Fiocruz-WHO Flaviviridae CORC

Flaviviridae

Research & Development Roadmap

March, 2026

FIOCRUZ
World Health Organization
R&DBlueprint
Powering research to prevent epidemics

Summary

Abbreviations

ADE: Antibody-Dependent Enhancement

AI: Artificial Intelligence

CHIM: Controlled Human Infection Model

CORC: Collaborative Open Research Consortium

CZS: Congenital Zika Syndrome

DAA: Direct-Acting Antiviral

DENV: Dengue virus

DENV-1 to DENV-4: Dengue virus serotypes 1 to 4

EMA: European Medicines Agency

FDA: Food and Drug Administration (United States)

FV CORC: Flaviviridae Collaborative Open Research Consortium

GBS: Guillain-Barré Syndrome

HTA: Host-Targeting Agent

IVM: Integrated Vector Management

JEV: Japanese encephalitis virus

LMICs: Low- and Middle-Income Countries

MCM: Medical Countermeasure

NLP: Natural Language Processing

PPPR: Pandemic Prevention, Preparedness and Response

R&D: Research and Development

RCCE: Risk Communication and Community Engagement

RT-PCR: Reverse Transcription Polymerase Chain Reaction

SLEV: St. Louis encephalitis virus

TBEV: Tick-borne encephalitis virus

TPP: Target Product Profile

USUV: Usutu virus

WHO: World Health Organization

WNV: West Nile virus

YFV: Yellow fever virus

ZIKV: Zika virus

Preamble

The Collaborative Open Research Consortium (CORC) represents an innovative global strategy coordinated by the World Health Organization (WHO) Research and Development (R&D) Blueprint for Epidemics. The formation of CORCs signifies a critical shift in paradigms regarding Pandemic Prevention, Preparedness and Response (PPPR), transitioning from a single pathogen focus on an approach centered on prototypes derived from both viral and bacterial families. This strategy aims to expand the current breadth of knowledge by moving beyond well-studied pathogens, utilizing prototype agents as "pathfinders" and leveraging scientific expertise to advance PPPR. This strategy is pivotal to support the implementation of the WHO pandemic agreement, recently approved at the 78th World Health Assembly.

The overarching purpose of the CORCs is to coordinate an open global scientific network, to promote and accelerate R&D cooperation, advancing epidemic and pandemic prevention, preparedness and response (PPPR), and to orient strategic allocation of resources. The Consortium is committed to a representative and equitable participation, improving global access to scientific knowledge, information, and Medical Countermeasures (MCMs).

The Flaviviridae CORC (FV CORC) encompasses pathogens of significant concern, including dengue virus (DENV), Zika virus (ZIKV), yellow fever virus (YFV), West Nile virus (WNV), St. Louis encephalitis virus (SLEV) and Japanese encephalitis virus (JEV). It was officially inaugurated by the World Health Organization (WHO) and the Oswaldo Cruz Foundation (Fiocruz) on February 24, 2025, with the objective of enhancing PPPR in the context of One Health and Climate Change perspectives. This is achieved through interdisciplinary collaborative research, sharing scientific knowledge, and expediting the development of MCMs to address epidemic and pandemic threats.

To date, the FV CORC has comprised approximately 500 attendees, encompassing scientists, stakeholders, international organizations, networks, funders, and private sector representatives from 51 nations spanning five continents, with 54% originating from low- and middle-income countries (LMICs). Inclusion and representativeness constitute core values central to this initiative. Furthermore, a team of Thematic Coordinators and the Core Group played an indispensable role in the development and validation of this document. Consequently, the current R&D roadmap represents a collaborative endeavor of this global workforce, whose contributions were essential for its realization.

Thank you!

Scope

The Flavivirus Research and Development roadmap presents the key challenges and necessary actions for enhancing Prevention, Preparedness, and Response to epidemics and pandemics. It emphasizes the prioritized research needs and establishes timelines aimed at accelerating the development and ensuring equitable access to MCMs. Consequently, this roadmap provides a comprehensive framework for coordinated implementation and evidence-based decision-making for policymakers, the scientific community, public health institutions, funding organizations, and other stakeholders.

Human pathogens belonging to *Orthoflavivirus* genus (*Flaviviridae* family) pose a significant threat to low- and middle-income countries, where health disparities and limited access to healthcare interventions exacerbate the burden of disease. This document underscores the necessity of fostering equitable participation, knowledge sharing, and capacity building. Enhancing local infrastructure and forging partnerships is crucial for ensuring that scientific advancements are accessible to the marginalized. Furthermore, the integration of regulatory measures and public health initiatives must be concurrently addressed in conjunction with the progress of scientific research.

Executive Summary

The *Orthoflaviviruses*, which belong to the family *Flaviviridae*, consist of small, enveloped RNA viruses that are highly relevant to public health. These viruses include the dengue virus (DENV), Zika virus (ZIKV), yellow fever virus (YFV), Japanese encephalitis virus (JEV), St. Louis encephalitis virus (SLEV), and West Nile virus (WNV). These arthropod-transmitted viruses possess the ability to induce severe, life-threatening diseases in humans, which typically manifest as hemorrhagic fever (in the cases of DENV and YFV) or encephalitis (as seen with ZIKV and WNV). Noteworthy, WNV demonstrates a significant capacity to cross species barriers, wherein migratory birds serve as reservoir hosts, raising significant veterinary concerns and posing threats to human populations.

Recent outbreaks have led to infections impacting up to 400 million individuals annually, resulting in significant socioeconomic consequences, particularly for vulnerable communities. The transmission and potential for epidemics of *Orthoflavivirus* infections are further exacerbated by climate change, urbanization, global travel, altering vector ecologies and other drivers, thus creating a complex epidemiological framework that aggravates existing health disparities.

To combat these urgent health threats, it is essential to advance vaccines, diagnostics, and therapeutics; however, these efforts face challenges due to existing knowledge gaps. A cohesive research and development ecosystem is essential, integrating multidisciplinary methodologies with eight specific R&D priorities pivotal for enhancing prevention, preparedness, and response strategies against flavivirus outbreaks. This R&D roadmap focuses on crucial areas of concentration, including the implementation of robust and efficient public health surveillance systems, community-derived interventions and community engagement, advancing genomic investigations to acquire insights into the dynamics of viral evolution, and utilizing immunological discoveries to improve clinical management approaches and the formulation of medical countermeasures. Furthermore, an in-depth understanding of vector ecology will inform targeted interventions. Moreover, improving vaccine and diagnostic capabilities, developing therapeutics, and streamlining regulatory pathways are crucial steps to ensure equitable access to these vital interventions.

The significance of an integrated One Health approach is underscored. By fostering international collaboration and facilitating knowledge exchange, the global response to flavivirus health threats can be substantially reinforced. Addressing these interrelated challenges through collaborative initiatives is crucial for mitigating the impact of flavivirus ongoing and new outbreaks and enhancing public health outcomes.

Introduction

The *Orthoflaviviruses*, which belong to the family *Flaviviridae*, consist of small, enveloped RNA viruses that are highly relevant to public health. These viruses include the dengue virus (DENV), Zika virus (ZIKV), yellow fever Virus (YFV), Japanese encephalitis virus (JEV), St. Louis Encephalitis Virus (SLEV), and West Nile Virus (WNV). These arthropod-transmitted viruses possess the ability to induce severe, life-threatening diseases in humans, which typically manifest as hemorrhagic fever (in the cases of DENV and YFV) or encephalitis (as seen with ZIKV and WNV). Noteworthy, WNV demonstrates a significant capacity to cross species barriers, wherein migratory birds serve as reservoir hosts, raising significant veterinary concerns and posing threats to human populations.

Over the past decades, DENV, ZIKV, YFV, and WNV have emerged, spread and caused multiple outbreaks and epidemics worldwide. Other *Orthoflaviviruses* such as JEV, tick-borne encephalitis virus (TBEV) and Usutu virus (USUV), remain potential threats and are emerging in new geographic regions of the world. *Orthoflaviviruses* are currently distributed globally, infecting up to 400 million people annually, imposing high socioeconomic costs and environmental impact particularly to the most vulnerable populations.

The epidemic potential and transmission of *Orthoflaviviruses* are influenced by multiple interconnected drivers. Factors such as climate change, rapid and unplanned urbanization, increased global trade and travel, and evolving vector ecology have intensified global transmission, enabling geographic expansion and co-circulation of multiple arboviruses in a transforming epidemiological landscape on a global scale. This convergence of global forces interacts with social and environmental determinants of health — such as poverty, inadequate housing, poor sanitation, and limited access to care — increasing transmission risk and exacerbating health disparities, particularly in marginalized communities and isolated areas. Furthermore, data gaps and surveillance fragmentation continue to hinder timely response, especially in low-resource settings. Incomplete, inconsistent, and underreported epidemiological data jeopardize effective risk assessments, modeling efforts, and outbreak forecasting, emphasizing the need for harmonized, integrated surveillance frameworks that incorporate epidemiological, clinical, genomic and environmental data. Strengthening local capacity, community engagement, and investment in public health infrastructure is critical for building resilience and ensuring long-term impact, especially in the face of recurring or overlapping outbreaks.

The primary goal of the FV CORC is to speed up the development and equitable distribution of effective MCMs for preparedness and response to epidemics and pandemics. This focus covers vaccines for prevention, diagnostics for case detection, and therapeutics to lower morbidity and mortality. Each area faces unique yet interconnected challenges, such as complex immunology affecting vaccine design and narrow therapeutic windows complicating drug development. Progress in foundational sciences and navigating regulatory challenges are critical for any MCM. The burdens from key viruses emphasize this urgency. DENV, with four serotypes, causes about 100 million symptomatic cases yearly. ZIKV poses severe risks due to neurological complications and congenital anomalies, while areas previously affected face outbreak risks as immunity diminishes. YFV is a re-emerging threat in Africa and the Americas, and notably, there are no licensed human vaccines for WNV or ZIKV, nor approved virus-specific treatments for flavivirus infections.

The most critical advancements over the upcoming decade will emerge from the establishment of a coherent R&D ecosystem and integrated monitoring strategies under a comprehensive One Health approach, which is crucial for creating a robust framework to guide collaboration and action. The framework that outlines these prioritized research needs is summarized in this R&D Roadmap, which functions as the strategic blueprint and a significant contribution to the effective execution of the WHO Pandemic Agreement.

Research & Development Priorities

1. FROM SIGNALS TO ACTION: PUBLIC HEALTH, SURVEILLANCE & EPIDEMIOLOGICAL INTELLIGENCE

Knowing the dynamics of transmission rates that are on the rise, identifying which viral genetic strains are emerging and spreading, as well as analyzing how vector and reservoir distributions are evolving, is essential for informing downstream health strategies and interventions. It is critical to emphasize that surveillance activities must be implemented in a systematic and continuous manner, ensuring they are both sustainable and aligned with actionable mitigation strategies, which extend beyond the epidemic or pandemic periods. Global health protection should be recognized as a primary goal.

In order to facilitate effective identification, monitoring, and response to emergent health threats, it is imperative to enhance global early warning systems. Recent advancements in artificial intelligence (AI), data science, and digital epidemiology possess the potential to utilize the extensive volumes of data routinely collected by health systems. By incorporating these with various external data sources, the accuracy and predictive validity of surveillance can be significantly improved. Contemporary health surveillance necessitates the provision of timely, granular, data-driven insights. Realizing such integration is feasible in specific contexts; however, the actualization of modern public health surveillance continues to be a substantial challenge in numerous countries.

1.1. Primary challenges

Silent zones in surveillance data. The surveillance data has silent zones, whit no samples or information, indicating that surveillance systems need to be strengthened to have representative data from each country, and each region inside a country. Moreover, the generation of data from each sample (human health, environment, veterinarian) needs to be time efficient and shared in real time for early detection of possible public health events and thus activation of the prevention and response programs and systems. To have a continuous acquisition of data, the surveillance system needs also to be sustainable and constant overtime.

Fragmentation of data across global and national systems and platforms. A fundamental barrier is the lack of information and/or interoperability between healthcare databases, public health surveillance systems, and other critical data sources (e.g., genomic, environmental, veterinary, and social media data). This siloed data architecture, even for bona fide health data, severely impairs the synthesis of effective epidemiological intelligence, from a One Health perspective, and hinders unified situational awareness.

Inability to process multilingual and unstructured data for global surveillance. Effective global surveillance requires the capacity to analyze information from diverse cultural and linguistic contexts, including unstructured sources like news reports and informal online discussions. While advances in Natural Language Processing (NLP) offer potential, robust, cross-culturally applicable tools are not yet widely deployed or validated for public health use.

The proliferation of disinformation and the challenges of algorithmic bias. The rise of intentional deception and disinformation on social media platforms presents a significant obstacle to detecting genuine public health signals. Concurrently, concerns regarding AI explainability, fairness, and inherent algorithmic bias inhibit the trust and integration of automated tools into public health decision-making systems.

Constraints posed by data privacy, sovereignty, and ethical governance. Strict privacy protection laws and the imperative to respect data sovereignty—often rooted in distinct cultural norms—create challenges for cross-jurisdictional data sharing. Developing governance models that balance rapid data analysis for timely response with stringent ethical and privacy requirements remains an unresolved operational hurdle.

Lack of integration between surveillance outputs and operational decision-support. There is a critical disconnect between surveillance systems that generate early alerts and the operational frameworks for healthcare resource allocation.

1.2. Knowledge gaps

Biogeography plays a crucial role in understanding the phylogenetic diversity and geographic distribution patterns of *Orthoflavivirus*. Beyond human populations, these patterns are also influenced by the circulation of reservoir hosts including non-human primates, birds, rodents, and bats. Such insights are essential for assessing the risk and susceptibility of countries to epidemic outbreaks. Additionally, it is imperative to rigorously evaluate the environmental factors influencing viral distribution and dissemination, especially in regions that have historically been underrepresented in research and surveillance efforts.

Representative geographic information on flavivirus diversity and its prevalence among various hosts, including humans, vectors, and animal reservoirs such as non-human primates, birds, bats, and rodents, which play a crucial role in maintaining the wildlife cycle. Furthermore, it is essential to examine the environmental impact on viral distribution and dissemination, particularly in regions that are often neglected in research.

