Zika Virus Research and Development (R&D) Roadmap

Roadmap purpose: To provide a 10-year framework for prioritizing research activities aimed at advancing the development, licensure, manufacture, deployment, and assessment of medical countermeasures (MCMs)—diagnostics, therapeutics, and vaccines—against Zika virus (ZIKV) disease. By highlighting key knowledge gaps, identifying strategic goals and milestones, and encouraging synergistic research and development (R&D) activities, the roadmap will serve as a valuable tool to advance the existing complex field of ZIKV MCM research and stimulate overall investment in R&D and in implementation activities.

Vision statement: To ensure that robust MCMs to detect, prevent, and control human ZIKV clinical disease, including congenital anomalies and neurodevelopmental disabilities associated with congenital ZIKV infection, are readily available and accessible for use in areas of known or potential ZIKV transmission. These MCMs include: (1) accurate, standardized, and validated diagnostics; (2) safe and effective treatments aimed primarily at preventing congenital ZIKV infection; and (3) safe and effective vaccines to prevent disease, disability, and death.

INTRODUCTION

ZIKV is a mosquito-borne flavivirus that was first isolated in 1947 from a sentinel rhesus monkey in the Zika Forest of Uganda (Dick 1952). Only a handful of ZIKV disease cases in humans had been identified prior to a 2007 outbreak in the State of Yap, Federated States of Micronesia, during which an estimated 73% of the population was infected (Duffy 2009, Petersen 2016). Subsequently, ZIKV caused an outbreak in French Polynesia during 2013-14, followed by outbreaks on other Pacific islands (Petersen 2016). In 2015, ZIKV was identified in Brazil, and the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) in February 2016 after neurodevelopmental anomalies in infants were linked to congenital ZIKV infection (Pierson 2018, Petersen 2016, WHO Fifth Meeting of Emergency Committee). The WHO ended the PHEIC declaration in November 2016. Although the epidemic in the Americas has waned and ZIKV incidence in the region has declined dramatically, ZIKV remains a global public health concern. Since 1947, autochthonous, mosquito-borne transmission of ZIKV had been documented in 87 countries and territories across four of the six WHO Regions (Africa, the Americas, South-East Asia, and the Western Pacific) (WHO Zika Epidemiology Update). In July 2019, the first probable case of autochthonous, mosquito-borne ZIKV transmission was identified in France, increasing ZIKV’s reach to a fifth WHO Region (WHO Zika Virus Disease France). ZIKV transmission is possible in additional “at risk” areas where the virus, competent mosquito vectors, and human populations previously unexposed to ZIKV are co-located (WHO Zika Epidemiology Update).

ZIKV is primarily transmitted via Aedes (Stegomyia) species mosquitoes; however, person-to-person transmission can occur via sexual contact, vertical transmission from mother to fetus during pregnancy, and transfusion of blood and blood products (Gregory 2018, Runge-Ranzinger 2019). The potential for transmission via breast milk from mother to infant also may occur (Dupont-Rouzeyrol 2016, Pang 2020).
In adults, ZIKV infection is asymptomatic in 50% to 80% of cases, and those with symptoms generally experience a mild febrile or rash illness (Pierson 2018, CDC Symptoms). Guillain-Barré Syndrome (GBS) was first linked to ZIKV infection during the 2013–14 outbreak in French Polynesia (Cao-Lormeau 2016, Oehler 2014, Petersen 2016); other more serious clinical presentations (e.g., organ failure, meningitis, encephalitis) also can occur (Pierson 2018).

The most pressing issue regarding ZIKV infection is the virus’s potential for teratogenic effects on a developing fetus, such as fetal demise, congenital anomalies, and neurodevelopmental disabilities (Pierson 2018, CDC Zika and Pregnancy). Infants born with congenital ZIKV infection may exhibit a range of findings (including microcephaly and brain and eye anomalies), and those exhibiting a specific combination of findings (e.g., severe microcephaly, limited joint movement, decreased brain tissue) may be diagnosed with congenital Zika syndrome (CZS) (CDC CZS, Moore 2017). The full spectrum of congenital ZIKV infection requires further clarification through longitudinal studies. Since congenital ZIKV infection is the most pressing public health issue associated with ZIKV, documenting and preventing adverse outcomes associated with pregnancy is of highest priority in this roadmap.

ZIKV exhibits a degree of sequence identity with other flaviviruses, especially dengue viruses (DENV), that circulate in overlapping geographic areas (Andrade 2018). There is a theoretical concern that ZIKV vaccines or natural ZIKV infection could promulgate more severe disease with subsequent non-ZIKV flavivirus infection due to flavivirus co-circulation. Antibody-dependent enhancement (ADE) is one suggested mechanism for why this may occur. ADE is a phenomenon associated with immune response to flaviviral structural proteins in which prior infection with one flavivirus results in the development of an antibody response that is sufficient to bind but not neutralize another flavivirus, and instead amplifies viral replication, which can lead to more severe disease. This has been demonstrated in cell culture and in small animal models for ZIKV, and has been suggested in one human cohort (Bardina 2017, Dejnirattisai 2016, Katzelnick 2020, Langerak 2019). By contrast, some studies suggest cross-protection (Subramaniam 2020). Additional data are needed to understand potential immunologic interactions between infection with ZIKV and related flaviviruses.

The ZIKV R&D roadmap is a key component of the WHO R&D Blueprint initiative for accelerating research and product development of MCMs to enable effective and timely emergency response to infectious disease epidemics. ZIKV is designated as one of the Blueprint’s “priority diseases” (defined as diseases that are likely to cause severe outbreaks in the near future and for which few or no MCMs exist) and is, like COVID-19, unique among the WHO priority diseases in that ZIKV is global in distribution. The Blueprint initiative calls for the development of R&D roadmaps to align and stimulate R&D of new or improved countermeasures, such as more accurate diagnostic assays, novel therapeutics, and effective vaccines. The scope of R&D addressed in this ZIKV roadmap ranges from basic research to late-stage development of MCMs to prevent and control ZIKV outbreaks and endemic disease in humans. The roadmap is organized into four main sections: cross-cutting issues (for areas that apply to more than one MCM category), diagnostics, therapeutics, and vaccines. (Note: These topics are not presented in order of public health priority.)
Considerable progress has been made in ZIKV research since the start of the 2015-16 outbreak, as evidenced by the volume of recently published literature, the organization of global consortia (e.g., ZikaPLAN, ZIKAction, ZIKAlliance), and the development of key research agendas and a target product profile (TPP) for ZIKV diagnostics (PAHO Research Agenda, WHO Research Agenda, WHO Diagnostic TPPs). The roadmap’s strategic goals and aligned milestones focus on high-priority achievements that are most needed during the next 10 years to address the challenges that still exist for ZIKV MCM development. As with all of the WHO R&D Blueprint priority diseases, funding to move MCMs forward is a critical issue. Without adequate funding, it will be difficult to achieve the goals and milestones identified in this roadmap; therefore, international partners will need to work together to creatively identify the resources required to realize the important objectives outlined in this R&D roadmap. As a living document, the roadmap will be revised periodically to reflect scientific progress and to identify gaps and barriers in achieving the milestones. Roadmap milestones will be tracked over time, with assessment of progress and updating as needed.

The COVID-19 pandemic will likely provide valuable lessons over the next few years that may be useful for this roadmap, especially if resources or technologies developed to address the COVID-19 pandemic can be leveraged for ZIKV MCM R&D. It is also possible that diversion of resources to the COVID-19 pandemic response and to other infectious disease issues that may arise in the wake of the pandemic could have a significant impact on meeting the goals and milestones in this roadmap. It will be important going forward, therefore, to balance the resources needed to accomplish the ZIKV R&D milestones with resource availability to the greatest degree possible.

Other aspects of public health preparedness and response, in addition to R&D for diagnostics, therapeutics, and vaccines, are critical to successful ZIKV infection prevention and control. Examples include implementing effective vector control, ensuring access to contraception methods during ZIKV outbreaks as a public health measure, promoting effective community engagement, implementing adequate infrastructure to deploy MCMs, and promoting workforce development and training in endemic and at-risk regions. Many of these issues are beyond the scope of this R&D roadmap but should be addressed as part of a broader public health control strategy.

Certain milestones are identified as high priority in this R&D roadmap. Though all R&D roadmap milestones are considered important to ZIKV MCM R&D, there are a number that are of utmost importance. For the purposes of this document, a high priority milestone identifies an area that is considered critical for public health and must be addressed first and swiftly. Prioritization helps ensure the most effective use of resources for optimal health impact and provide critical information to make better global health investment decisions, particularly when those decisions are not straightforward.

**CROSS-CUTTING ISSUES**

**Primary Challenges, Key Needs, and Knowledge Gaps**

*Issue: Disease characteristics and epidemiology*
Primary Challenges

- ZIKV infection is often asymptomatic or involves only mild non-specific symptoms (e.g., fever, rash, myalgia, arthralgia, conjunctivitis) that resemble those characteristic of other infections, which creates challenges for epidemiological surveillance, accurate and timely diagnosis, assessing the overall burden of ZIKV infection, and conducting clinical efficacy studies of candidate vaccines (Koppolu 2018, Lindsey 2020, Mitchell 2019, Musso 2019, Silva 2018).

- The incubation period following exposure to ZIKV can be as short as 3 days and the period of viremia following symptom onset averages from 3 to 5 days. Therefore, the availability of accurate diagnostic tools and therapeutics, especially for pregnant women and in areas of flavivirus co-circulation, is critical (Krow-Lucaı̈ 2017, Fourié 2018, Ng 2018).

- Future genetic evolution of ZIKV strains could potentially result in altered virulence phenotype(s) (Koppolu 2018).

- Global ZIKV distribution may vary over time with changes in vector dynamics and host immunity (Liu-Helmersson 2019).

- Mathematical modeling to estimate ZIKV transmission and spread is complex due to multiple factors (e.g., vector dynamics, population immunity, weather) (Towers 2016) and co-circulation of other flaviviruses.

Key Needs

- Although WHO published interim case definitions for ZIKV disease in 2016 toward the goal of global standardization for classification and reporting, no internationally adopted clinical criteria are available for surveillance of ZIKV illness or congenital infection. The sensitivity of some case definitions has been questioned and different case definitions have been used for surveillance purposes (Chow 2017, WHO Interim Case Definitions). Additionally, the current WHO and Pan American Health Organization (PAHO) ZIKV case definitions only identify 20% to 30% of laboratory-confirmed ZIKV cases in children (Burger-Calderon 2020). Additional efforts are needed to develop consensus on a set of case definitions for surveillance that could be applied in different geographic settings.

