EDITORIAL

Prevention of Dengue Deaths, Bangladesh Perspective

Overview: Dengue virus is a mosquito-borne pathogen that causes up to about 100 million cases of disease each year, placing a major public health, social, and economic burden on numerous low-income and middle-income countries. Major advances by investigators, vaccine developers, and affected communities are revealing new insights and enabling novel interventions and approaches to dengue prevention and control. While dengue fever is endemic in the South Asian country, with infections typically peaking during the monsoon season between July and September, this year the uptick in cases started much earlier – toward the end of April. A prolonged monsoon season that saw warmer temperatures combined with irregular, heavy rainfall created ideal breeding conditions for the Aedes mosquito, which carries the dengue disease.

In a sense, this neglected tropical disease has taken the world by surprise, with few coherent and coordinated efforts, at national or international levels, undertaken to hold dengue at bay and reverse these alarming trends. Compared with the situation 50 years ago, the worldwide incidence of dengue has risen 30-fold. More outbreaks are explosive in ways that severely disrupt societies and drain economies. Today, dengue ranks as the most important mosquito-borne viral disease in the world. Epidemics of dengue result in human suffering, strained health services and massive economic losses. In some countries like Bangladesh, the burden of dengue is comparable to that of tuberculosis and other communicable diseases with high disease burdens; unexpected surges in cases and the challenge to health systems of triaging thousands of cases without knowing which severe cases will require hospital care are additional challenges.

As of 15 October 2023, Cumulatively 231,204 cases including 1,122 deaths have been reported since January 2023. September was the highest in terms of reported cases and deaths and have been reported from all the 64 districts of the country. This makes it the largest outbreak of dengue fever reported in the country in terms of number of reported cases including deaths and the nationwide spread. The scale, urgency and seasonality have also brought additional pressure on the health system. The influx of patients has strained the country's health care system and hospitals have faced a shortage of beds and staff to care for them. Fatalities from the outbreak are almost four times higher than last year, when 281 people died. In September alone, there were more than 79,600 reported cases and 396 deaths, according to Bangladesh health authorities. There is also growing concern about the outbreak spilling into the cooler months. Last year, dengue cases only peaked in October with most deaths recorded in November. Dengue is under-reported, but the actual number of dengue infections per year is estimated to be as high as 390 million (95% credible interval, 284–528 million), of which 96 million (67–136 million) manifest clinically. The staggering reported number of cases and deaths in Bangladesh by year is shown in the table below-

Table-I

Dengue cases, deaths, and case fatality rate in Bangladesh for 2018, 2019, 2021, 2022 and 2023

Year	Cases	Death	Case Fatality Rate
2018	10,148	26	0.26%
2019	101,354	164	0.16%
2021	28,429	105	0.37%
2022	62,382	281	0.45%
2023 (as of 15 October)	231,204	1,122	0.50%

Data source: DGHS (*data for 2020 is limited due to COVID-19)

Dengue mortality can be reduced by implementing early case detection and appropriate management of severe cases; reorienting health services to identify early cases and manage dengue outbreaks effectively; and training health personnel, along with appropriate referral systems, at primary health-care levels. Dengue morbidity can be reduced by implementing improved outbreak

prediction and detection through coordinated epidemiological and entomological surveillance; promoting the principles of integrated vector management and deploying locally-adapted vector control measures including effective urban and household water management. Effective communication can achieve behavioural outcomes that augment prevention programmes. Research will continue to play an important role in reversing the trend in dengue, a neglected tropical disease, by improving methods and systems for surveillance, prevention and control.

The Global strategy for dengue prevention and control, advice on how to move from a reactive response to an emergency situation to proactive risk assessment, early warning systems, and preventive measures, guided by entomological as well as epidemiological surveillance. Above all, the Global strategy emphasizes many new opportunities, opened by country experiences and recent research, also on vaccines, that can be seized to reduce morbidity and mortality, rationalize the disease response, and build capacities that increase resilience to future outbreaks.

A complex disease like dengue demands a multipronged response that engages government ministries well beyond the health sector. The Global strategy promotes coordinated action among multi-sectoral partners, an integrated approach to vector management, and sustained control measures at all levels. Its guiding principle is to harmonize prevention, entomological and epidemiological surveillance, and case management with existing health systems, ensuring that efforts are coherent, sustainable, cost-effective and ecologically sound. The overall message is upbeat and encouraging. Despite the complex clinical manifestations of this disease, its management is relatively simple, inexpensive and highly effective in saving lives, provided correct and timely interventions are instituted. When these interventions are in place, mortality from dengue can be reduced to zero. Let us make this our overarching – and broadly shared – goal.

