced facilities, entitled Centre for Clinical Management of Dengue and Dengue Haemorrhagic Fever, had been opened at Negombo General Hospital.

Enumerating the steps taken by the MOH to identify and rectify the deficiencies in the clinical management of dengue patients, he said that strict monitoring and audit processes had been introduced and regular mortality reviews were being conducted.

Referring to the Five-Year National Strategic Plan for 2011–2020 for the control of dengue being implemented currently by the MOH, he said that the main strategies under this plan were: disease surveillance; case management; vector surveillance and integrated vector control; social mobilization; outbreak response and communication; intersectoral coordination, and research.

He acknowledged the many challenges in reversing the trend of increasing epidemics which required commitments and obligations from all stakeholders. The opportunities presented by promising advances in vector control technology, diagnostics, evidence-based clinical management and possible introduction of a dengue vaccine soon should be fully exploited.

He concluded with the hope that participants would share their country experiences in the clinical management of dengue and discuss ways to further improve it, and wished them all success.

4. Technical update

Professor Dr Pratap Singhasivanon, Dean, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, and Dr Paba Palihawadana, Chief Epidemiologist, MoH, Sri Lanka were nominated as Chair and Co-Chair respectively, while Dr Kalpana Baruah, Joint Director, National Vector-Borne Disease Control Programme, Ministry of Health and Family Welfare, India, was nominated as Rapporteur.

Early detection of dengue cases and their treatment is essential to prevent deaths. The first ever WHO guidelines (1974) for classification and management of DF/DHF were developed on the basis of observation of the Thai children admitted to the Children's Hospital in Bangkok. These guidelines were updated later on. The 1997 guidelines were adopted by the WHO South-East Asia Region and other regions. In DF, towards the end of the febrile period or immediately after deffervescence, the generalized rash fades and localized clusters of petechia may appear which is characterized by scattered pale round areas of normal skin. Haemorrhagic complications, bradycardia and convalescence rash are common during this period. The relative duration or severity of DF/DHF varies between individuals, as well as from one epidemic to another. DF complicated by

haemorrhage must be differentiated from DHF. During the first few days, the illness resembles classical DF, but a maculopapular rash is less common. On rare occasions, severe bleeding has caused deaths in some epidemics of DF. A positive tourniquet test and a tendency to bruise at venipuncture sites are always present in DHF and the liver is usually enlarged, soft and tender. In more severe cases, shock occurs when a critical volume of plasma is lost through leakage, which is often preceded by warning signs. A rapid and progressive decrease in platelet count to about 100 000 cells/mm and a rising haematocrit above the baseline may be the earliest sign of plasma leakage. This is usually preceded by leukopenia (= 5000 cells/mm). Warning signs usually precede the manifestations of shock and appear towards the end of the febrile phase, usually between days 3 to 7 of illness. The TDR (2009) guidelines do not differentiate between DF and DHF. The warning signs for severe and probable dengue are also unclear and overlapping. Hence, the 1997 WHO guidelines (expanded in 2011) should be used by the countries.

Dr Anon Srikiatkhachorn, Consultant in Allergy-Immunology, Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, Thailand, touching upon various dengue diagnostics, mentioned that viral isolation and characterization is the gold standard. Understanding the natural pathogenesis of dengue is useful in deciding the diagnostics. More practical approaches are antibody detection which is a preferred method when acute sample is taken after 2–3 days, then antigen detection using nonstructural protein 1 (NS1) and if the sample is taken after 5–6 days, immunoglobulin M (IgM) can be detected. Increase in sensitivity of antibody assays between admission and post-admission samples demonstrates the importance of convalescent samples. The most accurate and timely diagnosis can be provided by molecular methods. Differentiation of antigenically similar agents is possible by this method. He presented the genomic sequence of DENV serotypes and said that understanding of DENV evolutionary dynamics could be very informative for the development of vaccine and anti-viral drugs. However, safety in diverse populations (genetically and geographically distinct), age, flavivirus spectrum (primed and unprimed), and non-inferiority (immunity) outside trial would be crucial. He also mentioned that high levels of genetic diversity may impact vaccination in future.

Many commercial rapid diagnostic kits are also used; however, many of these are prone to false positives and negatives due to poor sensitivity and specificity. He cautioned that the current rapid tests on the market do not perform as indicated in their package inserts. If used, the results should be confirmed by another assay. It is always good to test rapid kits against a gold standard assay to check their performance.