Data integration and interoperability. The transformation of fragmented, heterogeneous data into actionable epidemiological intelligence represents one of the greatest challenges in modern public health surveillance. While the volume of health-related data has increased—ranging from electronic health records and genomic sequences to environmental sensors and social media streams—the capacity to integrate, analyze, interpret and forecast these diverse data sources in real-time remains severely limited. The fundamental scientific gap lies not merely in data collection, but in the development of robust methodologies for data harmonization, quality assessment, and synthesis across vastly different formats, languages, and governance frameworks.

Multilingual and unstructured data processing. Effective global surveillance requires the capacity to analyze information from diverse cultural and linguistic contexts, including unstructured sources like news reports and informal online discussions. Robust, cross-culturally applicable tools for natural language processing are not yet widely deployed or validated for public health use, limiting the ability to detect early signals from non-traditional data sources.

Balancing analytical power with ethical constraints. The need to balance analytical power with privacy preservation, algorithmic fairness, and protection against disinformation creates requirements that often pull in opposing directions and for which there are no established solutions. Concerns regarding AI explainability, fairness, and inherent algorithmic bias inhibit the trust and integration of automated tools into public health decision-making systems, while the rise of intentional deception and disinformation on social media platforms presents a significant obstacle to detecting genuine public health signals.

Integration of surveillance with operational response. There remains a critical disconnect between surveillance systems that generate outbreak alerts and the operational frameworks for healthcare resource allocation. Without progress in linking detection to decision-support tools, even the most comprehensive data collection efforts will fail to deliver the early warning and situational awareness needed for effective outbreak response.

Sustainability of surveillance systems. Research is needed to determine how surveillance systems can be designed to remain operational and effective during inter-epidemic periods, maintaining the infrastructure and expertise needed for rapid scaling when outbreaks occur. This includes developing sustainable funding models, career pathways for surveillance professionals, and low-cost technologies that can be maintained locally without external dependence.

1.3 Key needs

- Expansion of detection and genomic surveillance of Orthoflaviviruses in neglected areas and hosts, including vectors and reservoirs, and integrating virus evolution data into predictive models. Apply an unbiased approach through metagenomics to uncover coinfection, divergent lineages, and novel *Orthoflaviviruses*.

- Enhancement of early warning systems to facilitate prompt action. The technological framework for cloud-based data integration and high-performance computing is crucial to the advancement of interoperable data platforms that seamlessly amalgamate epidemiological data, health records, genomic information, ecological factors, climatic variables, wastewater analysis, and social media interactions into comprehensive predictive models.

- Improvement of quantitative forecasting mathematical frameworks for predictive scenario analysis, coupled with real-time, evidence-based dashboards and resource-allocation instruments, is crucial to ensure that surveillance findings lead directly to prompt and effective detection, monitoring, and response.

- Advancement of understanding of the impact of socio-environmental factors on human health, alongside the formulation and customization of strategies to implement participatory surveillance, particularly among marginalized and hard-to-reach populations and geographical areas.

- Reinforcement of Field Epidemiology Training Programs by integrating data science modules.

- Development of multilingual tools and natural language processing (NLP) techniques is critical for enhancing global epidemic intelligence and ensuring cross-cultural applicability.

- Adoption of a federated learning architecture to facilitate privacy-preserving data sharing. It is also imperative to establish a comprehensive framework that encompasses policy, legal, and regulatory support to guarantee timely integrated surveillance while concurrently protecting individual privacy.

- Implementation of direct funding to support science research focused on the translation of evidence into action within outbreak settings. Increase in communication between basic, implementation, translational, and clinical research for better exchange of data and complementary action between research and public health actions.

1.4 Strategic goals and milestones

Strategic Goal 1 Establish integrated, real-time data surveillance systems for early detection and response	**Year**
Milestones	
Map regulatory capacity and surveillance infrastructure in Orthoflaviviruses endemic countries to identify needs and targets for investment	**1**
Intensify genomic sequencing of Orthoflaviviruses in neglected areas and hosts, including vectors and reservoirs, and integrating virus evolution data into predictive models	**1-5**
Prioritize metagenomic surveillance in biodiversity hotspots to identify pathfinders - viruses with high diversity but low current human incidence	**1-2**
Integrate epidemiological data, health records, genomic information, ecological factors, climatic variables, wastewater analysis, social media interactions and other sources of information into multifaceted predictive models, enhancing early warning systems and facilitating prompt action	**1-5**
Implement a comprehensive multi-country vector–reservoir mapping framework linked to climate variability and land-use data	**2-4**
Integrate different surveillance systems with standardized protocols and data sharing	**2-5**
Consolidate regional One Health surveillance systems integrating amplifying hosts, vectors, and human cases	**2-5**
Strategic Goal 2 Build sustainable capacity for advanced surveillance in low-resource settings	**Year**
Milestones	
Promote capacity building and sustained strengthening (training, technology transfer) at the global level	**1-5**
Support local infrastructure development that is resilient and sustainable, enabling countries to maintain genomic surveillance independently	**2-5**
Enhance the understanding of socio-environmental factors on human health, as well as formulating and customizing strategies to implement participatory surveillance, particularly among marginalized and hard-to-reach populations and geographical areas	**2-4**
Develop regional laboratory networks for biobanking and sharing of specimens	**3-5**

2. VIRAL EVOLUTION AND ECO-EVOLUTIONARY GENOMICS THAT CONNECTS "SEQUENCE TO CONSEQUENCE" UNDER A ONE HEALTH PERSPECTIVE

Although much knowledge has been generated for some Orthoflaviviruses infecting humans, substantial gaps remain, particularly in the understanding of their circulation in reservoirs and vectors within the sylvatic cycle, and how host-virus coevolution drives viral genomic evolution in natural settings. In addition, uncertainties persist regarding vector adaptation, genomic and lineage changes accompanying the sylvatic-to-urban transition, and the evolutionary pressures imposed by interventions such as Wolbachia-based control or vaccination programs. Filling these knowledge gaps is essential for anticipating future risks, particularly as climate change, rapid urbanization, and global travel create new ecological opportunities for Orthoflaviviruses to emerge or re-emerge.

Genomic surveillance has outpaced functional insight: sequences accumulate, but phenotypes (transmissibility, virulence, immune escape, vector competence) often remain unknown. This is especially problematic for understanding sylvatic-to-urban transitions and how interventions (vaccines, Wolbachia-based control, insecticides) shape viral evolution.

Thus, enhancing genomic knowledge from the Orthoflaviviruses identified in underrepresented regions, populations, and hosts (such as vectors and reservoirs) is essential. This includes applying unbiased approaches (metagenomics) to uncover coinfection, divergent lineages, and novel Orthoflaviviruses. Additionally, integrating virus evolution data into multi-source models that combine genomics, ecology, and epidemiology is vital to better comprehend the transmission dynamics of these pathogens and to inform sustainable prevention and control strategies.

2.1 Primary challenges

Fragmented data and disciplinary silos hinder integrative analysis. A lack of synergy between virology, ecology, and epidemiology, compounded by restricted sharing of genomic data and standardized metadata, impedes the study of complex processes such as sylvatic-to-urban transition. This fragmentation limits the development of predictive models that integrate genomic, climatic, and epidemiological data to forecast transmission dynamics and emergence risk.

Inadequate and biased genomic surveillance. Genomic surveillance remains uneven across and within regions, with substantial heterogeneity in both geographic coverage and sampling strategies. This bias toward human clinical data creates a significant gap in understanding viral evolution within natural reservoir hosts and enzootic vectors. The lack of systematic serosurveillance further limits the ability to contextualize viral circulation and evolution within population with differing immunity landscapes.

A critical gap between genomic data and functional insight. The rapid generation of viral sequences has outpaced phenotypic characterization. The functional consequences of observed genomic changes - such as those affecting transmissibility, virulence, or immune escape—often remain unknown, limiting the actionable intelligence gained from surveillance. This gap is exacerbated by a scarcity of 3D structural data to mechanistically link genetic variation to changes in key virus-host interactions.

Limited empirical understanding of viral adaptation in real-world contexts. Despite high adaptive potential, there is sparse data on how Orthoflaviviruses evolve in response to specific selective pressures, such as those imposed by vaccines, *Wolbachia*-based biocontrol, or vector control. The genomic determinants of efficient urban transmission and the role of immune escape variants in driving epidemic patterns are poorly quantified.

2.2 Knowledge gaps

Sylvatic cycles and viral diversity: The remarkable genetic diversity of flaviviruses, shaped by millions of years of co-evolution with their vertebrate hosts and arthropod vectors, represents both a remarkable biological phenomenon and a profound challenge for pandemic preparedness. While tens of thousands of DENV genomes from human clinical cases have been sequenced, understanding of viral diversity in sylvatic cycles—where these viruses originated and continue to evolve in interaction with wildlife reservoirs and enzootic vectors—remains fragmentary at best. This is not merely an academic gap; the sylvatic cycles serve as permanent reservoirs from which new viral lineages can emerge into human populations, as demonstrated by the repeated spillovers of sylvatic dengue viruses in Southeast Asia and West Africa.

Sylvatic-to-urban transition: The evolutionary pathways that enable an flavivirus to transition from an enzootic cycle maintained in non-human primates and forest-dwelling mosquitoes to sustained urban transmission involving humans and peridomestic vectors like *Aedes aegypti* are poorly understood. The specific genomic signatures and evolutionary pathways that facilitate this transition have not been identified, limiting the ability to predict which viruses pose the greatest emergence risk.

Adaptation to selective pressures: How viral populations evolve in response to the selective pressures imposed by population immunity, and whether immune escape variants that could render current vaccines less effective can be anticipated, remains unknown. Similarly, the impact of interventions such as *Wolbachia*-based biocontrol, insecticides, and vaccination programs on viral evolutionary trajectories has not been systematically studied, and frameworks for predicting escape variants are lacking.

Functional consequences of genetic variation: The rapid generation of viral sequences has outpaced phenotypic characterization. The functional consequences of observed genomic changes—such as those affecting transmissibility, virulence, vector competence, or immune escape—often remain unknown, limiting the actionable intelligence gained from surveillance. This gap is exacerbated by a scarcity of 3D structural data to mechanistically link genetic variation to changes in key virus-host interactions.

Integration of genomic and epidemiological data: How disparate genomic, environmental, and health systems data can be operationally integrated into predictive models for outbreak risk and viral spread remains a methodological challenge. Investment in centralized analytic platforms, bioinformatic capacity, and multidisciplinary teams is needed to develop and maintain integrative models that can forecast transmission dynamics and emergence risk in real-time.

2.3 Key needs

- Building equitable and sustainable capacity for genomic surveillance and information, particularly in historically underrepresented regions and populations, as well as within vectors and reservoirs, thereby strengthening the One Health approach.
- Creation of cloud-based platforms for real-time genomic data sharing and evolutionary analysis.
- Reinforcement of predictive modeling techniques that integrate genomic, clinical, ecological, environmental, climatic, and epidemiological inputs for the purpose of forecasting viral emergence and spread.
- Implementation of comprehensive metagenomic surveillance in biodiversity hotspots to identify pathfinder viruses with pandemic potential.
- Development of reverse genetics systems for all major flaviviruses to enable functional characterization of emerging variants, alongside structural biology pipelines.

- Reinforcement of research on viral diversity in sylvatic reservoirs and vectors, while also establishing sentinel surveillance sites at sylvatic-urban interfaces for the early detection of spillover events.
- Implementation of long-term studies to monitor viral evolution in response to public health interventions is a critical component of effective surveillance strategies.

2.4. Strategic goals and milestones

Strategic Goal 1 Establish comprehensive genomic surveillance and functional characterization platforms	**Year**
Milestones	
Establish a "Pathogenic Shift" database that maps genetic variation to clinical outcomes, specifically targeting neuro-invasive and congenital phenotypes	**1-5**
Develop predictive models for spillover by linking sylvatic genomic signatures with environmental stressors (Climate Change/Urbanization)	**1**
Support local infrastructure development that is resilient and sustainable, enabling countries to maintain genomic surveillance	**2**
Strategic Goal 2 Advance understanding of virus evolution driven by intervention pressures (e.g., vaccines, Wolbachia-based control)	**Year**
Milestones	
Integrate virus evolution data into multi-source predictive models (genomic, ecological, climatic, epidemiological inputs)	**2**
Implement multi-country vector–reservoir mapping linked to climate and land-use data	**2-4**

3. QUANTITATIVE IMMUNE CORRELATES OF PROTECTION AND RISK ANCHORED IN LONGITUDINAL COHORTS AND DEEP IMMUNOPHENOTYPING

A sophisticated understanding of viral immunology is the foundational cornerstone for developing safe and effective MCMs against Orthoflaviviruses-associated diseases. The immune response to these arthropod-transmitted pathogens is a double-edged sword: while it can confer lasting protection, it can also increase risk of severe disease in a subsequent flavivirus infection through mechanisms like antibody-dependent enhancement (ADE), among others. This complexity, compounded by widespread pre-exposure and co-circulation of multiple flaviviruses, directly impacts vaccine design, diagnostic specificity, and therapeutic strategy. Advancing MCMs is therefore impossible without deciphering the precise rules governing protective versus pathological immunity.

The mechanisms that underpin the pathogenesis of Orthoflavivirus *infections in humans and the molecular basis of cross-immunity among multiple flaviviruses are still not fully elucidated, despite being critical for a more comprehensive understanding of the dynamics and kinetics of infections -- including the long-term dynamics of cross-reactive immunity following prior infections/vaccinations. Significant advances in this field involve translating Orthoflavivirus immunology knowledge into quantitative markers that could orient both MCMs and disease prevention.*

Correlates expedite timelines for vaccines and therapeutics, reduce uncertainty, and enable faster iteration of candidates without compromising safety. The absence of CoPs demands the execution of large, extended, and financially burdensome efficacy trials. The establishment of cohesive cohort and biobank networks utilizing uniform immune assays facilitates the immunobridging process and allows for the definition of safety margins regarding ADE and other mechanisms of enhancement.

3.1. Primary challenges

Incomplete understanding of immune correlates of protection and disease risk. Despite decades of research, there are poorly defined, quantitative immunological correlates to reliably predict vaccine efficacy or safety. The determinants of whether an immune response leads to protection or pathogenesis—particularly the tipping point between neutralizing and infection-enhancing antibodies—remain poorly characterized, hindering rational vaccine design and evaluation.