Diagnostic and therapeutic targets for dengue

Though most dengue patients do not enter the critical stage, there is uncertainty on which patients might progress to severe dengue. Identification of imminent severe dengue is crucial to allow timely management of shock and bleeding, facilitate early referrals, and reduce mortality. Availability of a predictive test for severe dengue that is simple, sensitive, and can provide rapid point of care diagnosis will avoid unnecessary hospitalization, save resources, and reduce time spent on repeated laboratory tests. To inform healthcare decisions for timely clinical management, the biomarker should be applied early upon hospital admission to patients at risk of progressing to severe dengue, especially in dengue warning sign patients. However, such a test is currently unavailable. There are several potential clinical biomarkers that need to be explored further to allow timely recognition of severe dengue. Continued research, funding, and resource allocation are crucial for development of such predictive tests. In fact, genetic testing is costly. It is a high technology that requires staff with good training and high experience in molecular biology. Lack of specific treatment for dengue infection highlights the compelling need for innovative therapeutic strategies. Advancing research on the role of inflammatory mediators in dengue pathogenesis can offer potential therapeutic targets.

Lessons from successful dengue control programs

In 2011, Lahore city of Pakistan experienced its most serious dengue epidemicin response, a Central Emergency Response Committee integrating multidisciplinary efforts of health, agriculture, environment, and horticulture ministries was established. A Dengue Expert Advisory Group identified suspected dengue patients referring them to public hospitals for standardized diagnostic test and treatment. Data from each confirmed case was entered in a centralized patient tracking system. Technological initiatives included implementation of online surveillance systems, global positioning systems, phone-based surveillance system, and toll-free help line for citizens. Health infrastructure was revamped with establishment of isolation wards and high dependency units (HDUs), extra allocation of beds, and recruitment of healthcare professionals. Medical practitioners and public health managers received training from Sri Lanka and Thailand and acted as master trainers to train local professionals.

Semarang City in Indonesia, which reports one of the highest numbers of dengue cases in Central Java, is another example of successful dengue control program.

To control the rising dengue incidence, the Governmental Health Office recruited dengue surveillance workers (DSWs) to improve environmental management through community participation, education, organization, and vector control. The success of DSWs work was demonstrated through the decline in dengue hemorrhagic fever (DHF) incidence from 92.4 per 100,000 inhabitants in 2014 to 18.14 per 100,000 inhabitants in 2017, coexisting with 3 years in which DSWs were entrusted to work in the Semarang municipality.

Lessons from such successful dengue control programs should be considered as stepping-stones for developing dengue control strategies in Bangladesh settings. Collaborative multi-sectoral (health, education, environment, policy, and community) efforts are needed to build a strong dengue prevention framework to lead the global march against dengue.

Double challenge of dengue and COVID 19

The dual problem of Coronavirus Disease 2019 (COVID-19) caused by novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and DENV is an important public health issue, especially for developing countries that have overburdened public health infrastructure, economic obstacles, and limited diagnostic capability. Misdiagnosis and coinfection with both COVID-19 and dengue is a serious concern due to similar clinical and laboratory characteristics. Cases of coinfection have been reported in Singapore, Thailand, Malaysia, Brazil, and Southeast Asia. Cross-reactivity between DENV and SARS-CoV-2 antibodies on serology tests, although unlikely, presents another diagnostic challenge. False positive dengue serological tests in COVID-19–positive patients were reported in Singapore and Israel. In Southeast Asia and South America, where both viruses are in cocirculation, 22% COVID-19 infections might be incorrectly diagnosed as dengue, complicating the management and treatment of both diseases. The delay in diagnosis and treatment is the most important risk factors contributing to the increase in dengue fatality rates. The pandemic highlights the pressing need for dengue preparedness through resource mobilization, environmental management, and the strengthening of public health infrastructure.

Dengue vaccines

The challenge of dengue vaccine development is providing protective antibodies against all 4 dengue serotypes to avoid possibly causing an antibody-dependent enhancement in further infections. Denvaxia is currently the only licensed vaccine with overall vaccine efficacy (60.3% to 60.8%) varying between DENV serotypes and age groups. However, it raised serious safety concerns as it might increase the risk of hospitalization in dengue-naïve vaccinees when they are exposed to the virus. At least 7 DENV vaccines have undergone different phases of clinical trials; however, Phase III clinical trials with only 2 vaccines, TV003/TV005 and TAK-003 (DENVAx), have shown promising results. The cumulative efficacy data of the DENVax vaccine 3 years post-vaccination shows an overall vaccine efficacy of 62% against virologically confirmed dengue. In baseline seronegative individuals, the DENVax effectiveness was 52.3% for DENV-3 and 83.4% for DENV-2. In baseline seronegative individuals, the vaccine was only effective against DENV-1 (43.5%) and DENV-2 (91.9%), but no efficacy was observed for DENV-3. The TV003/TV005 vaccine was licensed by the Butantan Institute in Brazil. The randomized placebo-controlled Phase II trial showed that it was safe and induced robust, balanced neutralizing antibody responses against the 4 DENV serotypes. A Phase III clinical trial for the TV003/TV005 is currently being conducted in Brazil, and results for this trial are still not available. A universal, highly effective, and safe dengue vaccine is imperative to improve its uptake.

