

Dengue therapeutics consortium 2025: a global collaboration in action

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ABSTRACT

Dengue is a global health emergency, with annually increasing case numbers that overwhelm healthcare systems, an ever-expanding range of the mosquito vector, and no antiviral or host-directed treatments proven to alter the course of disease. This article reports on a meeting of the Dengue Therapeutics Consortium, which included attendees from 19 countries with backgrounds in basic science, clinical research, drug development, industry, clinical trial methodology and policy. We summarise the current state of dengue therapeutics research and highlight the necessary steps to ensure that patients have equitable access to affordable and effective treatments. We review the antiviral pipeline, including novel and repurposed antiviral candidates, and we propose both human challenge and rate of viral clearance studies as methods to rapidly screen for antiviral activity prior to larger phase 3 clinical trials. We review ongoing phase 2 and phase 3 clinical trials to evaluate repurposed host-directed therapies for patients with moderate and severe disease, and we suggest considerations for future trial design, such as factorial randomisation and the use of a core outcome set to maximise efficiency and enable evidence synthesis by meta-analysis. We consider that multisectoral collaboration will be essential to achieve our aim of effective treatments for dengue. This will include drug development aligned to target product profiles, conduct of clinical trials with endpoints acceptable to both patients and regulators and sustained commitment from the pharmaceutical industry, non-profit initiatives and policymakers to ensure that effective treatments reach those who need them the most.

INTRODUCTION

This report summarises a meeting of the Dengue Therapeutics Consortium, a hybrid event organised by the Oxford University Clinical Research Unit in Ho Chi Minh City, Vietnam on 25 and 26 February 2025.

In this article, we outline the major themes that emerged from the meeting, and key steps necessary to ensure that patients with dengue virus (DENV) infection have equitable and durable access to safe, affordable and effective treatments. Progress towards this goal will require collaboration at all stages of the pipeline, from drug discovery aligned to target product profiles, to open communication and collaboration between pharmaceutical partners and clinician researchers, through engagement with regulators and policy-makers, and of people with lived experience to ensure patient-centred care.

The global dengue emergency

DENV infection is the most common arthropod-borne infection worldwide. A changing climate, geographical expansion of the mosquito vector, urbanisation and movement of people are driving relentless increases in cases, with an estimated 110 million symptomatic infections globally per year.^{1,2} Countries affected by both endemic and epidemic dengue face annual strain on their health systems, often leading to significant

disruption. Simultaneous rises in the burden of non-communicable diseases, including obesity in endemic regions, are increasing the populations at risk of severe and complicated dengue. The associated economic burden, including healthcare costs, loss of productivity and expenses related to vector control, is projected to reach hundreds of billions of dollars by 2050.³ In late 2023, the WHO assigned the highest level of emergency to dengue, indicating that the situation demands a major to maximal global response. In June 2024, the WHO pathogens prioritisation framework identified dengue as a priority pathogen for all six WHO regions.⁴

Despite the considerable need, no antiviral or host-directed treatments have been proven to alter the course of disease in patients with DENV infection. As a neglected tropical disease, efforts to identify effective treatments have largely focused on exploring off-target effects of repurposed antiviral candidates or host-directed therapies. In this context, the Dengue Therapeutics Consortium was born, with the goal of bringing those actively working in the dengue therapeutics space together to share knowledge, ideas and resources, avoid unnecessary duplication and ultimately ensure that promising treatments can make it to patients who need them most.

The meeting

The meeting of the Dengue Therapeutics Consortium (25 and 26 February 2025) was a hybrid event organised by the Oxford University Clinical Research Unit and King’s College London, funded by a networking grant from the Academy of Medical Sciences. Building on two previous international dengue therapeutics workshops held in Ho Chi Minh City,^{5,6} the event brought together a diverse group of invited stakeholders working in Asia, the Americas, Europe and Australia. Attendees included scientists involved in drug discovery and basic science, physicians, biostatisticians and clinical trialists, experts in policy and ethics, partners from the pharmaceutical industry and the WHO and funding bodies (see online supplemental appendix for full list of attendees). The objectives of the meeting were to establish a dengue therapeutics clinical trial network and connect existing global networks to review the candidate drugs pipeline, to discuss linking the therapeutics development pathway from drug discovery to phase 3 trials and to discuss trial design and funding considerations for proposed platforms.

