Zika Virus
Research and Development (R&D) Roadmap

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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 ZIKV 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 2016a). The WHO ended the PHEIC declaration in November 2016 (Wilder-Smith 2020). Although the epidemic in the Americas has waned and ZIKV incidence in the region has declined dramatically, ZIKV remains a global public health concern, as evidenced by local outbreaks in Cuba (2017) and India (2018), and periodic cases associated with local transmission or travel (CDC Zika Statistics and Maps, ECDC 2021, Grubaugh 2019, Watts 2019). As of July 2019, 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 August 2019, three autochthonous, mosquito-borne ZIKV cases were identified in France, increasing ZIKV’s reach to a fifth WHO Region (Durand 2020, Giron 2019). 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-Rouzyrol 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: What we know about ZIKA and pregnancy). Infants born with congenital ZIKV infection may exhibit a range of findings, such as brain atrophy and asymmetry, abnormally formed or absent brain structures, hydrocephalus, neuronal migration disorders, hyperreflexia, irritability, tremors, seizures, brainstem dysfunction, and eye abnormalities (such as optic nerve hypoplasia or atrophy, other retinal lesions, cataracts, and intraocular calcifications) (CDC: CZS and other birth defects). Infants who exhibit a specific combination of five findings (microcephaly in which the skull is partially collapsed, decreased brain tissue, damage to the back of the eye, congenital contractures, and hypertonia restricting body movement) may be diagnosed with congenital Zika syndrome (CZS) (CDC: CZS and other birth defects, Moore 2017). The full spectrum and long-term sequelae of congenital ZIKV infection, however, requires further clarification through longitudinal cohort 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 facilitate development of 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 ZIKV and related flaviviruses following infection or vaccination.

The ZIKV R&D roadmap is a key component of the WHO R&D Blueprint initiative (WHO 2016b) 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. Furthermore, as natural immunity to ZIKV wanes in areas where outbreaks have occurred and naïve birth cohorts reach reproductive age, areas with past outbreaks will be at risk of recurrent outbreaks. Outbreaks in new areas have the potential to occur at any time, given the presence of
suitable mosquito vectors across much of the globe. Preparedness against future ZIKV outbreaks, therefore, is an ongoing urgent public health concern.

The Blueprint initiative calls for the development of R&D roadmaps to align and stimulate R&D of accurate diagnostic assays, novel therapeutics, and effective vaccines for individual priority pathogens, rather than developing broad countermeasures that are applicable to multiple pathogens (e.g., strategies tailored to multiple mosquito-borne flaviviruses or mosquito-vector control). The scope of R&D addressed in this roadmap ranges from basic research to late-stage development of specific 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.) Approval of new MCMs will require input from national regulatory authorities (NRAs), particularly if non-traditional approval pathways are to be utilized. This document mentions regulatory approval pathways from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as examples, but other NRAs will have their own approaches and expectations that will need to be taken into consideration when seeking regulatory approval of new MCMs in different countries and diverse geographic regions. Convergence of expectations for regulatory approval across NRAs would simplify the approval process; however, this may be difficult to achieve.

While other issues are critical to successful prevention and control of ZIKV disease, they are outside the scope of this roadmap, given the WHO R&D Blueprint framework is focused on diagnostics, therapeutics, and vaccines. One particularly high-priority area is the need for improved vector control; this was identified as a critical issue in the 2016 WHO Zika Virus Research Agenda (WHO 2016b), which highlighted the importance of establishing vector control surveillance systems in at-risk areas and evaluating community-directed interventions (such as the use of Wolbachia biocontrol methods, transgenic mosquitoes, etc.). Preliminary results of a recent trial supported by the World Mosquito Program (WMP) in Yogyakarta, Indonesia, found a 77% reduction in dengue incidence over a 2-year period following release of Wolbachia-carrying mosquitoes in the area (Callaway 2020). These results and other recent reports suggest that the use of Wolbachia-carrying mosquitoes could reduce the transmission of ZIKV and other arthropod-borne viruses (arboviruses) (such as dengue, chikungunya, and yellow fever viruses). Efforts are needed to further assess this approach and other next-generation strategies for vector control, but they are beyond the scope of this document. The recently adopted WHO Global Vector Control Response (2017-2030) provides further information to reduce the burden and threat ZIKV and other arboviruses through the application of effective, locally adapted, and sustainable interventions (WHO 2017a). Examples of other important issues that are critical to successful ZIKV infection prevention and control, but are also outside the scope of this document, include ensuring access to contraception methods during ZIKV outbreaks as a public health measure, implementing adequate infrastructure to deploy MCMs, and promoting workforce development and training in endemic and at-risk regions.