The complexity of cross-reactive immunity and its impact on MCMs. Prior exposure to encephalitic Orthoflavivirus (e.g., ZIKV, JEV) or fundamentally alters the response to subsequent infections or vaccinations. This phenomenon, encompassing immunological imprinting and epitope masking, complicates the development of vaccines that are safe and effective across all serostatuses and in regions with multiple co-circulating flaviviruses.

Significant challenges in serological diagnosis due to immune cross-reactivity. Cross-reactive antibodies between flavivirus serotypes and species severely complicate serodiagnosis. This obstacle is intensified by the expanding use of flavivirus vaccines, creating an urgent need for highly specific assays that can differentiate between flavivirus infections, DENV serotypes, and vaccine-derived immunity.

Limited understanding of the mechanisms driving severe disease. The biological pathways that determine why a subset of infections progress to severe outcomes (e.g., vascular leakage, neuroinvasive disease, congenital infection, severe hepatitis/hemorrhagic manifestations) remain incompletely defined, including the roles of host genetics, comorbidities, viral factors, and immune dysregulation.

Insufficient support for longitudinal cohorts and biobanks. Long-standing cohort studies and the resulting biobanks play an indispensable role in advancing research across these domains, particularly by facilitating the identification of immune correlates associated with protection and susceptibility, elucidating mechanisms of immunological imprinting, and aiding in the development of precise diagnostic assays capable of differentiating

among flavivirus infections.

Limitations of preclinical models for translating immunology to human outcomes. Animal models, while useful for mechanistic studies, only partially replicate human flavivirus immunology and disease. The imperfect correlation between preclinical results and human vaccine efficacy or pathogenesis models creates uncertainty in the translational pathway for new MCM candidates.

3.2. Knowledge gaps

Correlates of protection and disease risk. The immunology of Orthoflavivirus infection presents a fundamental paradox that has confounded vaccine development for decades: the same antibodies that can neutralize virus and provide protection can also, under specific conditions, enhance infection and exacerbate disease. This phenomenon of antibody-dependent enhancement (ADE) is not merely a theoretical concern—it has had real-world consequences, most notably in the experience with the first licensed dengue vaccine, where vaccination of seronegative individuals led to increased risk of severe disease upon subsequent infection. Additional mechanisms leading to enhanced disease have also been recently described, e.g. FcgRIIIA, IgA to NS1 activating neutrophils. Despite its clinical significance, the molecular and cellular determinants of the switch between protective and pathogenic antibody responses remain poorly understood. The thresholds of antibody concentration, affinity, and epitope specificity that determine whether a response is protective or enhancing have not been quantitatively defined for any Orthoflavivirus.

Role of T-cell immunity. The role of T-cell immunity in modulating the balance between protection and pathology- both in terms of direct antiviral effects and in regulating B-cell response remains largely unexplored. Understanding how CD4+, CD8+, and regulatory T-cells contribute to protection, ADE risk, and disease severity across different Orthoflaviviruses and serostatus backgrounds is essential for rational vaccine design.

Impact of pre-existing immunity. The complexity of pre-existing immunity in Orthoflavivirus-endemic regions, where individuals may have experienced multiple infections with different members of the genus and serotypes over their lifetime, as well as the increasingly complex history of flavivirus vaccines in both flavivirus-endemic and non-endemic countries, creates an immunological history that profoundly shapes responses to subsequent infections and vaccinations. How prior Orthoflavivirus exposures shape long-term B-cell and T-cell immunity, and how vaccines can be designed to overcome or leverage this immunological imprinting, remains poorly characterized.

Mechanisms of severe disease. The biological pathways that determine why a subset of infections progress to severe outcomes—including vascular leakage, neuroinvasive disease, congenital infection, and severe hemorrhagic manifestations—remain incompletely defined. The roles of host genetics, comorbidities, viral factors such as nonstructural protein 1 (NS1), and immune dysregulation in driving these outcomes have not been systematically characterized, and validated biomarkers to predict progression to severe disease are lacking.

Limitations of preclinical models: Animal models, while useful for mechanistic studies, only partially replicate human Orthoflavivirus immunology and disease. Which preclinical models best predict the safety and efficacy of novel flavivirus MCMs in diverse human populations, and how these models can be standardized and validated against human outcomes, remains an unanswered question that creates uncertainty in the translational pathway for new candidates.

3.3. Key needs

- Definition of quantitative, threshold-based immunological correlates of protection and disease risk for vaccine development and evaluation.
- Extension of studies on the mechanisms and long-term dynamics of cross-protection and enhancement

across Orthoflaviviruses.

- Identification of biomarkers or immune signatures for the early prediction of progression to severe disease for use in clinical trials and patient management (e.g., severe dengue or congenital Zika syndrome).
- Improvement of understanding the role of T-cell mediated immunity and host factors (e.g., comorbidities, age, host genetics) in modulating protection and disease severity.
- Mapping of B-cell and T-cell responses across different Orthoflavivirus exposures and vaccination statuses using systems immunology and single-cell sequencing approaches.
- Development of next-generation diagnostic assays with high specificity to distinguish between infections by different Orthoflaviviruses, DENV serotypes, and vaccine-induced immunity.
- Support for large-scale longitudinal cohort studies with deep immunological phenotyping across diverse geographic settings.
- Establishment and validation of improved preclinical models (e.g., humanized systems, organoids) that more accurately recapitulate human immune responses for MCM testing.
- Development of standardized panels of well-characterized clinical specimens representing different flaviviruses, serotypes, and immune histories.
- Design of humanized mouse models and lymphoid organoid systems for studying ADE and immune protection mechanisms.
- Establishment of international reference standards for neutralizing antibody assays and assays to measure enhancement risk.

3.4. Strategic goals and milestones

Strategic Goal 1 Define humoral and cellular correlates of protection and advance understanding of enhancement	**Year**
Milestones	
Identify biomarkers or immune signatures for the early prediction of progression to severe disease for use in clinical trials and patient management (e.g., severe dengue or congenital Zika syndrome)	**1-5**
Establish prediction thresholds for protection vs. disease risk - including the tipping point between neutralizing and infection-enhancing antibodies	**1-5**
Leverage seroepidemiological studies to indicate possible immune correlates of protection	**1-5**
Support long-term cohort studies required to improve epidemiological and immunological understanding of flaviviruses as well as to provide panels of well-characterized samples for development of diagnostics	**1-5**
Advance in-vitro and in-vivo models for evaluation of new vaccines including assessment of risk of enhancement	**1-5**
Refine the use of immunological assays, including neutralizing antibodies assays and availability of reference standards for specific viruses	**2-5**
Strategic Goal 2 Establish infrastructure for immunological studies	**Year**
Milestones	
Develop regional laboratory networks for biobanking and sharing of specimens	**2-5**
Ensure a network of clinical sites is available for post-approval safety studies and studies to monitor vaccine effectiveness in different setting/regions	**2-5**

4. VECTOR/RESERVOIR AND REAL-TIME ENTOMOLOGICAL SYSTEMS INTEGRATED INTO INTERVENTION-AWARE INTELLIGENCE

A comprehensive understanding of vectors and reservoir hosts is a non-negotiable prerequisite for predicting and preventing flavivirus outbreaks. The transmission cycle is an integrated ecological system where viral persistence and emergence are dictated by the interplay between arthropod vectors, vertebrate hosts, and environmental drivers. Critical gaps in our knowledge of enzootic cycles, the competence of secondary vectors, and the impact of anthropogenic change directly undermine the effectiveness of MCMs and public health interventions. Strengthening this foundational ecological knowledge is therefore essential for targeting surveillance, optimizing vector control, and accurately assessing the spillover risk that precedes human epidemics.

4.1. Primary challenges

Major gaps in understanding enzootic transmission cycles and reservoir hosts. For many *Orthoflaviviruses*, the identity of key amplifying hosts, the dynamics of viral maintenance in wildlife, and the frequency and mechanisms of spillover into human populations remain poorly characterized. This fundamental ecological ignorance limits our ability to predict hotspots and design interventions at the source.

The epidemiological role of secondary and cryptic vectors is largely undefined. Research has historically focused on primary vectors like *Aedes aegypti*. The vector competence, host preference, and ecological niche of many other mosquito species (e.g., in the genera *Haemagogus*, *Sabethes*) and potential arthropods like ticks are insufficiently studied, creating blind spots in risk assessment and control strategies, especially for sylvatic cycles.

Fragmented and non-standardized entomological surveillance. Existing vector monitoring systems are often inconsistent, lack integration with virological and environmental data, and fail to provide the spatiotemporal resolution needed to identify transmission hotspots or track vector population shifts in real time. This surveillance deficit cripples early warning and the evaluation of control measures.

Inadequate integration of ecological data with intervention strategies. There is a disconnect between the complex ecology of vectors and the design of control programs. The efficacy of tools like *Wolbachia*, insecticides, or genetic control is highly context-dependent, influenced by local vector species, insecticide resistance, climate, and community acceptance, yet these factors are rarely incorporated into scalable, adaptive management frameworks.

Inadequate support for evidence-based, community-derived interventions for vector control, as well as community engagement in local vector control and prevention strategies. Multiple studies, including cluster randomized control trials, have demonstrated that community-derived interventions and community participation in vector control activities can significantly reduce entomological infestation, serological evidence of infection, and self-reported dengue. However, support for these approaches is lacking. Authentic community engagement is critical for the success of sustainable vector control strategies.

4.2. Knowledge gaps

Enzootic transmission cycles. The ecological role played by flavivirus transmission is far more complex and dynamic than current surveillance systems can capture. While substantial knowledge has been accumulated about urban transmission cycles involving *Aedes aegypti* and humans, understanding of the sylvatic cycles that serve as the evolutionary and ecological reservoirs for most flaviviruses remains remarkably superficial. For viruses such as yellow fever, non-human primates are known to be involved, but the precise identity of key amplifying host species, their population dynamics, immunity patterns, and the conditions that promote

spillover to humans remain poorly characterized. For other zoonotic Orthoflaviviruses such as ZIKV and WNV, the full range of vertebrate hosts and their relative contributions to viral maintenance and amplification is even less clear.

Secondary and cryptic vectors. Research has historically focused on primary vectors like *Aedes aegypti*, leaving the vector competence, host preference, and ecological niche of many other mosquito species—including those in the genera *Haemagogus* and *Sabethes* that are critical for sylvatic cycles—insufficiently studied. The epidemiological significance of secondary and potential vector species in different ecological contexts has not been systematically assessed, creating blind spots in risk assessment and control strategies.

Ecological drivers of transmission. The ecological context- including climate, land use, biodiversity, deforestation, and urbanization- modulates vector competence, vector distribution, and transmission dynamics, yet it remains poorly understood. The impact of climate change and land-use alteration on vector species redistribution and the reshaping of transmission landscapes has not been adequately characterized, and predictive models that can forecast these changes are lacking.

Integration of entomological and virological surveillance: Existing vector monitoring systems are often inconsistent, lack integration with virological and epidemiological data, and fail to provide the spatiotemporal resolution needed to identify transmission hotspots or track vector population shifts in real time. How entomological and virological surveillance can be operationally integrated into real-time, actionable early warning systems that predict human outbreak risk remains an unresolved methodological challenge.

Intervention efficacy in ecological context: The efficacy of tools like *Wolbachia*, insecticides, and genetic control is highly context-dependent, influenced by local vector species, insecticide resistance, climate, and community acceptance. The ecological context and vector community composition that modulate the efficacy and sustainability of these interventions has not been systematically studied, and adaptive management frameworks that incorporate this complexity and heterogeneity are lacking.

4.3. Key needs

- Advancement of studies on drivers of enzootic transmission cycles for key *Orthoflaviviruses*.
- Expansion of comprehensive studies on vector competence and ecology of secondary and potential vector species.
- Establishment of interoperable platforms that merge human, vectors and reservoir hosts, and environmental data into actionable early warning.
- Establishment of adaptive, ecology-informed frameworks for Integrated Vector Management (IVM) that combine traditional and novel tools.
- Strengthening field and laboratory capacity in endemic regions for entomology and wildlife virology.
- Implementation of multi-country mapping of vector–reservoir distributions under current and future climate scenarios and land-use data.
- Creation of long-term ecological field sites in sylvatic settings across Africa, Asia, and the Americas.
- Development of "Ecology-informed" integrated vector management frameworks that explicitly account for local context, heterogeneity, and community acceptance (especially for tools like Wolbachia or genetic control).
- Improvement of strategies and mechanisms to effectively promote community engagement and community-derived interventions.
- Enhancement of affordable products and strategies to enhance individual protection, such as a novel generation of mosquito repellents.

4.4. Strategic goals and milestones

Strategic Goal 1 Elucidate enzootic transmission cycles and identify reservoir hosts	**Year**
Milestones	
Elucidate the structure and drivers of enzootic transmission cycles for key *Orthoflaviviruses*.	**2-4**
Implement multi-country vector–reservoir mapping linked to climate and land-use data	**2-4**
Conduct comprehensive studies on vector competence and ecology of secondary and potential vector species.	**3-5**
Strategic Goal 2 Build integrated, real-time surveillance capacity for vectors and reservoirs	**Year**
Milestones	
Integrate different surveillance systems with standardized protocols and data sharing across the board	**1-5**
Support resilient and sustainable local infrastructure, enabling countries to maintain genomic and entomological surveillance, as well as community-derived interventions and community engagement	**1**
Consolidate regional One Health surveillance systems integrating amplifying hosts, vectors, and human cases	**2-5**

5. VACCINES TO PREVENT ORTHOFLAVIVIRUS-ASSOCIATED DISEASES: SCALING ACCESS, IMPROVING BREADTH AND SAFETY, AND ACCELERATING LICENSURE

Vaccines continue to represent the most significant intervention in public health and the most impactful MCM for Orthoflaviviruses, with proven successes for yellow fever, Japanese encephalitis, and tick-borne encephalitis. However, the vaccine landscape is marked by critical asymmetries: while several platforms are licensed, major pathogens like Zika and West Nile lack approved vaccines, and existing dengue vaccines face limitations due to complex immunology and safety concerns.