- Successful R&D, deployment, and assessment of MCMs depend on current and accurate descriptive epidemiologic information on ZIKV illness and ZIKV seroprevalence, geographic area, and other population demographics. Improved surveillance (or dedicated prospective research with a surveillance focus and a global sharing perspective) is needed to determine the true incidence of disease in future outbreak settings.

- A better understanding of the role of Aedes (Stegomyia) species mosquitoes other than Aedes aegypti in driving ZIKV outbreaks (e.g., Ae. albopictus, Ae. hensilli) and their distributions are needed to inform risk mapping models forecasting future outbreak spread (Erbelding 2017, Kraemer 2019, Lessler 2016, WHO Efficacy Trials).

- Early identification and neurodevelopmental follow-up are needed for infants with congenital ZIKV infection and children infected during the first year of life to facilitate their access to support and rehabilitation services.

Knowledge Gaps
• Research is needed to identify the underlying mechanisms of ZIKV pathogenesis, tissue tropism, and receptor-mediated attachment of flaviviruses to different types of host cells that lead to severe outcomes of ZIKV infection such as CZS and other congenital anomalies and neurodevelopmental disabilities (Andrade 2018, Laureti 2018).

• More information is needed to determine what level of viremia leads to CZS and other significant congenital anomalies and neurodevelopmental disabilities, and to quantify the risk to a developing fetus if a pregnant woman is infected with ZIKV, including any variation in risk depending on trimester (Brasil 2020). Such information can inform whether or not therapeutic agents or vaccines need to result in sterilizing immunity and complete blockage of viral replication, or only require attenuating capacity.

• After circulating for decades in Africa and Asia largely without evidence of serious complications, ZIKV outbreaks in South and Central America in 2015-16 demonstrated the potential for severe congenital disease associated with ZIKV infection. Causes for the apparent increase in ZIKV pathogenicity need to be clarified (Langerak 2019). For example, the factors (e.g., environmental, immunologic, virologic, and host-related) that contributed to the high rates of CZS found in Brazil during the 2015-16 outbreak and a cluster of microcephaly cases in infants with suspected ZIKV infection in Angola in 2017-18 remain undefined (Miner 2017, Caine 2018, Koppolu 2018, Souza 2019, Vedovello 2019, WHO Zika Epidemiology Update).

• Ecological surveillance studies of ZIKV in mosquitoes and associated animal populations are needed to identify potential ZIKV animal reservoirs.

• Further research is needed to elucidate the processes by which ZIKV infiltrates, affects, and persists in the male and female reproductive tracts and fluids (e.g., semen, vaginal secretions) (Borges 2019, Epelboin 2017, Spencer 2018).

• Natural history studies are needed to clarify the length of time ZIKV persists in breast milk and whether or not ZIKV ribonucleic acid (RNA) in breast milk is infectious for breastfeeding children (Erbelding 2017, Regla-Nava 2019).

• Ongoing phylogenetic and evolutionary analyses of ZIKV strains are needed to monitor viral heterogeneity that may affect the epidemiologic and clinical features of disease and diagnostic test sensitivity over time (Beaver 2018, Charrel 2016, Pettersson 2018, WHO Technology Roadmap). Additionally, a system is needed for communicating sequencing results to key stakeholders (Charrel 2016, Collins 2019, de Jesus 2019).

**Issue: Resources and tools for MCM R&D**

**Primary Challenges**

• Waning of the 2015-16 ZIKV epidemic has created a diminishing market for MCMs for ZIKV prevention and control, which is a major challenge for maintaining interest among stakeholders, including funders, the scientific community, and the pharmaceutical industry for continuing development of MCMs (Erbelding 2017, Garg 2018).

• Demonstrating that a product provides meaningful benefit without undue risk in targeted populations (a key aspect of any regulatory pathway) can be prohibitively expensive for product developers in the absence of a predictable demand. This may serve as a disincentive for
generating ZIKV therapeutics and vaccines, particularly since assessment of products in target populations such as pregnant women may be limited to outbreak settings.

- While nonhuman primates (NHPs) are an important animal model for ZIKV infection (particularly for studying maternal-fetal transmission, clarifying pathogenesis, and assessing vaccines and therapeutics), ethical issues, high costs, limited availability, and husbandry requirements, constrain their use (Estes 2018, Phillips 2014).

- Preparedness for conducting clinical trials during future outbreaks poses significant challenges, particularly since the location and timing of the next outbreak are unknown and very difficult to predict (Erbelding 2017). In addition, these areas may not have expertise or experience with the conduct of clinical trials, or possess the necessary research support resources.

**Key Needs**

- Funding sources (such as public-private partnerships, government agencies, and philanthropic organizations) and industry incentives for non-dilutive funding are needed to encourage innovation and secure private-sector commitments to develop and manufacture ZIKV MCMs (Goncalves 2018).

- Enhanced clinical, laboratory, and public health infrastructure are needed in future outbreak settings to promote early detection, diagnosis, treatment, surveillance, and implementation of vaccination programs for ZIKV prevention and control.

- Enhanced capacity for data sharing and analysis is needed to support collaborative clinical research, including methods for collecting, standardizing, and sharing clinical data (Chua 2017).

- Standardized and well-characterized assays and reagents are needed for R&D of ZIKV MCMs (e.g., immunoassays for comparing the immune response to different vaccines and assays to serve as gold standards for evaluating outcomes, diagnostic tests, and establishing minimum standards for sensitivity and specificity) (Barrett 2018, Garg 2018, Richner 2018, Roberts 2018, Wilder-Smith 2018).

- Use of a Controlled Human Infection Model (CHIM) has been proposed for studying ZIKV pathogenesis, immunology, and MCM R&D (particularly vaccines). Although concerns have been raised for using a CHIM for ZIKV research (Hubert 2019, Shah 2017), given the current low incidence of ZIKV disease, a safe and ethical model could confirm immune correlates of protection and provide an avenue through which to evaluate ZIKV MCMs (Barrett 2018, Erbelding 2017, Palacios 2019, Pattnaik 2020, Wilder-Smith 2018, Vannice 2019). However, the parameters of using a CHIM for ZIKV MCM development still need to be defined.

- An inventory is needed of available animal models that most closely recapitulate the spectrum of CZS or other congenital anomalies associated with ZIKV infection. Additional research is then needed to refine and standardize appropriate animal models of ZIKV infection and illness (Clancy 2018, Estes 2018, Zanluca 2018). Benchmark parameters for challenge route, genetically defined strain, and dose also are needed, as they may impact pathogenesis (Azar 2018, Duggal 2019).

- Early and recurrent communications are needed between product developers and the appropriate national regulatory authorities (NRAs) or other regulatory agencies to obtain clarity and guidance on clinical trial requirements, regulatory pathways, and other considerations for
ZIKV MCMs during the pre-licensure and post-licensure periods. Regulatory pathways and NRA capabilities vary between countries and ZIKV has a wide geographic distribution; therefore, early engagement, potentially with support from WHO, is essential to identify country-specific regulatory considerations.

- Preparations are needed in all affected and at-risk geographic areas for public education to address concerns about safety and efficacy of candidate MCMs used during future outbreaks. Improved epidemiologic data will be critical to identifying these areas in advance.
- Target population(s) for use of specific MCMs need to be defined, taking into consideration the societal and economic impact of ZIKV disease outcomes for different populations. Defining target populations will also affect the risk-benefit analysis (e.g., immunizing women of child-bearing age to prevent disease in their children).
- For areas without expertise or the necessary resources for conducting clinical trials, training in the conduct of high quality and compliant clinical trials and building the required physical and other research support infrastructure (e.g., data management, cold storage) are needed.

Knowledge Gaps

- Additional research in animal models is needed to clarify the pathogenesis of ZIKV congenital transmission to effectively develop, evaluate, and license ZIKV interventions that prevent sequelae caused by congenital ZIKV infection (Erbelding 2017, Estes 2018).
- At present, pregnant rhesus macaques are a promising model for studying congenital ZIKV infection, as viremia levels in pregnant animals are similar to those reported in pregnant humans, but additional research is needed to verify that the pregnant rhesus macaque model is sufficient for MCM development (Caine 2018, Estes 2018).
- Social science and community engagement activities will be needed to effectively engage populations at risk for ZIKV exposure, including women who are or may become pregnant, to promote awareness and sensitization about ZIKV illness symptoms and prevention programs and to ensure participation in clinical trials and acceptance of ZIKV MCMs (PREVENT Working Group, Juarbe-Rey 2018, Nelson 2019).

Strategic Goals and Aligned Milestones

**Strategic Goal 1:** Ensure that adequate tools are available for conducting additional research on ZIKV virology, transmission, and pathogenesis to facilitate development of ZIKV MCMs.

**Milestones:**

1. By 2025, generate an inventory of available animal models that most closely recapitulate CZS or other congenital anomalies associated with ZIKV infection.
2. By 2026, (1) obtain further guidance from regulatory authorities on key characteristics that animal models require to support regulatory review of ZIKV MCMs, (2) develop consensus on the most appropriate animal model(s) that can be used to infer efficacy of vaccines and therapeutics in humans, and (3) define the criteria used for those animal models (such as route, dose, and strain). *(High priority milestone)*
3. By 2026, generate a well-developed, standardized CHIM for ZIKV (particularly for use in the absence of ongoing ZIKV outbreaks) and define parameters for use (e.g., challenge strain, challenge dose, route of challenge administration and delivery) (Erbelding 2017, Vannice 2019). *(High priority milestone)*

4. By 2027, (1) conduct a review of existing ZIKV assays and determine if currently available assays are adequate for ZIKV clinical, epidemiologic, surveillance, and research purposes (e.g., are regionally applicable, can assess population-based immunity, and can distinguish ZIKV from other flaviviruses); (2) identify any gaps in the existing landscape of assays; (3) generate new assays as needed based on the gap analysis; and (4) ensure that an international standard(s) is available to assess new or existing ZIKV assays. *(High priority milestone)*

5. By 2027, standardize and optimize the most relevant animal model(s) that adequately recapitulate the different ZIKV disease endpoints.

**Strategic Goal 2:** In collaboration with WHO and in line with national priorities, improve understanding of ZIKV epidemiology and ecology, particularly in the context of other flaviviruses, to estimate the relative risk and potential for global occurrence of future ZIKV outbreaks to facilitate development of Zika MCMs.

**Milestones:**

1. By 2023, review existing case definitions for the clinical manifestations of ZIKV disease, including for children, in the context of other flaviviruses, and generate a set of harmonized case definitions for surveillance, in collaboration with WHO and in line with national priorities, that could be applied in different geographic settings. Once these definitions are developed, promote international adoption to allow generation of consistent surveillance data across countries and regions.

