WHO Target Product Profiles for Treatments for Dengue Fever

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Abbreviations

AFRO	Regional Office for Africa
AMRO	Regional Office for the Americas
EMRO	Regional Office for the Eastern Mediterranean
ERF	Emergency Response Framework
GAP-f	Global Accelerator for Paediatric Formulations
HQ	Headquarters
NIHR	National Institute of Health and Care Research
PADO	Paediatric Drug Optimisation
R&D	Research and Development
SEARO	Regional Office for South East Asia
SPRP	Strategic Preparedness, Response and Resilience Plan
TPP	Target Product Profile
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WPRO	Regional Office for the Western Pacific

Dengue

Epidemiology

Dengue is the most important vector-borne viral infections in humans. It is caused by an *Aedes* mosquito-transmitted flavivirus with four serotypes. WHO named dengue one of the top ten threats to global health in 2019 following a ten-fold increase in reported cases from 500,000 to 5.2 million between 2000 and 2019 driven by climate change and globalisation. A further surge and geographical expansion in the wake of the COVID-19 pandemic saw dengue being graded the highest level of emergency under the WHO's Emergency Response Framework (ERF) in 2023. Over 14 million dengue cases and over 10,000 dengue-related deaths were reported in 2024, approximately double the 6.5 million cases and over 6800 deaths reported in 2023. Dengue is now endemic in more than 100 countries and half the world living in tropical and sub-tropical regions at risk.

Clinical Features

Dengue can cause an acute illness characterised by fever with headache, myalgia, and rash. This early non-severe febrile phase can in turn progress to late severe disease with vascular leak, bleeding, and shock. In some cases, this can result in further complications including multi-organ failure and death. Dengue patients also often report medium- to long-term health effects such as fatigue after resolution of acute infection.

Populations at higher risk of more severe outcomes and complications include young children, older adults, pregnant women, people with pre-existing comorbidities such as diabetes mellitus, and people with weakened immune systems. Secondary infections after a primary infection with a different serotype are also more likely to be more severe.

Clinical Management & Treatments in Development

There are no licensed treatments for dengue fever and supportive care remains the mainstay of clinical management as detailed in the WHO Clinical Management Guidelines for Arboviral Diseases (Dengue, Zika, Chikungunya, and Yellow Fever)[1]. The WHO Global Strategic Preparedness, Readiness and Response Plan (SPRP) for Dengue and Other *Aedes*-borne Arboviruses[2] highlighted the need for safe and effective medicines to prevent progression to severe disease, organ failure, and death. Several drug candidates (small molecules and monoclonal antibodies) are now in phase 2 trials for the treatment of non-severe dengue. There are no novel drugs in clinical development at present for severe dengue.

Target Product Profile Development

Purpose

WHO product profiles are intended to accelerate the development of neglected health products for the greatest and most urgent unmet public health needs. WHO target product profiles (TPPs) in particular are developed as the product pipeline matures and before phase 3 trials are finalised as a strategic reference document for product developers, regulatory agencies, procurement bodies, and funders to facilitate alignment between public health and R&D priorities. WHO TPPs provide guidance on minimally acceptable (essential) and preferred (optimal) criteria for a product to be implemented and accessible, including through WHO prequalification and policy recommendation processes. They specify the intended use, target populations, and desired attributes of products, prioritising access and affordability considerations at all stages of development. These dengue therapeutics TPPs are therefore developed to guide the clinical development of new drugs or combinations of drugs for the treatment of non-severe (early) and severe (late) dengue for wide implementation and access in dengue-endemic countries.

Methodology

The TPP development process follows the WHO Standard Procedure for TPPs, Preferred Product Characteristics, and Target Regimen Profiles (Second Edition)[3]. It is coordinated by Raman Velayudhan (lead technical officer) and Xin Hui Chan (consultant). The first expert development group meeting was conducted virtually on 27-28 March 2025 and 14 April 2025.

TPP Purpose

This TPP should guide the clinical development of new treatments for non-severe (early) dengue and severe (late) dengue prioritising equity and access for all patients. A new treatment for non-severe dengue should be a dispersible tablet with excellent bioavailability given in a short course of ≤7 days or single-dose injectable with high safety requiring no routine monitoring and pan-serotype efficacy in reducing symptom severity and duration, and ideally also reducing progression to severe dengue. For severe dengue, an intravenous drug which reduces development of and duration of organ failure requiring invasive organ support with a positive risk-benefit ratio is recommended. It is essential that reproductive toxicity studies for any dengue drug are conducted ahead of phase 3 trials to enable inclusion of pregnant and lactating women, an important dengue risk group, in pivotal studies. As with other pathogens, anti-infective research efforts for dengue should go hand-in-hand with development of rapid diagnostic tests for pathogen confirmation accessible to the target populations to facilitate a test-and-treat approach along with continued health and regulatory system strengthening to support implementation and access.