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 and support from national health authorities, it will be difficult to achieve the goals and milestones identified in this roadmap; therefore, international partners (including academia, industry, government scientists and regulators, and non-government organizations) will need to work together to creatively identify the resources required to realize the important objectives outlined in this R&D roadmap. Furthermore, efforts should be undertaken to ensure equitable implementation of the roadmap in different geographic regions, given that ZIKV is a global public health threat. 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.

Certain milestones are identified as high priority in this roadmap. Although all 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 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-Lucal 2017, Fourié 2018, Ng 2018, Ximenes 2019).

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

- Coinfection involving ZIKV and other flaviviruses can occur, since such viruses often co-circulate in at-risk areas; this may contribute to epidemiologic and clinical implications for improving understanding of ZIKV epidemiology and clinical features.

- Global ZIKV distribution may vary over time with changes in vector dynamics, potential for viral persistence in animal reservoirs following outbreaks, 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.

- The COVID-19 pandemic has reduced financial and worker resources from disease surveillance and public health prevention of other infections, such as ZIKV and other arboviral infections.

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 known risk areas (during and between outbreaks) and to monitor the
emergence of ZIKV in other geographic areas (particularly Africa and Asia). Improved surveillance and better diagnostic testing could potentially identify areas with stable endemic transmission that could serve as sites for evaluation of ZIKV MCMs.

- 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 2017b).

- Early identification and neurodevelopmental follow-up are needed for infants with congenital ZIKV infection or perinatal infection to facilitate their access to support and rehabilitation services. A biomarker for identifying in utero ZIKV infection would be useful in early identification of such infants.

- Well-characterized longitudinal observational studies involving existing cohorts of children need to continue to better understand the long-term sequelae associated with congenital or perinatal ZIKV infection.

**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 for developing fetuses, such as CZS and other congenital anomalies and neurodevelopmental disabilities (Andrade 2018, Laureti 2018).

- Research is needed to better understand vertical transmission, to include determining 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, Honein 2017, Pomar 2021). 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.

- More information is needed to determine the key factors (e.g., level of viremia, antibody titers, etc.) that lead to CZS and other significant congenital anomalies and neurodevelopmental disabilities. Such information will inform the development of potentially effective vaccines that may be based on attenuation or inactivation of ZIKV and which may cause an initial low transient rise in levels of viremia.

- Better understanding is needed of clinical syndromes after birth, including: (1) the natural history of children born with severe birth defects consistent with CZS, (2) the risk for and patterns of neurodevelopmental disabilities in children with congenital ZIKV infection but no apparent effects at birth, and (3) the risk for adverse health and developmental outcomes with postnatal infection in the neonatal or infant period.

- 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. 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

- The lack of detected congenital disease in Africa is not well understood and may be due to a variety of factors, including phenotypic variations between African and Asian strains, underreporting, misdiagnosis, or immune protection resulting from ZIKV or related African flavivirus infection prior to puberty (Aliota 2017, Haddow 2016).
- Because of the extensive serologic cross-reactivity between flaviviruses, more research is needed regarding the implications of coinfections with other flaviviruses on the epidemiology, clinical manifestations, and transmission of ZIKV; this may require large-scale observational clinical studies with detailed laboratory analysis.
- More research is needed to evaluate the potential risk of severe dengue or other flaviviral infection following a primary ZIKV infection and conversely.
- Ecological surveillance studies of ZIKV in arboreal mosquitoes and associated animal populations (such as nonhuman primates [NHPs]) are needed to identify potential ZIKV animal reservoirs and to clarify sylvatic transmission cycles in forested areas (Valentine 2019) to evaluate the potential for re-emergence of ZIKV. Experimental infections of potential reservoir hosts would also be useful as part of this research effort.
- Further research is needed to understand sexual transmission of ZIKV, including elucidating 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).
- Better understanding is needed regarding the viral, host, and immune factors involved in the pathogenesis of acute and long-term neurological complications, including GBS, triggered by ZIKV infection in adults (Muñoz 2016).
- 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, Hung 2021, Pettersson 2018, WHO Technology Roadmap). Additional information is needed to better elucidate genotypic and phenotypic differences between African and Asian strains of ZIKV, particularly with regard to their pathogenesis (Hung 2021), and 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, areas where future outbreaks occur may not have the expertise or experience to conduct clinical trials or possess the necessary research support resources.