2. By 2025, refine mathematical modeling to better predict possible future global spread of ZIKV and co-circulating flaviviruses (Wilder-Smith 2018).

3. By 2027, generate estimates of the regional burden of clinically apparent congenital ZIKV infection in Asia, Africa, and the Americas (e.g., through use of sentinel surveillance projects in defined sites) *(WHO Technology Roadmap)*.

4. By 2027, define risk estimates for the full spectrum of adverse outcomes associated with congenital ZIKV infection (to potentially include gestational age of the fetus at the time of infection, as feasible) *(WHO Technology Roadmap)*.

5. By 2028, develop and implement an approach for enhancing human ZIKV surveillance in areas where future outbreaks may occur that will differentiate ZIKV infection from other circulating flavivirus infections in the specific geographic areas.

**Strategic Goal 3:** Identify sources of private- and public-sector funding and develop appropriate incentives and competitions to promote R&D of ZIKV MCMs.

**Milestones:**
1. By 2026, develop a full public health value proposition to support the development and implementation of ZIKV MCMs specifically aimed at preventing adverse health outcomes associated with congenital ZIKV infection (Arora 2018, Bartsch 2020, Gregory 2019).

2. By 2026, generate a private-sector value proposition for Zika MCMs, in coordination with commercial entities, to encourage private investment and interest in developing, licensing, and producing ZIKV MCMs, particularly for the prevention of adverse health outcomes associated with congenital ZIKV infection. This should include flexible approaches to incentives (such as advance purchase agreements) to avoid commitment to produce large quantities of products when the risks and benefits have not been fully explored.

3. By 2027, create a funding plan, including incentives for researchers in academia and industry, for advancing ZIKV MCMs toward early and/or late clinical evaluation, licensure/approval, acceptance, and sustainable access.

Additional Priority Areas/Activities

Additional Research Needs

• Continue to generate and make available standardized and well-characterized assays and reagents to support preclinical and clinical ZIKV MCM research.

• Continue to conduct studies to estimate the population-based immunity to ZIKV by age group and over time in various regions in Asia, Africa, and the Americas (Henderson 2020, WHO Technology Roadmap).

• Continue to conduct preclinical research on the virology, pathogenesis, and immunology of ZIKV infections to inform development of MCMs.

• Define the mechanisms by which ZIKV infection results in CZS and other congenital anomalies and neurodevelopmental disabilities.

• Better define ZIKV disease transmission dynamics (including differences based on trimester of pregnancy, the role of sexual transmission, and the potential role of transmission from mother to infant via breast milk), as possible, given the current epidemiologic landscape of ZIKV infection.

• Continue to perform phylogenetic and evolutionary analyses of ZIKV strains to monitor potential genetic diversity of ZIKV over time.

• Monitor the geographic distribution of ZIKV mosquito vectors over time, which may influence outbreak forecasting efforts.

• Conduct social science research to determine effective community engagement strategies for ZIKV awareness and prevention and for ensuring participation in clinical trials and acceptance of ZIKV MCMs.

Product Development

• Promote early communication between developers and appropriate NRAs for clarity and guidance on the regulatory aspects of MCM development for ZIKV infection.

• Develop regulatory guidance in collaboration with WHO, and ensure access to oversight, review, and authorization from appropriate NRAs for ZIKV MCMs.
Key Capacities

- **Strengthen** infrastructure to support ZIKV surveillance, diagnosis, disease prevention, treatment activities, and clinical trial capacity in areas at risk of future outbreaks.

- **Improve** surveillance for congenital anomalies in areas at risk for future ZIKV outbreaks ([WHO Technology Roadmap](#)).

- **Develop** capacity to allow improved sharing and analysis of data related to MCM development for ZIKV infection.

- **Promote** preparedness for epidemic response as it relates to MCM development and evaluation in areas at risk for future outbreaks.

- **Develop** infrastructure in areas at risk of future ZIKV outbreaks to educate the public about safety and efficacy of experimental vaccines and therapeutics.

Policy and Commercialization

- **Secure** funding to complete development, licensure, manufacture, deployment, and use of MCMs for ZIKV infection.

- **Support** plans for adequate manufacturing, stockpiling, and subsequent distribution of ZIKV diagnostics, therapeutics, and vaccines to future outbreak settings.

- **Support** the development of affordable pricing mechanisms to promote accessibility of ZIKV MCMs in low- and middle-income countries (LMICs) in future outbreak settings. (Note: According to WHO, an “affordable and fair” price is one that can reasonably be paid by patients and health budgets and simultaneously sustains research and development, production, and distribution within a country [WHO Fair Pricing](#).)

- **Develop** risk communication plans to promote acceptance of ZIKV MCMs, as new products become available.

DIAGNOSTICS

Primary Challenges, Key Needs, and Knowledge Gaps

Issue: Diagnostic test development, use, and evaluation

Primary Challenges

- Flaviviruses show extensive serologic cross-reactivity and so accurate ZIKV-specific diagnostics are needed. DENV and ZIKV cross-reactivity, in particular, has been observed. Japanese encephalitis virus (JEV) and West Nile virus (WNV) can all also result in cross-reactivity with ZIKV in serological assays.

- Strain variation exists between different genotypes, which could potentially impact performance of molecular assays.

- Diagnosis of ZIKV infection usually involves nucleic acid amplification tests (NAATs) for ZIKV viral RNA or serologic tests for ZIKV immunoglobulin M (IgM) and neutralizing antibodies; however, these approaches have limitations ([Chua 2017, Herrada 2018, Michelson 2018, Musso 2019, Sharp 2019](#)). Both false positive and false negative results can occur with NAATs and nucleic acid testing is only useful during a short window when ZIKV viremia, which is several orders of...
magnitude lower than that of other arboviral infections, such as DENV and chikungunya virus, is present (averaging 3 to 5 days following illness onset) (Ng 2018). Serologic testing is limited because cross-reactivity to other flaviviruses can lead to false positive results and as ZIKV incidence declines, the rate of false positives increases. Also, IgM antibodies may persist for 6 months or more, which creates challenges for diagnosis of acute infection. Finally, equivocal IgM results require plaque reduction neutralization test (PRNT) confirmation, although PRNTs are still subject to cross-reactivity and cannot determine the timing of infection.

- The neutralization test, including PRNT, is the gold standard for differentiating antibody responses against different flaviviruses (e.g., differentiating DENV from ZIKV), but the technique takes extensive time (i.e., 7-10 days), is limited to reference laboratories, requires standardized reagents that can prove challenging to obtain, and the specificity of PRNT following sequential infections is limited (Chepkorir 2019, Chua 2017, Landry 2016, Goncalves 2018).
- To date, very few DENV and ZIKV diagnostic tests have been adequately evaluated using clinical specimens from both ZIKV-infected and DENV-infected populations (Goncalves 2018).
- Lack of access to biobanks of well-characterized clinical specimens (particularly from regions outside of the Americas) has led to delays in test optimization and validation, which can create a significant bottleneck for ensuring that diagnostic tests are available and can be adopted for use (Goncalves 2018, Peeling 2018). This issue may also impact test performance, owing to regional variations in virus strains and circulating flaviviruses.
- During outbreak events, emergency use authorization can be obtained to allow use and evaluation of diagnostic tests during an emergency. An Emergency Use Authorization (EUA) is available from the US Food and Drug Administration (FDA) and an Emergency Use Assessment and Listing (EUAL) is available from WHO. However, such authorizations end after the emergency situation is declared over or after licensure of the diagnostic test. Test developers must then seek full approval of their products through traditional pathways, which usually requires obtaining additional data. The lack of access to well-characterized samples creates challenges for obtaining the necessary data for full product approval (Goncalves 2018).
- Improved methods for in utero diagnosis are needed for earlier detection of congenital infection.
- During pregnancy, amniocentesis for NAAT testing can be performed when prenatal ultrasound findings are consistent with CZS, but the sensitivity and specificity of NAAT testing of amniotic fluid is unclear (CDC Testing Guidance).
- Although several diagnostic tests for detection of ZIKV IgM antibodies have been authorized for marketing by a regulatory authority (for example, US FDA Zika Virus Response, US FDA 501(k) Premarket Notification, US FDA News Release), it should be noted that no test authorized as of December 2020 fully meets the desired specificity and sensitivity characteristics outlined in the WHO TPP (WHO Diagnostic TPPs).
- The pathway to development of in-house assays and commercial tests kits for ZIKV varies substantially, including use of different calibration controls, which creates challenges for determining the relative accuracy sensitivity and specificity of different tests (Goncalves 2018).
• Local and international restrictions on the export of clinical samples limit opportunities for product validation outside of affected countries (Goncalves 2018).

• Secondary flavivirus infection (i.e., infection with a different flavivirus after prior flavivirus infection or vaccination) can cause a decreased IgM response and a rapid rise in neutralizing antibodies against multiple flaviviruses (antigenic sin), potentially confounding the ability to determine which flavivirus caused the most recent infection (Sharp 2019).

Key Needs

• Improved data sharing among researchers and product developers and tracking of diagnostic test development are needed to advance R&D of ZIKV diagnostics (Peeling 2018).

• Validated, available diagnostic assays are needed that meet the ASSURED criteria (Affordable, Sensitive, Specific, User-friendly, Rapid and Robust, Equipment-free, and Delivered to the end-user) and can be used in point-of-care settings (if test sensitivity and specificity are adequate) (Chua 2017, Goncalves 2018, Peeling 2018).

• Standardized, well-characterized, ethically-obtained clinical samples from different stages of ZIKV illness are needed to evaluate the performance characteristics of diagnostic assays (Baylis 2017, Peeling 2018, Roberts 2018). (Note: A virtual biobank is being developed through the ZikaPLAN consortium and ongoing support of this effort will continue to move this critical activity forward.)

• Many ZIKV diagnostic products still need to be standardized based on the use of well characterized clinical standards and in the context of other circulating flaviviruses that differ by geographic area.

• Standardized clinical trial protocols are needed in advance of future ZIKV outbreaks to facilitate clinical studies of promising diagnostic tests.

Knowledge gaps

• More data are needed, through prospective cohort studies that include pregnant women, non-pregnant persons, and infants with potential congenital ZIKV syndrome or exposure on ZIKV kinetics to inform ideal sample types, timing of sample collection, and diagnostic testing algorithms (Charrel 2016, Chua 2017, Herrada 2018).

