Advancing a priority arbovirus research agenda for global preparedness and response

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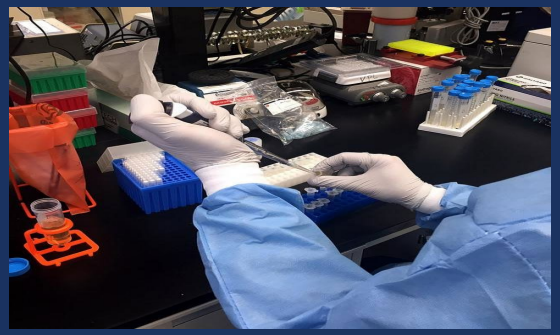

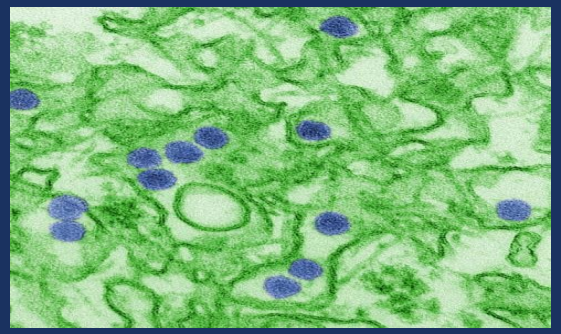

International Meeting on Zika and Mosquito-borne Arboviruses
London December 4-6, 2023

Meeting objectives:

- First 2 days: Advance a priority R&D agenda for Zika diagnostics, vaccines, and therapeutics
- Third day: Identify an integrated research strategy for mosquito-borne arboviruses

Hosted by the Wellcome Trust, London, UK

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Background: WHO R&D Roadmaps for priority pathogens with epidemic potential

Background: WHO R&D Blueprint for Priority Pathogens

- Strengthen preparedness for priority pathogens of epidemic potential that have few or no medical countermeasures, i.e., diagnostics, vaccines, therapeutics
- Generate R&D roadmaps for priority pathogens
  - Summarize key barriers and knowledge gaps
  - Identify specific, time-bound R&D goals and milestones
- Structured format and processes for review, public vetting, publication

Meeting background and approach

- 2019 -- Advanced draft of WHO ZIKV R&D roadmap completed
  - Structure: Diagnostics, Vaccines, Therapeutics, Cross-cutting Issues
  - Developed by CIDRAP with WHO Zika Taskforce, University of Texas Medical Branch, WHO Blueprint, and Wellcome Trust
  - Not finalized due to COVID-19. Draft posted on WHO Blueprint website.
- 2023 -- WHO Zika Taskforce reconvened
- Updated ZIKV R&D roadmap
- Dec 2023: Meeting of stakeholders - use roadmap as a platform to define research priorities to advance R&D for ZIKV diagnostics, therapeutics, and vaccines.

Zika Taskforce and Steering Group

Taskforce Members

- Kristina Adams Waldorf, Univ of Washington
- Joseph Bennie, FDA, Ghana
- Aaron Brault, CDC, USA
- Christiane Coelho, ANVISA, Brazil
- Nuno Faria, Univ of Cambridge, UK
- Eva Harris, UC Berkeley, USA
- Nagwa Hasanin, UNICEF
- Albert Ko, Yale School of Public Health, USA
- Yee-Sin Leo, NCID, Singapore
- Ziad Memish, Ministry of Health, Saudi Arabia
- Jairo Méndez-Rico, PAHO
- Kaitlyn Morabito, NIH, USA
- Manuela Mura, EMA, The Netherlands
- Lee Ching Ng, NEA, Singapore
- Kirk Prutzman, FDA, USA
- Ingrid Rabe, WHO, Geneva
- Henrik Salje, Univ of Cambridge, UK
- Erin Staples, CDC, USA
- Stephen Thomas, SUNY Upstate Medical Univ, USA
- Jessica Vanhomwegen, Institut Pasteur, France
- Jurai Wongsawat, Ministry of Public Health, Thailand
- Devy Emperador, FIND, Geneva (observer)

Wellcome Trust

- Ana Cehovin
- Petra Fay
- Josie Golding

UTMB

- Alan Barrett
- David Beasley
- Nigel Bourne

CIDRAP

- Tabitha Kazaglis
- Eve Lackritz
- Anje Mehr
- Nicolina Moua
- Michael Osterholm
- Julie Ostrowsky
- Angela Ulrich

Meeting Objectives

- Identify key research priorities and **specific, actionable activities** needed to advance a ZIKV research agenda.
- Comprehensive, coordinated approach.
- Promote visibility and investment to accelerate research needs.
- Building on Zika R&D focus, Wellcome Trust added review of priorities for an integrated arbovirus research strategy.