• Different countries have assigned different biosafety levels for working with ZIKV; this can be a challenge in countries where Biosafety Level-4 (BSL-4) containment is required.

**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, Durbin 2017, 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.
Benchmark parameters for challenge route, genetically defined strain, and dose also are needed, as they may impact pathogenesis (Azar 2018, Duggal 2019). For example, the intradermal route may be most likely to mimic natural infection.

- Early and recurrent communications are needed between product developers and the appropriate 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 to be used during future outbreaks. Improved surveillance and epidemiologic data will be critical to identifying these areas in advance (e.g., ongoing surveillance for ZIKV infection [to be differentiated from other flavivirus infections], serosurveillance surveys to define areas of risk, surveillance for CZS in neonates, etc.).

- 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 childbearing 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, along with efforts to sustain and maintain such infrastructure.

**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).

- Research is needed to identify the genetic determinants regarding the epidemiological fitness of different ZIKV strains.
**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 2023, generate an inventory of available animal models that most closely recapitulate CZS or other congenital anomalies associated with ZIKV infection and assess how different infecting strains (e.g., African vs. Asian lineage) influence the clinical presentation and outcome in those animal models.

2. By 2024, (1) obtain further guidance from regulatory authorities on key characteristics that animal models require to support regulatory approval 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, (3) define measurable endpoints for use of animal models (e.g., viremia, survival, CZS manifestations), and (4) define the parameters used for those animal models (such as route, dose, and virus/animal strain). *(High priority milestone)*

3. By 2024, (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 infection or past vaccination against 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) (or an update of the current international standard [NIBSC 2021] as needed) and validation panels are available to assess new or existing ZIKV assays. *(High priority milestone)*

4. By 2025, generate a well-developed, standardized CHIM for ZIKV (particularly for use in the absence of ongoing ZIKV outbreaks); define parameters for use (e.g., challenge strain, challenge dose, route of challenge administration and delivery, and exclusion criteria); and develop carefully considered risk mitigation strategies *(Durban 2017, Erbelding 2017, Vannice 2019)*. *(High priority milestone)*

5. By 2025, standardize and optimize the most relevant animal model(s) and reference virus strains for those models 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 2024, 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 sentinel surveillance projects [potentially combined with seroprevalence studies] 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. This may involve enhancing laboratory-based surveillance or developing acute febrile illness (AFI) syndromic surveillance with appropriate diagnostic testing for ZIKV and other infectious diseases as appropriate.

**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 2024, develop a full public health value proposition, as feasible based on existing data, 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 2024, generate a private-sector value proposition for ZIKV 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 2025, 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 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). This may help identify pockets of naïve populations and track the emergence of naïve cohorts or waning immunity in prior exposed cohorts. **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 for maternal transmission to fetuses or infants (including differences in vertical transmission based on trimester of pregnancy and the potential role of transmission from mother to infant via breast milk), as possible, given the current epidemiologic landscape of ZIKV infection.
- **Better define** the role of sexual transmission for ZIKV and its impact on ZIKV epidemiology, 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.
- **Improve understanding** of the differences between African and Asian strains of ZIKV and how that may impact the epidemiology and risk of infection in different areas.
- **Monitor** the geographic distribution of known and potential ZIKV mosquito vectors over time, which may influence outbreak forecasting efforts and identify areas of potential risk.
- **Continue to conduct** long-term follow-up to clarify the long-term sequelae of congenital or early childhood ZIKV infection to inform the full public health burden of ZIKV disease.
- **Improve** understanding of neurological consequences of ZIKV infection, particularly during future outbreaks (e.g., by improving surveillance for conditions such as GBS and enhancing provider awareness of such complications during future outbreaks).
- **Conduct** research into the pathogenesis of GBS and other neurologic sequelae following ZIKV infection.
- **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, adapted to different social and cultural contexts in dialogue with the involved communities.

**Product Development**

- **Promote** early communication between developers and appropriate NRAs for clarity and guidance on the regulatory aspects of MCM development for ZIKV infection, particularly in the absence of new outbreaks.
- **Develop** regulatory guidance in collaboration with WHO, and ensure access to oversight, review, and authorization from appropriate NRAs for ZIKV MCMs.
- **Explore** ways to strengthen the use of nontraditional approvals for emergency use authorizations during outbreaks or for licensure (such as the US FDA’s Animal Rule).
- **Consider** issues around development of harmonized regulatory pathways that could ease the need to obtain country-specific regulatory approvals.
Key Capacities

- **Strengthen** infrastructure to support ZIKV surveillance, diagnosis, disease prevention, treatment activities, and clinical trial capacity in areas at risk of future outbreaks, including enhancing communication between health authorities and rural communities.