• More information is needed regarding the performance characteristics (including sensitivity, specificity, limits of detection, cross-reactivity, and quantitative vs. qualitative data) for ZIKV assays, particularly for tests that received EUA/EUAL authorization, newer novel tests, and tests that are designed to detect other flaviviruses (e.g., DENV) in addition to ZIKV (Sharp 2019). The characteristics should be validated for different cohorts (e.g., infants, pregnant women, and non-pregnant persons).

• Further validation studies are needed of promising diagnostics during future ZIKV outbreaks, to include different geographic areas (Charrel 2016).

• More research is needed on next generation diagnostic technologies to identify sensitive, specific, and affordable tools that could be used in resource-limited settings either at the point of care (at the bedside) or near patient care (at the hospital laboratory). One such example is reverse transcription loop-mediated isothermal amplification (RT-LAMP)-based microfluidic

• More research is needed into new techniques of sample collection, processing, and storage to allow for more non-invasive sample collection techniques (e.g., saliva).

**Issue: Industry and infrastructure considerations**

**Primary Challenges**

• The unpredictable nature of ZIKV outbreaks brings uncertainty to industry and creates challenges for diagnostic companies to forecast demand and generate business models that allow return on investment (Goncalves 2018).

• Different diagnostic methodologies are appropriate for different use cases, which creates challenges for industry engagement: (1) surveillance and alerts (using high throughput assays such as IgM testing); (2) case detection and clinical diagnosis during outbreaks (using rapid, point-of-care testing for viral RNA, virus antigens, or IgM serology and confirmatory testing as needed using assays such as PRNT); (3) serosurveys to define prevalence (using surveillance tools with high specificity); (4) research to improve understanding of pathogenesis and monitor the impact of interventions (using a combination of surveillance tools and case detection tools); and (5) monitoring genomic diversity and changes in virus phenotypes of circulating ZIKV strains over time (using methods such as genomic sequencing and virus isolation) (CDC Testing Guidance, Charrel 2016, Chua 2017, de Jesus 2019, Peeling 2018).

• Limited laboratory resources constrain complex diagnostic testing in many of the countries affected by ZIKV and other flaviviruses, which creates market considerations (Shehu 2018).

• Regulatory oversight for diagnostic tools is variable and regulatory approval processes vary from country to country, which can impact marketing authorization and licensure (Goncalves 2018).

**Key Needs**

• Regulatory harmonization, increased information sharing, and enhanced transparency are needed between international and national regulatory agencies and manufacturers to expedite regulatory approval of ZIKV diagnostic tools (Goncalves 2018).

• Innovative financial incentives are needed to support scalable adoption of ZIKV diagnostic tests into national laboratory programs in areas at-risk for future ZIKV outbreaks (Goncalves 2018).

• Regular external quality assessments and proficiency testing programs are needed to monitor and evaluate performance of diagnostic assays in the field (Charrel 2016, Donoso 2018, Fischer 2018, Goncalves 2018, Peeling 2018).

**Knowledge Gaps**

• Research is needed to assess the current status of laboratory capacity to detect ZIKV in countries at risk for future ZIKV outbreaks (Charrel 2016).

**Strategic Goals and Aligned Milestones**
Strategic Goal 1: Foster an enabling environment to support ongoing research and evaluation of ZIKV diagnostics (Peeling 2018).

Milestones:
1. By 2024, review and revise, as appropriate, the WHO TPP for ZIKV diagnostics to ensure the TPP reflects current scientific knowledge (WHO Diagnostic TPPs).
2. By 2024, convene an expert working group (with membership that incorporates existing flavivirus workgroup expertise and expertise from affected countries) to meet in 2024, and then regularly thereafter, to review data on new assays/platforms for flavivirus diagnostic tests, identify research gaps, and define priority diagnostics by country that are missing from the market. Summaries of these reviews should be made publicly available.
3. By 2024, update the existing diagnostic landscape to provide current information (including performance characteristics) about ZIKV diagnostics that are commercially available and diagnostics that are in the pipeline to promote identification of current gaps (Peeling 2018).
4. By 2025, ensure that a virtual repository of clinical reference samples (including various sample types [e.g., serum, cerebrospinal fluid, urine, amniotic fluid] collected at different times after infection or illness onset) for ZIKV and other medically important flaviviruses as possible, to be used for assessing diagnostic agents, is operational in various geographic areas at risk for ZIKV emergence/reemergence (particularly in areas of the world other than the Americas) to reflect local/regional flavivirus epidemiology and to build up sustainable infrastructure in settings with limited resources and storage capacity. (High priority milestone)
5. By 2026, conduct several prospective studies in NHPs on ZIKV infection and immune response kinetics to further inform optimum sample types, timing of sample collection, and diagnostic testing algorithms.
6. By 2027, create a governance system for the virtual repository that is agreed upon through international collaboration and that promotes equitable access and sharing of specimens and data (e.g., through the ZikaPLAN consortium or other similar platform) (Goncalves 2018, Peeling 2018).
7. By 2027, define the use cases for ZIKV diagnostic testing, taking into consideration regional differences (e.g., ZIKV epidemiology and co-circulating flaviviruses), and determine the specific types of diagnostics that are needed for different use cases.
8. By 2028, develop guidance on the optimal clinical sample types, timing of sample collections, and diagnostic tests to be used for the different use cases.

Strategic Goal 2: Conduct standardized evaluation of ZIKV diagnostic tests that are currently available for use.

Milestones:
1. By 2023, complete standardized evaluations and additional validation as needed for at least 10 molecular or serologic ZIKV assays.
2. By 2026, complete additional in-country, regionally specific validation for ZIKV assays across a variety of use cases (e.g., clinical diagnosis, surveillance, etc.).
3. By 2026, create a mechanism to incentivize developers to pursue full regulatory approval of existing ZIKV assays.

4. By 2026, conduct at least one study that uses consistent methodology to compare the performance characteristics and relative accuracy of several different available diagnostic assays on different specimen types.

Strategic Goal 3: Develop highly sensitive and specific, cost-effective, and affordable molecular and serologic diagnostic tests for ZIKV (potentially including point-of-care tests) that align with the WHO TPP; are appropriately robust for the conditions in which they will be used and for different use case scenarios (e.g., emergency use, surveillance, clinical efficacy studies); can distinguish among flaviviruses in different geographic regions; and have minimal requirements for laboratory capacity and staff training.

Milestones:

1. By 2026, complete preclinical evaluation for at least two prioritized ZIKV-specific diagnostic assays, including at least one point-of-care diagnostic assay with adequate sensitivity and specificity, that align with the WHO TPP and can distinguish among flaviviruses in different geographic regions.

2. By 2026, develop a broadly agreed upon set of clinical trial protocols to assess ZIKV-specific diagnostic tests during the next ZIKV outbreak that will generate data needed for regulatory review.

3. During the next ZIKV outbreak, complete clinical trials for at least two prioritized ZIKV diagnostic assays that align with the WHO TPP.

4. By 2028, ensure that at least one well-validated ZIKV-specific diagnostic assay that aligns with the WHO TPP, can distinguish among flaviviruses in different regions, and can identify recency of infection is available for use in the general population (and specifically in pregnant women) in countries at risk of ZIKV outbreaks (either during outbreaks or during the inter-epidemic period to allow early outbreak identification). (High priority milestone)

5. By 2028, ensure that at least one well-validated ZIKV-specific point-of-care diagnostic assay that aligns with the WHO TPP is available for use in countries at risk of ZIKV outbreaks and develop guidelines for appropriate indications for use of point-of-care assays (such as for surveillance purposes in low-resource areas, for use in pregnant women when recommending treatment [if and when effective treatments become available], or as an initial screening test to identify asymptomatically infected pregnant women). (High priority milestone)

6. By 2029, ensure that at least one highly sensitive and specific serologic test is available to assess the presence/absence of ZIKV protective immunity in reproductive-aged women prior to pregnancy or during pregnancy. (High priority milestone)

7. By 2029, ensure that at least one ZIKV diagnostic assay has been approved for clinical use by an appropriate regulatory entity.

8. By 2029, ensure that at least one diagnostic test (or test combination) is available that is appropriate for use in clinical vaccine efficacy studies (i.e., that regulatory agencies will accept as definitive evidence of ZIKV infection). (High priority milestone)
9. By 2030, ensure that at least one well-validated ZIKV-specific diagnostic assay is available for diagnosis of congenital ZIKV infection. *(High priority milestone)*

**Strategic Goal 4:** Strengthen current laboratory infrastructure and capacity in at-risk countries according to national and regional priorities to enable rapid evaluation of diagnostic specimens during future ZIKV outbreaks.

**Milestones:**
1. By 2025, expand the regional availability of proficiency testing panels and protocols to assess laboratory performance for ZIKV testing (involving both serologic and molecular tools) in selected laboratories (such as national reference laboratories) in selected countries at risk for ZIKV outbreaks *(Goncalves 2018)*.
2. By 2026, conduct a global assessment of the laboratory capacity to detect ZIKV in different regions at risk for ZIKV outbreaks (to include Africa, Asia, and the Americas) *(Charrel 2016)*.
3. By 2027, convene an expert working group to develop an international reference laboratory response network for flavivirus detection (including ZIKV detection), which would include networks of in-country laboratories in at-risk areas *(Goncalves 2018)*.

**Additional Priority Areas/Activities**

**Additional Research Needs**
- Develop risk-benefit models to set accuracy targets that inform use of diagnostics when they do not meet the minimum criteria set forth in existing WHO TPPs *(Goncalves 2018)*.
- Continue to research the role of genomic sequencing/phylodynamic analyses as a potential surveillance tool for enhancing understanding of the epidemiology and evolution of ZIKV.
- Further assess the sensitivity and specificity of NAAT testing of amniotic fluid for CZS *(CDC Testing Guidance)*.

**Product Development**
- Continue to conduct validation studies on ZIKV diagnostic tests as they become available, including evaluation of diagnostic test suitability for new use cases (e.g., use in vaccination programs in areas with circulating DENV).
- Continue to determine the analytical characteristics (including sensitivity, specificity, and limits of detection) of novel diagnostic tests for ZIKV infection.

**Key Capacities**
- Identify innovative financial incentives and flexible funding schemes to achieve sustainable emergency preparedness for ZIKV diagnostics for use in outbreak settings *(Goncalves 2018, Peeling 2018)*.
- Develop diagnostic algorithms for CZS and ensure that affected areas have the capacity to follow them *(WHO Technology Roadmap)*.
- Promote scalable adoption of ZIKV diagnostic tools into national laboratory programs in areas at-risk for future outbreaks of ZIKV infection *(Goncalves 2018, Peeling 2018)*.
• Expand qualified field laboratory networks that have diagnostic capabilities in areas at risk for future ZIKV outbreaks (Goncalves 2018).

