

## Treatments for dengue: a Global Dengue Alliance to address unmet needs



Dengue is currently the most rapidly spreading mosquito-borne viral infection in the world, with half of the world's population at risk of becoming infected.<sup>1</sup> As a result of climate change, rapid urbanisation, and widespread international travel, the incidence of dengue is rapidly increasing, overwhelming health-care systems in many lower-income countries. Climate change has increased the burden of dengue in endemic countries and has also led to expansion of this infection to new territories in Europe and North America.<sup>2</sup>

Dengue is estimated to infect approximately 390 million individuals annually, with 96 million infections being symptomatic.<sup>1</sup> So far, the only strategy adopted to reduce the burden of dengue is vector control. Although techniques such as using *Wolbachia* bacteria to reduce dengue transmission by *Aedes* mosquitoes look promising,<sup>3</sup> it is evident that vector control alone is unlikely to be adequate to reduce the burden of dengue. The currently available dengue vaccines (CYD-TDV and TAK-003) have been shown to reduce hospitalisations, especially in dengue-seropositive individuals, but lack efficacy against some dengue virus serotypes.<sup>4</sup> Furthermore, CYD-TDV showed a higher incidence of severe dengue in dengue-naïve vaccine recipients, and both vaccines show some degree of waning immunity with time, especially in seronegative individuals.<sup>5,6</sup> Therefore, an integrated approach that comprises vector control, use of safe and effective vaccines, and an effective treatment is needed to face the growing challenges of dengue infection.

Efforts focused on finding a treatment have been scarce, with some investigator-led clinical trials conducted, and a few performed by pharmaceutical companies.<sup>7,8</sup> The importance of developing a treatment for dengue has largely been ignored.<sup>9</sup> The Drugs for Neglected Diseases initiative, which is focused on finding novel affordable treatment solutions for neglected tropical diseases since its inception in 2003, has recently formed a Global Dengue Alliance with several institutions in dengue-endemic countries, including the Faculty of Medicine at Siriraj Hospital, Mahidol University in Thailand; the Ministry of Health in Malaysia; the Translational Health Science and Technology Institute

in India; the Oswaldo Cruz Foundation in Brazil; and the Federal University of Minas Gerais in Brazil. The mission of this alliance is to accelerate research and development and deliver dengue therapeutics through an inclusive partnership. It aims to deliver a new treatment for dengue, within 5 years, from repurposed drugs and combinations (including novel antivirals from pharmaceutical companies). This alliance is co-created, co-owned, and co-funded by dengue-endemic countries, with a tiered governance mechanism allowing collaborative decision making at different levels. The organisations have formed a preclinical working group, a clinical working group, and a translational working group for effective communication and scientific planning. All three working groups feed into the Joint Steering Committee, which is responsible for delivering on the vision and mission of the alliance. The partners of this alliance share knowledge, experience, technologies, and capabilities to jointly validate preclinical assays with the ambition in the initial phase to identify currently available drugs that can be repurposed for use as dengue therapeutics. In parallel, clinical trials for these drug candidates are being designed using the expertise of clinicians in these countries who have been treating patients with dengue for many years, with initiation planned by the end of 2023.

Formation of this alliance is a major step towards developing a treatment for dengue, by aggregating resources from endemic countries, and ensuring engagement, scientific leadership, clinical guidance, and political interest in these countries. The different working groups and the steering committee coordinate efforts to address gaps in knowledge, such as epidemiology (specifically in Africa), biomarkers and diagnostics, clinical trials, and regulatory framework, while promoting open science. Although currently the alliance has a small number of partners, it is open to collaborations with new partners and key stakeholders in therapeutics and diagnostics.

Working with and aligning many partners and stakeholders to deliver objectives in a new model of collaboration is challenging, as is filling the existing knowledge gaps and need for integration, and

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leveraging information from different geographies and epidemiological settings. Furthermore, doing clinical trials aimed at treating dengue disease is challenging due to the seasonal nature of the disease, and with climate change, disease patterns could become more unpredictable. Although this approach is likely to accelerate development of a treatment, funding remains a challenge. With climate change becoming more of a concern in high-income countries, there is an increasing possibility that many global funding organisations will acknowledge the true burden of dengue, the devastation it causes to health systems and patients in endemic countries, and, therefore, the importance of funding initiatives to accelerate the development of new treatments for dengue.

We declare no competing interests.

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