Advancing the next generation of vaccines requires overcoming fundamental scientific barriers in immunology and clinical development, while leveraging novel platforms to create safer, broader, and more accessible products. A central focus for the forthcoming decade is threefold: (i) enhancing equitable access, programmatic delivery, and monitoring the effectiveness of current vaccines; (ii) utilizing and generating next-generation designs capable of delivering pan-Orthoflavivirus vaccines while ensuring an adequate safety margin regarding immune enhancement (ADE); and (iii) finalizing clinical development for Zika and West Nile vaccines despite their sporadic incidence.

5.1. Primary challenges

The risk of Antibody-Dependent Enhancement (ADE) and other mechanisms complicates vaccine design and deployment. This phenomenon, well-documented in dengue, poses a unique safety challenge. It necessitates strict serostatus-dependent use for some vaccines, complicates clinical trial design across populations with varying pre-exposure, and remains a concern for the development of vaccines against other Orthoflaviviruses with cross-reactive potential.

The absence of validated Correlates of Protection for key pathogens hinders development. For dengue, Zika, and West Nile viruses, there are no universally accepted immunological markers to predict clinical efficacy. This lacks forces reliance on large, long-term, and costly efficacy trials with clinical endpoints, creating a major barrier for outbreak-prone pathogens with sporadic incidence.

Unpredictable and episodic epidemiology disrupts clinical trial feasibility. The low and fluctuating incidence of viruses like Zika and West Nile outside of outbreak periods makes conducting traditional placebo-controlled efficacy trials logistically infeasible and ethically challenging, stalling the development pipeline despite promising candidates.

Significant gaps remain in the vaccine portfolio for high-threat pathogens. There are no licensed human vaccines for Zika or West Nile virus. Since dengue vaccines are already available and have demonstrated acceptable safety and efficacy, this sentence overstates the gap by implying the portfolio is largely absent. Also, current vaccines do not require pre-vaccination serostatus screening, so the 'ideal for all serostatuses' phrasing should be clarified. A more precise framing is that current vaccines show heterogeneous protection—with different performance by baseline serostatus/age/setting—and Phase III/field evidence is still insufficient to guarantee uniformly high protection against all four dengue serotypes across endemic contexts.

Technological and regulatory pathways for novel vaccine concepts are not fully established. Next-generation approaches, as T-cell-based vaccines (to avoid ADE) and pan-Orthoflavivirus vaccines, are in early development. Their advancement is hampered by a lack of standardized assays for cellular immunity, uncertain regulatory pathways for products without humoral correlates, and the inherent complexity of demonstrating efficacy for multi-pathogen targets.

5.2. Knowledge gaps

ADE and vaccine safety: The development of safe and effective Orthoflavivirus vaccines confronts a fundamental immunological paradox that has no parallel in most other vaccine targets: the immune response that protects against infection can also, under specific conditions, enhance disease. This phenomenon of ADE has profoundly shaped the vaccine landscape for Orthoflaviviruses, most notably in the experience with the first licensed dengue vaccine, where vaccination of seronegative individuals led to increased risk of severe disease upon subsequent infection. Despite its central importance, the quantitative parameters that determine whether antibody response is protective or enhancing remain poorly defined. What concentrations, affinities, epitope specificities, and Fc receptor engagement profiles distinguish protective from pathogenic antibodies? How does pre-existing immunity from prior Orthoflavivirus exposures, which is the norm in endemic regions—modulate these thresholds?

Correlates of protection for vaccine licensure: Beyond the ADE challenge, the absence of validated correlates of protection for most Orthoflaviviruses forces developers into a regulatory dilemma: vaccines cannot be licensed without efficacy data, but generating efficacy data requires large trials that may take decades to complete for pathogens with sporadic incidence. This is particularly acute for ZIKV and WNV viruses, where outbreaks are unpredictable and inter-epidemic periods can be long. Even for dengue, where incidence is high, the need to demonstrate efficacy against all four serotypes across diverse geographic settings and age groups creates extraordinary sample size requirements.

Alternative development pathways: Alternative development pathways—including controlled human infection models (CHIMs), immunobridging techniques, and accelerated regulatory approval based on established correlates of protection - have the potential to significantly alter this landscape. However, their regulatory acceptance is contingent upon the very correlates that remain undefined. Investigating how clinical development can be effectively finalized for vaccines targeting low-incidence, outbreak-prone Orthoflaviviruses, as well as identifying the optimal combinations of CHIMs, ring vaccination strategies, adaptive trial designs, and immunobridging methodologies, is of paramount importance. This requires immediate and thorough investigation to provide sufficient evidence for licensure.

Novel vaccine concepts. Compounding these challenges is the limited exploration of novel vaccine concepts that might circumvent ADE entirely, such as novel antigens (e.g., stabilized envelope dimer) that eliminate or mask epitopes (e.g., fusion loop) that generate enhancing antibodies, T-cell-based vaccines targeting conserved non-structural proteins, or pan-Orthoflavivirus vaccines that could provide broad protection with a single product. The optimal regulatory and clinical pathways to evaluate the efficacy of T-cell-based vaccines that do not induce neutralizing antibodies, and whether a single vaccine platform can provide durable protection against multiple Orthoflaviviruses, remain unanswered questions.

5.3. Key needs

- Refinement of clinical development strategies for Zika and West Nile vaccines to ensure efficacy can be rigorously demonstrated despite sporadic and unpredictable viral incidence.
- Discovery and validation of correlates of protection (CoP) for severe diseases caused by DENV, ZIKV, and WNV aim to facilitate accelerated licensure pathways. An international consortium could effectively validate CoP through a pooled analysis of existing trial data.
- Advancement of next-generation vaccine platforms (e.g., novel immunogens that avoid enhancing epitopes, T-cell-based, pan-Orthoflavivirus) designed to circumvent ADE and provide broader protection.
- Establishment of longitudinal follow-up cohorts is essential for the purpose of assessing the long-term effectiveness of protective measures and monitoring the risk of adverse events following immunization (ADE).

- Establishment of sustainable clinical trial site networks in areas affected by endemic diseases with suitable infrastructure, regulatory capabilities, and community involvement.
- Implementation of real-world effectiveness studies for gaining insights into how existing vaccines perform across various settings and populations, with a focus on coverage, durability, and safety under program conditions.
- Development of standardized reference reagents, immune assays, and specimen panels for cross-trial comparability.
- Establishment of regulatory-accepted alternative clinical development pathways, including Controlled Human Infection Models (CHIMs) and immunobridging strategies.
- Reinforcement of international standardization of regulatory criteria for facilitating the expedited approval processes of innovative Orthoflavivirus vaccines across regions that experience endemic outbreaks.

5.4. Strategic goals and milestones

Strategic Goal 1 Define Regulatory Pathways and Correlates of Protection	**Year**
Milestones	
Define regulatory pathways for Orthoflaviviruses vaccine approval according to different scenarios (including CHIMs, animal models, emergency use, accelerated approval based on correlates) with clear criteria for each pathway)	**1-5**
Define the criteria and the data that would support different pathways according to the scenarios.	**1-5**
Leverage seroepidemiological studies to indicate possible immune correlates of protection.	**1-5**
Consider the role of CHIMs for approval of vaccines, including development of standardized CHIM protocols and regulatory guidance	**1-5**
Strategic Goal 2 Advance Preclinical Testing and Long-Term Safety Assessment	**Year**
Milestones	
Advance *in-vitro* and *in-vivo* models for evaluation of new vaccines including assessment of ADE risk	**1-5**
Refine the use of immunological assays, including neutralizing antibodies assays and availability of reference standards for specific viruses	**2-5**
Promote evaluation of second-generation vaccines consisting of novel immunogens that eliminate epitopes that generate enhancing antibodies	**1-5**
Ensure background rates for incidence of Adverse Events of Special Interest (AESI) are determined in likely affected countries and regions	**1-5**
Establish a network of clinical sites is available for post-approval safety studies and studies to monitor vaccine effectiveness in different setting/regions	**2-5**
Strategic Goal 3 Harmonize Clinical Trial and Observational Studies Protocols	**Year**
Milestones	
Reach a consensus on the fundamental aspects of the methodology for both interventional and non-interventional clinical studies aimed at assessing their efficacy and effectiveness. This includes establishing uniform endpoints, precise case definitions, and robust statistical methodologies.	**2-5**

6. DIAGNOSTIC: MULTIPLEXED AND AFFORDABLE ASSAYS FOR DETECTION AND DIFFERENTIAL DIAGNOSTICS OF ORTHOFLAVIVIRUS INFECTIONS

Accurate, precise, accessible, and timely diagnostics are a foundational MCM essential for clinical management, identification of outbreaks and monitoring of epidemiological sceneries, and the evaluation of other countermeasures like vaccines and therapeutics. The diagnostic landscape for Orthoflaviviruses is uniquely challenged by antigenic cross-reactivity, co-circulation of multiple pathogens, and the short viremic window for molecular detection. These scientific hurdles are compounded by operational barriers of fragmented infrastructure, inequitable access, and complex regulatory pathways. Advancing diagnostic capabilities is therefore a critical cross-cutting priority to enable effective public health response, guide therapeutic intervention, and ensure the accurate monitoring of vaccine impact in endemic regions. Without accurate differentiation, surveillance is noisy, trials enroll the wrong patients, and vaccine impact becomes hard to measure.

6.1. Primary challenges

The complexity of differential diagnosis due to nonspecific presentation and extensive cross-reactivity. Orthoflavivirus infections are present as acute febrile illnesses indistinguishable from many other pathogens. Serological diagnosis is severely complicated by cross-reactive antibodies, especially in areas with multiple circulating Orthoflaviviruses, and by the phenomenon of "original antigenic sin." This leads to misdiagnosis, undermines surveillance accuracy, and complicates clinical trial enrollment and endpoint assessment. Furthermore, existing assays cannot reliably distinguish between natural infection and vaccine-induced immune responses, a gap that will widen with increased vaccine deployment.

The limited diagnostic window and performance of existing platforms. Molecular assays (RT-PCR), while sensitive and specific, are only useful during a brief viremic phase and are often inaccessible in resource-limited settings. Rapid point-of-care tests frequently suffer from inadequate sensitivity and specificity.

Inadequate and inequitable public health laboratory infrastructure. Effective diagnosis hinges on robust laboratory networks, which are often absent or fragmented in endemic regions. Limitations in specimen transport, cold chain, technical expertise, and data connectivity create major operational bottlenecks, hindering early detection, outbreak response, and the generation of standardized performance data needed for regulatory approval.

A fragmented and unsustainable development pathway for new diagnostics. The development of improved assays is hampered by a lack of well-characterized specimen panels for validation, inconsistent market incentives outside of outbreaks, and poor coordination between developers, researchers, and endemic country regulators. This results in a scarcity of optimal tests tailored to the needs of frontline health systems.

Heterogeneous and slow regulatory processes impede timely access. Regulatory requirements for diagnostics vary widely between countries and between epidemic and inter-epidemic periods. The slow adoption of reliance mechanisms and collaborative review pathways delays the availability of WHO-prequalified or stringently approved tests in areas where they are most urgently needed.

6.2 Knowledge gaps

Novel diagnostic targets. Despite numerous decades of research, diagnostic platforms capable of consistently addressing these questions in the hands of frontline health workers in resource-limited settings remain inadequate. The scientific gap is not solely technical but also fundamentally conceptual: antigenic targets that are sufficiently conserved within serotypes to enable detection while being sufficiently divergent between viruses to facilitate discrimination have not been fully identified and rigorously validated.

Cross-reactivity and diagnostic specificity. The diagnostic challenges presented by Orthoflaviviruses are rooted in the principles of virology and immunology: these viruses exhibit considerable structural homology such that antibodies generated against one strain frequently recognize other strains, leading to a complex network of cross-reactivity that complicates serological diagnosis. In regions where various Orthoflavivirus strains co-circulate, and populations possess intricate backgrounds of infection and vaccination; the interpretation of positive antibody tests becomes exceedingly challenging. Does a positive result indicate current infection with DENV, a previous infection with ZIKV, or YF live vaccine-induced immunity? The clinical and public health ramifications of this uncertainty are significant: misdiagnosis can result in improper clinical management, skewed surveillance data, and inaccurate assessments of vaccine efficacy.

Extending the diagnostic window. For molecular diagnostics, the challenge is distinct but equally fundamental: the brief window of viremia means that a negative PCR result does not rule out Orthoflavivirus infection. However, there is a lack of validated biomarkers of the host response that could extend the diagnostic window. What unique antigenic or biomolecular signatures—including host response biomarkers—can be leveraged to create highly specific diagnostic assays for differentiating between Orthoflavivirus infections and between natural infection and vaccine response is a question that requires systematic investigation.

Specimen panels for validation: The advancement of enhanced diagnostics is significantly constrained by the lack of well-characterized specimen panels that represent the full spectrum of Orthoflavivirus diversity—including different viruses, serotypes, genotypes, geographic variants, and time points post-infection—that are crucial for rigorous assay validation. Such panels require a coordinated international effort and regulation on consent requirements for use to effectively assemble, characterize, and make available to developers, but the necessary infrastructure and governance frameworks are currently not in place.

Regulatory and market barriers: Even when enhanced tests are developed, regulatory and market barriers significantly delay their availability in regions of greatest need, perpetuating a cycle where those most affected continue to have access to the poorest tools. What are the most effective models for sustainable financing and market shaping to ensure continuous diagnostic research and development as well as availability for outbreak-prone diseases with fluctuating incidence, and how can diagnostic data be seamlessly integrated with genomic, entomological, and clinical surveillance systems to create real-time early warning platforms? These remain unanswered questions that require coordinated global action.

6.3. Key needs

- Identification and validation of novel non-cross-reactive epitopes for serotype-specific and species-specific diagnostics.
- Advancement of highly sensitive and specific molecular and serological multiplex assays for accurately differentiating between co-circulating Orthoflaviviruses and their respective serotypes and genotypes, and for effectively distinguishing clinically significant infections from cross-reactive background responses or vaccine-induced immunity.
- Definition of key performance characteristics for multiplexed assays and Point-of-Care (POC) diagnostics to overcome extensive antibody cross-reactivity ("Antigenic Sin") and facilitate regulation.
- Advancement of cost-effective and highly sensitive and specific point-of-care (POC) platforms, which offer rapid, streamlined workflows with minimal technological requirements, to broaden the accessibility of precise diagnostic testing beyond reference laboratories. This initiative is particularly critical in endemic regions, as well as in settings with limited resources and during public health outbreaks.
- Strengthening of international laboratory networks, biorepositories and standardized specimen panels - linked to comprehensive clinical data- and guidance on managing appropriate consent for future use in

diagnostic testing is pivotal to validating tests, support multi-country evaluation networks, and accelerate regulatory approval through reliance/convergence mechanisms.