- **Promote** surveillance for birth defects in areas at risk for ZIKV outbreaks, according to current WHO recommendations ([WHO 2020](#), [WHO Technology Roadmap](#)). This is particularly important in Africa, since data are limited on the capacity for African lineage strains to cause congenital disease ([Musso 2019](#)).

- **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, to include planning for conducting research in pregnant women ([Ades 2020](#)).

- **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 2017c](#).)*

- **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), tick-borne encephalitis virus (TBEV), and West Nile virus (WNV) can all also result in cross-reactivity with ZIKV in serological assays (Jääskeläinen 2018, Sharp 2019).
- 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, Coutinho 2021, 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, and requires standardized reagents that can prove challenging to obtain (although a standard has been developed using an anti-Asian ZIKV antibody [[NIBSC 2021]] (Chepkorir 2019, Chua 2017, Landry 2016, Goncalves 2018). Furthermore, even with the PRNT test, the potential still exists for cross-neutralization against other related flaviviruses, particularly in highly endemic areas where sequential infections are likely to occur (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).
- 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/biorepositories 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 outbreaks, 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 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).

- Certain provisions of the Nagoya Protocol (United Nations Environmental Programme, Secretariat of the Convention on Biological Diversity 2011) could restrict international sharing of clinical specimens, viral isolates, and gene sequences necessary for developing and optimizing new diagnostics.

- 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).

- Infants born to mothers with documented ZIKV infection during pregnancy may not develop a sustained anti-ZIKV immunoglobulin G (IgG) neutralizing antibody response, even when vertical transmission is confirmed (Espindola 2021). Therefore, diagnosis of congenital infection is challenging and requires regular clinical follow-up to determine if infection sequelae develop over time.

- 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 September 2021 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).

**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). Efficient testing is needed during future outbreaks to evaluate the true burden of disease and inform the feasibility (and potentially timing of) clinical trials.
• A reliable biomarker for ZIKV congenital infection is needed for infants born to mothers who develop ZIKV infection during pregnancy (Espindola 2021).

• Improved methods for in utero ZIKV diagnosis are needed for earlier detection of congenital infection.

• 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). Samples must be sufficient in terms of volume for each sample and number of samples required for performing clinical studies. (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**

• Further research is needed to identify what factors (genetic, physiologic, viral-host interaction) predispose to ZIKV complications and determine whether or not any diagnostics (biomarkers or other tests) can adequately categorize infected individuals into risk categories for ZIKV-related complications, morbidity, and mortality.

• 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, Rosinger 2021, Ximenes 2019).

• 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, other promising tests (such as NS1 antigen tests for ZIKV), and tests that are designed to detect other flaviviruses (e.g., DENV) in addition to ZIKV (Bosch 2017, Sharp 2019). The characteristics should be validated for different cohorts (e.g., infants, pregnant women, and non-pregnant persons) and in different geographic regions.

• Further research is needed to determine if testing for other immunoglobulins, such as immunoglobulin A (IgA) or combinations of immunoglobulins, may improve performance of antibody testing for ZIKV (Warnecke 2019).

• Further validation studies are needed of promising diagnostics during future ZIKV outbreaks, to include different geographic areas (Charrel 2016). Validation of current or novel diagnostic tests is also needed for testing pregnant women with rash illness during non-outbreak periods and to detect congenital ZIKV infection in regions with multiple arboviruses.

• 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) (Herrada 2018).
Goncalves 2018, Priye 2017). Recent developments for COVID-19 diagnostics, including using CRISPR-based technology, can inform this effort (Ganbaatar 2021).

- 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 and the ability to differentiate between DENV and ZIKV); (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).

- Industry access to clinical samples and evaluation panels is limited; these are essential for providing clinical performance results and supporting submission of dossiers for regulatory approval.

- The uncertainty of a consistent market for ZIKV diagnostics that allows return on investment creates a significant challenge for industry partners to invest time and effort on test development, particularly between outbreaks, when future demand is unknown.

- Even though emergency use authorization can be obtained to allow use and evaluation of diagnostic tests during an emergency, once the emergency is over, it can be difficult for companies to transition to long-term approval.

- 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).

- The lack of regulatory convergence among countries is a significant challenge for development of diagnostic tests, in part due to the co-circulation of different combinations of flaviviruses in different geographic regions.

**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).
• Once new tests are approved and commercialized, post-market surveillance mechanisms need to be in place to ensure quality of tests over time and across different lots.

