



Zika Virus: Research Priorities for Preparedness and Response 1

Zika virus: advancing a priority research agenda for preparedness and response

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The 2015–16 Zika virus epidemic emerged in the Americas and rapidly spread throughout the region and beyond, showing the epidemic potential of this mosquito-borne *Orthoflavivirus* and its capacity to cause severe congenital malformations and neurological sequelae. WHO declared the Zika virus epidemic a public health emergency of international concern in 2016. Despite this declaration, there are no licensed Zika virus vaccines, therapeutics, or diagnostic tests appropriate for routine antenatal screening. To address this absence of essential tools to detect and mitigate the threat of future Zika virus outbreaks, a group of global experts developed a priority agenda for Zika virus research and development. This Series paper summarises crucial challenges and knowledge gaps and outlines a comprehensive strategy to advance research, surveillance, global capacity, policy, and investment for Zika virus preparedness and response.

Introduction

Zika virus is an *Orthoflavivirus* transmitted primarily by *Aedes* mosquitoes. Originally discovered in Uganda in 1947, for decades Zika virus infections were only identified in rare, sporadic cases of human disease in Africa and Asia. In 2007, large epidemics unexpectedly began to emerge in the Federated States of Micronesia and other Pacific islands.^{1,2} In 2015–16, the Zika virus epidemic emerged in the Americas and spread rapidly throughout the region and beyond, revealing the virus's devastating capacity to cause severe congenital malformations and other adverse pregnancy outcomes, as well as Guillain-Barré syndrome and other neurological sequelae in adults and older children.^{3–5} In response to this epidemic, WHO declared a public health emergency of international concern (PHEIC).⁶ WHO lifted the PHEIC in 2016 with the declaration, “we must be ready for the long haul”,⁷ a clear call for a long-term commitment to address this newly emerged pathogen. However, to this day, there are no licensed Zika virus vaccines, therapeutics, or diagnostics appropriate for routine antenatal screening. The absence of these essential tools hampers global capacity for surveillance, clinical diagnosis, prevention, and control, and is a crucial barrier to preparedness and response for future Zika virus epidemics.

Although the epidemic in the Americas has waned, Zika virus remains a global health threat. Autochthonous mosquito-borne Zika virus transmission has been documented in 92 countries and territories across the Americas, Asia, Africa, Europe, and the Pacific, and an additional 60 countries and territories have competent mosquito vectors, but have not yet documented Zika

Key messages

- To address the absence of Zika virus vaccines, therapeutics, and diagnostics, a group of global experts reviewed key challenges and knowledge gaps in Zika virus research and developed a priority research agenda for preparedness and response.
- Multiple novel strategies are under investigation to improve the specificity of serological assays; systematic, standardised evaluations of leading candidates are needed to inform and accelerate the development pipeline, including evaluation of multiplex and point-of-care diagnostics.
- Expanded research in Zika virus infection, pathogenesis, and immune response, using in-vitro methods, animal models, and controlled human infection model studies would advance research and development of Zika virus medical countermeasures during periods of low transmission.
- Strengthened systems for surveillance and national and regional laboratory capacity are needed to improve early detection of future outbreaks, monitor transmission and genomic epidemiology, and improve risk mapping for future research and response. Integrated approaches for Zika virus and other arboviruses for surveillance, vector surveillance, and laboratory testing would improve efficiencies and reduce costs.
- Overcoming complacency and building investment in research and development for Zika virus medical countermeasures and vector control will be essential for global preparedness and response against future epidemics.

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This paper is the first in a **Series** of four papers about Zika virus, to be published in conjunction with *The Lancet Microbe*.

All papers in the Series are available at <https://www.thelancet.com/series/zika-virus>

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virus transmission.^{8–11} Since the 2016 epidemic, outbreaks have occurred in new areas and low-level transmission continues to be reported in multiple countries worldwide.^{12–18} The threat of future Zika virus epidemics continues as there are many populations that are immunologically naive, new birth cohorts reach reproductive age, and epidemics of arthropod-borne viruses (arboviruses) escalate in frequency and severity.¹⁹ Preparedness against future Zika virus epidemics therefore remains an urgent public health issue. This Series paper summarises the underlying challenges for Zika virus research and development, identifies priority areas of research, and outlines a comprehensive strategy to advance Zika virus research and development for preparedness and response.