Key themes

The antiviral pipeline

Higher dengue viral loads and slower rate of clearance of DENV from the blood are both associated with increased risk of severe disease.^{7,8} As such, there may be a role for an effective antiviral administered early in symptomatic dengue to accelerate viral clearance. Until recently, all antiviral candidates evaluated in clinical trials for dengue had been repurposed from other viral diseases, for example, hepatitis C,^{9,10} or relied on off-target effects

of antiparasitic medications (eg, chloroquine and ivermectin)^{11,12}; none showed promise for dengue. This history underscores the importance of early pharmacodynamic validation prior to large, costly, phase 3 trials and stronger collaboration between academia and industry to develop dengue-specific antivirals to avoid repeating earlier pitfalls. Recently, progress has been made in the development of direct-acting antiviral compounds for dengue, including small molecules and monoclonal antibodies (figure 1).

Among the small molecules, the NS4B inhibitor EYU688 (Novartis) is currently under evaluation in a phase 2a clinical trial (ClinicalTrials.gov: NCT06006559). Trials of other small molecules, including AT-752 (Atea Pharmaceuticals)⁸ and Mosnodenvir (JNJ-1802, Janssen),¹³ have been discontinued; reprioritisation by Janssen led to early discontinuation of clinical trials investigating the latter as treatment and prophylaxis. Second generation NS4B inhibitors and compounds targeting NS5 polymerase and NS3 proteases are in development.

Two tetravalent monoclonal antibodies are currently in clinical trials; recruitment has completed for a phase 2 trial of Dengushield (VIS-513, Serum Institute of India, CRTI 2021/07/035290, results awaited). A phase 2 dose-ranging study investigating AV-1 in a controlled human infection model of attenuated DENV-3 has recently begun (AbViro, clinicaltrials.gov: NCT06799741), and other tetravalent monoclonal antibodies are in development.

Representatives from not-for-profit consortia presented their strategies for antiviral development. The Drugs for Neglected Diseases *initiative* (DND*i*) is a research organisation, which has partnered with institutions in dengue-endemic countries to form the dengue alliance. Together they are conducting preclinical profiling of therapeutics and plan to take promising candidates forward to clinical trials. The rapidly emerging antiviral drug development

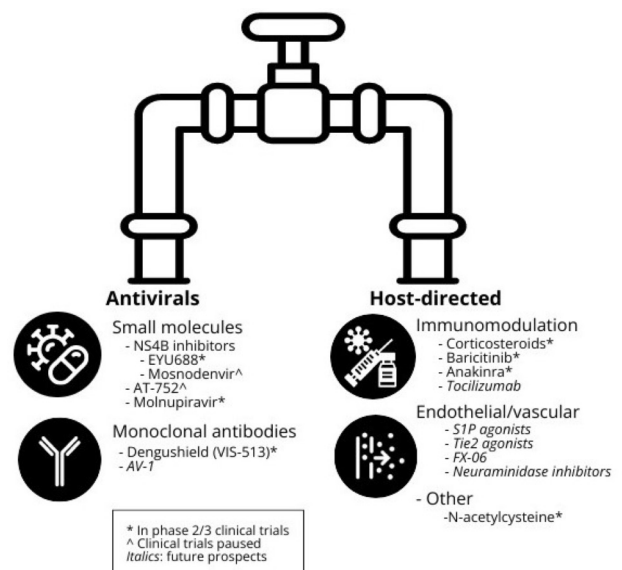


Figure 1 The dengue therapeutics pipeline—candidates in phase 2/3 clinical trials and future prospects.

initiative (READDI) is a non-profit biotechnology organisation working with academia, industry, government and philanthropy to develop antiviral compounds for viral diseases of pandemic potential, including dengue. Both DNDi and READDI are seeking to develop antivirals with broad activity across the flavivirus family. In addition to direct-acting antivirals, host-targeted antiviral compounds, such as ISLA-101 (ISLA Pharmaceuticals) and Xafty/Niclosamide (Hyundai Bioscience) and ion channel inhibitors, such as TMEM16F, are being evaluated. The utility of artificial intelligence in the selection of novel therapeutic targets and early drug development process was highlighted by several speakers.