Professor Siripen Kalayanarooj, Director, Queen Sirikit's National Institute of Child Health, Thailand, stressed that the steps for proper case management included: early clinical diagnosis; outpatient department (OPD) triaging; monitoring of general condition of the patient; proper intravenous (IV) fluid management; management of complications; early diagnosis of expanded dengue syndrome; and eventual discharge of the patient. Clinical diagnosis through case definition was explained with set criteria by WHO (2011) (high fever with any two of accompanying signs such as headache, retro-orbital pain, myalgia/arthralgia, rash, haemorrhagic manifestations, leukopenia, platelet count $<150\ 000/mm^3$ or haematocrit increase 5–10%). ''Warning signs" are still appropriate to be used in OPD triaging to decide on admissions, and when health workers are trained properly and implement this correctly, there is significant increase in quality of care. Screening and triaging during dengue outbreak is extremely important with simplified case definition (fever >3 days, leukopenia – white blood cell count $<5000/mm^3$, and platelet count $<100\ 000/mm^3$) and high-risk patients need to be identified early. Rapid laboratory tests are also crucial.

Recent studies were highlighted in regard to dengue classification, all of which stressed the need to attain the aim of lower CFR, less severe cases, more practical and applicable in places with limited resources. Some clinical guidance and evidence for decision-making in the clinical management such as close monitoring by nurse team, how to manage IV fluid properly, expanded dengue syndrome (multiple organ failure from prolonged shock, often occurs in co-morbid hosts or dual infections manifestations include encephalopathy and liver/renal failure) and criteria for discharge were outlined. In a study carried out on suspected dengue patients, the TDR (2009) classification was applied, using the data from the study case-report from each patient, even though the final diagnosis was based on the current WHO (1997) classification together with laboratory confirmation. Clinical and laboratory data between each group of patients

was compared and statistical analysis done. Based on the study, continued use of the current 1997 WHO classification was recommended, because the newly suggested TDR classification creates about twice the workload on health-care workers, as was evident from the last outbreak in Pakistan.

However, the current WHO classification needs to be modified to be simple and more user-friendly. Suggested modification is to address plasma leakage as a major criterion. Positive tourniquet test or bleeding symptoms can be combined as minor criteria. Unusual dengue is proposed to be added to the current WHO classification to cover those patients who do not fit in the current WHO classification.

During the discussion on the Bi-regional Strategic Plan for Dengue Prevention and Control 2008–2015, the need to strengthen and standardize disease reporting systems using standard case definitions was highlighted. This is realized through the development of the Asia–Pacific Dengue Strategic Plan which aims to reduce the disease burden due to vector-borne diseases to such an extent that they are no longer major public health problems. The vision of the Asia–Pacific Strategy is to reverse the rising trend of dengue to minimize its health, economic and social impact. The adoption of resolutions on dengue in the Meetings of the Regional Committees of the South-East Asia and Western Pacific regions in 2008 amply illustrated this commitment. The need for implementation and scaling up of integrated vector management (IVM) approach, country capacity strengthening in case management, surveillance and vector control, and developing a comprehensive guideline on prevention and control of dengue was also highlighted.

5. Country situation of dengue and experiences in using dengue classification in surveillance

5.1 Bangladesh

In 1964, dengue came to Dhaka city as *Dhaka fever* with great casualty. In 2000, a major outbreak occurred in three major cities - Dhaka, Chittagong and Khulna - with a total of 5551 reported cases and 93 deaths. At that time, preparation was not good enough to face the dengue/DHF and

haemorrhaegic symptoms. Since then, occurrence of dengue is a regular phenomenon every year with an upsurge every alternate to three years. Though the numbers of cases are fluctuating, Bangladesh has demonstrated appreciable competence in managing the cases with continued decline in mortality. Since 2007, there have been no reported deaths, except in the year 2011.

The national guidelines for management of dengue/DHF adapted the WHO (1997) classification and have been updated and re-printed in 2009. Training courses for doctors and nurses in clinical management and capacity building have been a major focus, especially in the tertiary care facilities of both the public and private sectors. Training of the health-care providers on dengue management and increased awareness of the people in general have contributed to low mortality. The prevalence of the circulating types of virus and the immunological process involved may also play a role in reduction of severe dengue. However, dengue has established itself as an endemic disease not only in the major cities, but also in small towns and semi-urban areas.