Approach

To address the absence of countermeasures to mitigate Zika virus transmission and disease, the University of Minnesota's Center for Infectious Disease Research and Policy (CIDRAP) and the Wellcome Trust, along with the Sealy Institute for Vaccine Sciences at the University of Texas Medical Branch (UTMB), convened a group of experts to develop a priority agenda to advance Zika virus research and development. The research agenda was built on the application of the draft WHO Zika Research and Development Roadmap,²⁰ originally developed by CIDRAP, UTMB, and WHO in 2021, with input from global experts, to accelerate research for medical countermeasures (ie, vaccines, diagnostics, and therapeutics) for priority pathogens with epidemic potential.

To develop the research agenda, CIDRAP conducted extensive literature reviews and convened the Zika Expert Workgroup, which comprised 26 global experts plus UTMB members working in Zika virus diagnostics, virology, immunology, pathophysiology, vaccine development, reproductive biology, epidemiology, regulatory systems, and public health. The Zika Expert Workgroup reviewed and updated the research priorities outlined in the draft WHO Research and Development Roadmap through a series of virtual meetings. CIDRAP, Wellcome, and UTMB then convened an invitational hybrid (ie, in-person and remote) meeting in London on Dec 4–6, 2023, attended by 130 key stakeholders from academia, national and multilateral public health organisations, industry, regulatory agencies, and philanthropic organisations from around the world. Scientific presentations and panel discussions reviewed the state of the science, and with participant discussion, identified priority activities needed to advance Zika virus medical countermeasures for global preparedness and response. This Series paper summarises content related to diagnostics, policy and investment, vector control, and cross-cutting issues, including global coordination and capacity building. The other papers in this Series cover content related to research priorities for development of

vaccines and monoclonal antibodies, non-human primate animal models, and sharing of specimens and data.^{21–23} As the original roadmap did not include content related to vector control, Wellcome and CIDRAP included a third meeting day to address research priorities for an integrated strategy for arboviruses, including vector biology, surveillance, and control. Proceedings of the arbovirus meeting will be published fully elsewhere.

Underlying challenges of Zika virus research and development

Multiple inter-related factors pose inherent challenges to the advancement of Zika virus research and development, which need to be addressed for the development of a comprehensive research strategy for preparedness and response.

Clinical symptoms and co-circulation with other arboviruses

An estimated 50–80% of Zika virus infections are asymptomatic; symptomatic disease is typically mild, characterised primarily by rash with or without low-grade fever, myalgia, arthralgias, and conjunctivitis.^{24–27} This non-specific clinical presentation is similar to that of other co-circulating arboviruses, such as dengue and chikungunya viruses, which creates challenges for early detection, surveillance, diagnosis, and research.^{27–30} In addition, Zika, dengue, and other orthoflaviviruses share extensive genetic and structural similarities, resulting in cross-reactive immune responses that hamper Zika virus serological diagnosis and immunological research.

Limitations of currently available diagnostics

Accurate diagnostics are central to Zika virus research, epidemiology, surveillance, and prenatal screening. Nucleic acid amplification testing remains the optimal method for diagnosing acute Zika virus infection due to its high specificity and ability to confirm infection. However, viral RNA is detectable in plasma for only about 1–7 days following symptom onset (and somewhat longer in urine and whole blood),^{31,32} limiting the utility of this test. In addition, the sensitivity of this test is diminished by the generally low viral load associated with infection. As most Zika virus infections are asymptomatic, the utility of nucleic acid amplification testing for routine screening during pregnancy is extremely limited; a negative test does not rule out recent infection. In addition, nucleic acid amplification testing of amniotic fluid does not reliably predict risk of congenital malformations.³³ Current nucleic acid amplification testing technologies are technically complex and expensive, limiting their use in many remote or low-resource settings.^{34,35}

IgM serological assays are potentially important to detect recent infections, as positive results are generally detectable from 1 to 12 weeks after infection, lengthening the time for diagnosis. However, Zika virus IgM can

persist for months or even more than a year. Therefore, a positive test might reflect an infection that preceded pregnancy.³⁶ The high propensity for Zika virus cross-reactivity with dengue virus and other orthoflaviviruses creates substantial challenges for serological diagnosis. The potential for immunological imprinting or so-called antigenic sin might create an additional barrier to serological differentiation of Zika virus and dengue virus infection.^{31,37} Plaque reduction neutralisation tests can help determine the infecting virus but take days to complete, are generally limited to use in reference laboratories, and might fail to confirm a substantial proportion of Zika virus-positive serological test results in individuals with previous *Orthoflavivirus* infection.^{31,38}

Most national and international testing guidelines do not recommend routine antenatal testing of asymptomatic patients because of the limitations of both molecular and serological Zika virus diagnostics.^{32,39} As most infections are asymptomatic, the limitations of current testing strategies reflect a crucial gap in detection of at-risk pregnancies, clinical management, and research.

