Editorial

Dengue in India: Towards a better understanding of priorities and progress

In January 2019, the World Health Organization (WHO) announced their new 5-year strategic plan, the Thirteenth General Programme of Work 2019–2023, to ensure that one billion more people in the world enjoy the benefits of better health and well-being (World Health Organization, 2019a). Among the 10 highest priority health issues presented, dengue was identified as one of the four main infections threatening global health (World Health Organization, 2019b). Concerted action against dengue was proposed by the WHO in 2012 with the aim of reducing dengue mortality by 50% and dengue morbidity by 25% by the year 2020 (World Health Organization, 2012). The five key elements needed to achieve the dengue public health targets identified by the WHO Global Strategy are diagnosis and case management, integrated surveillance and outbreak preparedness, sustainable vector control, future vaccine implementation, and basic operational and implementation research (World Health Organization, 2012).

India is poised to play a key role in contributing towards these targets. Based on global modeled data, an estimated 33 million clinically apparent dengue cases occur in India each year, contributing to a third of the total global dengue burden (Bhatt et al., 2013). Increasing numbers of dengue cases and fatalities are being reported in multiple urban and rural settings in India. These rapidly advancing dengue outbreaks result in severe disease that constitutes a leading cause of hospital admissions, with high case fatality rates. Furthermore, they place tremendous pressure on healthcare resources and have a heavy effect on society. Data from the Global Burden of Disease in 2013 and the WHO are similar in identifying India as an epicenter of dengue (Stanaway et al., 2016; World Health Organization, 2012). National data on dengue collected by the National Vector Borne Disease Control Programme (NVBDCP) in India estimate a smaller number of cases, in part because of the lack of a systematic national surveillance system.

In India, as in many areas of the world, advancement in the field of dengue control, which comes under the purview of the NVBDCP, has been impeded by a lack of financial and human resources, poor availability of point-of-care diagnostics, and ineffective mosquito control methods. A concerted national effort to establish sustainable surveillance systems in India, improve dengue and flavivirus diagnostics, develop innovative vector control, and facilitate the development and testing of dengue vaccines, could bring about a paradigm shift in global dengue control. This special supplement on ‘Dengue in India’ is a step towards this effort by bringing together researchers in India to highlight ongoing work relating to the epidemiology of dengue disease in India, including the disease burden, circulating serotypes, vector epidemiology, and economic burden of dengue disease in India, as well as reviewing the state of vaccine development, with a note on novel approaches being developed in India.

The dengue virus (DENV) is an RNA virus belonging to the genus flavivirus, and there are four serologically and genetically distinct serotypes, DENV1–4. Infection can occur with any of the four serotypes, and multiple sequential infections can occur. The immunopathogenesis of dengue is exceedingly complex, with the primary (or first) dengue infection with one serotype inducing homotypic antibodies (to the homologous infecting serotype), which generally provide long-term protection against the infecting serotype. This primary infection also produces heterologous antibodies that are weakly neutralizing and that provide only short-term heterologous protection. A secondary dengue infection with a second serotype can result in severe dengue, which is effected by viral binding to poorly neutralizing heterologous antibodies and enhanced viral uptake by host macrophages and dendritic cells via their Fc receptors, a phenomenon called antibody-dependent enhancement (ADE). To add to the complexity, ADE is likely to occur only when the heterologous antibody titers are within a specific range (Katzelnick et al., 2017). The non-structural protein 1 (NS1) is a viral factor that is likely to play a significant role in disease severity. Studies have indicated that NS1 can disrupt the host’s endothelial glycocalyx, leading to increased vascular permeability, which is associated with dengue-associated vascular leakage and ensuing shock (Beatty et al., 2015).

The march of dengue, unlike other ancient infectious disease scourges of mankind that have abated of late, has expanded relentlessly for the past several decades, and it currently affects over 120 countries, placing over four billion people at risk of dengue infection (Bhatt et al., 2013). The forces that sustain this expansion include rapid globalization, unplanned urbanization, and poor mosquito control.

The vast majority of dengue infections are clinically inapparent. Among the approximately 25% of those infected who have clinical manifestations, symptoms are often mild, but they may be moderate or severe in a small proportion, leading to death in 0.1–2.5% of all cases depending on host factors and access to care (Simmons et al., 2012). The 1997 clinical classification of dengue

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that was later modified in 2009 highlighted the importance of recognizing ‘warning signs’ with the potential to turn non-severe dengue into severe dengue; this had real practical value for triaging and clinical management of dengue (World Health Organization, 2009). Dengue disease manifestations may include a combination of damage to capillaries and the coagulation system. Early access to healthcare is critical, and appropriate management includes close monitoring for thrombocytopenia and disease progression and supportive care for shock, hemorrhage, and organ failure. Careful and precise replacement of fluid losses can be life-saving.

Success in reducing the public health burden of dengue will require a multi-pronged approach, with preventive measures that focus on vector control and dengue vaccines. Vector control measures include personal protection measures and environmental mosquito control. Novel vector control strategies using insect population transformation via bacterial or genetic manipulation are being evaluated in some countries (Carvalho et al., 2015; Hoffmann et al., 2011), and could provide a synergistic opportunity to improve prevention and control not only of dengue, but potentially for other Aedes-borne diseases as well. With such approaches, community engagement and community-led interventions have been found to be critical in producing an effect on reducing dengue cases (Andersson et al., 2015).