5.2 India

The disease situation, control strategy and case management in India was discussed. DENV was first isolated in 1945 at Calcutta in India. The first evidence of DF in the country was documented in 1956 from Vellore district, Tamil Nadu, while the first DHF outbreak occurred in 1963 in Calcutta (Kolkata, West Bengal). The country has become hyperendemic, as all the four serotypes i.e. DENV 1, 2, 3 and 4 are isolated in India. The risk of dengue has shown an increase in the recent years, spreading every year to newer geographical areas including peri-urban and rural areas. Transmission is perennial in the southern and western parts of the country, while seasonal in northern and eastern parts. Dengue is not confined to the paediatric group in India; all age groups of both the genders are affected.

Out of 35 states/union territories, 34 have reported cases and deaths due to dengue. Repeated outbreaks are reported from various states. The country experienced a major outbreak in 1996 with 16 517 cases and 545 deaths. Repeated outbreaks are reported from 2003 onwards with almost 12 000 cases and 200 deaths annually. Thereafter, cases are on the rise since 2009, (15 535 cases), 292 cases in 2010 and 50 222 in 2012 which

was the highest ever in the country in the last two decades. *Ae. aegypti* is the principal vector; however, at present *Aedes albopictus* has posed serious threats of dengue transmission in certain geographical regions endowed with sylvatic environment, particularly in the southern and north-eastern states.

A mid-term plan (with eight key elements), called the octalogue strategies, is implemented for prevention and control of dengue by the National Vector Disease Control Programme under the Ministry of Health and Family Welfare, Government of India. Key technical elements are diagnostic and case management, surveillance and outbreak response, sustainable vector control and research. To facilitate diagnosis, early case detection and management, 347 sentinel surveillance hospitals with laboratory support were established across the country and linked to 14 apex referral laboratories with advanced diagnostic facilities for back-up support. National guidelines for clinical management of dengue cases have been developed in tandem of WHO (1997) guidelines with national and international experts and sent to the states for circulation in all hospitals. Training on national guidelines was conducted for capacity building of doctors, which has been crucial in bringing down the CFR gradually from 3.3% in 1996 to 1.2% in 2007 and to 0.5% in 2012. The case management guidelines are under the process of updating. WHO case classifications are hotly debated; however, conclusions could not be drawn on which guidelines to follow.

5.3 Indonesia

Dengue was the leading cause of hospitalization and death among children in Indonesia. It was first reported in 1968 during an outbreak that occurred in Surabaya and Jakarta with 58 cases and 24 deaths (CFR: 41.3%). In subsequent years, the number of cases increased and reached 150 505 in 2010. Cases and deaths decreased thereafter, which is quite significant. In 2012, there were 90 245 cases and 816 deaths (CFR 0.9%). Dengue is now widely spread in most of the districts and municipalities, with Jakarta province, the islands of Bali and Java as the most endemic areas due to high population density. Four serotypes of DENV have been reported. Male to female proportion was 53.2 to 46.8 (MoH 2012). *Ae. aegypti* is the major vector, although *Ae. albopictus* has been reported as well.

The national dengue control programme aims to decrease the morbidity of DHF cases and reduce CFR with strong prevention and control of outbreaks. National indicators have been set up to reach dengue incidence below 55/100 000 population: CFR below 1% and free larvae index in houses to below 60%. Source reduction implementation with 100% coverage and DF/DHF case management has been standardized. The national programme also provides support to the districts/provinces in terms of policy and strategic planning, as since 2008, Indonesia has undergone decentralization process in governance with more district/province autonomy and resource allocation.

Clinical criteria of WHO (1997) dengue classification are followed. The multiplicity of WHO guidelines (1997, 2009 & 2011) is confusing. Increase of hematocrit 20% and platelet <100 000 is rarely taken into account as an indication of hospitalization in daily clinical practice. Tourniquet test is rarely performed due to false negative result. Laboratory sampling and testing is not done except in limited numbers in outbreaks or in cluster samples tested by serology and virus isolation by PCR.

5.4 Myanmar

Sporadic cases of dengue have been reported since the 1960s, with the first outbreak occurring in Yangon in 1970. By 1974, the disease had spread widely with cases reported from all states and divisions except Chin, affecting both urban and rural areas. There is an increasing number of cases reported (24 285 in 2009, compared with 1884 in 2000). The disease affects mainly young age group of 5–9 years. The transmission season spans the entire year, but is relatively high during the rainy season of June to August. Year 2010 saw 16 529 cases, which declined to 4783 in 2011 and 6121 cases were reported until October 2012.