There was consensus that, although the risk of treatment-emergent resistance may theoretically be lower than that seen in infections with more persistent viraemia (eg, HIV), a combination approach to antiviral therapy, ideally deploying compounds with different mechanisms of action, would be the optimal strategy to increase the barrier to development of resistance. However, there was uncertainty regarding the true risk of transmission of treatment-emergent resistant DENV due to the short duration of viraemia and potential fitness cost both in the human and *Aedes* mosquito vector.

Strategies to screen antiviral compounds for dengue

The participants recognised that the lack of a good animal model for DENV infection has impeded progress in selecting the most promising *in vitro* candidates to progress to phase 3 trials. Two different approaches were presented to overcome this obstacle, with the goal to screen out antivirals with low potential (ie, ‘fail fast, fail cheap’): dengue human challenge models and phase 2 platform trials evaluating rates of viral clearance from frequent viral density measurements (eg, the adaptive dengue antiviral platform trial (ADAPT), ClinicalTrials.gov: NCT06551844). While there are advantages and disadvantages to both, these strategies are intended only to improve the selection of candidate antivirals for larger phase 3 efficacy studies.

The dengue human infection model (DHIM) consortium—a collaboration between the State University of New York Upstate Medical University, the University of Maryland School of Medicine and the US Army—has developed models for DENV-1, 3 and 4, with a model for DENV-2 in development.^{14 15} DENV challenge models allow precise evaluation of antiviral action when administered before, at the time of and after challenge with an attenuated DENV strain. The controlled environment permits detailed profiling of infection and immunity following challenge. While the DHIM consortium studies enrol exclusively dengue naïve patients, a Controlled Human Challenge Model at Mahidol University, Bangkok has recently been approved to recruit patients in an endemic setting (ClinicalTrials.gov: NCT05476757). Candidates without antiviral potential in dengue may be efficiently screened out by DHIM models involving only a handful of patients, but any candidate showing promise

would need to be evaluated in patients with natural infection (ie, non-attenuated virus) prior to late-stage clinical trials. Ethical considerations surrounding DHIMs, especially in endemic low-middle income countries (LMIC) settings, were highlighted. Speakers noted that maintaining rigorous informed consent processes and independent oversight is crucial to safeguard vulnerable populations participating in these studies.

An alternative strategy is that adopted by ADAPT, which was built on methodology developed for the PLATCOV study for COVID-19.¹⁶ Led by the Oxford University Clinical Research Unit in Vietnam, ADAPT seeks to screen candidates for antiviral activity in humans naturally infected with dengue by comparing rates of viral clearance in those receiving treatment versus those receiving standard of care only. The rate of clearance is the estimated slope of a linear regression fitted to the serial log viraemia measurements. It is estimated that candidates without promising antiviral activity may be screened out by approximately 50 patients per arm. A team at the Federal University of Minas Gerais, Brazil is currently investigating the impact of Molnupiravir on the rate of viral clearance in patients with early symptomatic dengue in the Adapta-Arbo trial (Brazilian Clinical Trials registry: U1111-1306-1425).

Host-directed therapeutics

While there are efforts underway to develop novel antiviral medications for dengue, it is likely that host-directed therapies will be repurposed drugs since aberrant host pathways underlying severe disease are plausibly conserved between several different disease states. Advances in understanding of the immunopathology of dengue have highlighted that the hyperinflammatory response is a key determinant of disease severity.^{17 18} Therapeutics of interest include broadly acting immunomodulators, such as corticosteroids and janus kinase (JAK) inhibitors, and targeted immunomodulators, such as interleukin 1 and interleukin 6 inhibitors. Although immunomodulators are the priority candidates for upcoming trials, therapeutics that stabilise the endothelium and reduce vascular leakage are also desirable; potential candidates include the angiopoietin-1 mimetic vasculotide (AV-001, Vasomune therapeutics) and the vascular endothelial cadherin stabilising agent FX-06 (F4 pharma), but phase 2 trials would be required to demonstrate the safety and proof of concept prior to a larger phase 3 trial (figure 1).

Several phase 2 trials of host-directed therapies for dengue have been conducted. None have shown clinical benefit to date, but most have been underpowered for clinical efficacy outcomes, and have used surrogate outcomes, which may not have direct relevance to patient outcomes. Phase 2 trials of dexamethasone, anakinra (ClinicalTrials.gov: NCT05611710) and zanamivir (ClinicalTrials.gov: NCT04597437) are all ongoing. While small trials are unlikely to demonstrate clinical efficacy, they do allow in-depth mechanistic evaluation and detailed safety assessments, often in narrowly defined subgroups. Where

phase 2 data are considered necessary, seamless phase 2/3 designs may enable early termination for safety or futility while reducing the delays associated with ethics and funding applications and offering economies of scale.

