Conference Report

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Abstract

Background: The 7th Asia Dengue Summit (ADS), titled "Road Map to Zero Dengue Death", was held in Malaysia from 5 to 7 June 2024. The summit was co-organized by Asia Dengue Voice and Action (ADVA); Global Dengue and Aedes-Transmitted Diseases Consortium (GDAC); Southeast Asian Ministers of Education Tropical Medicine and Public Health Network (SEAMEO TROPMED); Fondation Mérieux (FMx); and the International Society for Neglected Tropical Diseases (ISNTD).

Objectives: Dengue experts from academia and research, as well as representatives from the Ministries of Health, Regional and Global World Health Organization (WHO), and International Vaccine Institute (IVI), came together to highlight the crucial need for an integrated approach for dengue control and achieve the target of zero dengue deaths.

Methods: With more than 50 speakers and delegates from over 28 countries, twelve symposiums, and three full days, the 7th ADS highlighted approaches to curb the growing danger of dengue. The summit included topics ranging from emerging dengue trends, insights from dengue human infection models, the immunology of dengue, and vaccine updates to antivirals and host-directed therapeutics.

Conclusions: The 7th Asia Dengue Summit reinforced the importance of an integrated, collaborative approach to dengue prevention and control. By bringing together diverse stakeholders and launching innovative initiatives such as the Dengue Slayers Challenge, the summit advanced the regional and global agenda to achieve zero dengue deaths. The exchange of knowledge and strategies at the summit is expected to contribute significantly to improved dengue management and community engagement in affected regions.

Keywords: dengue, vector control, vaccines, antigenic evolution, youth

Introduction

The Asia Dengue Voice and Action (ADVA) is a scientific working group dedicated to dengue control across the region through collaboration with academia, industry, and non-government organizations. One of the core

educational initiatives by the ADVA is the Asia Dengue Summit (ADS) held every year in collaboration with GDAC, SEAMEO TROPMED, FMx, and ISNTD. Following the inaugural conference held in 2016, every year, ADS focuses on key issues such as the growing global public health burden of dengue, outbreak prediction and surveillance, challenges in vaccination, travel-related dengue, and vector control. The 7th Asia Dengue Summit (7th ADS) was held in Malaysia from 5 to 7 June 2024. With 50 speakers and 550 delegates from over 28 countries, thirteen symposiums, and three full days, the 7th ADS highlighted approaches to curb the growing danger of dengue. The summit included topics ranging from emerging dengue trends, insights from dengue human infection models, the immunology of dengue, and vaccine updates to antivirals and host-directed therapeutics. Healthcare professionals, researchers, epidemiologists, and representatives from the Ministries of Health came together to highlight the crucial need for an integrated approach for dengue control to achieve the target of zero dengue deaths. In this special symposium, experts discussed dengue clinical scenarios, identified challenges, and shared clinical experiences to advance dengue case management. The inaugural ADVA Junior Achievement challenge highlighted the youth's potential in developing creative and innovative solutions for dengue control. This report summarizes key highlights from the speaker presentations during the 7th Asia Dengue Summit.

Wolbachia Success Stories

The World Mosquito Program's (WMP) Wolbachia innovation is a safe, self-sustaining, one-time intervention operational across three continents and has shown promising results in reducing dengue incidence. The Wolbachia (wMel) method works by introducing the naturally occurring bacteria, Wolbachia, into the Aedes aegypti mosquito population and rendering them incapable of transmitting diseases such as dengue, Zika, chikungunya, and yellow fever. The World Health Organization (WHO) Vector Control Advisory Group (VCAG) has endorsed the public health value of the Wolbachia innovation against dengue. The AWED trial (Applying Wolbachia to Eliminate Dengue) was the first cluster randomized controlled trial to evaluate the efficacy of the large-scale deployment of Wolbachia-infected Aedes aegypti mosquitoes in reducing the incidence of dengue at a single site in Yogyakarta, Indonesia. The primary analysis of the AWED trial showed positive results with a 77% reduction in the incidence of virologically confirmed dengue (VCD) versus the untreated arm and an 86% reduction in hospitalized VCD in wMel-treated clusters compared to untreated areas.

A secondary analysis of the AWED trial demonstrated an 83% reduction in the incidence of notified dengue hemorrhagic fever (DHF) during the fully treated versus untreated periods. Furthermore, there was an 83% reduction in the application of insecticide spraying in wMel intervention areas, and a 39.6% reduction in the annual cost of insecticide spraying in Yogyakarta city.

Following the launch of the Wolbachia Malaysia project in 2017, wAlbB-carrying Ae. aegypti were deployed in eleven dengue hotspots in the Klang Valley around Kuala Lumpur. Data collected from twenty high-rise residential areas with Wolbachia release demonstrated a 62.4% reduction in dengue fever incidence. So far, Wolbachia deployments have been carried out across forty localities in eight states in Malaysia, with the Malaysian Ministry of Health planning further coverage of dengue hotspots as a national rollout program.