**Policy and Commercialization**

• Promote regulatory harmonization, information-sharing, and transparency between national and international regulatory agencies involved in regulatory approval of ZIKV diagnostic tests.

• Develop additional guidance on specimen collection once more information is available about ZIKV kinetics.

• Develop public health guidance for use of any point-of-care diagnostic tests that are generated and made available.

**THERAPEUTICS**

**Primary Challenges, Key Needs, and Knowledge Gaps**

**Issue: ZIKV infection and disease considerations**

**Primary Challenges**

• No licensed therapeutic agents are available to treat or prevent illness caused by any flavivirus.

• ZIKV is unique among flaviviruses in that the virus can be sexually transmitted, necessitating therapeutic treatments that can reduce the risk of transmission to sexual partners (Caine 2018, Erbelding 2017).

• No specific therapies are available to treat ZIKV clinical illness, to prevent ZIKV from crossing the placental barrier, or to treat developing fetuses in utero (da Silva 2018, Wilder-Smith 2018).

• No specific treatment is available for infants born to ZIKV-infected mothers, although a therapeutic agent could be helpful in reducing viral loads, preventing further nervous system damage, and improving clinical outcomes (Erbelding 2017).

• Different therapeutic approaches may be needed for different patient populations. Examples of populations to consider include healthy non-pregnant adults who may be suitable for pre-exposure prophylaxis or early post-exposure prophylaxis to prevent ZIKV infection; pregnant women who may require pre-exposure prophylaxis, early post-exposure prophylaxis, or treatment of clinical illness to prevent in utero transmission; neonates born to infected mothers who may require therapy to lessen the effects of congenital ZIKV infection; and healthy ZIKV-infected adults who may require therapy to prevent complications of ZIKV infection or to accelerate viral clearance (Erbelding 2017, Wilder-Smith 2018).

**Key Needs**

• Safe, easily-administered, well-tolerated, and effective therapeutic agents are needed that: (1) treat ZIKV infection in pregnant women; (2) prevent vertical transmission of ZIKV to developing fetuses without causing teratogenic effects (potentially by decreasing viral loads in the maternal circulation); and (3) treat infants with congenital ZIKV infection to reduce disease manifestations or progression.

• Additional research is needed to establish if there is a public health need for therapeutic agents that would be used to prevent vertical transmission from lactating women to their infants or to...
eliminate ZIKV infectious particles from male and female reproductive tracts and fluids for the 
prevention of sexual transmission.

- ZIKV therapeutic agents with potential to effectively treat other flavivirus infections (e.g., DENV, 
  yellow fever virus [YFV], JEV, WNV) are needed, owing to virus geographic overlap, symptom 
similarity, lack of diagnostics capable of quickly differentiating between these viruses in the 
field, and necessity of early treatment. This approach could provide a cost-effective and 
sustainable strategy for ensuring that treatment options are available (Bernatchez 2019, Wilder-
Smith 2018).

**Knowledge Gaps**

- Research is needed to better understand the determinants and predictors of congenital 
anomalies and neurodevelopmental disabilities associated with congenital ZIKV infection to help 
identify therapeutic agents that could prevent or mitigate sequelae associated with congenital 
ZIKV infection (Wilder-Smith 2018).

**Issue: Therapeutic agents**

**Primary Challenges**

- A therapeutic agent’s ability to cross the blood-brain barrier and prevent or reduce the negative 
  impact of ZIKV transmission to a developing fetus without teratogenic effects will be critical in 
determining whether that agent moves forward into clinical trials (Erbeling 2017, Munjal 2017, 
Saiz 2019).

- Although numerous therapeutic agents, involving a variety of anti-ZIKV approaches (e.g., entry 
  receptor inhibitors, viricidal agents, protease inhibitors, fusion inhibitors, replication inhibitors), 
are being evaluated as possible ZIKV therapeutic agents, most are still in discovery or preclinical 
in vitro development and very few have been assessed in animal models. Extrapolation of in 
vitro results to in vivo settings is difficult (Bernatchez 2019, Saiz 2019, Souza 2019).

- Very few phase 1 clinical trials have been initiated for ZIKV therapeutic agents or agents with 
potential anti-ZIKV activity (NIH Zika Therapy Clinical Trials, NIH NCT03891420); therefore, 
additional clinical research is needed before such drugs can enter phase 3 clinical efficacy trials.

- Because studies evaluating possible ZIKV therapeutics have used different methodologies, viral 
strains, and cell types, conflicting results have been reported for the same therapeutic agent 
(Saiz 2019).

- The majority of data on therapeutic use during pregnancy are collected after a drug has been 
licensed (i.e., through post-marketing studies). Developing therapeutics that do not cause harm 
to developing fetuses but can prevent congenital ZIKV infection and CZS will prove challenging 
for drug development and clinical trial design.

- Various monoclonal antibodies (mAbs) have shown promise as ZIKV therapeutic and 
prophylactic candidates. These biologics have a number of advantages; they are specific, can be 
used in combination with other therapies, their production can be quickly scaled up, and 
promising results have been found in both in vitro and animal challenge models (Abbink 2018, Li 
2018, Sun 2017, Wilder-Smith 2018). However, mammalian cell-produced mAbs are time-
consuming and costly to develop, involve concerns regarding possible emergence of resistance to monospecific mAbs, and may theoretically increase the risk of severe disease due to ADE or other immunologic mechanisms following subsequent infection with other flaviviruses (Sun 2017). These drawbacks to mAbs could potentially be addressed by identifying mAbs with targeted neutralizing activity, administering mAb cocktails, or through engineering therapeutic antibodies to mitigate the potential risk of ADE (such as through removal of the Fc receptor binding portion for recombinant mAbs) (Magnani 2017, Sun 2017).

**Key Needs**

- A TPP for ZIKV therapeutics is needed that captures the spectrum of clinical indications for ZIKV therapies (Bernatchez 2019).
- Biomarkers are needed for evaluating the anti-ZIKV activity of potential therapeutic agents.
- Numerous agents with possible anti-ZIKV activity have been identified by screening libraries of bioactive molecules, identifying drugs known to have antiviral activity for repurposing against ZIKV, and testing natural compounds (Saiz 2019). A clearly defined selection process is needed to determine which possible therapeutic agents should advance through preclinical and early clinical research.
- Several therapeutics that are being evaluated as possible anti-ZIKV agents (e.g., sofosbuvir, niclosamide, azithromycin, memantine, nitazoxanide) are already licensed. However, data on use in pregnant women are unavailable for most of these agents and risk-benefit evaluations for use during pregnancy are needed (Cairns 2018, Cao 2017, Souza 2019).
- As potential therapeutic candidates advance through the therapeutic pipeline, protocols for conducting clinical efficacy trials of promising therapeutic candidates in ZIKV-affected areas will be needed, especially during future outbreaks. This process will require harmonized protocols that can be used across multiple geographic sites and potentially across multiple outbreaks.

**Knowledge Gaps**

- Preclinical and clinical data are needed on the safety, tolerability, and efficacy of investigational therapeutic agents, particularly in special populations such as pregnant and lactating women and infants (Bernatchez 2019).
- Preclinical and clinical data are needed on the safety, tolerability, and efficacy of administering combinations of investigational therapeutic agents (e.g., mAbs and antiviral compounds), particularly in special populations.
- Preclinical and clinical data are needed on the safety and efficacy of investigational therapeutic agents to prevent the development of congenital anomalies *in utero*.
- Additional research is needed to develop mAbs that maximize the potential benefits of this approach and minimize the potential downsides, including generating mAb products that are affordable in LMICs at risk for ZIKV (Sun 2017).
- Further research is needed on the potential for repurposing existing drugs (such as sofosbuvir, niclosamide, and nitazoxanide) for ZIKV treatment (particularly for pregnant women), including identifying the mechanisms of action for antiviral effects (Cao 2017, Cheng 2016, Souza 2019). A systems biology approach may be useful for this research (Cheng 2016).
Strategic Goals and Aligned Milestones

**Strategic Goal 1:** Support development and preclinical/early clinical evaluation of novel therapeutic agents (such as mAb cocktails) for the prevention and treatment of congenital ZIKV infection.

*Milestones:*

1. By 2024, develop a TPP for ZIKV therapeutics that identifies optimal and desirable characteristics for ZIKV therapeutic agents, including prevention of vertical transmission and treatment of infected infants.
2. By 2026, create and implement a transparent prioritization process for moving investigational ZIKV therapeutic agents through the therapeutic pipeline.
3. By 2027, complete preclinical evaluation (including NHP studies) of the preliminary safety (including teratogenicity), tolerability, and efficacy of more than one promising mAb candidate for prophylaxis or treatment of congenital ZIKV infection. *(High priority milestone)*
4. By 2030, complete early clinical evaluation of the preliminary safety (including teratogenicity) and tolerability of at least one promising mAb candidate or combination therapy for prophylaxis or treatment of congenital ZIKV infection, to include phase 1 and phase 2 clinical trials. *(High priority milestone)*
5. By 2031, develop a plan to pursue regulatory approval (through efficacy trials or other mechanisms) of any novel therapeutic candidates that successfully complete phase 1 and phase 2 clinical trials.

**Strategic Goal 2:** Further assess the potential to repurpose existing, licensed drugs that demonstrate antiviral activity for use as treatment for or prevention of ZIKV infection.

*Milestones:*

1. By 2025, identify one to three existing, licensed drugs that represent the most promising candidates for drug repurposing as treatment for or prevention of ZIKV infection.
2. By 2029, complete preclinical evaluation in suitable animal models to assess safety (including use during pregnancy) and efficacy of these agents.
3. By 2031, complete at least phase 1 clinical trials for drug safety during pregnancy (including teratogenicity) for at least one of the most promising repurposed agents that may be suitable for treatment of pregnant women.

**Strategic Goal 3:** Develop strategies for assessing clinical efficacy of novel or repurposed therapeutic agents for treatment of ZIKV infection, once promising agents are further along in the development process.

*Milestones:*

1. By 2025, complete a protocol for conducting clinical efficacy trials of promising therapeutic candidates for treatment of ZIKV infection and develop plans for operationalizing the protocol for use during future outbreaks.
2. By 2025, complete a protocol for conducting clinical trials of promising therapeutic candidates for use as prophylactic therapy and develop plans for operationalizing the protocol for use during future outbreaks.

3. By 2028, identify and evaluate one or more biomarkers that are suitable for evaluating antiviral activity of potential therapeutic agents to be used for different clinical indications.