- Encouragement of extensive research to systematically identify and evaluate optimal models for diagnostic network enhancement in resource-limited settings.
- Promotion of regulatory convergence, reliance mechanisms, and collaborative multi-country evaluations to accelerate diagnostic approval and rollout.
- Implementation of integrated data systems that connect diagnostic results with genomic, clinical, and surveillance data for real-time public health intelligence.
- Exploration of innovative financing strategies to ensure diagnostic R&D and to secure availability for outbreak-prone diseases.

6.4. Strategic goals and milestones

Strategic Goal 1 Establish standardized frameworks for Global Diagnostic Evaluation and Regulatory Approval	**Year**
Milestones	
Define key performance characteristics for multiplexed assays and ensure engagement of regulators in defining the regulatory strategy	**1-5**
Review and update WHO TPPs and conduct a landscape analysis of commercially available tests for clinical diagnosis	**1**
Set up multi-country networks for joint evaluation of IVDs and establish a regulatory reliance or convergence mechanism for emergencies	**2**
Obtain regulatory approval of IVDs based on data from joint evaluations and collaborative review	**3**
Strategic Goal 2 Build Sustainable Infrastructure and Resources for Diagnostic Validation	**Year**
Milestones	
Elaborate on the strategic framework and specific criteria for the systematic collection of samples and biobanking, specifically outlining the types of specimens to be meticulously gathered and archived	**1-5**
Develop comprehensive regional laboratory networks for the purpose of enhancing biobanking and sharing of specimens, as well as establishing standardized protocols for the evaluation of diagnostic assays	**2**
Secure sustainable funding mechanisms available for laboratory capacity building, diagnostics R&D, evaluation, and implementation	**3**
Strategic Goal 3 Promote Integrated Clinical Research and Data Synergy	**Year**
Milestones	
Integrate in vitro diagnostic (IVD) development and validation efforts with therapeutic and vaccine clinical trials/studies wherever feasible	**1-5**
Develop novel biomarkers or immune signatures for the early identification of individuals who are at risk of advancing to severe dengue, maternal Zika infection, and congenital Zika syndrome	**2**

7. THERAPEUTICS THAT COMBINE DIRECT-ACTING ANTIVIRALS + HOST-TARGETING APPROACHES, ENABLED BY BETTER MODELS AND "STANDING" TRIAL INFRASTRUCTURE

The development of effective therapeutics remains the most critical unmet need within the Orthoflavivirus MCM portfolio. While supportive care via fluid and case management is the current standard to reduce severity, iatrogenia, and mortality, there are no approved antiviral or immunomodulatory treatments specifically for dengue, Zika, or other Orthoflavivirus-associated diseases. This gap is particularly acute for severe disease, which is driven by a complex, biphasic pathogenesis: an initial viral replication phase followed by a potentially lethal immunopathological phase. The successful development of effective therapies must navigate a narrow therapeutic window, integrated strategies (direct-acting antivirals and host-targeting agents), and the challenges of conducting clinical trials for outbreak-prone diseases. Research in therapeutics must also focus on deriving clinical dosing schedules from preclinical pharmacokinetics (PK) to address the limited time between peak viremia and immunopathology onset. Filling this therapeutic void is essential to reduce mortality, alleviate healthcare burden, and complement vaccine and diagnostic strategies.

7.1. Primary challenges

The narrow therapeutic window for direct-acting antivirals (DAAs). Viral replication peaks early in the course of infection, often occurring prior to clinical presentation. This situation results in a very narrow timeframe (typically <5 days post-symptom onset) for antiviral intervention to exert a significant impact on clinical outcomes. Such circumstances pose challenges to trial design and may constrain the standalone efficacy of direct-acting antivirals (DAAs), thereby necessitating their combination with agents that target later stages of the disease.

The complex biphasic pathogenesis requires distinct therapeutic strategies. Effective treatment must address both the initial viremic phase and the subsequent immunopathological phase responsible for severe disease (e.g., plasma leakage in dengue). This complexity demands combination therapies (DAA + host-targeting agent) or multi-mechanism drugs, vastly complicating preclinical modeling, clinical trial design, and regulatory pathways.

The lack of predictive animal models for severe disease. Preclinical development is hindered by the absence of animal models that fully recapitulate the severe immunopathology seen in humans. This makes it difficult to evaluate candidate therapeutics for efficacy against the most clinically relevant endpoints, increasing the risk of failure in costly human trials.

Extreme challenges in clinical trial design and feasibility. Conducting traditional efficacy trials is profoundly difficult due to the unpredictable, episodic nature of outbreaks, the short therapeutic window, and the need for rapid patient enrollment and intervention. For Orthoflaviviruses with low incidence, such as ZIKV, the feasibility of conducting clinical trials is significantly restricted. These hurdles deter investment and slow progress.

Insufficient commercial investment and fragile R&D pipelines. The perceived market limitations for outbreak-prone diseases affecting primarily low- and middle-income countries, combined with high developmental risks, have led to strategic withdrawals by large pharmaceutical companies. This underscores the necessity for sustained public and philanthropic funding and global coordination to advance candidates.

7.2. Knowledge gaps

Narrow therapeutic window. The absence of any approved antiviral therapy for Orthoflavivirus infections represents one of the most glaring gaps in the global medical countermeasure portfolio - a gap that becomes more striking when contrasted with the remarkable success in developing therapeutics for other viral diseases. The narrow therapeutic window for direct-acting antivirals is perhaps the most daunting challenge: viral replication peaks very early in infection, often before patients seek care, meaning that even a highly effective

antiviral may have limited clinical impact if administered after this window has closed.

Biphasic pathogenesis and combination therapy. This challenge is compounded by the biphasic nature of severe Orthoflavivirus disease, where the initial viral replication phase is followed by an immunopathological phase characterized by cytokine storm, vascular leakage, and shock that can progress even after virus has been cleared. Effective treatment may therefore require combination approaches—a direct-acting antiviral to reduce the initial viral load, coupled with an immunomodulator to dampen the pathogenic host response—but developing and testing such combinations adds layers of complexity to an already difficult enterprise. What combination of a direct-acting antiviral and a host-targeting agent can effectively treat Orthoflavivirus infection by addressing both early viremia and late-stage immunopathology, and what are the optimal timing, dosing, and duration for such combination regimens, remains unknown. Further, viral factors, such as NS1, which induces endothelial permeability, vascular leak, and virus dissemination in multiple Orthoflaviviruses (e.g., DENV, ZIKV, WNV, YFV) dengue), can be targeted to reduce severe disease manifestations.

Predictive preclinical models: The preclinical models used to evaluate candidates have uncertain predictive value, as many do not recapitulate the severe disease phenotypes seen in humans. A compound that reduces viral load in a mouse model may have no impact on vascular leakage in a patient, and validated biomarkers that could bridge this gap are lacking. Which preclinical models and biomarkers can reliably predict the efficacy of therapeutic candidates against severe Orthoflavivirus disease outcomes in humans require systematic investigation?

Clinical trial feasibility. Clinical trial design for Orthoflavivirus therapeutics confronts extraordinary challenges: outbreaks are unpredictable, the enrollment window is narrow, and sample size requirements for endpoints like severe disease are large. How robust clinical trials for Orthoflavivirus therapeutics can be feasibly conducted given these challenges, and what trial designs are most appropriate for different scenarios, has not been established.

Sustainable development models. These hurdles have proven insurmountable for the traditional pharmaceutical development model, which relies on predictable markets and clear regulatory pathways. What sustainable R&D and financing models can ensure the progression of promising therapeutic candidates through the "valley of death" between discovery and clinical proof-of-concept, and how real-time genomic surveillance and pharmacovigilance can be integrated to monitor for the emergence of antiviral resistance, requires innovative approaches to public-private partnership and global coordination.

7.3. Key needs

- Establishment of robust high-throughput screening platforms for DAA and HTA discovery, including the utilization of repurposing libraries. This approach aims to enhance the advancement of combination therapeutic strategies that specifically target both viral replication, viral factors, and immunopathology.
- Formulation and development of Pan-Antivirals (targeting conserved viral proteins) and Host-Targeted Therapies (HTAs), as no approved treatments currently exist.
- Advancement and validation of enhanced preclinical models that more accurately reflect human severe disease. This involves the development and qualification of animal models that effectively recapitulate severe dengue characterized by vascular leakage, Zika associated with congenital syndrome, and West Nile virus leading to neuroinvasive disease. Innovations in trials - such as adaptive/master protocol trials and trial-ready clinical networks in endemic regions, potentially complemented, where ethical and ap propriate, by CHIMs to speed proof-of-concept.
- Creation of sustainable, globally coordinated R&D consortia with harmonized protocols and shared resources to de-risk development.

- Establishment of standing clinical trial networks in endemic regions with master protocols for rapid activation during outbreaks.
- Development of accurate Orthoflavivirus models to optimize dosing regimens for the narrow therapeutic window.
- Implementation of integrated pharmacovigilance and genomic surveillance to monitor treatment efficacy and potential drug resistance.
- Incentive of public-private partnerships to sustain the therapeutic development pipeline.

7.4. Strategic goals and milestones

Strategic Goal 1 Define Target Product Profiles and Accelerate Candidate Pipeline	**Year**
Milestones	
Contribute to finalization of TPP for antivirals and host-directed therapies	**2**
Establish a regulatory-aligned framework for the 'rolling review' of combination Direct-Acting Antivirals (DAAs) and Host-Targeting Agents (HTAs) to address the lack of existing therapeutic benchmarks	**2**
Engage with developers of antivirals and host-directed therapies to build a coordinated pipeline	**1-5**
Encourage data sharing and real-time collaboration platforms between public health authorities of different countries to globalize genomic surveillance data and monitor potential emergence of drug resistance	**3**
Strategic Goal 2 Advance Preclinical Models and Evaluation Platforms	**Year**
Milestones	
Advance *in vitro* and *in vivo* models for evaluation of new antivirals and host-directed therapies	**2-3**
Standardize and optimize the most relevant animal models and reference virus strains that adequately recapitulate the different Orthoflavivirus disease endpoints	**3**
Agree on the core elements of the design of randomized clinical efficacy and safety trials through international consensus	**1-5**
Consider the role of CHIMs for advancing antiviral candidates	**1-5**
Harmonize trials design and readouts within the CORC; share expertise, protocols, biological/viral reagents, and in vitro/in vivo models	**2**
Strategic Goal 3 Ensure Sustainability	**Year**
Milestones	
Implement a funding strategy for the sustainability of the consortium including key public-private partnerships and diversified funding sources	**2**

8. COMPLIANCE AND REGULATION

Robust and agile regulatory pathways are the critical bridge that transforms scientific discovery into accessible MCMs. For Orthoflaviviruses, this process is fraught with unique challenges, including the lack of validated correlates of protection, the risk of antibody-dependent enhancement (ADE), and the episodic nature of outbreaks that complicate traditional clinical trials. A fragmented global regulatory landscape, coupled with a near-total absence of approved therapeutics, further delays the availability of tools in regions where the burden is greatest. Harmonizing regulatory approaches, validating novel trial methodologies, and fostering international collaboration are therefore cross-cutting imperatives to ensure equitable and timely access to vaccines, diagnostics, and treatments.

8.1. Primary challenges

The absence of correlates of protection and the risk of ADE complicate vaccine development. For key viruses like dengue, the lack of validated immunological markers to predict clinical protection necessitates long and costly efficacy trials. This challenge is magnified by the risk of ADE, which demands extensive safety monitoring and creates unique hurdles for vaccine design and regulatory approval.

The infeasibility of traditional clinical trial designs during inter-epidemic periods. The unpredictable and sporadic nature of Orthoflavivirus outbreaks makes conducting conventional large-scale, placebo-controlled efficacy trials logistically difficult and ethically problematic during periods of low transmission, stalling the development pipeline for both vaccines and therapeutics.

A fragmented global regulatory environment creates gaps and delays. Divergent regulatory requirements and review processes across countries and regions lead to duplication of efforts, increased costs, and delayed access for endemic countries, undermining global equity in MCM availability.

A critical deficit of robust preclinical models and translational tools. The limited use and regulatory acceptance of standardized animal models and Controlled Human Infection Models (CHIMs) for Orthoflaviviruses restricts the ability to generate early, high-quality efficacy data, increasing the risk and cost of subsequent clinical development phases.

Therapeutic and diagnostic development is hindered by a lack of infrastructure. The complete absence of approved antivirals and host direct drugs reflects a major R&D gap. Development is slowed by inadequate biobanking networks, a lack of standardized clinical specimens for assay validation, and the technical difficulty of creating multiplex diagnostics that can differentiate between Orthoflaviviruses in co-circulation settings.

8.2. Knowledge gaps

Alternative clinical trial designs. The episodic nature of Orthoflavivirus outbreaks means that traditional trial designs, which require enrolling thousands of participants and following them until sufficient cases accumulate, can take years or decades to complete, if they can be completed at all. How alternative clinical development pathways—including controlled human infection models, adaptive trial designs, ring vaccination, and immunobridging—can be rigorously validated and gain global regulatory acceptance for flaviviruses remains an open question that requires urgent attention.

Correlates of protection for regulatory pathways. The pathway from promising candidate to licensed medical countermeasure is particularly tortuous for Orthoflavivirus products, reflecting a series of interconnected scientific and regulatory challenges for which solutions remain elusive. At the heart of the problem lies the absence of validated correlates

of protection for most Orthoflavivirus diseases. For vaccines against Orthoflaviviruses-associated human diseases such as severe dengue, immunological benchmarks that can predict clinical efficacy with sufficient confidence to support accelerated approval pathways have not been established. This requires relying on large-scale, long-term efficacy trials with clinical evaluation criteria that are truly effective for infectious diseases with unpredictable and sporadic incidence.

ADE safety assessment. This regulatory and clinical development challenge is compounded by the unique safety concerns posed by antibody-dependent enhancement, which necessitates not only demonstration of efficacy but also extensive safety monitoring to rule out the risk of enhanced disease in vaccinees who subsequently become infected. What constitutes sufficient evidence to rule out ADE risk, and what duration and scale of follow-up is needed, has not been definitively established.