  Included topics of vectors, vector control, climate change, and interactions of host-virus-vector-animal reservoirs that were not part of the WHO R&D structure for medical countermeasures.

The need for a priority research agenda for Zika diagnostics, therapeutics, and vaccines

- February 2016 - WHO declared a Public Health Emergency of International Concern (PHEIC) due to emergence of ZIKV epidemic in the Americas and discovery of associated microcephaly and Guillain-Barré syndrome.
- November 2016 - WHO lifted the PHEIC with the declaration of the Director General, "***We must be ready for the long haul***," a clear statement of the long-term commitment required to address this newly-emerged pathogen.

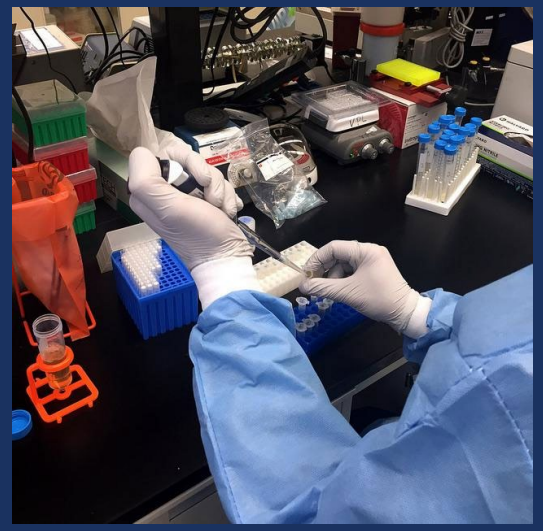
The need for a priority research agenda for Zika diagnostics, therapeutics, and vaccines

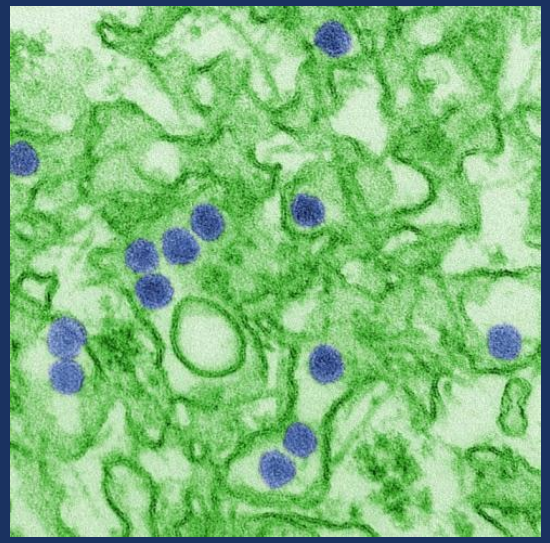
- Ultimately, 91 countries and territories have documented autochthonous, mosquito-borne ZIKV transmission.
- No vaccines, therapeutics, or diagnostics for routine antenatal screening.
- Risk of complacency after a global epidemic.
- Critical time to develop countermeasures now to be prepared for re-emergence in the future.

Unique challenges of Zika R&D

- Unlike other priority pathogens, disease is generally mild or asymptomatic. Ultimate goal is to prevent ZIKV infection of the fetus.
- Co-circulation and co-infection with other arboviruses.
- Low transmission and uncertainty of future transmission patterns:
  - Limits research opportunities
  - Uncertain markets for industry investment
  - Low visibility and investment