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 and technical limitations (WHO Diagnostic TPPs). This process should include input and review by industry partners.
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 2024, create a plan for a virtual biorepository network that is agreed upon through international collaboration and that promotes equitable access and sharing of specimens and data (Goncalves 2018, Peeling 2018). The plan should promote standardization of various parameters (e.g., types of specimens to be included, methods for sample characterized, storage, archiving, etc.).
5. By 2025, ensure that a virtual biorepository network 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 and representative of different regional populations) 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)*

6. By 2026, conduct several prospective studies in NHPs (or other suitable animal models as appropriate) on ZIKV infection and immune response kinetics to further inform optimum sample types, timing of sample collection, and diagnostic testing algorithms.

7. By 2026, create a mechanism to incentivize developers to pursue full regulatory approval of existing ZIKV assays.

8. 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 to facilitate definition of diagnostic algorithm(s) for different geographic regions.

9. By 2028, develop guidance on the optimal clinical sample types, timing of sample collections, and diagnostic tests (i.e., a diagnostic algorithm) 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 several molecular or serologic ZIKV assays depending on flaviviruses co-circulating in particular geographic areas (with assay readouts reported in International Units using the International Standards for antibody and viral RNA).

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, conduct at least one multi-site evaluation 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 (including past infection with a non-ZIKV flavivirus).

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

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)*

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 asymptotically infected pregnant women). *(High priority milestone)*

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)*

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

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)*

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, 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)*.
2. 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)*.
3. By 2026, conduct mapping of laboratories in at least several at-risk countries to determine capacity and referral systems for ZIKV diagnosis. This information can then be used to improve diagnostic testing capacity in those countries, based on the mapping results.
4. By 2027, convene an expert working group to develop and explore funding for 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](#)).
- **Continue research to identify a** reliable biomarker of ZIKV congenital infection ([Espindola 2021](#)).
- **Strengthen** research into biomarkers and other diagnostics which can prognosticate or categorize infected individuals into risk groups for ZIKV-related complications, morbidity, and mortality.
- **Continue to research** new technology and assay formats that may eventually allow development of multiplexed diagnostic tests to allow specific diagnosis of different flaviviruses or potentially other arboviruses.
- **Continue to research** the role of additional immunoglobulins (such as IgA) or combinations of immunoglobulins in improving performance of ZIKV antibody testing.

**Product Development**

- **Continue to conduct** validation studies on ZIKV diagnostic tests, as feasible based on disease incidence, 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 promising diagnostic tests for ZIKV infection.
- **Assess and address** the impact of the Nagoya Protocol on sharing of clinical specimens, viral isolates, and gene sequences in relation to development of diagnostic tests for ZIKV.

**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](#)).
- **Promote** manufacturing of low-cost diagnostic assays in regions with limited resources, including Africa, South America, to support continuity of supply across different areas of the globe.
- **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.

• **Determine** the utility and potential settings where it may be appropriate to incorporate serological testing for ZIKV (i.e., early in pregnancy and at the end of pregnancy) into TORCH screening (TORCH screening currently includes toxoplasmosis, other agents [e.g., HIV, hepatitis viruses, varicella, parvovirus], rubella, cytomegalovirus, herpes simplex, and syphilis).

• **Promote** mechanisms to ensure affordable pricing of ZIKV diagnostic tests to low-resourced countries, such as procurement through WHO or other United Nations (UN) agencies at negotiated pricing.

• **Develop** guidance on use of diagnostic tests (including point-of-care tests): (1) during pre-conception counseling for women of reproductive age, (2) during prenatal examinations for pregnant women, and (3) for use in children with ZIKV in utero exposure, with and without ZIKV associated birth defects. Such guidance is important to ensure adequate and equitable health care and to aid in the development of evidence-based public health interventions.
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, Magalhaes 2021, Rosenberg 2019).
• 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

• 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 (Erbelding 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. Based on studies with other pathogens mAbs with half-life extension technologies could potentially be used for prophylaxis against maternal infection or for prevention of vertical transmission during outbreaks. mAbs 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

- 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.
• 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.

• Research is needed to determine whether or not interruption of maternal viremia during different trimesters of pregnancy correlates with reduced risk of congenital ZIKV infection. Research is also needed to determine if mAbs that eliminate maternal viremia soon after infection completely reduce, partly reduce, or have no impact on congenital infection; this should also be examined by trimester of pregnancy, since maternal antibodies do not cross the placenta during the first trimester.