Regulatory fragmentation and equity. Across all MCM types, the fragmentation of regulatory requirements across different countries and regions creates inefficiencies that disproportionately affect LMICs, where the burden of Orthoflavivirus disease is highest but regulatory capacity is often most limited. How regulatory processes can be streamlined across endemic and non-endemic countries to ensure rapid, equitable access to new MCMs without compromising safety or efficacy standards remains an unresolved policy and operational challenge.

Infrastructure for MCM evaluation. For therapeutics, the situation is even more challenging, as the narrow window for antiviral intervention and the biphasic nature of severe disease create complexities in trial design and endpoint selection that have no established solutions. The lack of standardized preclinical models, well-characterized specimen panels, and global biobanking networks further hinders the development and validation of both therapeutics and diagnostics.

8.3. Key needs

- Establishment of internationally accepted correlates of protection and safety for Orthoflavivirus vaccines.
- Conduction of regulatory science research on CHIM validation and acceptance.
- Definition of regulatory pathways that utilize alternative data streams and animal models, especially when traditional efficacy trials are infeasible (e.g., for low-incidence viruses).
- Development and evaluation of reliance mechanisms, as well as regulatory convergence and harmonization across regions to facilitate joint regulatory reviews, to establish criteria and to expedite global approval of MCMs, while incorporating the core elements for the design of both interventional and non-interventional clinical studies.
- Qualification of standardized preclinical models and translational science for therapeutics.
- Establishment of global specimen biorepositories and reference standards to accelerate diagnostic and therapeutic development.
- Creation of international consortia to standardize and validate immune assays for correlates of protection, including induced by vaccination.
- Organization of virtual biorepositories with standardized collection protocols and linked clinical metadata.
- Development of master protocols for adaptive trial designs acceptable to multiple regulators globally.
- Reinforcement of initiatives of coaching for regulatory scientists in emerging economies on flavivirus-specific product evaluation.
- Development of emergency use authorization frameworks harmonized across regions.

8.4. Strategic goals and milestones

Strategic Goal 1 Ensure Regulatory Alignment and Preparedness	**Year**
Milestones	
Promote regulatory convergence (e.g., reliance, joint reviews, harmonization mechanisms) to facilitate rapid authorization and approval globally	**1-5**
Strengthening regulatory capacity across nations through training programs, twinning arrangements, and improved emergency preparedness frameworks	**1-5**
Map regulatory capacity in flavivirus endemic countries to identify needs and targets for investment	**1**
Define regulatory pathways for different scenarios (including use of CHIMs, animal models, and emergency use authorization) with clear criteria for each pathway	**1-5**
Strategic Goal 2 Establish infrastructure for regulatory science and MCM evaluation	**Year**
Milestones	
Develop regional laboratory networks for biobanking and sharing well-characterized specimens with associated clinical data	**2**
Clarify strategy for samples collection and biobanking, including the types of specimens to be collected and archived, standardized protocols and governance frameworks	**1-5**
Secure sustainable funding mechanisms available for laboratory capacity building, diagnostics R&D, evaluation, and implementation	**2**

Acknowledgements

We sincerely recognize Dr. Ana Maria Henao Restrepo and the WHO R&D Blueprint for Epidemics as well as the Oswaldo Cruz Foundation (Fiocruz) team for their collaborative partnership and support throughout this significant journey. We also extend our gratitude for the crucial contributions made by all experts who participated in the thematic consultations held in June and July 2025, including the 13 speakers and 13 panelists, who generously shared their knowledge and insights with us. We are particularly appreciative of Dr. Jairo Mendez Rico, regional advisor for Viral Diseases at PAHO and WHO, for summarizing all the scientific sessions. Lastly, we wish to express our gratitude to our CORC team, in particular to the Scientific Coordinators of thematic areas, and the Core Group, for their indispensable contributions and unwavering support for this initiative.

Flaviviridae CORC Team

Coordinator		
Name	Institution	Country
Maria de Lourdes A. Oliveira	Oswaldo Cruz Foundation	Brazil
Technical Advisory Team (Fiocruz)		
Name	Institution	Country
Aline Matos	Oswaldo Cruz Foundation	Brazil
Ana Maria Bispo	Oswaldo Cruz Foundation	Brazil
Flavia Barreto	Oswaldo Cruz Foundation	Brazil
Gabriel da Luz Wallau	Oswaldo Cruz Foundation	Brazil
Patrícia Bozza	Oswaldo Cruz Foundation	Brazil
Ricardo Khouri	Oswaldo Cruz Foundation	Brazil
Thiago Moreno	Oswaldo Cruz Foundation	Brazil
Tulio Campos	Oswaldo Cruz Foundation	Brazil
Valdileia Veloso dos Santos	Oswaldo Cruz Foundation	Brazil
Viviane Boaventura	Oswaldo Cruz Foundation	Brazil
Operational Team (Fiocruz)		
Name	Institution	Country
Carlos Ripardo	Oswaldo Cruz Foundation	Brazil
Cristiane Boar	Oswaldo Cruz Foundation	Brazil
Fernando Conte	Oswaldo Cruz Foundation	Brazil
Leandro Amparo	Oswaldo Cruz Foundation	Brazil
Luiza Silva	Oswaldo Cruz Foundation	Brazil
Natalia Pacheco	Oswaldo Cruz Foundation	Brazil
Paola Hushi Lopes	Oswaldo Cruz Foundation	Brazil
Paula Reges	Oswaldo Cruz Foundation	Brazil

Thematic Coordinators		
Name	Institution	Country
Alex Pauvolid-Corrêa	Federal University of Viçosa	Brazil
Andre Siqueira	Oswaldo Cruz Foundation	Brazil
Anna-Bella Failloux	Pasteur Institute	France
Claudia ND Santos	Oswaldo Cruz Foundation	Brazil
Elzinandes Azeredo	Oswaldo Cruz Foundation	Brazil
Ethel Maciel	Brazilian Ministry of Health	Brazil
Eva Harris	University of California, Berkeley	United States of America
Felix Drexler	Charité University	Germany
Flavia Barreto	Oswaldo Cruz Foundation	Brazil
Gabriel da Luz Wallau	Oswaldo Cruz Foundation	Brazil
Laurent Chatel-Chaix	Institute National de la Recherche Scientifique	France
Luiz Augusto Galvão	Oswaldo Cruz Foundation	Brazil
Manoel Barral-Netto	Oswaldo Cruz Foundation	Brazil
Marcelo Moreira	National Health Surveillance Agency	Brazil
Marco Cavaleri	European Medicines Agency	International Organization
Mariane Branco	Federal University of Rio de Janeiro	Brazil
Marta Giovanetti	Campus Bio-Medico University	Italy
Maurício Barreto	Oswaldo Cruz Foundation	Brazil
Neelika Malavige	University of Sri Jayewardenepura	Sri Lanka
Patrícia Alvarez	Oswaldo Cruz Foundation	Brazil
Patricia Bozza	Oswaldo Cruz Foundation	Brazil
Philippe Desprès	University La Réunion	France
Rafael Freitas	Oswaldo Cruz Foundation	Brazil
Rosanna Peeling	London School of Hygiene and Tropical Medicine	United Kingdom
Sergio Sosa-Estani	Drugs for Neglected Diseases initiative	International Organization
Sotiris Missailidis	Pasteur Institute	France
Thiago Moreno	Oswaldo Cruz Foundation	Brazil

The Core Group		
Name	Institution	Country
Andre Siqueira	Oswaldo Cruz Foundation	Brazil
Chang-Kweng Lim	National Institute of Infectious Diseases	Japan
Claudia ND Santos	Oswaldo Cruz Foundation	Brazil
Cristina Domingo Carrasco	Robert Koch Institute	Germany
Elvis Temfack	Africa CDC	Ethiopia
Eva Harris	University of California, Berkeley	United States of America
Felipe Naveca	Oswaldo Cruz Foundation	Brazil
Felix Drexler	Berlin University	Germany
Gabriel da Luz Wallau	Oswaldo Cruz Foundation	Brazil
Gamou Fall	Pasteur Institute Dakar	Senegal
Janine Boniatti	Oswaldo Cruz Foundation	Brazil
Luiz Antonio Camacho	Oswaldo Cruz Foundation	Brazil
Luiz Augusto Galvão	Oswaldo Cruz Foundation	Brazil
María Alejandra Morales	Instituto Nacional de Enfermedades Virales Humanas Dr Julio Maiztegui	Argentina
María Guzman	Pedro Kouri Tropical Medicine Institute	Cuba
Miguel Martinez	University of Barcelona	Spain
Patricia Bozza	Oswaldo Cruz Foundation	Brazil
Philippe Desprès	University La Réunion	France
Rafael Freitas	Oswaldo Cruz Foundation	Brazil
Rebecca Grais	Pasteur Institute	France
Ricardo de Godoi Ferreira	Oswaldo Cruz Foundation	Brazil
Sandra López Vergès	Gorgas Memorial Research Institute for Health Studies	Panama
Sonia Pagliusi	Geneva University	Switzerland
Sotiris Missailidis	Pasteur Institute	France

References

Abbasi E. Arboviral Diseases in a Changing World: Evolutionary Dynamics, Host–Vector Interactions, and Novel Control Strategies. https://home.liebertpub.com/vbz. 2025 Sep 16. doi:10.1177/15303667251376450 PubMed PMID: 40955762.

Ackermann-Gäumann R, Lang P, Zens KD. Defining the "Correlate(s) of Protection" to tick-borne encephalitis vaccination and infection – key points and outstanding questions. Front Immunol. 2024 Jan 22;15:1352720. doi:10.3389/fimmu.2024.1352720 PubMed PMID: 38318179.

Ali S, Khan AW, Taylor-Robinson AW, Adnan M, Malik S, Gul S. The unprecedented magnitude of the 2017 dengue outbreak in Sri Lanka provides lessons for future mosquito-borne infection control and prevention. Infect Dis Health. 2018 Jun 1;23(2):114–20. doi:10.1016/j.idh.2018.02.004 PubMed PMID: 38715304.

Bettis AA, L'Azou Jackson M, Yoon IK, Breugelmans JG, Goios A, Gubler DJ, et al. The global epidemiology of chikungunya from 1999 to 2020: A systematic literature review to inform the development and introduction of vaccines. PLoS Negl Trop Dis. 2022 Jan 1;16(1). doi:10.1371/JOURNAL.PNTD.0010069 PubMed PMID: 35020717.

Bifani AM, Chan KWK, Borrenberghs D, Tan MJA, Phoo WW, Watanabe S, et al. Therapeutics for flaviviral infections. Antiviral Res. 2023 Feb 1;210:105517. doi:10.1016/j.antiviral.2022.105517 PubMed PMID: 36592668.

Bournazos S, Gupta A, Ravetch J V. The role of IgG Fc receptors in antibody-dependent enhancement. Nat Rev Immunol. 2020 Oct 1;20(10):633–43. doi:10.1038/s41577-020-00410-0 PubMed PMID: 32782358.

Cardona-Ospina JA, Henao-SanMartin V, Acevedo-Mendoza WF, Nasner-Posso KM, Martínez-Pulgarín DF, Restrepo-López A, et al. Fatal Zika virus infection in the Americas: A systematic review. International Journal of Infectious Diseases. 2019 Nov 1;88:49–59. doi:10.1016/j.ijid.2019.08.033 PubMed PMID: 31499212.

Cardona-Ospina JA, Roy V, Marcano-Jiménez DE, Bos S, Duarte E, Zambrana J V., et al. IgA-driven neutrophil activation underlies post-Zika severe dengue disease in humans. medRxiv. 2025 Feb 18. doi:10.1101/2025.02.11.25322002 PubMed PMID: 40162272.

Cardona-Ospina JA, Roy V, Marcano-Jiménez DE, Bos S, Duarte E, Zambrana J V., et al. IgA-driven neutrophil activation underlies severe dengue disease after primary Zika virus infection in humans. Nature Immunology 2026 27:1. 2026 Jan 2;27(1):126–34. doi:10.1038/s41590-025-02363-9 PubMed PMID: 41482554.

Carver S, Bestall A, Jardine A, Ostfeld RS. Influence of hosts on the ecology of arboviral transmission: potential mechanisms influencing dengue, Murray Valley encephalitis, and Ross River virus in Australia. Vector Borne Zoonotic Dis. 2009 Feb 1;9(1):51–64. doi:10.1089/vbz.2008.0040 PubMed PMID: 18800866.

Cavaleri M, de Sousa CMA, Hacker A, Higgs ES, Lumpkin MM, Maia CS, et al. A roadmap for fostering timely regulatory and ethics approvals of international clinical trials in support of global health research systems. Lancet Glob Health. 2025 Apr 1;13(4):e769–77. doi:10.1016/S2214-109X(24)00515-1 PubMed PMID: 40155114.

Cella E, Cunha M V., Alcantara LCJ, Lourenço J, Giovanetti M. Strengthening arbovirus surveillance: bridging gaps for global health preparedness. Trends Microbiol. 2025 Nov 1;33(11):1185–95. doi:10.1016/j.tim.2025.03.010 PubMed PMID: 40280792.

Costa LB, Barreto FK de A, Barreto MCA, Santos THP dos, Andrade M de MO de, Farias LABG, et al. Epidemiology and Economic Burden of Chikungunya: A Systematic Literature Review. Tropical Medicine and Infectious Disease 2023, Vol 8,. 2023 May 30;8(6). doi:10.3390/tropicalmed8060301 PubMed PMID: 37368719.

da Silva LMI, Maciel-de-Freitas R, Paiva MHS, da Luz Wallau G. Horizons of the Future: Preparedness and Response. Curr Top Microbiol Immunol. 2025;447:363–87. doi:10.1007/82_2025_292 PubMed PMID: 40392280.

de Almeida MT, Merighi DGS, Visnardi AB, Boneto Gonçalves CA, Amorim VM de F, Ferrari AS de A, et al. Latin America's Dengue Outbreak Poses a Global Health Threat. Viruses. 2025 Jan 1;17(1). doi:10.3390/v17010057 PubMed PMID: 39861846.