Access and Affordability

Access to new essential treatments for neglected tropical diseases is a core part of universal health coverage. Developers should commit to an access strategy that promotes availability at fair prices. A fair price is one that is affordable for health systems and patients, but at the same time provides sufficient market incentive for industry to invest in innovation and the production of quality essential health products. To ensure access to patients in many countries, developers are invited to collaborate with WHO and the Medicines Patent Pool where appropriate.

Target Product Profiles for Treatment of Dengue Fever

a) Non-severe Dengue

TPP Domain	Minimal	Optimal	Notes
Treatment Indication	Treatment of confirmed[4] non-severe[1] dengue		Test-and-treat approach recommended.
Target Population	All age groups including young children and older adults People on or with immunosuppression People with diabetes mellitus, obesity[5], and other risk factors predisposing to more severe dengue outcomes People from all geographical regions	Pregnant and lactating women All age groups including young children and older adults People on or with immunosuppression People with diabetes mellitus, obesity[5], and other risk factors predisposing to more severe dengue outcomes People from all geographical regions	Live-attenuated vaccine-complementing protection, particularly of groups at higher risk of developing severe disease from dengue infection and who are also frequently excluded from clinical trials[6].
Efficacy	Pan-serotype efficacy in primary and secondary dengue -Reduction in time to resolution of acute symptoms of fever, pain, and nausea/vomiting [primary outcome] compared to standard-of-care with supportive measures	Pan-serotype efficacy in primary and secondary dengue -Reduction in time to resolution of acute symptoms of fever, pain, and nausea/vomiting [primary outcome] -Reduction in progression to severe dengue [secondary outcome] compared to standard-of-care with supportive measures	Direct clinical outcomes over surrogate measures[7] recognising low rate of severe and fatal outcomes from non-severe dengue in the general population.
Safety	No serious adverse drug reactions[8]. Well-tolerated with no routine monitoring required. No accumulation in or exacerbation of hepatic or renal impairment, or cardinal dengue complications (bleeding, vascular leak, and shock).	No serious adverse drug reactions[8]. Well-tolerated with no routine monitoring required. No accumulation in or exacerbation of hepatic or renal impairment, or cardinal dengue complications (bleeding, vascular leak, and shock).	High safety including in groups at higher risk of developing severe disease from dengue infection and who are also frequently excluded from clinical trials[6].

	No clinical risk of drug-related antibody-dependent enhancement. Reproductive toxicity studies completed before phase 3 trials.	No risk of drug-related antibody-dependent enhancement. No foetal toxicity in pre-clinical data. Safe during breastfeeding.	
Interactions	No clinically significant drug-drug interactions with commonly prescribed drugs in the patient population	No drug-drug interactions with commonly prescribed drugs in the patient population	Interaction studies including in groups at higher risk of developing severe disease from dengue infection and who are also frequently excluded from clinical trials[6].
Treatment Duration	≤7 days	≤3 days	Comparable to core oral anti-infectives for common severe acute infections on the WHO Essential Medicines List[9] (i.e. oral antimalarials and oral antibiotics for treatment of uncomplicated malaria and uncomplicated bacterial infections).
Dose Frequency	2-3x/day	≤1x/day	
Route	Oral or single-dose parenteral (intravenous or subcutaneous)	Oral	
Formulation	Tablet with appropriate dispersible formulation[10] as demonstrated by acceptability study, or injectable	Tablet with appropriate dispersible formulation[10] as demonstrated by acceptability study	
Food Requirements	Requirement to be taken before or after meals, or with specific foods.	No specific food requirements.	
Stability & Storage	Suitable for all climactic zones, including International Council for Harmonisation Zone IVb (30°C and 75% relative humidity) and cycling of temperatures. Shelf-life of ≥24 months. Oral: No special storage or transport requirements. No cold chain requirements. Injectable: If cold chain needed, compatible with current vaccine cold chain requirements (2-8°C).	Suitable for all climactic zones, including International Council for Harmonisation Zone IVb (30°C and 75% relative humidity) and cycling of temperatures. Shelf-life of ≥36 months. Oral: No special storage or transport requirements. No cold chain requirements.	

Pricing	Compatible with wide access in dengue-endemic countries	Compatible with wide access and rapid scale-up in dengue-endemic countries	Cost-effectiveness analyses incorporating all aspects of drug procurement, delivery, and administration (including monitoring requirements) specific to drug modality and mechanism of action are recommended.