Surveillance, epidemiology, and unpredictable patterns of transmission

Infrastructure for Zika virus surveillance and laboratory testing is absent or insufficient in many parts of the world and has been further eroded since the 2015–16 epidemic due to waning transmission and competing health priorities. Insufficient infrastructure to monitor for infections hinders global capacity for early detection and response, as well as research in epidemiology, transmissibility, and pathogenicity. Major questions remain regarding modelled projections of future Zika virus outbreaks, hampering the identification and development of research sites in preparation for future epidemics. Little is known about the pre-epidemic Zika virus lineages that circulate in Africa and Asia, including their epidemiology and effects on pregnancy outcomes.

Protection of the developing fetus

The most pressing health issue related to Zika virus infection is the risk to pregnancy outcomes, including severe congenital malformations, neurodevelopmental disabilities, fetal loss, preterm birth, and stillbirth.^{24,40–42} Zika virus infection is unique among WHO priority pathogens in that the primary target for prevention and treatment is protection of the developing fetus. Developing interventions that mitigate the effects of congenital infection poses unique challenges. Identification of traditional endpoints in clinical trials is problematic given that Zika virus infection is generally asymptomatic, microcephaly occurs in 5% or less of affected pregnancies, and correlates of protection remain unknown.^{43–45} Adverse pregnancy outcomes, such as fetal loss and preterm birth, are relatively common in the

general population. Demonstrating the protective effects of Zika virus medical countermeasures against the background rates of pregnancy complications can be difficult. Multiple milder neurological sequelae in congenitally infected infants have been identified, such as learning disabilities and behavioural disorders; delineation of long-term sequelae and pathogenicity have not been fully elucidated.^{46,47}

Availability of specimens for research and development

One of the greatest barriers to developing Zika virus medical countermeasures is the low availability of specimens. Panels of well characterised clinical samples are needed to develop and evaluate diagnostic assays and identify targets for vaccines, monoclonal antibodies, and therapeutics.⁴⁸ Barriers and strategies to improve sharing of specimens and associated data are discussed in depth in Series paper 4.²³

Priorities to advance a Zika virus research agenda

Multiple barriers can be addressed through specific and actionable activities that would drive Zika virus research and development, with the goal of developing medical countermeasures that are available for use worldwide.

Research priorities for Zika virus diagnostics

Several molecular and serological assays have been approved for commercial use or received emergency use authorisations.^{49–52} However, independent, standardised evaluations of assay performance have yet to be conducted or have yielded inconsistent or suboptimal results.^{53–57} Evaluations of assay sensitivity, specificity, and cross-reactivity are needed, including use of well characterised clinical standards.^{56,58,59} Evaluation of multiplex platforms is an important component of this scope of work, given the common co-circulation of Zika, dengue, chikungunya, yellow fever, and other arboviruses. In addition, advancing research and development for point-of-care diagnostics remains a priority to improve availability of accurate, practical, and affordable tests for use worldwide. Numerous rapid and simple tests are commercially available or under development for detecting Zika virus antigen and IgM, IgG, and combination IgM–IgG antibodies.^{60,61} Evaluations are needed for different populations, such as infants, during pregnancy, from multiple geographical areas, and those with serial orthoflavivirus infections.³⁸ The potential effect of strain variations on molecular assay performance warrants further monitoring.⁶²

Given serological cross-reactivity between orthoflaviviruses, novel assays are needed with improved specificity that are practical for use worldwide. Methods under investigation include measuring antibodies to Zika virus and dengue virus that target specific antigens, such as NS1 and domains I and III of the envelope protein,^{38,63–66} and investigation of novel targets, such as

Zika virus IgA or combinations of IgA and other immunoglobulins.⁶⁷ Studies are also needed on the use of alternative specimen types (eg, saliva, urine, amniotic fluid, and cerebrospinal fluid) for both molecular and serological methods.

Building a coordinated agenda for research and development of Zika virus diagnostic

An important first step to advance research and development of diagnostics is to conduct a comprehensive landscape review of assays that are commercially available or in the development pipeline, including point-of-care and multiplex assays. The review would compile data on assay performance, ability to distinguish Zika virus from other *Orthoflavivirus* infections, and utility for different uses (eg, clinical diagnosis, epidemiology, surveillance, and research). The results of the landscape review would guide evaluations of leading candidates and future test development.