The goal of the national dengue control programme is to reduce mortality and morbidity caused by dengue. Strategies encompass components such as effective disease and vector surveillance systems; selective, stratified and integrated vector control; emergency preparedness capacity for outbreaks with appropriate contingency plans; prompt case management, and awareness of the community through IEC; and strengthening the health facilities for health sector development. Referral network system in public and private sectors has been established.

Capacity-building through training of medical officers in IEC and of basic health services staff on effective disease and vector surveillance, epidemic preparedness and case management as appropriate is a priority activity.

The vector control measures are evidence-informed and aim to control vector populations based on IVM principles. Operational research on effectiveness of larvicide was carried out in eight townships. Surveillance is done through weekly reporting and a hospital-based surveillance system is established by the township health department. There is a clear flow of information from the focal point to States/Division VBDC team and to the Central VBDC, then to the MoH.

5.5 Sri Lanka

The first official record of serologically-confirmed dengue in Sri Lanka was in 1962 and the first outbreak was noted in 1965. The country has become dengue-endemic since 1989, and in 1996, the disease was mandated to be notifiable. Since 2000, every year, around 5000 cases have been reported and cyclical epidemics occurred in 2002, 2004, 2006 and 2009. In 2009, the number of cases was 35 008 with 350 deaths. The high morbidity continued in 2010 and 2011, with 34 097 and 28 473 cases, respectively. Until October 2012, a high number of 38 426 cases were reported with 154 deaths. Although notification through health information system is in place, underreporting from the private sector is evident.

The national dengue control programme was then established. Activities in the country strategy cover key areas such as: disease surveillance (by strengthening early notification at OPD/wards); capacity building, establishing peripheral laboratories; proper case management; developing guidelines and training manuals for clinicians, training and death reviews; IVM including space spraying, entomological surveillance, and legislation for mosquito control. Intersectoral coordination was done by ensuring partnerships between different stakeholders; and social mobilization activities included development of district COMBI plan, campaign through 'dengue weeks' and holding media seminars.

The importance of dengue vector control is evident; thus activities such as insecticide fogging and source reduction (larval) were put in place. Insecticide resistance is a concern and will be monitored. Trained

volunteers visit households to eliminate breeding sites. Emergency response includes measures to rapidly reduce the number of infective mosquitoes and proper management of patients.

Political commitment to tackle dengue is shown through the constitution of a Presidential Task Force in 2010 with members from various ministries and local governments. However, several areas such as proper collection and disposal of solid waste, water storage management, interministerial and intersectoral cooperation, need strengthening.

5.6 Thailand

Dengue was reported in Thailand as early as 1949. The first outbreak occurred in 1958 in Bangkok with 2706 cases (attack rate 10.6/100 000 population) and 296 deaths (CFR 10.9%). The fluctuation has shown an increasing trend over the years. In 2008 and 2009, the number of cases and deaths were 89 626 and 56 651 and 102 and 50, respectively. In 2010, a huge increase was noted with 115 768 cases and in 2011, 65 971 cases. All serotypes are in circulation. The age groups of 10–14 and 15–24 years were the most affected. Mosquito *Ae. aegypti* is the predominant vector in the country.

In view of this major public health problem, national policies and control programmes were established, with key strategies and activities ranging from surveillance (passive, active surveillance, serosurveillance, vector surveillance); IVM (strengthening of *Aedes* larvae abatement programmes); case management (intensive training of physicians and nurses in clinical diagnosis and disease management; and distributing national clinical practice guidelines through government hospitals); social mobilization (establishing advisory groups to develop educational materials, empowering individuals and communities; providing training on community mobilization, conducting public education campaigns, big cleaning day); and quite importantly, updating knowledge and research (organization of international conferences on DF/DHF, application of new tools to diagnose DF/DHF, carrying out dengue vaccine trials).

Outbreak control is achieved through enhanced surveillance by mobilizing general practitioners around clusters for increased alertness, improved reporting, setting up flows to send samples to the Medical

Sciences Department for laboratory confirmation and serotyping, epidemiological investigation and determining epidemiological links of seemingly unrelated cases. Multisectoral networking and partnership for dengue prevention and control is initiated.

Thailand has experienced DF/DHF epidemics every two to four years till the end of the twentieth century. During the epidemic that occurred during 1997–1998, 228 878 cases were reported to the Ministry of Public Health.

Thailand has been a model for other endemic countries in the application of guidelines to reduce CFR among DHF patients. From the early 1960s, when the CFR was generally above 10% and in some outbreaks as high as 44%, it has been reduced to less than 0.5% by 1998. Between 2007 and 2011, the CFR has been around 0.001% or less.