Zika Diagnostics:
Key Challenges and Research Priorities





Zika diagnostics: key challenges

- Diagnostics are foundation of research, preparedness, and response: surveillance, early detection, forecasting, clinical diagnosis, R&D, clinical trials, evaluating public health measures, etc.
- Majority of ZIKV infections asymptomatic or mildly symptomatic
- Nucleic acid amplification tests (NAATs):
  - High specificity but narrow window of detectable RNA
  - Limited utility for identifying asymptomatic infections and for routine screening in antenatal care

Zika diagnostics: Limitations of serology

- IgM detected generally 1-12 weeks post-infection.
- IgM may persist for months; positive test may reflect infection prior to pregnancy.
- Cross-reactivity with other flaviviruses and "antigenic sin."
- PRNT is labor-intensive, limited to reference laboratories, and may fail to confirm etiologic flavivirus.
- Lack of approved tests for alternate specimen types (CSF, urine, amniotic fluid).

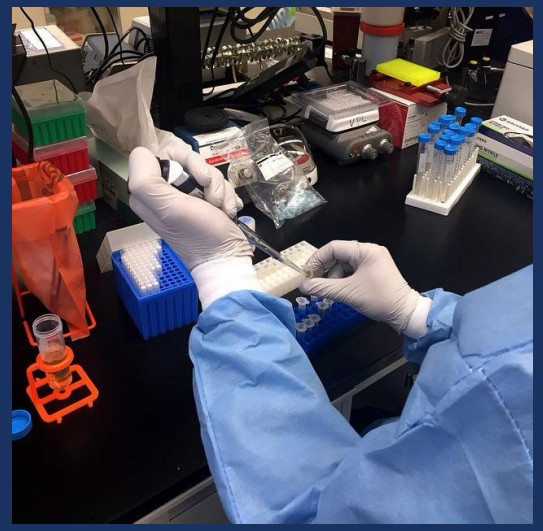
Zika diagnostics accessible for global use

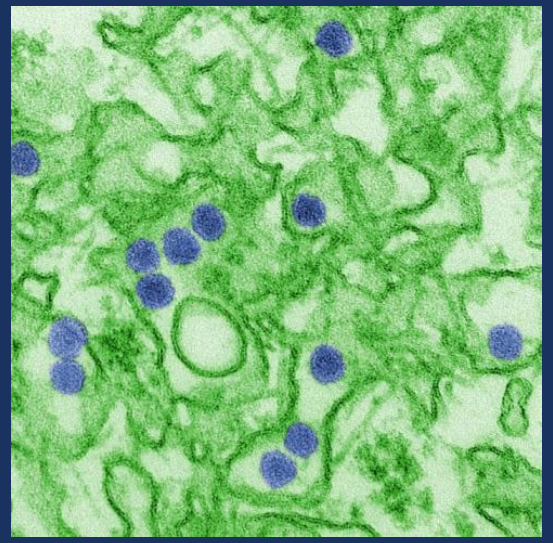
Development of rapid and simple tests

- Need for point-of-care diagnostics in clinical settings with limited lab capacity
- Challenges with specificity and false positives
- Logistical challenges for reference laboratories; increased burden of confirmatory testing

Multiple NAAT and serologic assays approved under emergency use authorizations but not validated by standardized evaluations.

Zika Vaccines, Therapeutics, Prophylaxis: Key Challenges and Research Priorities





Key challenges for ZIKV vaccine R&D

- Complex immunologic interactions with other flavivirus infections.
- Potential ADE safety signal.
- Mechanisms of protective immunity of flavivirus vaccines poorly understood. Neutralizing Ab's often used as correlate of protection.
- Need to better elucidate roles of neutralizing, non-neutralizing, and T-cell mediated immune responses.
- Prevention of congenital infection unrealistic endpoint of clinical trials.
- Majority of adult infections asymptomatic/mildly symptomatic.
  - Difficult to assess clinical endpoints and benefit for regulatory approval.

ZIKV vaccine R&D

- Multiple candidates in preclinical and Phase I and II clinical trials, multiple platforms.
- Non-standardized methods, endpoints.
- Unknown market demand. Unstable funding.
- Need to clarify target populations, non-traditional regulatory pathways.

Table 1. Zika vaccine candidate platforms and components.