The formation of a global expert working group, including representation from affected countries, would drive research and development of Zika virus diagnostics. Using results of the diagnostic landscape review, the group would identify priority candidates to be validated by multicountry, multiregion evaluations, across various use cases, and in outbreak situations. A unified approach would align research efforts and build a clear plan for building global laboratory capacity. Review and update of the WHO target product profiles for Zika diagnostics⁶⁸ would help set clear direction for researchers and developers.

Improving early detection of adverse birth outcomes

Elucidation of the full spectrum and long-term sequelae of congenital Zika virus infection, the molecular pathways of in-utero infection and pathogenesis, and factors that influence infant outcomes remain scientific priorities. Estimates of the effects of maternal Zika virus infection on birth outcomes vary widely and little information is available to guide counselling of those infected in pregnancy.⁶⁷ Ultrasound can identify severe structural defects but fail to detect functional or milder structural anomalies. Prenatal ultrasound is not available in many settings and training and interpretation can be inconsistent.⁶⁹ Infants with documented in-utero exposure sometimes do not develop a sustained IgG antibody response, even when vertical transmission is confirmed, further complicating postnatal diagnosis.^{70,71} As with other teratogens, no biomarkers are available that predict infant outcomes following in-utero Zika virus exposure. Studies are underway to identify potential biomarkers;^{72,73} well controlled clinical evaluations will be needed.

Multiple factors can affect detection and reporting of both infection and pregnancy outcomes. Congenital Zika syndrome has been known to occur following both asymptomatic and symptomatic infections,⁷⁴ and

multiple milder sequelae have been identified through long-term follow-up.⁴⁶ Some infants identified as asymptomatic at birth have had reduced postnatal brain growth and other defects suggestive of disease progression after birth.⁷⁵ Confounding variables, such as nutritional deficiencies and teratogenic exposures, are not consistently controlled for in studies. Long-term investigations of children with known in-utero exposure, with well characterised comparison groups, would better define the full spectrum of disease in children who are congenitally and postnatally infected and guide research in identification of potentially protective factors.^{30,76}

Advancing research in infection, transmission, immunology, and pathogenesis

Identifying targets for vaccines, monoclonal antibodies, and therapeutics requires a comprehensive understanding of the underlying mechanisms of fetal Zika virus infection, pathogenesis, tissue tropism, host receptors, and immune responses, particularly in pregnancy.^{77,78} Zika virus preferentially infects neural, placental, and testicular cells, including fetal neural progenitor cells, although the exact mechanisms of these tissue tropisms are not fully understood. The CNS, gravid uterus, and testis are all target tissues of Zika virus infection but are also immune privileged sites, which adds further complexity to the development of medical countermeasures targeting prevention and treatment of CNS complications, fetal infection, and sexual transmission.^{79,80} Research is needed to further delineate mechanisms of viral cell entry, immune responses, immunological interactions with other *Orthoflavivirus* infections, and durability of protective immunity following infection. This research would further complement studies of factors, such as viral load and gestational age at infection, that affect risk of adverse pregnancy outcomes.⁸¹ In addition, research is needed to identify factors involved in the pathogenesis of Guillain-Barré syndrome and other neurological complications in adults and children who are infected postnatally.⁸²⁻⁸⁴

Mechanistic studies of Zika virus host receptors, immunology, and pathogenesis can be advanced using animal models and in-vitro methods, thus enhancing preparedness during times of low incidence. Important preclinical investigations can be conducted in animal or other non-clinical models in preparation for human trials.⁸⁵ Compiling an inventory of animal models that most closely recapitulate the spectrum of human disease will accelerate this agenda. Defining standardised methods in animal research, including challenge routes, viral strains, doses, natural history of disease, immune correlates of protection, and endpoints for assessing efficacy will allow greater comparability between preclinical studies. Non-human primate models will be crucial to advance an understanding of Zika virus infection and pregnancy; a

summary of research priorities related to the use of non-human primates is included in Series paper 3.²³

Controlled human infection model studies are an important and feasible strategy to advance Zika virus research and development, particularly during times of low transmission. Controlled human infection model studies can enable investigations of human immune responses, immunological interactions between Zika virus and other orthoflaviviruses, immune correlates of protection, and host response following a known time of infection.⁸⁶ Controlled human infection model studies can be used to investigate vaccine safety and immunogenicity, and contribute important information to regulatory approvals, including via non-traditional pathways.^{87,88} Zika virus controlled human infection model protocols have been implemented that mitigate potential risk to study participants and the general population.⁸⁶