6. Clinical management of dengue at peripheral (health centres), secondary (district hospitals) and tertiary health facilities

6.1 India

Prof Ashutosh Biswas, Professor of Medicine from All India Institute of Medical Sciences (AIIMS), New Delhi, who is actively involved in case management and clinical research in DF/DHF, said that AIIMS hospital, a tertiary care hospital and medical college, usually becomes overloaded with DF patients during epidemics. Only severe and complicated DF cases are admitted in the hospital.

In one of the studies, the impact of two different classifications developed by WHO and TDR was compared. To examine the severity of DF patients, 80 cases of DF/DHF were enrolled in the study according to two classifications and TDR. According to WHO classification, 30 severe patients with shock and 50 with non-shock and non-severe could be classified compared to 46 severe and 34 non-severe according to TDR classification. It is interesting to note that the number of severe cases jumped from 30 to 46 when TDR classification was applied. It was found

that the inflated number (46) was mostly due to introduction of misclassification in clinical settings, where it was practically difficult to categorize such as ascites, pleural effusion and bleeding into severe and non-severe group. Therefore, sixteen more patients were added in the severity group from non-shock, irrespective of severity of pleural effusion, ascites and organ involvement.

Molecular research work on the pathogenesis of DF/DHF was also presented. Dr Biswas has been working on trans-membrane protein human thrombomodulin (TM) also known as BDCA-3 or CD141, mainly expressed by vascular endothelial cells. Severity of capillary leakage is mostly dependent on severity of inflammation of capillary endothelial cells. He has also been working on different cytokines and chemokines to correlate the severity of DF and DHF. He found some of the risk factors were associated with severity of DF. Elevated STM (soluble thrombomodulin) and Interleukin 6 (IL-6) were found to be the predictors of severity of DF. Till date, we do not have any molecular or biomarkers to predict the severity of DF. If these molecular markers are proved in a study with larger sample size, it would be a great contribution in the field of diagnosis and management of severe DF.

Dr Janani Shankar, Paediatrician, shared her experiences in case management in a private hospital in south India. She mentioned that TDR (2009) guidelines are followed in the hospital classification, though the Indian national guidelines are based on WHO (1997) guidelines.

6.2 Indonesia

Dr Sri Rezeki Harun Hadinegoro Paediatrician, Faculty of Medicine, University of Indonesia, Jakarta, made a presentation about harmonization between the two WHO guidelines.

She emphasized the importance of differentiating between DF and DHF. DF has no plasma leakage, no hypovolemic shock and has good outcome; bleeding is usually mild. The sign of DHF is plasma leakage with increasing haematocrit above 20 per cent. The key to differentiation between DF and DHF, according to her, is monitoring during the early shock phase (day 3–5 of illness).

In DF, after fever ceases, the patient will have good clinical condition with good appetite; while in case of DHF, after fever ceases, clinical conditions worsen and are generally followed by hypovolemic shock.

The low fatality rate in Indonesia was because the denominators mixed up DHF plus DF; whereas it should be total dengue deaths, divided only by DHF cases. If the last denominator is used, the CFR will increase from 1.5 % to 4.9%.

From the analysed data of dengue outbreaks (1998 and 2004) in Jakarta, she showed that 16.1% was DF, 70.5% was DHF and 13.1% was DSS. The above data shows the importance of setting up triage system and one-day care unit (ODC) in hospitals in order to reduce the mortality. By using triage system in ODC Unit, it reduces 76% hospitalized suspected dengue cases. ODC is very useful, particularly in outbreak situation.

6.3 Sri Lanka

Dengue case classifications are important in early detection of suspected cases for surveillance, early diagnosis for clinical management and for disease burden studies. However, he concentrated on the classification in clinical practice. In Sri Lanka, over the past several years, those who treat dengue patients have classified cases in two different ways: while the majority try to split and differentiate DHF from DF (splitting) early in real-time before attempting to treat; a minority consider dengue as one disease entity with different clinical presentations with unpredictable outcome/ complications (lumping).