• 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 2023,** develop a TPP that identifies optimal and desirable characteristics for ZIKV therapeutic agents and identifies priority populations for use of therapeutics (e.g., pregnant women and infants).
2. **By 2024,** create and implement a transparent prioritization process for moving investigational ZIKV therapeutic agents through the therapeutic pipeline.
3. **By 2024,** conduct a workshop to define a development strategy (from preclinical research to approval) for novel therapeutics that prioritizes populations to be studied, sets expectations regarding the regulatory requirements for authorization/approval, and lays out strategies for moving therapeutics forward in the context of different epidemiologic scenarios (i.e., what can be accomplished in the absence of future outbreaks, what efforts are needed to be prepared for clinical trials when future outbreaks occur, etc.).
4. **By 2025,** develop and implement a plan for data sharing regarding development of therapeutic agents for treatment of ZIKV infection (particularly single mAb or mAb cocktails) as they move through preclinical and clinical development.
5. **By 2026,** complete preclinical evaluation in NHPs (using standardized ZIKV challenge strains) 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)*
6. **By 2028,** complete early clinical evaluation (i.e., phase 1 and 2 clinical trials) to assess the preliminary safety and tolerability of at least one promising mAb candidate or combination therapy for prophylaxis in pregnant women or women of reproductive age, or for treatment of congenital ZIKV infection. *(High priority milestone)*
7. **By 2029,** 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 2024,** identify one to three existing, licensed drugs that represent the most promising candidates for drug repurposing as treatment for or prevention of ZIKV infection (based on criteria identified in the TPP from the previous strategic goal).
2. **By 2028,** complete preclinical evaluation in suitable animal models to assess safety (including teratogenicity) and efficacy of these agents.
3. **By 2029,** complete phase 1 clinical trials for safety and efficacy in non-pregnant persons for at least one of the most promising repurposed agents that may be suitable for treatment of pregnant women (based on animal model data).
4. By 2031, complete phase 1 clinical trials for drug safety in pregnant women for at least one of the most promising repurposed agents that may be suitable for treatment during pregnancy (based on animal model data).

**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 2026, 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.
2. By 2027, 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.
3. By 2027, 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.

**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.

• **Ensure** that post-marketing pharmacovigilance strategies are in place when new biologics become available, particularly for evaluating use of new therapeutics in pregnant women.

**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) (although it is possible that areas of endemic transmission could be identified with better surveillance and better diagnostic testing; such areas could then potentially serve as study sites for clinical trials).
- The unpredictable nature of ZIKV outbreaks creates challenges in planning for future clinical trials and related efforts. Having trial protocols in place when a new outbreak emerges would expedite critical research vaccine research (Castanha 2020).
- In the absence of outbreaks, a regulatory pathway to licensure for ZIKV vaccines has not been established.
- 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. Alternative approaches, (e.g., test-negative case-control study designs) may be more feasible in assessing vaccine efficacy (Anders 2018). 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 2017b), 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, vaccine stockpiles for ready deployment following phase 1/2 safety/immunogenicity studies, 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 (such as use of the US FDA Animal Rule or Accelerated Approval pathways [US FDA 2011, US FDA 2015]) 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 (Castanha 2020, 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 2017b).

A transparent framework is needed for selecting promising vaccine candidates to be further evaluated in phase 2b/phase 3 clinical trials (WHO 2017b).

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).

Studies are needed to evaluate the impact of ZIKV vaccines on the occurrence of DENV and other flavivirus infections (particularly on symptomatic and severe dengue). Similarly, studies are needed to assess the impact of DENV vaccines on ZIKV occurrence and transmission.

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 unclear (Culshaw 2017, Langerak 2019, Poland 2018, Wen 2019). Specifically, cross-reactive 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, Katzelnick 2020, Langerak 2019, Morabito 2017).

**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, particularly for use in pregnant women (Thomas 2016).

• Researchers and vaccine developers/manufacturers may not be incentivized to engage in ZIKV vaccine R&D because of the challenges with developing effective vaccines and 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).

• Public-private partnerships may be needed to mitigate or to de-risk industry efforts in developing new vaccines.

**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). This information is critical to shaping vaccine development approaches.

• 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).
• More research is needed on the potential interactions of candidate ZIKV vaccines and those of other flaviviruses, such as JEV, YFV, and TBEV.
• 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). Additionally, the spectrum of potential ADE manifestations needs to be further defined in this context (e.g., enhancement of vertical transmission). If an ADE effect is identified in humans, it will need to be addressed in a licensure pathway for any candidate vaccines. However, 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 (Bodalto-Corrêa 2021, 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).
- Social science research is needed to determine whether target populations (e.g., pregnant women or women of child-bearing age) will be amenable to vaccination and under what circumstances (e.g., during outbreaks only, during inter-outbreak periods, etc.).