Platform technology	Type
Live attenuated	• Infectious clone based with mutations • Codon pair de-optimized • Plasmid-launched live attenuated vaccine • Chimeric prM + E based on either dengue, Japanese encephalitis or yellow fever backbones • Single round replicating viruses
Inactivated	• Formalin-inactivated purified whole virus particle
Recombinant protein	• N-terminal 80% envelope protein • N-terminal 90% envelope protein • Envelope protein domain III • NS1
Virus-like particles (VLPs)	• prM + E protein
Live vectored	• Measles virus • Vaccinia
None-live vectored	• Replication deficient chimpanzee adenovirus • Replication deficient human adenovirus • Replication defective rhesus adenovirus • Replication defective poxvirus
DNA	• prM + E • prM + E + NS1
RNA	• prM + E

*prM = pre-membrane; E = envelope; NS1 = nonstructural protein 1

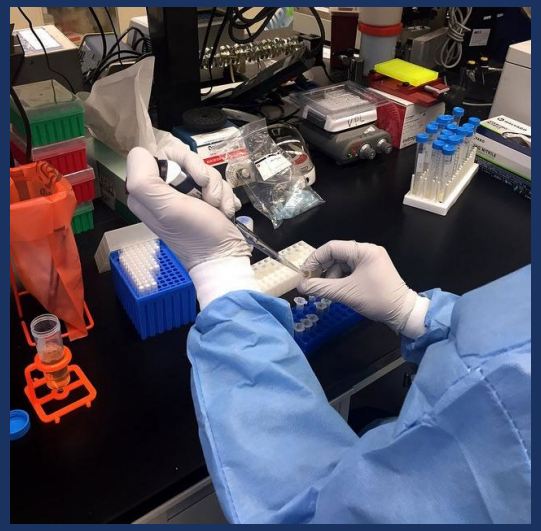
Source: Thomas and Barrett, Human Vacc & Immun. 2020

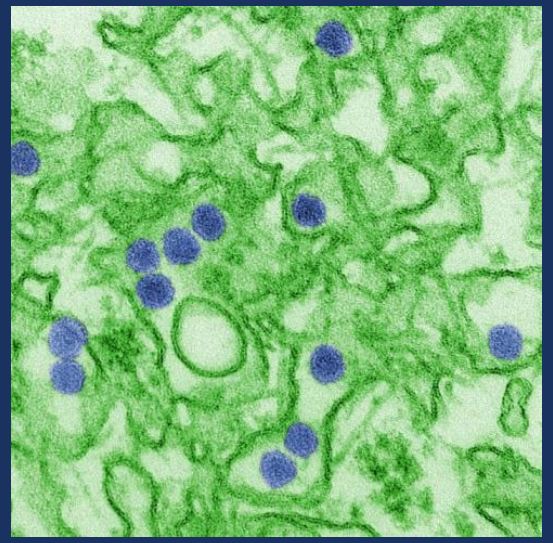
Defining regulatory pathways for vaccines and therapeutics

Multiple unique considerations for ZIKV regulatory approvals:

- Potential use in pregnant women or women who may become pregnant
- Prevention of congenital Zika infection - large sample size collected over years
- US FDA – likely stepwise approach:
  - Approval via accelerated pathway for adults. Animal rule alone unlikely.
  - Post-marketing studies to monitor population immunity and congenital Zika infection
- Different countries/regions with different regulatory requirements
- Prepare now for future outbreaks

Systematic Approaches to Accelerate R&D for Zika Diagnostics, Vaccines, Therapeutics





Biorepositories and sharing specimens

Need for sharing well-characterized clinical specimens

- Address restrictions of export of clinical specimens, protection of country interests, intellectual property, human subjects
- Models of agreements in Americas (PAHO), Europe (EU), Africa (Africa CDC)
- Proposed strategies:
  - Regional specimen sharing with legal agreements; define how quality samples are collected, stored, utilized.
  - Potential for industry agreements with countries if product commercialized.

Create systems for collection of standardized, well-characterized specimens

Develop standardized collections of well-characterized specimens for R&D, diagnostic assessments, laboratory proficiency programs.