Dengue vaccines, when they become available, should be integrated with mosquito control to prevent epidemic transmission. Although vaccinations are cost-effective public health measures, vaccine hesitancy is a global public health concern. Factors contributing to vaccine hesitancy include complacency, inconvenience, safety, and lack of confidence. Vaccine hesitancy has become a major issue more so during the COVID-19 pandemic due to spread of misinformation about the vaccines. Continuous vaccine advocacy by engaging medical community, policy makers, public, and media will be crucial in gaining public confidence and maintaining vaccination programs. Overcoming vaccine hesitancy will require coordinated communication strategies based on transparency timely credible science-based information and understanding of human behavior.

Vector control

The control of *Aedes* mosquitoes is one of the options for the primary prevention of dengue. Most vector control methods available for public health use are not very productive, not implemented to high quality, and not routinely implemented. Therefore, dengue vector control aims to reduce vector densities as much as possible and maintain them at low levels. Chemical methods widely used are organophosphates, such as Fenitrothion and Malathion, and different pyrethroid derivates. However, the use of chemical insecticides is declining because of the development of insecticide-resistant strains and unforeseen side effects on human health and the ecosystem. Temephos, an organophosphorous substance, and Pyriproxyfen, a broad-spectrum insect growth regulator, are widely used for larviciding. Both chemicals are not toxic in drinking water when used with the prescribed dosage. However, they require a regular application.

Novel vector control techniques such as the Incompatible Insect Technique (IIT) and the Sterile Insect Technique (SIT) are currently being studied for public health use. IIT relies upon Wolbachia-infected male mosquitoes that cannot generate viable offspring after mating with a wild-type female. Wolbachia can spread naturally in this population once released into the wild mosquito population. Similarly, SIT uses gamma-irradiation to produce large-scale random damage to the insect chromosomes. When released into the wild, it can suppress and ultimately eliminate wild mosquito populations. However, this approach requires a constant release of irradiated sterile male insects that need substantial financial and human resources. To achieve the WHO 2021–2030 global target for dengue control, there is an urgent need for endemic countries to develop the infrastructure to support integrated, multi-sectoral prevention and control programs cosponsored by government at the local, state, and national levels (health, environment, and education ministries), the private sector, and the community.

Future actions for Bangladesh:

The epidemiology of dengue will continue to change. Although *Ae. aegypti* is the dominant urban vector, *Ae. albopictus* can also cause outbreaks, especially in less tropical areas. Flexibility, ingenuity, and imagination will be required to control dengue in the face of these challenges. Changes in climatic conditions, patterns of human settlement, movement, and population density, distribution of the two main mosquito vectors, and water-management technologies have all influenced the occurrence of dengue outbreaks. The competitive relationship between the two main vectors, *Ae. aegypti* and *Ae. Albopictus*, may lead to future changes in the epidemiology of the disease.

Reversing the trend requires commitments and obligations from partners, organizations and countries, as well as leadership by WHO and increased funding. Fund-raising is probably best addressed by a combined effort, with consideration for dengue as a public health problem in countries with substantial local and national funding resources that must be effectively channelled through sound technical support. Dengue prevention and management can now exploit opportunities presented by promising advances in vector control technology interventions, diagnostics, prognostic systems for triage, evidence-based clinical interventions and candidate vaccine developments. In order to realize these opportunities, we need to ensure they are implemented, coordinated and adequately resourced.

Just as new strategies and vaccines are devised for prevention and control of DENV, there is always a gap left in the form of challenges and limitations for perfect implementation of such strategies. Since prevention and control strategies to counter dengue have not shown satisfactory results in reducing disease transmission, the utilization of vaccines as cost-effective and potential resistance has become the main priority to restore public health. In Bangladesh, we have deficiency everywhere-Leadership, Health System Weakness', multi-stakeholder collaborations, implementation of National Guideline based Integrated Vector Control, improved access to diagnosis and management and improved case management of hospitalized Severe Cases could improve morbidity and mortality from Dengue Syndromes. As the strategies grow and are used in an integrated manner with other methods, advanced combinations have also predicted attenuation of vector population. With more research and experimentation of novel methods and

techniques, the future could enjoy better control with protective immunity to DENV. Bangladesh need to take urgent necessary steps to overcome the misery of Dengue on its population.

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