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 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 2026, develop a consensus statement on “preparing at risk”, to address issues such as stockpiling (for use during future outbreaks) of candidate vaccines that have been evaluated through phase 1/2 safety and immunogenicity testing. This could also include an assessment regarding the utility of the US FDA’s Animal Rule, or similar approaches, to compensate for the lack of phase 3 efficacy data.
5. 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)
6. By 2028, ensure that the necessary requirements are in place to allow licensure of candidate ZIKV vaccines through alternative regulatory approval pathways (such as the US FDA’s Animal Rule or Accelerated Approval pathways [US FDA 2011, US FDA 2015]). (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 or via the EMA Accelerated Assessment process).

**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 in areas where future ZIKV outbreaks emerge. (High priority milestone)
4. By 2026, generate a comprehensive list of ZIKV vaccine candidates and apply the process identified in milestone 1 to determine the most promising candidates for moving forward into clinical studies and for future funding considerations.
5. By 2026, convene a workshop to develop a consensus statement on a risk assessment for disease enhancement with ZIKV vaccines, similar to what was done for COVID-19 vaccines in 2020 (Lambert 2020).
6. 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 2024, 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 2025, establish a reference panel of sera to aid the standardization of serum neutralization tests for evaluating ZIKV vaccines on the assumption that neutralizing antibodies will be the correlate of protection.
4. By 2026, complete preclinical research on at least three promising ZIKV vaccine candidates that demonstrate efficacy in suitable animal models.
5. By 2026, complete DART studies on at least three promising ZIKV vaccine candidates.
6. 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.
7. By 2027, advance at least three vaccine candidates into phase 2/expanded phase 2 trials in defined populations.
8. 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).
9. By 2028, ensure that at least two vaccine candidates are available that are suitable for phase 3 clinical trials or alternative efficacy assessment approaches.
10. 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)
11. 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 (Bodalo-Corrêa 2021, 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.
- **Conduct** research on the potential interactions of vaccines for other flaviviruses such as DENV, JEV, YFV, and TBEV with vaccines developed for ZIKV.
- **Refine** vaccine dosing regimens for use of vaccines in pregnant women.

**Product Development**

- **Apply** any relevant lessons learned from development of COVID-19 vaccines to development of ZIKV vaccines.
• **Track** current and potential developers and manufacturers of ZIKV vaccines (including by region) to ensure an adequate pipeline for vaccine development.
• **Identify** potential financial resources for clinical trials in the event of new ZIKV outbreaks.
• **Drive** information exchange between diagnostic testing developers, vaccine developers, and clinical trial centers to promote efficacy evaluation of vaccine candidates.
• **Continue** to clarify for vaccine developers how alternative regulatory pathways may be applied for licensure of ZIKV vaccines in the absence of ongoing transmission.
• **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](https://www.preven.org/)).
• **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](https://www.who.int/zh/treatment/zika-virus)).
• **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**

• **Conduct** social science research to determine whether target populations (e.g., pregnant women or women of child-bearing age) in at-risk areas will be amenable to vaccination and under what circumstances (e.g., during outbreaks only, during inter-outbreak periods, etc.).
• **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](https://www.who.int/zh/treatment/zika-virus)).
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## 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 3:** By 2024, (1) obtain further guidance from regulatory authorities on key characteristics that animal models require to support regulatory approval 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, (3) define measurable endpoints for use of animal models (e.g., viremia, survival, CZS manifestations), and (4) define the parameters used for those animal models (such as route, dose, and strain).

- **Milestone 4:** By 2024, (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 infection or past vaccination against 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) (or an update of the current standard [NIBSC 2021] as needed) and validation panel are available to assess new or existing ZIKV assays.

- **Milestone 5:** By 2025, generate a well-developed, standardized CHIM for ZIKV (particularly for use in the absence of ongoing ZIKV outbreaks); define parameters for use (e.g., challenge strain, challenge dose, route of challenge administration and delivery, and exclusion criteria); and develop carefully considered risk mitigation strategies (Durban 2017, Erbelding 2017, Vannice 2019).

### Diagnostics

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

- **Milestone 5:** By 2025, ensure that a virtual biorepository network 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 and representative of different regional populations) 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 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; 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 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).

- **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 asymptotically 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.