Please see Appendix 1 for additional recommendations and notes from expert development group discussions.

b) Severe Dengue (including Dengue with Warning Signs)

TPP Domain	Minimal	Optimal	Notes
Treatment Indication	Treatment of confirmed[4] severe[1] dengue		Test-and-treat approach recommended.
Target Population	All age groups including young children and older adults People on or with immunosuppression People with diabetes mellitus, obesity[5], and other risk factors predisposing to more severe dengue outcomes People from all geographical regions	Pregnant and lactating women All age groups including young children and older adults People on or with immunosuppression People with diabetes mellitus, obesity[5], and other risk factors predisposing to more severe dengue outcomes People from all geographical regions	Live-attenuated vaccine-complementing protection, particularly of groups at higher risk of developing severe disease from dengue infection and who are also frequently excluded from clinical trials[6].
Efficacy	Pan-serotype efficacy in primary and secondary dengue -Reduction in duration of organ failure requiring invasive organ support [primary outcome] compared to standard-of-care with supportive measures	Pan-serotype efficacy in primary and secondary dengue -Reduction in duration of organ failure requiring invasive organ support [primary outcome] -Reduction in mortality [secondary outcome] compared to standard-of-care with supportive measures	Direct clinical outcomes over surrogate measures[7] noting the low rate of fatal outcomes in severe dengue in the general population.
Safety	Overall acceptable risk-benefit profile in the target population. No clinical risk of antibody-dependent enhancement. Minimal risk of reactivation of endemic chronic infections (e.g. tuberculosis, hepatitis B, and strongyloidiasis). Minor dose adjustments required in organ failure. Reproductive toxicity studies completed before phase 3 trials.	No serious adverse drug reactions[8]. No risk of antibody-dependent enhancement. No routine screening or monitoring required. No dose adjustments required in organ failure. No foetal toxicity in pre-clinical data. Safe during breastfeeding.	High safety including in groups at higher risk of developing severe disease from dengue infection and who are also frequently excluded from clinical trials[6].

Interactions	No clinically significant drug-drug interactions with commonly prescribed drugs in the patient population	No drug-drug interactions with commonly prescribed drugs in the patient population	Interaction studies including in groups at higher risk of developing severe disease from dengue infection and who are also frequently excluded from clinical trials[6].
Treatment Duration	7-10 days	<7 days	Comparable to core parenteral anti-infectives for common severe acute infections on the WHO Essential Medicines List[9] (i.e. parenteral antimalarials and parenteral antibiotics for treatment of severe malaria and severe bacterial infections).
Dose Frequency	2-3x/day	1x/day	
Route	Intravenous		
Formulation	Injectable		
Stability & Storage	Suitable for all climactic zones, including International Council for Harmonisation Zone IVb (30°C and 75% relative humidity) and cycling of temperatures. Shelf-life of ≥24 months. Injectable: If cold chain needed, compatible with current vaccine cold chain requirements (2-8°C).	Suitable for all climactic zones, including International Council for Harmonisation Zone IVb (30°C and 75% relative humidity) and cycling of temperatures. Shelf-life of ≥36 months. Injectable: No special storage or transport requirements. No cold chain requirements.	
Pricing	Compatible with wide access in dengue-endemic countries	Compatible with wide access and rapid scale-up in dengue-endemic countries	Cost-effectiveness analyses incorporating all relevant aspects of drug procurement, drug delivery, and drug administration (including monitoring requirements) specific to drug modality and/or mechanism of action are recommended.

Please see Appendix 1 for additional recommendations and comments from expert development group discussions.

Appendix 1: Expert Development Group Meeting Notes

TPP Domain	Meeting 1	Meeting 2
Treatment Indication	**Non-severe Dengue & Severe Dengue** Consensus recommendation for a test-and-treat approach, recognising complexities around: • Resources to access virological confirmation, particularly in outbreak settings • Turnaround time for test results[4] relative to need for early initiation of antiviral treatment • Sensitivity, specificity, and predictive value of rapid diagnostic tests[4], particularly for secondary infections with 30-40% missed[11,12] by commonly used NS1 antigen point-of-care tests • Clinical diagnosis alone for a non-specific acute febrile illness, particularly with atypical presentations more likely in the important risk group of older adults • Antiviral stewardship and risk-benefit assessment in the absence of pathogen-based confirmation	To follow
Target Population	**Non-severe Dengue & Severe Dengue** Expert recommendations to: • Move pregnant and lactating women from minimal to optimal target population in favour of adding requirement for reproductive toxicity studies before phase 3 trials • Add obesity to list of risk factors predisposing towards severe dengue The expert development group recognised the: • Importance of prioritising groups at higher risk of severe dengue in clinical development of and access to treatments particularly where drug supplies may be limited, such as in outbreaks • Limitations of using warning signs and existing biomarkers to predict progression to severe dengue	To follow
Efficacy	**Non-Severe Dengue & Severe Dengue**	To follow