Both the WHO (2011) and TDR (2009) classifications had been evaluated in terms of all three entities and possible clinical end points arrived at. Implications of classifications on case management as per WHO (2011) – DF & DHF (splitting); facilitates early diagnosis and proactive management of DHF; clinical end-point altered through early intervention, whereas TDR (2009) classification as dengue without severe signs, dengue with severe signs and severe dengue (lumping) allows the disease to evolve – a reactive management of severe disease - clinical end-points mixture (natural and iatrogenic). Therefore, the implications of classifications would result in facilitating early diagnosis and proactive management, whereby clinical end-points could be altered, or allowing the disease to evolve and

initiating reactive management based on severity where the end-points would probably be a mixture. One group diagnoses clinical end points and manages cases accordingly. Majority actively looks for fluid leak and provides fluid therapy judiciously, based on haemodynamic status of each patient. In terms of surveillance, diagnosis and management, both classifications have advantages and disadvantages. So, one may not be able to get one classification to do both. Therefore, they would not reject either and try to use both intelligently to prevent mortality and minimize morbidity.

Dr Lak Kumar Fernando, Paediatrician**,** from Negombo General Hospital, Sri Lanka, described his experiences on clinical management of dengue cases citing examples of managing a few cases at the Centre for Clinical Management of Dengue and Dengue Haemorrhagic Fever. The management of dengue in both children and adults is more or less the same. Management of DF and DHF patients needs close observation and monitoring. All the cases should be examined actively for fluid leak and fluid therapy provided judiciously, based on the haemodynamic status of each patient. He said the majority of deaths reported were due to negligence of patients such as seeking treatment after developing DHF or DSS.

7. Case management, dengue classification (2009) and experiences in the Western Pacific Region in using the guidelines

7.1 Singapore

Dr Yee-Sin Leo, Director, Institute of Infectious Disease and Epidemiology, Singapore, mentioned that Singapore's worst outbreak to date occurred in 2005, when confirmed cases reached 14 006 and 27 people died of the illness. This year, only two deaths have been reported, but by the number of cases, officials expect the current outbreak to exceed the previous record. Because of intensive vector control over the years, the population may be having low immunity, making them vulnerable to outbreaks. Influx of population not exposed to dengue also increases the threat. Singapore

has experienced yet another epidemic. With more than 13 000 cases reported as of mid-July 2013, this could possibly be one of the worst outbreaks in Singapore's history. Dengue claimed its first death in May 2013 and since then; four others have died of dengue. Of these five deaths, 80% occurred in patients older than 60 years. The last epidemic from 2004 to 2005 saw more than 14 000 cases with 27 reported deaths. However, cases are fewer now. Singapore follows the WHO 1997 guidelines for case classification. DF and DHF cases are reported separately.

7.2 Viet Nam

Dr Tran Tinh Hien, Director of Clinical Research, Oxford University Clinical Research Unit Ho Chi Minh City, Viet Nam, presented his clinical experiences of dengue case management. He said if DF and DHF are different, then there should be two different virus strains. In-depth study is needed for host genetics characteristics and genomic analysis to understand these complex phenomena. He described the role of platelet count, fluid management and supportive therapy for case management. About haemorrhage, he observed that it is more severe in adults than children. He concluded that dengue infection is not yet understood completely and requested for finalization of classification for dengue.

8. Field visit to the Centre of Clinical Management of Dengue and Dengue Haemorrhagic Fever, Negombo, Sri Lanka

On 14 August 2013, all the participants were taken to the recently opened state-of-the-art Centre for the Clinical Management of Dengue and Dengue Haemorrhagic Fever, Negombo. While welcoming the participants, Dr LakKumar Fernando, paediatrician-in-charge of the hospital mentioned that the hospital is unique and acclaimed as the first in the country for management of DF and DHF in both adults and children. The 17-bedded hospital is well-equipped for monitoring all "vitals" such as blood pressure, heart rate, oxygen saturation and temperature of patients by individual machines attached to each bed. Besides, it has the facility of infusion pumps to combat fluid leakage after accurate electronic calculation of individual needs, critical in the management of DHF cases. The Centre not

only offers care for dengue patients, but also a regional training centre for specialist doctors. The hospital has 17 beds, but has the capacity to increase up to 20. In addition to the consultant paediatrician Dr Fernando, the hospital has a dedicated work force of 6 doctors, 10 nurses and 5 staff. Negombo had been reporting the highest number of dengue patients when compared to any city or place in the country and is a major contributory factor for the high numbers in the Western Province. During the visit, all the beds, both paediatric (5) and adult (12) were occupied by dengue patients.

9. Harmonization of dengue classification

For harmonizing dengue case classification and case management as well as reporting system, the following issues were discussed:

- harmonization of dengue case classification and case management;
- review of the implication of difference in reporting system and recommend for uniformity of reporting system;
- recommendation for monitoring and evaluation of clinical management; and establishment of a network of experts on case management of dengue.