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<table>
<thead>
<tr>
<th>Therapeutics</th>
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<tbody>
<tr>
<td><strong>Strategic Goal 1:</strong> Support development and preclinical/early clinical evaluation of novel therapeutic agents (such as mAb cocktails) for the prevention and treatment of congenital ZIKV infection.</td>
</tr>
<tr>
<td><strong>Milestone 5:</strong> By 2026, complete preclinical evaluation in NHPs (using standardized ZIKV challenge strains) of the preliminary safety (including teratogenicity), tolerability, and efficacy of more than one promising mAb candidate for prophylaxis or treatment of congenital ZIKV infection.</td>
</tr>
<tr>
<td><strong>Milestone 4:</strong> By 2028, complete early clinical evaluation (i.e., phase 1 and 2 clinical trials) of the preliminary safety and tolerability of at least one promising mAb candidate or combination therapy for prophylaxis in pregnant women or women of reproductive age, or for treatment of congenital ZIKV infection.</td>
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<tr>
<th>Vaccines</th>
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<tr>
<td><strong>Strategic Goal 1:</strong> Develop the capability to use alternative approaches for evaluating and</td>
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<tr>
<td><strong>Milestone 5:</strong> 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</td>
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</table>
| Licensing candidate ZIKV vaccines (e.g., through the US FDA Accelerated Approval Program or the EMA Accelerated Assessment). | ZIKV vaccines (e.g., for use in animal challenge studies with subsequent extrapolation to humans) (Vannice 2019).

- **Milestone 6:** By 2028, ensure that the necessary requirements are in place to allow licensure of candidate ZIKV vaccines through alternative regulatory approval pathways (such as the US FDA’s Animal Rule or Accelerated Approval pathways [US FDA 2011, US FDA 2015]). |

**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 in areas where 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 10:** 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 11:** 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**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADE</td>
<td>Antibody-dependent enhancement</td>
</tr>
<tr>
<td>AFI</td>
<td>Acute febrile illness</td>
</tr>
<tr>
<td>ASSURED</td>
<td>Affordable, Sensitive, Specific, User-friendly, Rapid and Robust, Equipment-free, and Delivered to the end-user</td>
</tr>
<tr>
<td>BSL</td>
<td>Biosafety Level</td>
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<tr>
<td>CHIM</td>
<td>Controlled Human Infection Model</td>
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<tr>
<td>CZS</td>
<td>Congenital Zika syndrome</td>
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<tr>
<td>DART</td>
<td>Development and reproductive toxicology</td>
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<tr>
<td>DENV</td>
<td>Dengue virus</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>EUA</td>
<td>Emergency Use Authorization</td>
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<tr>
<td>EUAL</td>
<td>Emergency Use Assessment and Listing</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GBS</td>
<td>Guillain-Barré Syndrome</td>
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<tr>
<td>IgA</td>
<td>Immunoglobulin A</td>
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<tr>
<td>IgG</td>
<td>immunoglobulin G</td>
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<tr>
<td>IgM</td>
<td>Immunoglobulin M</td>
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<tr>
<td>JEV</td>
<td>Japanese encephalitis virus</td>
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<tr>
<td>LMICs</td>
<td>Low- and middle-income countries</td>
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<tr>
<td>mAb</td>
<td>Monoclonal antibody</td>
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<tr>
<td>MCM</td>
<td>Medical countermeasure</td>
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<tr>
<td>NAAT</td>
<td>Nucleic acid amplification test</td>
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<tr>
<td>NHP</td>
<td>Nonhuman primate</td>
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<tr>
<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>-------------</td>
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<tr>
<td>NRA</td>
<td>National regulatory authority</td>
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<tr>
<td>PAHO</td>
<td>Pan American Health Organization</td>
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<tr>
<td>PHEIC</td>
<td>Public Health Emergency of International Concern</td>
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<tr>
<td>PPC</td>
<td>Preferred product characteristic</td>
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<tr>
<td>PRNT</td>
<td>Plaque reduction neutralization test</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and development</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
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<tr>
<td>RT-LAMP</td>
<td>Reverse transcription loop-mediated isothermal amplification</td>
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<tr>
<td>TPP</td>
<td>Target Product Profile</td>
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<tr>
<td>TBEV</td>
<td>Tick-borne encephalitis virus</td>
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<td>UN</td>
<td>United Nations</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WMP</td>
<td>World Mosquito Program</td>
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<td>WNV</td>
<td>West Nile virus</td>
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<tr>
<td>YFV</td>
<td>Yellow fever virus</td>
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<td>ZIKV</td>
<td>Zika virus</td>
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