The first dengue vaccine to be licensed (CVD-TDV) is a recombinant tetravalent live-attenuated product with target dengue proteins expressed on a yellow fever virus backbone. Early data from large carefully conducted dengue vaccine trials in Asia and Latin America showed favorable safety and efficacy results (Capeding et al., 2014; Villar et al., 2015). However, when these results were re-evaluated with baseline serological status at the time of immunization, it was found that vaccinated seronegative children of any age were at higher risk of hospitalization for severe dengue compared to age-matched and serostatus-matched controls (non-recipients of the vaccine) (Hadinegoro et al., 2015; Sridhar et al., 2018). These observations suggest that the vaccine can be given safely only to individuals who have had one or more dengue infections in their lifetime. Taking into consideration these new data, and recognizing the potential public health benefit of even a partially efficacious dengue vaccine, the WHO in September 2018 recommended that individuals 9–45 years of age living in dengue-endemic areas may receive the vaccine as long as the individual shows evidence of a past dengue infection (World Health Organization, 2018). However, the quest for an appropriate point-of-care serological test for pre-vaccination screening is still in progress.

Two other promising vaccine candidates are in phase II and III trials, with clinical efficacy and safety results expected to become available in 2019 through 2021 (Pang et al., 2017). One of these candidates, another live-attenuated vaccine (TV003/TV005) developed by the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, has been licensed to three well-established manufacturers in India, and this vaccine candidate is being prepared for early clinical trials. Several other dengue vaccine candidates are in development and are in various preclinical and clinical stages (Silva et al., 2018).

This special supplement reporting studies focusing on dengue in India comes at a crucial time as countries deliberate on ways to effectively control this disease. The overall goal of this collection of articles is to integrate research findings within India and prepare a platform for future activities, particularly those under the leadership of the Indo-US Vaccine Action Program (VAP), the Department of Biotechnology (DBT), and the Indian Council of Medical Research (ICMR).

The first two papers address dengue seroprevalence and incidence, respectively. Murhekar et al. report dengue seroprevalence among individuals presenting with fever between 2014 and 2017, within a network of 52 laboratories across India supported by the ICMR. The results show a wide variation between the regions of India, indicating likely heterogeneity, but this may be better addressed by study designs that include a denominator population. Leveraging an existing prospective cohort that was established for surveillance of enteric fever in India, Rose et al. nested testing of dengue within this cohort. They report a high intensity of dengue transmission among febrile children in the community in southern India. Both of these studies reveal the compelling need for systematic surveillance to be established in conjunction with other surveillance activities in India in order to monitor dengue outbreaks and disease endemicity, particularly asymptomatic or mild infections. The next article by Ravi et al. reveals DENV to be the third most common cause of acute encephalitis syndrome, after Japanese encephalitis and scrub typhus. While all three articles described above report a distinct seasonality for dengue in the post-monsoon period, it is noteworthy that dengue was detected throughout the year. Understanding the evolving epidemiology and clinical presentation of dengue will have important implications in the diagnosis and case management strategy to be employed for regional dengue control.

Two papers describe dengue virological diversity and phylogeny. In the article by Kar et al., we see that dengue viral titers were highest among individuals with severe dengue compared to mild or moderate disease, although viral replication kinetics were similar in all groups. Ahamed et al. used phylogenetic analysis to demonstrate the emergence of new lineages and genotypic variations in DENV-1 and DENV-2 that may have influenced the magnitude of dengue epidemics in southern India during the outbreaks of 2012–2013 and 2014–2015. This research is critical for our understanding of DENV evolution, which can directly influence serotype-specific responses and consequently impact transmission dynamics and dengue vaccine efficacy. Chandele et al. explored homotypic and heterotypic immune responses and dengue-specific memory B cells in non-symptomatic adults, revealing, not surprisingly, a great degree of variation among individuals.

The next two articles present important new research on the economic burden of dengue. Panmei et al. report high direct dengue costs stratified by severity of illness. Using hospital and patient billing records, they show that dengue deaths have a higher cost than severe hospitalized non-fatal dengue, and that up to 90% of costs may be out-of-pocket expenditure, revealing an unacceptable burden on individuals and society. In the second paper, using updated incidence figures from the Global Burden of Disease 2018 for dengue in India, Hariharan et al. highlight the substantial increase in India’s dengue economic burden compared to previous estimates. Direct and indirect costs of dengue in India together now total over three billion dollars and are reflective of the higher incidence and greater number of case fatalities in India in 2018 compared to 5 years earlier. More detailed cost estimates are needed and will be an essential component for understanding the burden of illness and for supporting the planning of health services and policy.

This supplement also addresses areas relevant to the future of dengue control. The controlled human infection model (CHIM) and specifically the dengue human challenge model (DHCM) are important modalities for vaccine development and the assessment of safety and immunogenicity in a smaller controlled setting. Ethical and practical issues abound in India and must be addressed, as outlined by Rose and Shekhar. Finally, this supplement contains an elegant summary by Swaminathan et al. of the currently available licensed dengue vaccine, those vaccine candidates close to licensure, and those in the development pipeline, including an account of the indigenous tetravalent dengue vaccine DSV4 based on a yeast-expressed virus-like particle platform being developed in India.
The way forward in dengue control is to obtain full commitment from global stakeholders in addressing a complex disease with solutions that include integrating disease surveillance, clinical management, vector control, and vaccination methods. For India, complete support from all aspects of the government, including health, science, infrastructure, sanitation, and regulatory agencies will be critical to achieving the WHO dengue control targets. An important research gap is the establishment of prospective cohorts and systematic serosurveillance to study viral patterns and immunomediating phenomena that can inform scientists, funders, and policy-makers on appropriate dengue control strategies. In bringing together experts from India and the world to discuss and implement dengue control strategies, the VAP partners, NIAD, DBT, and ICMR have done commendable service in advancing dengue knowledge in India towards the common goal of global dengue control. With a rapidly evolving disease, new approaches to surveillance and innovative research on dengue vaccines undertaken by one of the highest dengue burden regions in the world have never been more important.

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