10. Conclusion

Harmonization of the WHO classification revised in 2011 by the WHO Regional Office for South-East Asia with the TDR (2009) classification is done by addressing plasma leakage as the major pathophysiology that may lead to severe disease first. After signs of plasma leakage are observed, warning signs (2009) should be applied. The two classifications can be made parallel and interchangeable between each classification as follows:

(1) DF (2011) is equal to mild dengue (2009).

(2) DF without/with unusual haemorrhage (2011) is equal to moderate dengue with warning signs (2009).

(3) DHF with plasma leakage/expanded dengue syndrome is equal to severe dengue (2009).

11. Recommendations

- DHF/DSS should continue to remain as the most important category in the disease classification of dengue illness.
- A uniform reporting system based on DF and DHF classification should be proposed to all Member States on arrival of the final diagnosis. The final diagnosis should be clearly stated. For surveillance purpose, any 'unusual dengue' category must be reported.
- A formal Regional Expert Group on Clinical Management, representing all Member States, should be established which would be coordinated by WHO.
- Networking among the expert groups on clinical management within the countries should be fostered.
- Intercountry cooperation networking pertaining to any development in disease and management as well as promotion of collaborative research should be extended to experts.
- TDR (2009) guidelines should be harmonized with the WHO (1997) guidelines and revised WHO (2011) guidelines on the following basis:
  - recognize plasma leakage first, using WHO (1997) or (2011) dengue guidelines;
  - then apply warning signs TDR (2009) in order to prevent shock, complications of fluid overload or organ(s) failure.
- Dengue case classification should be harmonized as follows:
  - DF and DHF are two different clinical entities of dengue infections: DF is without plasma leakage, DHF is with on-going plasma leakage;
  - DF does not progress to DHF;
  - DHF or DSS is the same disease with different degree of plasma leakage;

- Standard criteria for diagnosis and management should be standardized.
- A standardized recording and reporting system should be established in countries:
  - uniformity of reporting system is a must – based on final diagnosis
  - reporting system should follow the International Classification of Diseases (10th revision) (ICD10): (A 90 – DF; A 91 – DHF; A 91a – DSS; A99 – unconfirmed dengue)
- Intercountry cooperation, new genotype sharing of information should be extended.
- One or two focal points from each country should be identified, and country representatives must be consulted on all issues related to clinical management and guideline formation.

Annex 1

Agenda

(1) Opening

(2) Technical update

(3) Situation of dengue and experiences in using dengue disease classification in surveillance

(4) Clinical management of dengue at peripheral (health centres), secondary (district hospital) and tertiary health facilities

(5) Case management, dengue classification (2009) and experiences in the Western Pacific Region in using the guidelines

(6) Harmonization of dengue disease classification and case management

(7) Field visit to the Centre for Clinical Management of Dengue and Dengue Haemorrhagic Fever, Negombo

(8) Conclusion

(9) Recommendations

Annex 2
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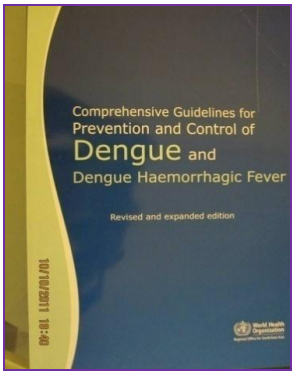
Annex 3

Dengue case classification – WHO



- DF
- DHF
- DSS
- Expanded dengue syndrome

Dengue fever

Probable diagnosis:

- Acute febrile illness with two or more of the following:
- headache
- retro-orbital pain
- myalgia
- arthralgia/bone pain
- rash
- haemorrhagic manifestations
- leucopenia (wbc =5000 cells/mm)
- thrombocytopenia (platelet count <150 000 cells/mm^3)
- rising haematocrit (5 – 10%)

and at least one of the following:

- supportive serology on single serum sample: titre =1280 with haemagglutination inhibition test, comparable IgG titre with enzyme-linked immunosorbent assay, or testing positive in IgM antibody test;
- occurrence at the same location and time as confirmed cases of DF.

Confirmed diagnosis:

Probable case with at least one of the following:

- isolation of DENV from serum, CSF or autopsy samples;
- fourfold or greater increase in serum IgG (by haemagglutination inhibition test) or increase in IgM antibody specific to DENV;
- detection of DENV or antigen in tissue, serum or cerebrospinal fluid by immunohistochemistry, immunofluorescence or enzyme-linked immunosorbent assay;
- detection of DENV genomic sequences by reverse transcription-polymerase chain reaction.