Dengue: global situation, surveillance and progress – 2024 update [Internet]. [cited 2026 Mar 19]. Available from: https://www.who.int/publications/i/item/who-wer10052-665-678

Dias B de P, Barbosa CC, Ferreira CS, Mayra Soares Alves dos Santos S, Arrieta OAP, Malta WC, et al. Challenges in Direct Detection of Flaviviruses: A Review. Pathogens. 2023 May 1;12(5):643. doi:10.3390/pathogens12050643 PubMed PMID: 37242313.

Ferraguti M, Magallanes S, Mora-Rubio C, Bravo-Barriga D, Marzal A, Hernandez-Caballero I, et al. Implications of migratory and exotic birds and the mosquito community on West Nile virus transmission. Infect Dis. 2024;56(3):206–19. doi:10.1080/23744235.2023.2288614 PubMed PMID: 38160682.

Franklinos LHV, Jones KE, Redding DW, Abubakar I. The effect of global change on mosquito-borne disease. Lancet Infect Dis. 2019 Sep 1;19(9):e302–12. doi:10.1016/S1473-3099(19)30161-6 PubMed PMID: 31227327.

Gomes da Silva P, Seixas dos Reis JA, Nogueira Rodrigues M, da Silva Ardaya Q, Mesquita JR. Serological Cross-Reactivity in Zoonotic Flaviviral Infections of Medical Importance. Antibodies (Basel). 2023 Mar 1;12(1). doi:10.3390/antib12010018 PubMed PMID: 36975365.

Gularte JS, Strottmann DM, Spilki FR, Zanluca C. Diagnostic Techniques for Dengue Virus. Curr Top Microbiol Immunol. 2026;447:179–225. doi:10.1007/82_2025_307 PubMed PMID: 40495084.

Guthid S, Hanley KA, Althouse BM, Boots M. Ecological processes underlying the emergence of novel enzootic cycles: Arboviruses in the neotropics as a case study. PLoS Negl Trop Dis. 2020 Aug 1;14(8):e0008338. doi:10.1371/journal.pntd.0008338 PubMed PMID: 32790670.

Katzelnick LC, Gresh L, Halloran ME, Mercado JC, Kuan G, Gordon A, et al. Antibody-dependent enhancement of severe dengue disease in humans. Science. 2017 Nov 17;358(6365):929–32. doi:10.1126/science.aan6836 PubMed PMID: 29097492.

Kaur J, Butt ZA. AI-driven epidemic intelligence: the future of outbreak detection and response. Front Artif Intell. 2025 Jul 30;8:1645467. doi:10.3389/frai.2025.1645467

Kim YC, Reyes-Sandoval A. Recent Advances in Vaccine Development for Flaviviruses and Alphaviruses. Vaccines (Basel). 2025 Aug 1;13(8):808. doi:10.3390/vaccines13080808 PubMed PMID: 40872895.

Kuczera D, Assolini JP, Tomiotto-Pellissier F, Pavanelli WR, Silveira GF. Highlights for Dengue Immunopathogenesis: Antibody-Dependent Enhancement, Cytokine Storm, and Beyond. J Interferon Cytokine Res. 2018 Feb 1;38(2):69–80. doi:10.1089/jir.2017.0037 PubMed PMID: 29443656.

Kuhn RJ, Barrett ADT, Desilva AM, Harris E, Kramer LD, Montgomery RR, et al. A Prototype-Pathogen Approach for the Development of Flavivirus Countermeasures. J Infect Dis. 2023 Oct 18;228(Supplement_6):S398–413. doi:10.1093/infdis/jiad193 PubMed PMID: 37849402.

Lackritz EM, Ng LC, Marques ETA, Rabe IB, Bourne N, Staples JE, et al. Zika virus: advancing a priority research agenda for preparedness and response. Lancet Infect Dis. 2025 Jul 1;25(7):e390–401. doi:10.1016/S1473-3099(24)00794-1 PubMed PMID: 40024263.

McCain K, Vicco A, Morgenstern C, Rawson T, Naidoo TM, Bhatia S, et al. A systematic review and meta-analysis of Zika virus epidemiology. Nature Health 2026 1:3. 2026 Feb 13;1(3):355–67. doi:10.1038/s44360-025-00051-4

Moir M, Sitharam N, Hofstra LM, Dor G, Mwanyika G, Ramphal Y, et al. Identifying genomic surveillance gaps in Africa for the global public health response to West Nile virus: a systematic review. Lancet Microbe. 2025 Oct 1;6(10). doi:10.1016/j.lanmic.2025.101176

Mousavi FS, Shenagari M, Reza Hashemnia SM, Zandi M. Climate change and arboviruses_a growing threat to public health. New Microbes New Infect. 2024 Dec 1;62:101532. doi:10.1016/j.nmni.2024.101532 PubMed PMID: 39649021.

Musso D, Ko AI, Baud D. Zika Virus Infection — After the Pandemic. New England Journal of Medicine. 2019 Oct 10;381(15):1444–57. doi:10.1056/nejmra1808246 PubMed PMID: 31597021.

Narayan R, Tripathi S. Intrinsic ADE: The Dark Side of Antibody Dependent Enhancement During Dengue Infection. Front Cell Infect Microbiol. 2020 Oct 2;10:580096. doi:10.3389/fcimb.2020.580096 PubMed PMID: 33123500.

Operational Guide Using the Web-Based Dashboard : Early Warning and Response System (EWARS) for Dengue Outbreaks [Internet]. 2020 [cited 2026 Mar 19]. Available from: https://iomc.info/publications/i/item/operational-guide-using-the-web-based-dashboard-early-warning-and-response-system-(ewars)-for-dengue-outbreaks

Ostrowsky JT, Katzelnick LC, Bourne N, Barrett ADT, Thomas SJ, Diamond MS, et al. Zika virus vaccines and monoclonal antibodies: a priority agenda for research and development. Lancet Infect Dis. 2025 Jul 1;25(7):e402–15. doi:10.1016/S1473-3099(24)00750-3 PubMed PMID: 40024262.

Patiño L, Benítez AD, Carrazco-Montalvo A, Regato-Arrata M. Genomics for Arbovirus Surveillance: Considerations for Routine Use in Public Health Laboratories. Viruses 2024, Vol 16,. 2024 Aug 1;16(8). doi:10.3390/v16081242 PubMed PMID: 39205216.

Paz-Bailey G, Adams LE, Deen J, Anderson KB, Katzelnick LC. Dengue. The Lancet. 2024 Feb 17;403(10427):667–82. doi:10.1016/S0140-6736(23)02576-X PubMed PMID: 38280388.

Pierson TC, Diamond MS. The continued threat of emerging flaviviruses. Nature Microbiology 2020 5:6. 2020 May 4;5(6):796–812. doi:10.1038/s41564-020-0714-0 PubMed PMID: 32367055.

Power GM, Vaughan AM, Qiao L, Clemente NS, Pescarini JM, Paixão ES, et al. Socioeconomic risk markers of arthropod-borne virus (arbovirus) infections: a systematic literature review and meta-analysis. BMJ Glob Health. 2022 Apr 15;7(4). doi:10.1136/bmjgh-2021-007735 PubMed PMID: 35428678.

Salem GM, Galula JU, Wu SR, Liu JH, Chen YH, Wang WH, et al. Antibodies from dengue patients with prior exposure to Japanese encephalitis virus are broadly neutralizing against Zika virus. Communications Biology 2024 7:1. 2024 Jan 24;7(1):15-. doi:10.1038/s42003-023-05661-w PubMed PMID: 38267569.

Sarker A, Dhama N, Gupta RD. Dengue virus neutralizing antibody: a review of targets, cross-reactivity, and antibody-dependent enhancement. Front Immunol. 2023 Jun 2;14:1200195. doi:10.3389/fimmu.2023.1200195 PubMed PMID: 37334355.

Sharma K, Syeda S, Shah SM, Kori SA, Shetty P, Kazi S, et al. Overcoming barriers to medical countermeasures: Strengthening global biosecurity. Hum Vaccin Immunother. 2025;21(1):2483043. doi:10.1080/21645515.2025.2483043 PubMed PMID: 40132079.

Simmonds P, Becher P, Bukh J, Gould EA, Meyers G, Monath T, et al. ICTV Virus Taxonomy Profile: Flaviviridae. J Gen Virol. 2017 Jan 1;98(1):2. doi:10.1099/jgv.0.000672 PubMed PMID: 28218572.

Singh P, Khatib MN, Ballal S, Kaur M, Nathiya D, Sharma S, et al. West Nile Virus in a changing climate: epidemiology, pathology, advances in diagnosis and treatment, vaccine designing and control strategies, emerging public health challenges - a comprehensive review. Emerg Microbes Infect. 2025;14(1). doi:10.1080/22221751.2024.2437244 PubMed PMID: 39614679.

Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, Machabert T, et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. New England Journal of Medicine. 2018 Jul 26;379(4):327–40. doi:10.1056/nejmoa1800820 PubMed PMID: 29897841.

Srivastava S, Jayaswal N, Gupta P, Sridhar SB, Jaiswal P, Tariq Mohd, et al. The Yellow Fever Vaccine Journey: Milestones and Future Directions. Vaccines 2026, Vol 14,. 2026 Jan 4;14(1):65. doi:10.3390/vaccines14010065

Sufi Aiman Sabrina R, Muhammad Azami NA, Yap WB. Dengue and Flavivirus Co-Infections: Challenges in Diagnosis, Treatment, and Disease Management. Int J Mol Sci. 2025 Jul 1;26(14):6609. doi:10.3390/ijms26146609 PubMed PMID: 40724859.

Tornimbene B, Leiva Rioja ZB, Barral-Netto M, Castillo-Salgado C, Djordjevic I, Kraemer M, et al. Data integration and synthesis for pandemic and epidemic intelligence. BMC Proc. 2025 Mar 1;19(Suppl 4):12. doi:10.1186/s12919-025-00321-9 PubMed PMID: 40269901.

Tripathi A, Chauhan S, Khasa R. A Comprehensive Review of the Development and Therapeutic Use of Antivirals in Flavivirus Infection. Viruses 2025, Vol 17,. 2025 Jan 7;17(1). doi:10.3390/v17010074 PubMed PMID: 39861863.

Vasilakis N, Cardosa J, Hanley KA, Holmes EC, Weaver SC. Fever from the forest: prospects for the continued emergence of sylvatic dengue virus and its impact on public health. Nature Reviews Microbiology 2011 9:7. 2011 Jun 13;9(7):532–41. doi:10.1038/nrmicro2595 PubMed PMID: 21666708.

Vatti A, Monsalve DM, Pacheco Y, Chang C, Anaya JM, Gershwin ME. Original antigenic sin: A comprehensive review. J Autoimmun. 2017 Sep 1;83:12–21. doi:10.1016/j.jaut.2017.04.008 PubMed PMID: 28479213.

Wei Y Lou, Wu Z, Li R Le, Tang F. Review of selected mosquito-borne diseases: arboviruses (dengue, chikungunya, Zika, West Nile, Japanese encephalitis, yellow fever) and parasitic diseases (malaria, lymphatic Filariasis). Front Public Health. 2026 Jan 21;13:1712094. doi:10.3389/fpubh.2025.1712094

Wilder-Smith A, Ooi EE, Horstick O, Wills B. Dengue. The Lancet. 2019 Jan 26;393(10169):350–63. doi:10.1016/S0140-6736(18)32560-1 PubMed PMID: 30696575.

World Health Organization. Global vector control response 2017–2030- 2 October 2017. Organización Mundial de la Salud [Internet]. 2017 [cited 2026 Mar 19];57. Available from: https://www.who.int/publications/i/item/9789241512978

Yen PS, Failloux AB. A Review: Wolbachia-Based Population Replacement for Mosquito Control Shares Common Points with Genetically Modified Control Approaches. Pathogens 2020, Vol 9, Page 404. 2020 May 22;9(5):404. doi:10.3390/PATHOGENS9050404 PubMed PMID: 32456036.

Yitbarek S, Chen K, Celestin M, McCary M. Urban mosquito distributions are modulated by socioeconomic status and environmental traits in the USA. Ecol Appl. 2023 Jul 1;33(5). doi:10.1002/eap.2869 PubMed PMID: 37140135.

Annexes

1- CORC Thematic Meeting 1 – Agenda

Agenda for CORC Call
Thematic Meeting #1 Date: 02 June 2025
8:00am– 01:00pm (Brasilia) | 01:00– 06:00pm (CEST) | 04:00am– 9:00am (PDT)

Time (BRT)	Duration (min)	Topic	Speakers
8:00 8:10	10′	Opening remarks	Lourdes Oliveira (Brazil) Ana Maria Restrepo (WHO)
8:20 8:40	20′	**Lecture 1:** *Prototype flaviviruses: a brief review and main challenges and perceptions, under the perspective of PPPR*	**Chair:** Philippe Despres (France)
8:40 9:10	30′	**Panel 1:** Driving questions should include (without being restricted to) • Main drivers of clinical and epidemiological changing patterns • Major public health challenges • Main research gaps and priorities	**Moderator:** Felix Drexler (Germany) **Panelists** • Pedro Vasconcelos (Brazil) • Laura Martin-Sancho (UK) • Cristina Cassetti (USA)
9:20 9:40	20′	**Lecture 2:** *Genetic diversity and viral evolution: evolvability in multiple hosts – reservoirs, vectors and humans*	**Chair:** Nuno Faria (UK)
9:40 10:10	30′	**Panel 2.** Driving questions should include (without being restricted to): • Challenge on selection pressure and immune escape variants • Innovative approaches and tools • Genomic surveillance and data-sharing • Main challenges and recommendations to fulfil R&D gaps	**Moderator:** Josefina Campos (WHO) **Panelists** • Louis Lambrechts (France) • Gabriel Wallau (Brazil) • Marta Giovanetti (Italy) • Gilberto Santiago (USA)
10:10 10:30	20′	**Lecture 3.** *Viral and vaccine-induced immunity*	**Chair:** Leah Katzelnick (USA)
10:30 11:00	30′	**Panel 3** Driving questions should include (without being restricted to): • Cross-protection and potential enhancement between serotypes and FV and implications for vaccine design, diagnostics • Alternative vaccine antigens and design • Antibody dynamics by antigen/epitope • Role of T cells protection and vaccines • Correlates of protection and risk	**Moderator:** Eva Harris (USA) **Panelists** • Neelika Malavige (Sri Lanka) • Pierre Roques (France) • Jose Moreira (Brazil) • Laura Rivino (UK) • Michael Diamond (USA)
11:00 11:20	20′	**Lecture 4.** *Diagnostic and Innovative surveillance approaches*	**Chair:** Rosanna Peeling (UK)
11:20 11:50	30′	**Panel 4** Driving questions should include (without being restricted to): • Challenges and improvements in differential diagnosis • Critical data and information-sharing • Forecasting of surges	**Moderator:** Jairo Mendez (PAHO) **Panelists** • Patricia Sequeira (Brazil) • Bridgette Jeanne Billioux (USA)