Additional Priority Areas/Activities

Additional Research Needs

- Define the determinants and predictors of congenital anomalies and neurodevelopmental disabilities associated with congenital ZIKV infection to inform development of ZIKV therapeutics.
- Further elucidate the pathophysiology of viral persistence and the impact on ZIKV sexual transmission to inform the development of therapeutic agents.
- Identify which therapeutic treatments may safely be used in combination to treat ZIKV infection and prevent the risk of congenital ZIKV infection and associated abnormalities.
- Determine whether or not specific anti-ZIKV mAbs or mAb cocktails increase the potential risk of severe disease (i.e., ADE) following subsequent infection with other flaviviruses and assess the timeframe for mAb decay in the host and the timeframe following mAb administration where ADE might occur if such a risk exists.
- Research the rate of viral persistence in infants and associated clinical outcomes to determine if therapeutic agents could ameliorate the effects of congenital ZIKV infection.
- Determine if promising therapeutic agents are protective against other flaviviruses to facilitate development of treatment options suitable for multiple infections.
- Assess, on an ongoing basis, whether or not ZIKV strain differences will affect the response to therapeutic candidates and results from clinical trials as promising agents move through the drug pipeline.

Product Development

- Continue to identify small-molecule therapeutic agents with anti-ZIKV properties for preclinical and clinical research and move them through the therapeutic pipeline.
- Promote early communication between developers and appropriate NRAs for clarity and guidance on the regulatory aspects of therapeutic drug development and assessment for ZIKV infection.
- Promote development of therapies that are targeted to treatment of more than one flavivirus.

Key Capacities

- Ensure that a coordinated process is in place to assess efficacy of promising therapeutic agents.

Policy and Commercialization

- Develop guidance to inform the use of ZIKV therapeutic treatments as appropriate for different use cases (e.g., pregnant and lactating women with ZIKV exposure, ZIKV-naïve persons traveling to areas where future ZIKV outbreaks are occurring) as therapies become available.
Secure funding to complete development, licensure, manufacture, and deployment of affordable therapeutics for ZIKV infection.

VACCINES

Primary Challenges, Key Needs, and Knowledge Gaps

Issue: Assessment of candidate ZIKV vaccines

Primary Challenges

- The currently low incidence of ZIKV infection creates challenges for conducting future phase 2 or 3 clinical vaccine trials with adequate statistical power to demonstrate vaccine efficacy (Erbelding 2017, Pattnaik 2020).

- A WHO workshop in 2017 determined that “virologically confirmed ZIKV illness is a convenient and feasible primary end point for a vaccine efficacy trial.” However, since ZIKV illness is often associated with mild symptoms that may be challenging to detect, and 50% to 80% of ZIKV infections are asymptomatic, using symptomatic illness as a clinical endpoint in vaccine efficacy trials will require large sample sizes. Additionally, vaccine efficacy trials will likely only be feasible in the setting of major outbreaks and will necessitate an active trial surveillance component (Erbelding 2017, Musso 2019). In addition, congenital ZIKV infection occurs too infrequently to be chosen as primary clinical endpoints (WHO Efficacy Trials), although these conditions could be monitored via post-marketing surveillance of any licensed vaccines.

- In future outbreak settings, rapid initiation of clinical efficacy studies for candidate ZIKV vaccines will be essential to capture peak disease incidence before the incidence naturally declines (Erbelding 2017). This will require rapid, specific diagnostics to be available prior to vaccine evaluation, along with protocols and field resources that can be rapidly mobilized.

- Traditional vaccine efficacy studies may be challenging or infeasible, given the current epidemiology of ZIKV; therefore, alternative approaches to licensure may be necessary (Vannice 2019).

- Different candidate ZIKV vaccine platforms have varying advantages and disadvantages, which complicates vaccine selection for advancement to clinical trials and advanced vaccine assessment (Wilder-Smith 2018). For example, the safety assessment and regulatory requirements for live, attenuated, replicating-competent ZIKV vaccines will likely require additional data compared to non-replicating vaccine platforms (Wilder-Smith 2018).

Key Needs

- A definitive immune surrogate of protection is desirable for vaccine assessment (which could potentially be used for animal studies, human challenge studies, or field studies), and its development should be pursued through the ongoing nonclinical and clinical evaluation of vaccine candidates.

- In the absence of ZIKV outbreaks, alternative approaches will be needed for vaccine licensure; this will require not only an immune surrogate of protection, but also at least one animal model that has demonstrated relevance to human ZIKV disease and is reasonably likely to predict clinical benefit in humans. A generic, vetted, and agreed-upon core protocol for ZIKV vaccine
efficacy trials is needed for use, as appropriate, in multiple sites in advance of future outbreaks
to allow rapid implementation when outbreaks occur (WHO Efficacy Trials).

- A transparent framework is needed for selecting promising vaccine candidates to be further
evaluated in phase 2b/phase 3 clinical trials (WHO Efficacy Trials).
- Post-marketing assessments will be needed for any approved ZIKV vaccines and strategies for
these evaluations need to be developed, particularly with regard to vaccine adverse event
surveillance and potential safety signals (Vannice 2019).

**Knowledge Gaps**

- Several candidate ZIKV vaccines have entered phase 1 and phase 2 clinical trials (NIH Vaccine
Clinical Trials, Pattnaik 2020, Thomas 2020). Additional studies, however, are needed to
continue to move the current candidates (and any additional promising vaccine candidate) from
preclinical evaluation through the ZIKV vaccine pipeline, particularly through late phase 2 clinical
trials involving expanded safety and immunogenicity assessments (Vannice 2019).
- Field studies in areas at risk for future outbreaks (or during future outbreaks) are needed to
determine if the immune response (or vaccine performance profile) for ZIKV vaccines is different
between persons with and without prior flavivirus immunity (Shan 2018, Thomas 2016).

**Issue: Ongoing vaccine development**

**Primary Challenges**

- Asymptomatic infection in pregnant women with presumed low levels of viremia may result in
congenital ZIKV infection (Paixão 2018); therefore, ZIKV vaccines will need to be highly effective
or be able to induce sterilizing immunity to prevent ZIKV vertical transmission during pregnancy.
- Vaccine developers use different neutralization assays, which creates challenges for comparing
vaccine candidates (Barrett 2018).
- Different vaccine constructs or different levels of vaccine efficacy may be needed to provide
protection against different modes of ZIKV transmission and to protect population groups with
distinctly different infection risks (e.g., pregnant women, fetuses, women and men of
childbearing age, prepubescent children, those with past exposure to ZIKV or other flaviviruses)
(Poland 2018).
- ZIKV occurs in geographic areas where other flaviviruses co-circulate. This adds complexity to
the development and clinical trial assessment of ZIKV vaccines, since the immunologic
implications of cross-reactive immune responses between ZIKV and other flaviviruses are
antibodies to flaviviruses may pose potential risks for more severe disease (i.e., ADE) as was
suggested in at least one human cohort (Katzelnick 2020). The occurrence of ADE following
natural infection or potentially vaccination has been demonstrated for DENV and is a concern
for ZIKV, particularly for subsequent DENV infection following ZIKV vaccination (Poland 2018,

**Key Needs**
• WHO developed a TPP for ZIKV vaccines intended for use in outbreak settings (WHO UNICEF ZIKV Vaccine TPP) and a set of preferred product characteristics (PPCs) for ZIKV vaccines for endemic use (WHO PPC). However, a TPP for preventive use is also needed to facilitate development of vaccines targeted to broader, routine use in at-risk areas (Thomas 2016).

• Researchers and vaccine developers/manufacturers may not be incentivized to engage in ZIKV vaccine R&D due to the complicated and country-specific regulation and oversight involved with vaccine clinical trials, approval, licensing, and distribution. Additionally, concerns regarding risks of vaccines promulgating more severe disease through ADE or other mechanisms and risks of involving pregnant women in research studies (e.g., possible harm to women, developing fetuses, and the children born to women participating in research) may deter ZIKV vaccine R&D. Governing, advisory, and financial leaders (e.g., NRAs, advisory committees, funders) should consider implementing incentives to address vaccine R&D deterrents, such as regulatory fee exemptions, tax credits, expedited patent review, and trial insurance and indemnification programs (PREVENT Working Group).

Knowledge Gaps

• Additional research is needed to determine if sterilizing immunity (or elimination of detectable viremia) is required to prevent seeding of the placenta and subsequent vertical transmission and to determine the neutralization titer needed to achieve that level of immunity (Barrett 2018, Garg 2018, Richner 2018).

• More research is needed in appropriate animal models to determine whether or not: (1) vaccination after onset of pregnancy can prevent vertical transmission, (2) a different regimen is needed for pregnant women, and (3) vaccination of pregnant women requires both cellular and humoral immunity, which may involve unique vaccine constructs (Shan 2018).

• Further efforts are needed to define and characterize the epitopes responsible for virus-specific neutralizing antibodies (Shan 2018).

• More research is needed to determine if pre-existing cross-reactive antibodies to co-circulating flaviviruses dampen the effectiveness of ZIKV vaccines (Poland 2018, Richner 2018).

• Further research is needed to characterize the ability of anti-ZIKV immunity (through natural infection or vaccination) to cause more severe disease through ADE or other immune mechanisms for other flavivirus infections, particularly DENV infection, since the geographic distributions for these viruses often overlap (Culshaw 2018, Langerak 2019, Poland 2018, Richner 2018, Shan 2018, Thomas 2016). Specifically, clinical studies are needed to examine these risks and to develop an overall understanding of the potential for ADE in the context of ZIKV vaccination in populations where flaviviruses co-circulate (Andrade 2018, Katzelnick 2020, Langerak 2019, Pattnaik 2020). Since ADE could be an uncommon event, this issue may be difficult to assess in clinical trials and post-marketing safety studies will be needed.

• Research is needed to fully characterize the mechanisms of ZIKV-induced adaptive immunity, including the roles of neutralizing and non-neutralizing antibodies, and T cell-mediated immune responses (Culshaw 2017, Poland 2018, Shim 2019, Subramaniam 2020).

Issue: Programmatic implementation
Primary Challenges
- The substantial global temporal and spatial heterogeneity of ZIKV infection incidence creates challenges for developing cohesive strategies for implementation of ZIKV vaccination programs.
- Many research questions still need to be addressed for elucidating the immunologic response to ZIKV infection, identifying the optimal platforms and attributes for ZIKV vaccines, clarifying critical issues around vaccine safety, and determining risk-benefit profiles for different vaccination strategies.