Building on many of the themes discussed at the meeting, the DEN-HOST trial will be a randomised, adaptive, phase 3, placebo-controlled trial to evaluate host-directed therapeutics in patients hospitalised with moderate or severe dengue. With funding from the Wellcome Trust and the PREPARE network (Singapore Ministry of Health), this will be a multisite, multicountry trial across dengue-endemic regions in Latin America and Asia. Trial sites will build on the existing research capacity within the OUCRU, PREPARE and International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) networks; the trial will have regional coordinating centres and a strong focus on local capacity building. The trial will employ factorial randomisation and will begin with three treatment comparisons: dexamethasone, baricitinib and N-acetylcysteine, the latter for a subgroup of patients with liver injury. However, it is anticipated that the platform will evaluate more treatments in the future.

Clinical trial design considerations

Although dengue is indeed a neglected disease in terms of number of clinical trials to inform treatment, the trials that have been done have been mostly markedly underpowered to detect meaningful clinical outcomes. Synthesis of trial data has not been possible due to the use of disparate and non-comparable outcomes. ISARIC's DEN-CORE project sought to remedy the latter problem through the development of a standardised core outcome measurement set for phase 3/4 clinical trials in dengue.¹⁹

In addition to these steps, at the meeting, there was much discussion on how the design and conduct of clinical trials can facilitate high-quality evidence generation, with adequately powered comparisons to definitively answer efficacy questions. It was agreed that platform trials are the most powerful ways to achieve this; the addition of new treatment comparisons adds only marginal expense to a multicentre international trial, for which much of the running cost is fixed (figure 2).

Speakers explored different ways of reducing the cost associated with large clinical trials. It was highlighted that most clinical trials collect large amounts of data that are neither necessary nor ultimately used by investigators; cost of staff time and data storage may be reduced by reducing data collection requirements to those truly necessary for the determination of efficacy. ISARIC has developed consensus case record forms to target dengue clinical data collection on critical elements and support the use of machine-readable data standards.²⁰ It was recommended that protocols are streamlined to ensure that processes are not unduly arduous, especially for trials running in stretched healthcare systems during dengue outbreaks. The RECOVERY trial was cited as an example

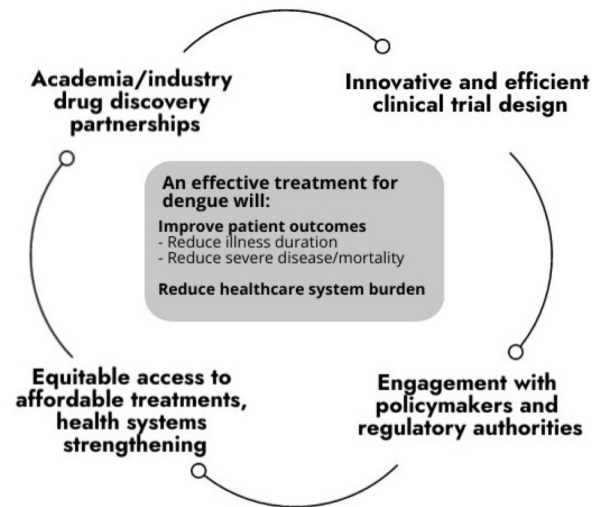


Figure 2 A multisectoral framework to support development and delivery of effective dengue therapeutics.

of a lean protocol, which could be deployed widely by busy clinicians during the COVID-19 pandemic in both high- and low-resource settings; the low burden imposed by the trial was a significant factor in the ability to recruit many patients and generate high-quality data at pace.²¹

Methods of enriching the trial population by recruiting patients at higher risk of poor outcomes and, thus, reducing the sample size required were explored, including selection based on baseline biomarkers, demographic factors and/or clinical decision support tools. Although these strategies have been used successfully in other fields, they are relatively nascent in dengue; predictors ideally need to be simple and readily available so that randomisation is not delayed, perform well and be externally validated for the target study population. It was agreed that a concerted effort to determine probabilities of transition from uncomplicated dengue to hospitalisation, ICU admission and mortality across different geographical settings and demographics would be very valuable to help calculate sample and effect sizes for future clinical trials.