Build global research networks collecting specimens from:

- Patients infected with ZIKV and other flaviviruses
- Geographically diverse areas
- Different patient populations: pregnant women, adults, neonates
- Different specimen types: blood, saliva, urine, amniotic fluid, CSF
- Standardized protocols for specimen collection, processing, and storage; characterized according to time after infection or symptom onset

Zika diagnostics: Evaluation and validation of existing diagnostics

Activities:

- Landscape review of diagnostics that are commercially available or in the pipeline.
- Convene expert working group: review landscape analysis, summarize gaps, and identify priorities.
- Complete standardized evaluations of assays, using standardized panels with geographic diversity, reported in International Units using International Standards. Include specimens coinfected/previously infected with other flaviviruses.
- Explore use of easy-to-collect specimens (e.g. saliva), new approaches (e.g. IgA), multiplex platforms for co-circulating arboviruses.

Animal models: key activities

Animal models of high importance in context of pregnancy research and low ZIKV transmission

- Inventory of animal models that best recapitulate congenital Zika infection.
- Investigate mechanisms of infection, pathophysiology, protective immunity, ZIKV kinetics, R&D for vaccines and therapeutics (including different viral strains).
- Correlates of protection for fetal infection, "sterilizing immunity"
- Define measureable endpoints that can be standardized across studies (viral load, immune response, malformations).

Controlled human infection models (CHIM) for Zika and other flaviviruses

Prominent role for CHIM studies to accelerate R&D during low ZIKV transmission

- ZIKV kinetics and immune response, by different sample types (blood, urine, saliva, cervical)
- R&D platform for vaccines, diagnostics, therapeutics
- Immunologic interactions of flaviviruses
- ZIKV CHIM studies approved and underway by Anna Durbin et al., Johns Hopkins Univ.
  - Identified strategies to mitigate risk for secondary sexual and mosquito-borne transmission. Enroll only women on highly-effective contraceptive methods.

Preparing research sites in advance of ZIKV re-emergence

- Establish global research networks with standardized and pre-approved protocols
- Geographically diverse research sites with co-circulating flaviviruses
- Engagement and planning with regulatory and public health agencies in countries at risk for re-emergence
- Identify and prioritize research candidates for diagnostics, vaccines, therapeutics
- Plan staffing, laboratory, and data management capacity
- Early engagement of governments, women, communities

Need for longitudinal cohorts

Longitudinal cohorts of pregnant women, infants, adults

- Durability of immune response
- Correlates of immune protection
- Interactions of ZIKV, DENV, and other flaviviruses: clinical, immunologic, epidemiologic
- Clinical sequelae of congenitally exposed infants, children
- Build community engagement
- Laboratory and research infrastructure for outbreak response

Need to identify strategies for long-term investment in the context of integrated arbovirus research.

Strengthen epidemiology and surveillance for preparedness and response

Data needed for early detection, response, forecasting, clinical outcomes, measurement of population-level immunity, response

- Enhance systems for early detection, monitoring, and evaluation of interactions of ZIKV, DENV, and co-circulating flaviruses
- Global data and laboratory capacity to support surveillance
- Track genetic epidemiology and inform forecasting models.
- Investigate novel strategies, e.g. wastewater surveillance
- Build investment for integrated arbovirus surveillance and control

Building global laboratory capacity for preparedness and response

- Conduct assessment of laboratory capacity in countries at risk for ZIKV
- Global mapping of reference labs
- Establish international reference laboratory networks for ZIKV/arboviruses
- Proficiency testing programs
- Anticipate assay selection, standardized protocols to evaluate diagnostics before the next outbreak

Programs to accelerate Zika R&D

- Update target product profiles (TPPs) and use cases for vaccines and therapeutics, including prophylaxis
  - Relevant to different geographic settings and capacity
- Ensure international standards and validation panels are available to assess new and existing diagnostics

Policy and investment for ZIKV and arbovirus R&D

Ultimately, need investment to accelerate R&D:

- Advance Zika research as part of an integrated arbovirus strategy
- Develop a full public health value proposition / cost-benefit analyses of medical countermeasures
- Investigate potential for advance purchase agreements
- Meetings and work groups to monitor pipeline, facilitate coordination and efficiencies
- Investigate strategies for protections related to legal liability of products used in women of reproductive age.

Advance visibility and engagement of governments, foundations, the public

- Collaborate with NASEM and other stakeholders