Key Needs
- ZIKV vaccines are needed that are low-cost and suitable for wide-scale use in LMICs (Garg 2018, Poland 2018). Examples of suitability issues include ease of administration, simple dosing schedules, and manageable cold-chain requirements.
- Data from developmental and reproductive toxicology (DART) studies are needed for candidate vaccines before clinical trials involving pregnant or lactating woman are conducted.
- Strategies for using ZIKV vaccines will be needed once vaccines become available (Thomas 2016). Issues include determining whether or not vaccines will be intended for reactive use during outbreaks or for preventive use in areas at risk for future outbreaks, identifying target populations for vaccination, and clarifying what routes of transmission vaccines will be expected to prevent.

Knowledge Gaps
- More information is needed to determine whether or not vaccination programs can interrupt epidemic transmission, and if so, what type of vaccination strategy is needed to do so (Poland 2018).
- More information is needed regarding the durability of immunity induced by different vaccine candidates in flavivirus-naïve and flavivirus-immune recipients, since nonclinical studies to date have involved relatively short follow-up timelines (Barrett 2018). This will inform development of vaccination strategies.
- Modeling research is needed to define triggers for initiating a vaccination program in response to a ZIKV outbreak (WHO Technology Roadmap).
- Further research is needed to determine whether or not achieving high titers of neutralizing antibodies in flavivirus-naïve and flavivirus-immune recipients will require multiple doses of vaccine or use of novel vaccine approaches, such as heterologous prime-boost strategies using two different vaccine platforms (Barrett 2018).

Strategic Goals and Aligned Milestones

Strategic Goal 1: Develop the capability to use alternative approaches for evaluating and licensing candidate ZIKV vaccines (e.g., through the US FDA Accelerated Approval Program or the European Medicines Agency [EMA] Accelerated Assessment).

Milestones:
1. By 2025, generate standardized definitions for vaccine adverse events of interest for ZIKV vaccines to be used for post-marking surveillance (WHO Technology Roadmap).

2. By 2026, identify the best biomarker for protection against in utero infection in an appropriate animal pregnancy model (Vannice 2019).

3. By 2026, develop consensus on methodologic approaches for post-marketing evaluation of ZIKV vaccines, particularly with regard to detecting uncommon outcomes (such as CZS) and potential vaccine adverse events, such as ADE for subsequent flavivirus infections (particularly DENV infections).

4. By 2028, identify an immune correlate/surrogate of protection that aligns with an international standard and is able to predict a reasonable likelihood of clinical benefit for one or more ZIKV vaccines (e.g., for use in animal challenge studies with subsequent extrapolation to humans) (Vannice 2019). (High priority milestone)

5. By 2028, ensure that the necessary requirements are in place to allow licensure of candidate ZIKV vaccines through alternative regulatory approval pathways. (High priority milestone)

**Strategic Goal 2:** Enhance preparedness for conducting clinical vaccine efficacy studies in the event of future ZIKV outbreaks (e.g., conducting confirmatory trials if one or more ZIKV vaccines are licensed via the US FDA Accelerated Approval Program).

**Milestones:**

1. By 2024, determine a transparent process and criteria for identifying vaccine candidates that are most suitable to move forward into clinical efficacy trials (to be initiated during future outbreaks).

2. By 2025, address ethical and regulatory issues for including and excluding pregnant and lactating women in ZIKV vaccine efficacy/effectiveness studies (PREVENT Working Group).

3. By 2025, establish a harmonized protocol (i.e., with a consistent set of end points, target populations, and trial design) for vaccine efficacy studies to be used across multiple study sites, as appropriate, and obtain ethical approvals in advance, to allow rapid implementation when future ZIKV outbreaks emerge. (High priority milestone)

4. By 2029, ensure that adequate supplies of selected vaccine candidates are readily available for performing phase 3 clinical efficacy trials or confirmatory phase 4 efficacy studies when outbreaks occur.

**Strategic Goal 3:** Further evaluate ZIKV vaccine candidates through preclinical and clinical research and promote licensure of ZIKV vaccines for different target populations.

**Milestones:**

1. By 2025, publish a TPP for ZIKV vaccines for preventive/routine use that complements the existing PPC document (WHO Technology Roadmap).

2. By 2025, review the current status of the ZIKV vaccine pipeline to identify gaps for moving ZIKV vaccines through the pipeline and create a pathway for addressing the gaps.

3. By 2026, complete preclinical research on at least three promising ZIKV vaccine candidates that demonstrate efficacy in suitable animal models.

4. By 2026, complete DART studies on at least three promising ZIKV vaccine candidates.
5. By 2027, complete at least three phase 1 clinical trials, as appropriate, using different vaccine candidates in healthy volunteers to assess vaccine safety and immunogenicity.

6. By 2027, advance at least three vaccine candidates into phase 2/expanded phase 2 trials in defined populations.

7. By 2027, conduct at least one study in an at-risk area to determine if the vaccine performance profile for one or more candidate ZIKV vaccines is different in persons with and without prior flavivirus immunity (particularly DENV immunity).

8. By 2028, ensure that at least two vaccine candidates are available that are suitable for phase 3 clinical trials or alternative efficacy assessment approaches.

9. By 2029, engage with regulatory authorities to ensure that at least one ZIKV vaccine that induces rapid onset of protective immunity is licensed for use (or approved for emergency use) during future outbreaks and is targeted to healthy adults. (High priority milestone)

10. By 2031, engage with regulatory authorities to ensure that at least one ZIKV vaccine that induces rapid onset of protective immunity is licensed for use during future outbreaks and is targeted to pregnant women. (High priority milestone)

Strategic Goal 4: Improve understanding of the humoral and cell-mediated immune responses to ZIKV infection to inform vaccine development.

Milestones:
1. By 2026, conduct nonclinical studies using several different candidate vaccines in appropriate animal models using standardized assays to determine what level of immunity is needed to prevent vertical transfer of ZIKV following maternal infection (e.g., determine whether or not sterilizing immunity is needed).

2. By 2027, conduct studies in appropriate animal model(s) using several different candidate vaccines to determine if vaccination after onset of pregnancy can prevent vertical transmission.

3. By 2028, conduct nonclinical studies using several different candidate vaccines to determine if ZIKV antibodies generated through vaccination contribute to ADE with subsequent DENV infection or infection with other flaviviruses.

Additional Priority Areas/Activities

Additional Research Needs

- **Continue to characterize** the mechanisms of ZIKV-induced adaptive immunity in humans, including the roles of neutralizing and non-neutralizing antibodies, and T cell-mediated immune responses (Culshaw 2017, Poland 2018, Shim 2019).

- **Conduct** clinical assessments to determine vaccine performance in different at-risk population groups for candidate ZIKV vaccines that reach advanced stages of development.

- **Refine** vaccine dosing regimens for use of vaccines in pregnant women.

Product Development

- **Complete** efficacy assessment for one or more promising ZIKV vaccine candidates, either through traditional clinical efficacy studies or through alternative approaches.
• Encourage governing, advisory, and financial leaders to develop incentives to stimulate ZIKV vaccine R&D, such as exemption from regulatory fees and indemnification programs (PREVENT Working Group).

• Continue to assess promising vaccine candidates for preventive, routine use in at-risk areas (once the TPP for routine use is available).

Key Capacities

• Develop capacity to conduct post-marketing surveillance in areas targeted for ZIKV vaccination for ongoing assessment of vaccine efficacy, particularly in preventing rare complications, and ongoing assessment of vaccine safety (e.g., vaccine safety in special populations such as pregnant women).

• Strengthen capacity to conduct clinical trials during future outbreaks, using outbreak forecasting and modeling to predict areas of highest risk.

• Ensure access to low cost vaccine manufacturing using current Good Manufacturing Practices for commercial production of ZIKV vaccines (WHO Technology Roadmap).

• Support plans for adequate manufacturing and stockpiling of the most promising candidate ZIKV vaccines for further clinical evaluation and use when outbreaks occur.

Policy and Commercialization

• Provide guidance on vaccination strategies for various target populations that align with vaccine attributes, once vaccines are available.

• Define triggers for initiating a ZIKV vaccination program in response to future ZIKV outbreaks, using modeling techniques.

• Develop guidance for community sensitization to vaccine acceptance and promotion within the community (WHO Technology Roadmap).
BACKGROUND INFORMATION


Andrade DV, Harris E. Recent advances in understanding the adaptive immune response to Zika virus and the effect of previous flavivirus exposure. Virus Res 2018;254:27-33 [Abstract]


Barrett ADT. Current status of Zika vaccine development: Zika vaccines advance into clinical evaluation. NPJ Vaccines 2018 Jun;3:24:s41541-018-0061-9 [Full text]


CDC (Centers for Disease Control and Prevention). Congenital Zika syndrome & other birth defects. Last reviewed 2020 Apr 23 [Webpage]

CDC. What we know about Zika and pregnancy. Last reviewed 2020 Apr 23 [Webpage]

CDC. Zika symptoms. Last reviewed 2019 May 21 [Webpage]

CDC. Zika virus testing guidance. Last reviewed 2019 Dec 9 [Webpage]

Charrel RN, Leparc-Goffart I, Pas S et al. Background review for diagnostic test development for Zika virus infection. Bull World Health Organ 2016 Aug 1;94(8):574-584D [Full text]


Chua A, Prat I, Nuebling CM, et al. Update on Zika diagnostic tests and WHO’s related activities. PLoS Negl Trop Dis 2017 Feb;11(2) (Epub ahead of print) [Full text]


Culshaw A, Mongkolsapaya J, Screaton G. The immunology of Zika virus. F1000Res 2018 Feb 19;7:203 [Full text]


Duggal NK, McDonald EM, Weger-Lucarilli J, et al. Mutations present in a low-passage Zika virus isolate result in attenuated pathogenesis in mice. Virology 2019 Apr;530:19-26 [Full text]


Garg H, Mehmetoglu-Gurbuz T, Joshi A. Recent advances in Zika virus vaccines. Viruses 2018 Nov 14;10(11):631 [Full text]


Krow-Lucal ER, Biggerstaff BJ, Staples JE. Estimated incubation period for Zika virus disease. Emerg Infect Dis 2017 May;23(5):841-5 [Full text]


Landry ML, St. George K. Laboratory diagnosis of Zika virus infection. Arch Pathol Lab Med 2016 Oct 20 (Epub ahead of print) [Full text]


Miner JJ, Diamond MS. Zika virus pathogenesis and tissue tropism. Cell Host Microbe 2017 Feb 8;21(2):134-42 [Full text]


Munjal A. Advances in developing therapies to combat Zika virus: current knowledge and future perspectives. Front Microbiol 2017 Aug 3;8:1469 [Full text]


Ng DHL, Ho JF, Chow A, et al. Correlation of clinical illness with viremia in Zika virus disease during an outbreak in Singapore. BMC Infect Dis 2018;18:301 [Full text]