Factorial randomisation was proposed as the most efficient way to evaluate multiple therapies concurrently while also having the potential to detect qualitative interactions between treatments. Factorial trial designs would also permit efficient evaluation of combination host-directed treatments (eg, immunomodulation plus endothelial stabilising therapies) with or without antiviral interventions. Although there was broad agreement with these principles, several participants stated that local clinicians and ethics committees are unfamiliar with the practice of factorial randomisation, and that while in principle, factorial or basket trial designs reduce the time and cost associated with repeated ethical applications, in practice, new ethical approval is often required for each additional treatment comparison added at each site. The importance of early engagement with ethics committees, offering

educational opportunities to support understanding of newer clinical trial design, and the potential for connecting local ethics committees at a regional level for exchange of experience were raised. In addition to engagement with ethics committees, the importance of engagement with local clinicians to develop local clinical trial capacity was emphasised. Investing time and money to develop local clinical trials operations, infrastructure and monitoring will be key to ensuring that the trials leave a legacy of capacity.

Policy and translation

Several important themes emerged through the meeting, essential to ensure that efforts in drug discovery and clinical trials are readily translatable to clinical practice. The WHO target product profile for dengue is being developed to assist developers to make sure that drug candidates in development fulfil the minimally acceptable criteria for patients, funders and regulators. In addition, the importance of using outcomes for clinical trials, which are both important to patients and acceptable to regulators, was stressed, and engagement with regulatory bodies during the development process may help to ensure that outputs can be translated to clinical practice in a timely fashion. A representative from WHO emphasised the need for clinical trials to be conducted across geographical boundaries, with designs that address multiple pressing research questions concurrently. Development of the most recent clinical guidelines on the management of arboviral infections highlighted more questions than answers, and most recommendations were based on either low or very low certainty of evidence.²² Representatives from DNDi and Novartis Global Health highlighted their critical role in ensuring equitable access to effective therapeutics; there is little value in developing and approving a therapeutic that cannot be deployed at scale or afforded in endemic regions where it is most needed. In addition to affordability, substantial systemic barriers remain to equitable access to treatment in dengue-endemic regions. These include fragmented regulatory frameworks, limited pharmacovigilance capacity, delayed drug registration, supply chain challenges and resource constraints within overstretched health systems. Achieving equity will require regulatory harmonisation, affordable procurement and investment in health system capacity (figure 2).

Multisectoral collaboration to support future platform trials

The Dengue Therapeutics Consortium presents an opportunity for multisectoral collaboration (figure 2). Philanthropic organisations, such as the Wellcome Trust, have shown strong commitment to tackling infectious diseases sensitive to environmental change, including vector-borne viruses. Their funding pipeline spans from early translational work and Phases 1–2 trials to effectiveness studies aimed at changing

global guidelines. Pharmaceutical and biotechnology companies, such as Novartis, GSK Global Health and READDI, are leading discovery and drug development efforts with a strong commitment to ensuring that end products are affordable and accessible. In parallel, research consortia, such as the DNDi and the Dengue Alliance, are leading multisectoral collaborative efforts to develop, evaluate and translate novel and repurposed treatments to prevent progression to severe dengue.

Established research networks for pandemic preparedness and response, including ISARIC, PREPARE and the Cohorts Network to be activated Globally In Outbreaks, have sites in dengue-endemic settings and are ideally placed to build capacity and sustain site readiness in the interepidemic period and streamline regulatory and ethical processes for rapid trial (re)-activation during outbreaks. The European Clinical Research Alliance is an EU-funded academia-driven network of ‘warm bases’, which can rapidly activate to recruit patients during dengue outbreaks, which are increasingly common in Europe. Consortia, such as Strategies and Treatments for Respiratory Infections and Viral Emergencies, have demonstrated that it is possible to pivot infrastructure and expertise in clinical trials from one epidemic disease to another.

Aligning the interests of multisectoral stakeholders through a well-coordinated platform trial could accelerate the development and validation of urgently needed therapies while also strengthening research capacity and resilience in dengue-endemic regions.

CONCLUSION

Through global collaboration, capacity building and open communication, the Dengue Therapeutics Consortium has shared goals to prioritise research to select the most promising therapeutic candidates, harmonise methodologies, data tools and core outcome sets to generate robust evidence in diverse settings and eventually translate effective treatments into clinical practice for all patients who need them.

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