Dengue Early Warning Tools

Strong vector surveillance systems are crucial to developing early warning systems to prompt intervention strategies to minimize public health impacts. Meteorological parameters and entomological parameters are used as predictors in dengue forecasting models.

DenMap, a web-based dengue surveillance system, is an excellent example of a real-time system for monitoring dengue outbreaks in Malaysia. The e-Notifikasi database (notified cases) and e-Dengue database (registered cases) in Malaysia enable the notification of dengue cases to the Ministry of Health within 24 hours, facilitating the development of a rapid geocoding and visualization application. DenMap generates a quick, real-time visual display of notified and registered cases on Google Maps, providing an early warning of dengue hotspots, clusters, and spatial and temporal distributions of cases.

The early warning and response system (EWARS), established in Mexico in 2012, underwent further development in 2014 to validate prediction algorithms using epidemiological, entomological, and meteorological alarm indicators. In 2018, Mexico incorporated EWARS into its national platform for integrated epidemiological surveillance. Over 17 countries, including several in the Southeast Asia and Western Pacific regions, are either implementing or in the process of integrating EWARS into their national dengue control programs. Recent evidence from the National Vector Control Program in Mexico validating the efficacy of EWARS highlights that adequate and timely responses to alarm signals play a crucial role in notably reducing dengue outbreaks and hospitalizations.

Insights from the Dengue Human Infection Models (DHIMs)

There are significant gaps in the current dengue countermeasure portfolio. As of now, there are no antivirals or monoclonal antibodies approved for the prevention or treatment of dengue. Challenges include the presence of four dengue serotypes, a lack of clarity on immunological and pathologic profiles, difficulty in measuring immune response, and the absence of accurate animal models that replicate human infection. A consortium of investigators was established with the objective of developing safe dengue human infection models (DHIMs) to analyze the clinical, virologic, immunologic, and serologic features of mild dengue in a controlled and safe environment.

In a recent study, a phase 1, open-label assessment of the DENV-1 live-virus human challenge strain (DENV-1-LVHC strain 45AZ5) in twelve healthy adult volunteers resulted in an uncomplicated dengue illness that was well-tolerated. Another phase 1 study using DENV-3 strain CH53489 showed mild-to-moderate dengue in all participants. These DHIMs represent a unique opportunity to understand immune correlates of DENV infection and to assess the benefit of candidate countermeasures.

Potential Biomarkers for Severe Dengue

Ongoing research to identify clinically usable biomarkers to predict severe dengue has shown promising results. A 20-gene set identified by Robinson et al. was validated across different cohorts. Another machine learning model using eight genes predicted severe dengue progression.

Immune profiling revealed that early innate immune activation and specific T cell activity are key in severe cases. Differences are exaggerated in children. Circulating microRNA expression patterns such as miR-574-5p and miR-1246 have shown promise as prognostic markers. However, further validation in large, diverse cohorts is required, and the assays must be affordable and rapid for field use.

Dengue Vaccine Update

CYD-TDV (Dengvaxia™) is only recommended for seropositive individuals aged 6 years and older due to safety concerns.

TAK-003, another tetravalent vaccine, has been prequalified by WHO and is being introduced in Brazil. Multi-dose vials are being planned to increase production.

The Butantan dengue vaccine showed efficacy in phase 3 trials and is under extended follow-up. A modified mRNA vaccine targeting dengue proteins has shown T cell activation and protection in animal models.

Dengue Monoclonal Antibody Update

NS1 protein is a promising target for antivirals. Anti-NS1 monoclonal antibodies have shown efficacy in animals.
Other promising antibodies target the EDIII region of the virus. VIS513, developed in India, was found safe in a first-in-human trial in Australia.

Dengue Therapeutics and Antivirals

Development of direct-acting antivirals (DAAs) and host-directed antivirals (HDAs) continues. DAAs offer specificity but may lead to resistance. HDAs are less prone to resistance but may have lower efficacy.

JNJ-1802 is the first DENV antiviral with confirmed safety in humans. Repurposed drugs like metformin, rupatadine, and montelukast are also under clinical testing.

The Dengue Alliance

Current dengue management is reactive. There is a need for affordable antiviral therapies. The Dengue Alliance, launched in 2022, is a partnership of institutions from endemic countries including India, Malaysia, Thailand, and Brazil. The Alliance is working to develop new treatments using repurposed drugs and novel antivirals within five years.

Engaging Youth in Dengue Control

The Young ADVA program, launched in 2023, aims to involve youth in dengue control. In collaboration with Junior Achievement, the ADVA/JA Dengue Slayers Challenge was held across five countries with 459 students. The event received wide media coverage and demonstrated youth engagement as a tool for community awareness.

Conclusions

Translating research into clinical impact is key to achieving zero dengue deaths. Integrated, multisectoral collaboration is critical.

Tools such as vaccines, antivirals, and vector control must be implemented effectively. Strong leadership, policies, political will, and community trust are essential.

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