PAHO (Pan American Health Organization). PAHO/WHO regional research agenda related to Zika virus infection. 2016 [Full text]
Paixão ES, Teixeira MG, Rodrigues LC. Zika, chikungunya and dengue: the causes and threats of new and re-emerging arboviral diseases. BMJ Glob Health 2018 Jan 4;3:e000530 [Full text]


Pierson TC, Diamond MS. The emergence of Zika virus and its new clinical syndromes. Nature 2018;560(7720):573-81 [Abstract]


Roberts CC, Maslow JN. Assay challenges for emerging infectious diseases: the Zika experience. Vaccines (Basel) 2018 Oct 2;6(4):E70 [Full text]

1414 Saiz J-C. Therapeutic advances against ZIKV: a quick response, a long way to go. Pharmaceuticals (Basel) 2019 Aug 30;12(3):E127 [Full text]
1420 Shan C, Xie X, Shi P-Y. Zika virus vaccine: progress and challenges. Cell Host Microbe 2018 Jul 11;24(1):12-7 [Full text]
1438 Souza INO, Barros-Aragão FGQ, Frost PS, et al. Late neurological consequences of Zika virus infection: risk factors and pharmaceutical approaches. Pharmaceuticals (Basel) 2019 Apr 17;12(2):60 [Full text]
1453 Thomas SJ, Barrett A. Zika vaccine pre-clinical and clinical data review with perspectives on the future development. Hum Vaccin Imunother 2020 Jul 23;1-13 [Abstract]
US FDA (US Food and Drug Administration). FDA authorizes marketing of first diagnostic test for detecting Zika virus antibodies. 2019 May 23 [Webpage]

US FDA. 510(k) premarket notification. Last updated 2019 Oct 7 [Webpage]

US FDA. Zika virus response updates from the FDA. Last updated 2020 Feb 20 [Webpage]


WHO (World Health Organization). Efficacy trials of ZIKV vaccines: endpoints, trial design, site selection. 2017 [Full text]

WHO. Fair pricing forum: informal advisory group meeting. 2017 [Full text]

WHO. Fifth meeting of the emergency committee under the International Health Regulations (2005) regarding microcephaly, other neurological disorders and Zika virus. 2016 Nov 18 [Webpage]

WHO. Preferred product characteristics (PPC) for Zika vaccines for endemic use. 2019 [Full text]

WHO. Target product profiles for better diagnostic tests for Zika virus infection. 2016 Apr 13 [Full text]

WHO. Zika epidemiology update. 2016 Apr 13 [Full text]

WHO. Zika vaccine development technology roadmap. 2019 Apr [Full text]

WHO. Zika virus disease - France. 2019 Apr 13 [Webpage]

WHO. Zika virus disease: interim case definitions. 2016 [Webpage]

WHO. Zika virus research agenda. 2016 Oct [Full text]


Zanluca C, de Noronha L, Duarte dos Santos CN. Maternal-fetal transmission of the Zika virus: an intriguing interplay. Tissue Barriers 2018 Jan 2;6(1):e1402143 [Full text]
### Cross-Cutting Issues

**Strategic Goal 1:** Ensure that adequate tools are available for conducting additional research on ZIKV virology, transmission, and pathogenesis to facilitate development of ZIKV MCMs.

- **Milestone 2:** By 2026, (1) obtain further guidance from regulatory authorities on key characteristics that animal models require to support regulatory review of ZIKV MCMs, (2) develop consensus on the most appropriate animal model(s) that can be used to infer efficacy of vaccines and therapeutics in humans, and (3) define use criteria for those animal models (such as route, dose, and strain).

- **Milestone 3:** By 2026, generate a well-developed, standardized CHIM for ZIKV (particularly for use in the absence of ongoing ZIKV outbreaks) and define parameters for use (e.g., challenge strain, challenge dose, route of challenge administration and delivery) (*Erbelding 2017, Vannice 2019*).

- **Milestone 4:** By 2027, (1) conduct a review of existing ZIKV assays and determine if currently available assays are adequate for ZIKV clinical, epidemiologic, surveillance, and research purposes (e.g., are regionally applicable, can assess population based immunity, and can distinguish ZIKV from other flaviviruses); (2) identify any gaps in the existing landscape of assays; (3) generate new assays as needed based on the gap analysis; and (4) ensure that an international standard is available to assess new or existing ZIKV assays.

### Diagnostics

**Strategic Goal 1:** Foster an enabling environment to support ongoing research and evaluation of ZIKV diagnostics (*Peeling 2018*).

- **Milestone 4:** By 2026, ensure that a virtual repository of clinical reference samples (including various sample types [e.g., serum, cerebrospinal fluid, urine, amniotic fluid] collected at different times after infection or illness onset) for ZIKV and other medically important flaviviruses as possible, to be used for assessing diagnostic agents, is operational in various geographic areas at risk for ZIKV emergence/reemergence (particularly in areas of the world other than the Americas) to reflect local/regional flavivirus epidemiology and to build up sustainable infrastructure in settings with limited resources and storage capacity.

**Strategic Goal 3:** Develop highly sensitive and specific, cost-effective, and affordable molecular and serologic diagnostic tests for ZIKV (potentially including point-of-care tests) that align with the WHO TPP;

- **Milestone 4:** By 2028, ensure that at least one well-validated ZIKV-specific diagnostic assay that aligns with the WHO TPP, can distinguish among flaviviruses in different regions, and can identify recency of infection is available for use in the general population (and specifically in pregnant women) in countries at risk of ZIKV.
are appropriately robust for the conditions in which they will be used and for different use case scenarios (e.g., emergency use, surveillance, clinical efficacy studies); can distinguish among flaviviruses in different geographic regions; and have minimal requirements for laboratory capacity and staff training.

- **Milestone 5**: 2028, ensure that at least one well-validated ZIKV-specific point-of-care diagnostic assay that aligns with the WHO TPP is available for use in countries at risk of ZIKV outbreaks and develop guidelines for appropriate indications for use of point-of-care assays (such as for surveillance purposes in low-resource areas, for use in pregnant women when recommending treatment [if and when effective treatments become available] or as an initial screening test to identify asymptomatically infected pregnant women).

- **Milestone 6**: By 2029, ensure that at least one highly sensitive and specific serologic test is available to assess the presence/absence ZIKV protective immunity in reproductive-aged women prior to pregnancy or during pregnancy.

- **Milestone 8**: By 2029, ensure that at least one diagnostic test (or test combination) is available that is appropriate for use in clinical vaccine efficacy studies (i.e., that regulatory agencies will accept as definitive evidence of ZIKV infection).

- **Milestone 9**: By 2030, ensure that at least one well-validated ZIKV-specific diagnostic assay is available for diagnosis of congenital ZIKV infection.

### Therapeutics

**Strategic Goal 1**: Support development and preclinical/early clinical evaluation of novel therapeutic agents (such as mAb cocktails) for the prevention and treatment of congenital ZIKV infection.

- **Milestone 3**: By 2027, complete preclinical evaluation (including NHP studies) of the preliminary safety (including teratogenicity), tolerability, and efficacy of more than one promising mAb candidate for prophylaxis or treatment of congenital ZIKV infection.

- **Milestone 4**: By 2030, complete early clinical evaluation of the preliminary safety (including teratogenicity) and tolerability of at least one promising mAb candidate or combination therapy for prophylaxis or treatment of congenital ZIKV infection, to include phase 1 and phase 2 clinical trials.

### Vaccines

**Strategic Goal 1**: Develop the capability to use alternative approaches for evaluating and licensing candidate ZIKV vaccines (e.g., through the US FDA Accelerated Approval Program or the European Medicines Agency [EMA] Accelerated Assessment).

- **Milestone 4**: By 2028, identify an immune correlate/surrogate of protection that aligns with an international standard and is able to predict a reasonable likelihood of clinical benefit for one or more ZIKV vaccines (e.g., for use in animal challenge studies with subsequent extrapolation to humans) (Vannice 2019).

- **Milestone 5**: By 2028, ensure that the necessary requirements are in place to allow licensure of candidate ZIKV vaccines through alternative regulatory approval pathways.
| Strategic Goal 2: Enhance preparedness for conducting clinical vaccine efficacy studies in the event of future ZIKV outbreaks (e.g., conducting confirmatory trials if one or more ZIKV vaccines are licensed via the US FDA Accelerated Approval Program). | • **Milestone 3**: By 2025, establish a harmonized protocol (i.e., with a consistent set of end points, target populations, and trial design) for vaccine efficacy studies to be used across multiple study sites, as appropriate, and obtain ethical approvals in advance, to allow rapid implementation when future ZIKV outbreaks emerge. |
| Strategic Goal 3: Further evaluate ZIKV vaccine candidates through preclinical and clinical research and promote licensure of ZIKV vaccines for different target populations. | • **Milestone 9**: By 2029, engage with regulatory authorities to ensure that at least one ZIKV vaccine that induces rapid onset of protective immunity is licensed for use (or approved for emergency use) during future outbreaks and is targeted to healthy adults.  
• **Milestone 10**: By 2031, engage with regulatory authorities to ensure that at least one ZIKV vaccine that induces rapid onset of protective immunity is licensed for use during future outbreaks and is targeted to pregnant women. |
### APPENDIX 2

#### ACRONYMS

- **ADE** Antibody-dependent enhancement
- **ASSURED** Affordable, Sensitive, Specific, User-friendly, Rapid and Robust, Equipment-free, and Delivered to the end-user
- **CHIM** Controlled Human Infection Model
- **CZS** Congenital Zika syndrome
- **DART** Development and reproductive toxicology
- **DENV** Dengue virus
- **EMA** European Medicines Agency
- **EUA** Emergency Use Authorization
- **EUAL** Emergency Use Assessment and Listing
- **FDA** Food and Drug Administration
- **GBS** Guillain-Barré Syndrome
- **IgM** Immunoglobulin M
- **JEV** Japanese encephalitis virus
- **LMICs** Low- and middle-income countries
- **mAb** Monoclonal antibody
- **MCM** Medical countermeasure
- **NAAT** Nucleic acid amplification test
- **NHP** Nonhuman primate
- **NRA** National regulatory authority
- **PAHO** Pan American Health Organization
- **PHEIC** Public Health Emergency of International Concern
- **PPC** Preferred product characteristic
1561  PRNT  Plaque reduction neutralization test
1562  R&D  Research and development
1563  RNA  Ribonucleic acid
1564  RT-LAMP  Reverse transcription loop-mediated isothermal amplification
1565  TPP  Target Product Profile
1566  WHO  World Health Organization
1567  WNV  West Nile virus
1568  YFV  Yellow fever virus
1569  ZIKV  Zika virus