		• Main challenges and innovative approaches for PPPR • Standardization of protocols	• Daniele Medeiros (Brazil) • María Guzman (Cuba)
11:50 12:20	20´	**Lecture 5.** *Vectors & Reservoirs*	**Chair:** Rafael Freitas (Brazil)
12:20 12:40	30´	**Panel 5** Driving questions should include (without being restricted to): • Role of entomovirological surveillance • Vector control strategies • Vector resistance • Environmental research and surveillance including the impacts of climate change • Main research gaps and priorities	- **Moderator:** Esther Schnettler (Germany) **Panelists** • Khamsing Vongphayloth (Laos) • Steven Sinkins (UK) • Ary Hoffman (Australia) • Renke Lühken (Germany)
12:40 12:50	10´	Wrap up	Jairo Mendez (PAHO)
12:50 13:00	10´	Closing remarks	Lourdes Oliveira (Brazil) Ana Restrepo (WHO)

Name	Institution	Country
Ana Maria Henao Restrepo	World Health Organization	International Organization
Ary Hoffman	University of Melbourne	Australia
Bridgette Billioux	National Institutes of Health	United States of America
Cristina Cassetti	National Institutes of Health	United States of America
Daniele Medeiros	Evandro Chagas Institute	Brazil
Esther Schnettler	Bernhard Nocht Institute for Tropical Medicine	Germany
Eva Harris	University of California, Berkeley	United States of America
Felix Drexler	Berlin University	Germany
Flavia Barreto	Fiocruz	Brazil
Gabriel Wallau	Fiocruz	Brazil
Gilberto Santiago	Centers for Disease Control and Prevention	United States of America
Jairo Mendez	Pan American Health Organization	International Organization
Jose Moreira	Butantan Institute	Brazil
Josefina Campos	World Health Organization	International Organization
Khamsing Vongphayloth	Pasteur Institute Laos	Laos
Laura Martin-Sancho	Imperial College London	United Kingdom
Laura Rivino	University of Bristol	United Kingdom
Leah Katzelnick	National Institutes of Health	United States of America
Louis Lambrechts	Pasteur Institute	France
Lourdes Oliveira	Fiocruz	Brazil
María Guzman	Pedro Kouri Tropical Medicine Institute	Cuba
Marta Giovanetti	Campus Bio-Medico University	Italy
Michael Diamond	Washington University School of Medicine	United States of America
Neelika Malavige	University of Sri Jayewardenepura	Sri Lanka
Nuno Faria	Imperial College London	United Kingdom
Patricia Sequeira	Fiocruz	Brazil
Pedro Vasconcelos	Para State University	Brazil
Philippe Despres	University La Réunion	France
Pierre Roques	Pasteur Institute Guinée	Guinea
Rafael Freitas	Fiocruz	Brazil
Renke Lühken	Bernhard Nocht Institute for Tropical Medicine	Germany
Rosanna Peeling	London School of Hygiene and Tropical Medicine	United Kingdom
Steven Sinkins	University of Glasgow	United Kingdom

2- CORC Thematic Meeting 2 – Agenda

Agenda for CORC Call
Thematic Meeting #2 Date: 18/06/2025
8:00– 11:20 am (Brasilia) | 01:00– 04:20pm (CEST) | 04:00am– 7:20am (PDT)

Time (BRT)	Duration (min)	Topic	Speakers
8:00-8:10	10′	Opening remarks	Flavia Barreto (Brazil) Ana Maria Henao Restrepo (WHO)
8:10-8:30	20′	**Lecture 1:** *Overview of the global epidemiology*	**Chair:** Diana Alvarez (WHO)
8:30-9:10	40′	**Panel 1** Driving questions should include (without being restricted to): • Epidemiological studies: best models and mitigation of data gaps • Models and dynamics of disease transmission • Risk assessment • Disease burden • Impact/ effectiveness of control measures • Main research gaps and priorities	**Moderator:** • José Cerbino Neto (Brazil) **Panelists** • Claudio Henriques (Brazil) • Claudio Struchiner (Brazil) • Colin Carlson (US)
9:10-9:30	20′	**Lecture 2:** *Socioeconomic and environmental impacts of disease: Gaps, challenges and opportunities for action*	**Chair:** Enny Paixão (UK)
9:30-10:00	30′	**Panel 2** Driving questions should include (without being restricted to): • Social determinants of health • Innovative approaches for socioeconomic and environmental impact analysis • Mitigation measures • Community engagement • Main research gaps and priorities	**Moderator:** Luiz Augusto Galvão (Brazil) **Panelists** • Carl Kendall (US) • Duane Gubler (Singapore) • Elizabeth Brickley (UK) • Fernando Bozza (Brazil) • Marcia Lenzi (Brazil) • Maurício Barreto (Brazil)

10:00-10:20	20′	**Lecture 3:** *Integrated data-based surveillance, innovative approaches for epidemiological intelligence and early alert systems*	**Chair:** Manoel Barral-Netto (Brazil)
10:20-10:50	30′	**Panel 3** Driving questions should include (without being restricted to): • Integrative surveillance frameworks (epi, clinical, genomic, wastewater) • Innovative approaches for math modelling and epidemiological intelligence • Methods for predicting epidemiological trends for timely intervention • One health approaches	**Moderator:** Tim Dallman (WHO) **Panelists** • Mariane Branco (Brazil) • Michael Busch (US) • Miguel Martinez (Spain) • Judith Wong (Singapore)
10:50-11:10	20′	Wrap up	Jairo Mendez (WHO)
11:10-11:20	10′	Closing remarks	Ana Maria Henao Restrepo (WHO) Patrick Lydon (WHO)

Name	Institution	Country
Ana Maria Henao Restrepo	World Health Organization	International Organization
Carl Kendall	Tulane University Celia Scott Weatherhead School of Public Health and Tropical Medicine	United States of America
Claudio Henriques	Oswaldo Cruz Foundation	Brazil
Claudio Struchiner	Getúlio Vargas Foundation	Brazil
Colin Carlson	Yale University School of Public Health	United States of America
Diana Alvarez	World Health Organization	International Organization
Duane Gubler	Duke-NUS Medical School	Singapore
Eline Van Damme	Institute of Tropical Medicine Antwerp	Belgium
Elizabeth Brickley	The London School of Hygiene & Tropical Medicine	United Kingdom
Enny Paixão	The London School of Hygiene & Tropical Medicine	United Kingdom
Fernando Bozza	Oswaldo Cruz Foundation	Brazil
Flavia Barreto	Oswaldo Cruz Foundation	Brazil
Jairo Mendez	Pan American Health Organization	International Organization
José Cerbino Neto	Oswaldo Cruz Foundation	Brazil
Judith Wong	Environmental Health Institute Microbiology & Mol EPI Division	Singapore
Lourdes Oliveira	Oswaldo Cruz Foundation	Brazil
Luiz Augusto Galvão	Oswaldo Cruz Foundation	Brazil
Manoel Barral-Netto	Oswaldo Cruz Foundation	Brazil
Marcia Lenzi	Oswaldo Cruz Foundation	Brazil
Mariane Branco	Federal University of Rio de Janeiro	Brazil
Maurício Barreto	Oswaldo Cruz Foundation	Brazil
Michael Busch	University of California San Francisco	United States of America
Miguel Martinez	University of Barcelona	Spain
Mostafa Vaziri	Pasteur Institute of Iran	Iran
Patrick Lydon	World Health Organization	International Organization
Tim Dallman	World Health Organization	International Organization

3- CORC Thematic Meeting 3 – Agenda

Final Agenda for CORC Call
Thematic Meeting #3 Date: 30/07/2025
8:00 – 12:25 am (Brasília) | 01:00 – 05:25 pm (CEST) | 04:00 – 8:25 am (PDT)

Time (Brasília)	Duration (min)	Topic	Speakers
8:00-8:10	10´	Opening remarks	Flavia Barreto (Brazil) Ana Maria Henao-Restrepo (WHO)
8:10-8:30	20´	Lecture 1 *An overview of available flavivirus vaccines*	Chair: Kent Kester (US)
8:30-9:10	40´	*Panel 1* - Driving questions should include (without being restricted to): • Innovation in vaccine technology platforms and administration technologies • How to navigate the challenges of the valley of death • Challenges of clinical trial design and opportunities for improvement • Pharmacovigilance and adverse events • Main research gaps and priorities to accelerate MCMs *-How to simplify clinical trials protocols?* *-Which are the regulatory considerations on evidence generation for prototype FV vaccine(s) during an outbreak?* *-What evidence from an individually randomized clinical trial would contribute to address the additional data needs?*	Moderator: Sushant Sahastrabuddhe (IVI) Panelists • José Moreira (Brazil) • Sebastian Ulbert (Germany) • Sotiris Missailidis (France)

9:10-9:20	**10´**	**Lecture 2** *Multidisciplinary decision-making strategy on drug for clinical development: the international alliances experience.*	**Chair:** Peter Sjö (DNDi)
9:20-9:40	20	***Panel 2.1*** - Driving questions should include (without being restricted to): • Druggable targets: from the Direct acting antivirals and host-related targets • Tissue distribution of the compounds and time frame of opportunity: what we know and do now know on the flavivirus phisiopathology ? • Drug repurposing vs innovation, in light of the access to low and middle income countries to medicines	**Moderator:** Thiago Moreno (Brazil) **Panelists** • Jingyue Ju (US) • Johan Neyts (Belgium) • Yi Shi (China)
9:40-9:50	**10´**	**Lecture 3** *What is needed for clinical development of treatments?*	**Chair:** Andre Siqueira (DNDi)
9:50-10:10	20´	***Panel 2.2*** - Driving questions should include (without being restricted to): • What models of collaboration are most effective in the current global health context? • Have the key definitions been established to support the design of clinical trials for therapeutic development (e.g., endpoints, trial designs, and operational frameworks in the context of rapidly evolving diseases)?	**Moderator:** Sergio Sosa-Estani (DNDi) **Panelists** • Estevão Portela (Brazil) • Marnix Van Loock (Belgium) • Neelika Malavige (Sri Lanka)

10:10-10:30	**20´**	**Lecture 4** *IVD research, development and implementation*	**Chair:** Thirumalaisamy Velavan (Germany)
10:30-11:10	40´	*Panel 3* - Driving questions should include (without being restricted to): • Point of care assays • Molecular assays/platforms • Serological assays • Limitations	**Moderator:** Jairo Mendez (WHO) **Panelists** • Carolina Lázari (Brazil) • Chang-Kweng Lim (Japan) • Patricia Alvarez (Brazil) • Rosanna Peeling (UK)
11:10-11:30	**20´**	**Lecture 5.** *Compliance & regulation of medical countermeasures*	**Chair:** Marco Cavaleri (EMA)
11:30-12:10	40´	*Panel 4* – Driving questions should include (without being restricted to): • Regulatory requirements for FV MCMs in epidemic and inter-epidemic periods • Minimum evidence for clinical trials: how to simplify protocols among sanitary emergencies? • Recommendations on trial designs and farmacovigilance • Gaps and opportunities to advance and accelerate MCM regulation	**Moderator:** Dean Smith (Canada) **Panelists** • Anuradha Poonepalli (Singapore) • Marcelo Moreira (Brazil) • Rubina Bose (India) • Ilaria Dorigatti (UK)
12:10-12:20	10´	**Wrap up**	Jairo Mendez (WHO)
12:20-12:25	5´	**Closing remarks**	Thiago Moreno (Brazil) Ana Maria Henao-Restrepo (WHO)

Name	Institution	Country
Andre Siqueira	Oswaldo Cruz Foundation (FIOCRUZ)	Brazil
Anuradha Poonepalli	Health Sciences Authority	Singapore
Carolina Lázari	University of São Paulo	Brazil
Chang-Kweng Lim	National Institute of Infectious Diseases	Japan
Dean Smith	Health Canada	Canada
Estevão Portela	Oswaldo Cruz Foundation (FIOCRUZ)	Brazil
Flavia Barreto	Oswaldo Cruz Foundation (FIOCRUZ)	Brazil
Ilaria Dorigatti	Imperial College London	United Kingdom
Jairo Mendez	Pan American Health Organization (PAHO)	International Organization
Jingyue Ju	Columbia University	United States
Johan Neyts	University of Leuven	Belgium
José Moreira	National Health Surveillance Agency (ANVISA)	Brazil
Kent Kester	Coalition for Epidemic Preparedness Innovations (CEPI)	International Organization
Lourdes Oliveira	Oswaldo Cruz Foundation (FIOCRUZ)	Brazil
Marcelo Moreira	National Health Surveillance Agency (ANVISA)	Brazil
Marco Cavaleri	European Medicines Agency (EMA)	International Organization
Marnix Van Loock	Johnson & Johnson	Belgium
Neelika Malavige	University of Sri Jayewardenepura	Sri Lanka
Patrick Lydon	World Health Organization (WHO)	International Organization
Patrícia Alvarez	Oswaldo Cruz Foundation (FIOCRUZ)	Brazil
Peter Sjö	Drugs for Neglected Diseases initiative (DNDi)	International Organization
Ricardo Gazzinelli	Oswaldo Cruz Foundation (FIOCRUZ)	Brazil
Rosanna Peeling	London School of Hygiene and Tropical Medicine (LSHTM)	United Kingdom
Rubina Bose	Central Drugs Standard Control Organization	India
Sebastian Ulbert	Fraunhofer Institute for Cell Therapy and Immunology	Germany
Sergio Sosa-Estani	Drugs for Neglected Diseases initiative (DNDi)	International Organization
Sotiris Missailidis	Pasteur Institute	France
Sushant Sahastrabuddhe	International Vaccine Institute (IVI)	International Organization
Thiago Moreno	Oswaldo Cruz Foundation (FIOCRUZ)	Brazil
Thirumalaisamy Velavan	University of Tübingen	Germany
Yi Shi	Chinese Academy of Sciences	China