	Expert recommendations that: • Selection of outcomes and endpoints for phase 3 trials should take into account sample size considerations to support trial feasibility • Clinical or radiological findings used for clinical decision-making in patient care would not be suitable for regulatory decision-making for pivotal clinical trials without additional evaluation and validation **Non-Severe Dengue** Consensus recommendations that: • Reduction in time to resolution for acute signs and symptoms would be acceptable as a predefined primary composite outcome to demonstrate a direct clinical antiviral effect for regulatory decision-making drawing on experience with acute respiratory viral infections. The expert development group recognised the public health importance of reduction in morbidity and related functional impairment from non-severe dengue and the low frequency of severe dengue. However, further careful selection and definition of symptoms as well as validation of any novel measurement tools would be required for the development of such a composite measure. • Hospitalisation for a dengue-related reason as an objective resource utilisation measure was noted to be important to record as a secondary outcome although experts noted the wide variation in thresholds for hospitalisation across geographical regions and resource settings including outbreaks • Viraemia proxy measures for progression to severe dengue would not be acceptable as a primary outcome for regulatory decision-making but would be relevant in evaluation of rebound for both antiviral and immunomodulator drugs • Further research on the frequency and natural history of post-dengue cardiovascular and neuropsychiatric complications was considered necessary to define an appropriate outcome	

	Severe Dengue Consensus recommendation that: • The number of systems requiring invasive organ support, the type of organ support used, and the duration this organ support be recorded as measures for organ failure Seeking feedback from dengue drug developers during the public consultation phase was recommended to learn from recent clinical trials. Following public consultation, a second expert development group meeting will be conducted to consider efficacy outcomes in greater detail towards the end of 2025.	
Safety	**Non-severe Dengue & Severe Dengue** Consensus recommendations for: • Assessing the risk of antibody-dependent enhancement • Requirements for routine screening (e.g. for endemic infections) and monitoring being barriers to access to be avoided as far as possible	To follow
Interactions	No changes recommended	To follow
Resistance	**Non-severe Dengue & Severe Dengue** Consensus recommendations for: • Development of combination therapies to reduce the risk of emergence of resistance • Further research to characterise if and how genetic mutations would translate into clinically significant resistance in mosquitoes and humans Section removed in absence of suitable pre-clinical proxy marker of resistance for regulatory decisions.	To follow
Treatment Duration	**Non-severe Dengue** Expert recommendations to: • Extend minimal treatment duration from 5 days to ≤7 days • Reduce optimal treatment duration from 3 days to ≤3 days	To follow
Dose Frequency	**Non-severe Dengue & Severe Dengue** Consensus recommendation that requirements for higher dose frequencies are barriers to access to be avoided as far as possible.	

	Non-Severe Dengue Expert recommendation to reduce optimal dose frequency from 1x/day to ≤1x/day.	
Route	**Non-severe Dengue** Consensus recommendation on preference for the oral route recognising: • Need for further evidence on the efficacy, safety, pharmacokinetics, and acceptability of the rectal, sublingual, and transdermal routes in acute non-severe dengue fever **Severe Dengue** Consensus recommendation on preference for the intravenous route recognising: • Challenges with enteral absorption in patients with vascular leak • Concerns about bleeding risk with nasogastric tube insertion • Use of both peripheral and central venous access in severe dengue depending on clinical need and resource availability	
Formulation	**Non-severe Dengue** Consensus recommendation for dispersible tablet formulation to support access for all age groups and people with comorbidities which affect the ability to swallow capsules. Further detail to be added following Paediatric Drug Optimization (PADO) process led by WHO Global Accelerator for Paediatric Formulations (GAP-f)[10].	
Food Requirements	No changes recommended.	
Stability & Storage	**Non-severe Dengue & Severe Dengue** Expert recommendation for requirement for stability during cycling of temperatures as would be expected during transport.	To follow
Pricing	**Non-severe Dengue & Severe Dengue** Consensus recommendation for central procurement, delivery, and administration of dengue therapeutics by regional and/or national government health systems supported by appropriate staff training to facilitate safe and equitable access to all.	To follow

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