Dengue haemorrhagic fever

All of the following:

- acute onset of fever of two to seven days duration;
- haemorrhagic manifestations, shown by any of the following: positive tourniquet test, petechiae;
- ecchymoses or purpura, or bleeding from mucosa, gastrointestinal tract, injection sites, or other locations;
- platelet count =100 000 cells/mm;
- objective evidence of plasma leakage;
- due to increased vascular permeability shown by any of the following:
    - rising haematocrit/haemoconcentration =20% from baseline;
    - decrease in convalescence;
    - evidence of plasma leakage such as pleural effusion, ascites or hypoproteinaemia/ albuminaemia.

Dengue shock syndrome (DSS)

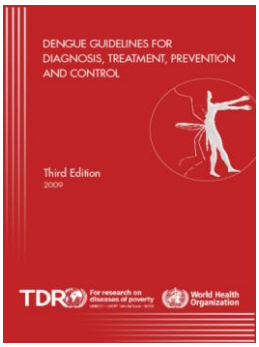
Criteria for dengue haemorrhagic fever as above with signs of shock including:

- tachycardia, cool extremities, delayed capillary refill, weak pulse, lethargy or restlessness, which may be a sign of reduced brain perfusion.

- pulse pressure =20 mmHg with increased diastolic pressure, e.g. 100/80 mmHg.
- hypotension by age, defined as systolic pressure <80 mmHg for those aged <5 years or 80 to 90 mmHg for older children and adults.

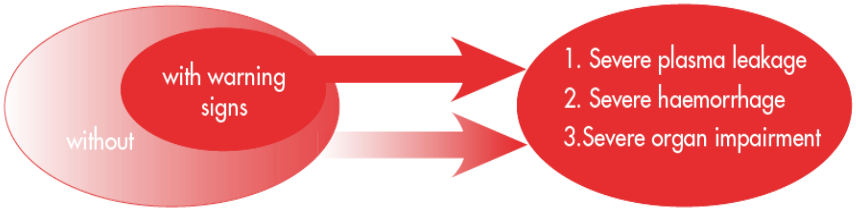
Annex 4

Dengue case classification – TDR+WHO



- Dengue (D)
- Dengue ± warning signs (D ± WS)
- Severe dengue (SD)

DENGUE ± WARNING SIGNS **SEVERE DENGUE**



CRITERIA FOR DENGUE ± WARNING SIGNS

Probable dengue

live in /travel to dengue endemic area.
Fever and 2 of the following criteria:

- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Leukopenia
- Any warning sign

Laboratory-confirmed dengue

(important when no sign of plasma leakage)

Warning signs*

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargment >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)

CRITERIA FOR SEVERE DENGUE

Severe plasma leakage

leading to:

- Shock (DSS)
- Fluid accumulation with respiratory distress

Severe bleeding

as evaluated by clinician

Severe organ involvement

- Liver: AST or ALT >=1000
- CNS: Impaired consciousness
- Heart and other organs

World Health Organization
Regional Office for South - East Asia

INFORMAL EXPERT CONSULTATION ON CASE MANAGEMENT OF DENGUE

Colombo, Sri Lanka
12 - 14 August 2013

Dengue is the fastest-growing arborvirus infection with a rapidly evolving epidemiology. During the past 50 years, the worldwide incidence of dengue has risen 30-fold. The World Health Organization estimates that 50 100 million dengue infections occur each year in 100 tropical and subtropical countries where almost half the world's population lives. Approximately 1.8 billion (more than 70%) of the population at risk for dengue worldwide live in Member States of the WHO South-East Asia and Western Pacific regions, which bear nearly 75% of the current global disease burden due to dengue. Except for the Democratic People's Republic of Korea, all 10 countries including India are endemic for dengue.

Incidence of dengue is increasing as the disease spreads and explosive outbreaks are occurring in newer geographical areas. Mortality is the highest during the initial period of the outbreak or epidemic. Children in particular are at high risk of mortality as a result of complications and lack of access to prompt treatment.

The interventions that are currently available have been relatively effective for more than two decades, but there is clearly a need for the development of new and improved diagnostic, preventive and therapeutic tools.

In contribution to ongoing efforts to manage the dengue cases effectively in the Region, a three-day informal expert consultation on case management of DF/DHF was held in Colombo, Sri Lanka, from 12 to 14 August 2013. The experts recommended harmonization and synchronization of the dengue case classification of WHO guidelines 2011 with TDR guidelines 2009.

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