Person-to-person transmission of Zika virus warrants further investigation.^{89,90} Infectious virus can persist in the testis for 6 months or more, but the contribution of sexual transmission to the overall incidence of Zika virus infection is unknown. Animal model studies suggest sexual transmission might adversely affect fetal development more than mosquito-borne transmission.⁹¹ Information is needed on the processes by which Zika virus infiltrates, infects, and persists in the male reproductive tract.^{80,92} In addition, studies are needed that evaluate the persistence of Zika virus RNA in breastmilk and potential transmission to infants.^{93–95}

Strengthening infrastructure for Zika virus preparedness and response

A comprehensive and coordinated agenda is needed to build national and regional capacity for Zika virus research for preparedness and response.

Strengthening systems to monitor global Zika virus transmission and disease

Specific actions can be implemented to better monitor global transmission, improve early detection and response, and identify sites for future research.

In most areas of the world, Zika virus surveillance systems do not have sufficient sensitivity for early detection of outbreaks or monitoring trends in endemic areas. Microcephaly is likely to be a rare and late signal to use for detection of Zika virus outbreaks. Alternative strategies are needed to adequately track patterns of transmission and disease, including active surveillance, serosurveys, sentinel surveillance, and laboratory-based surveillance. Special systems will be needed in sub-Saharan Africa to detect rare occurrences of African lineage infections through active case finding to support research related to genetic sequencing, in-vitro investigations, and clinical research of obstetric and paediatric populations.^{96,97} Novel strategies to monitor for Zika virus infections, such as wastewater surveillance, are

needed to improve early detection of Zika virus re-emergence.^{98–100} Adopting standardised methods for genomic surveillance and facilitating sharing of sequence data, as well as expanding Zika virus genomic epidemiology studies, will provide important information about Zika virus transmissibility and a foundation to investigate vaccine candidates, Zika virus pathogenicity, and diagnostic test performance over time.^{62,101–106}

Given the scarce resources available for Zika virus surveillance, strategies are needed to improve country and regional infrastructure through increased efficiencies and reduced costs, such as implementing integrated surveillance for multiple arboviruses, building on existing systems and laboratories for other pathogens, and centralising reference laboratory testing and data systems at the country and regional levels. A review of national and regional reference laboratories for Zika virus diagnostic testing is needed to guide development of networks and ensure availability of equipment, reagents, and trained staff. Standardised methodologies for serosurveys, stratified by age cohorts and based on assessments of serological assays, would serve to elucidate patterns of Zika virus transmission worldwide.

Standardised clinical case definitions form the foundation of global surveillance. WHO interim case definitions, first published in 2016 and updated by the Pan American Health Organization in 2023,^{107,108} need to be implemented and evaluated for global use, coupled with evaluations of laboratory testing algorithms,^{32,39} in areas with co-circulating arboviruses and in paediatric populations.¹⁰⁹

The reasons for the emergence of Zika virus as a pathogen of epidemic potential remain poorly understood. Further research is needed to delineate how changes in the viral genome, host factors, and vector competence contributed to changes in Zika virus transmissibility and pathogenicity.^{96,110–112} Linking surveillance and epidemiological data with entomovirological and vector surveillance information (eg, geographical distribution, vector density, vector competence, and vector dynamics) will serve to identify key drivers of Zika virus outbreaks and inform risk mapping, forecasting of future epidemics, and preparation of research sites.¹¹³

Building research sites for clinical trials and cohort studies

Important efforts were advanced during the 2016 epidemic to develop standardised protocols and research networks,^{42,114–119} but these initiatives have not been fully actualised due to the rapid decline in Zika virus transmission and funding. Therefore, it is important to finalise protocols and build research infrastructure now, in preparation for future Zika virus re-emergence.¹²⁰ A landscape review of available research networks, cohorts, pregnancy registries, protocols, and standard operating procedures will serve to guide future research

coordination and standardisation, including standardisation of data on demographics, clinical outcomes, specimen collection, follow-up intervals, testing algorithms, ascertainment of gestational age, fetal neuroimaging, neurodevelopmental assessment in infants and children, sampling methods for population-based serosurveys, and potential co-factors. Established research sites and cohorts are well positioned worldwide to implement Zika virus research studies; continued investment will be foundational to research preparedness and response.

Many essential research questions will need to be addressed by longitudinal cohort studies, such as Zika virus incidence, kinetics, durability of the immune response,^{121,122} clinical sequelae, immune correlates of protection, and immunological interactions of serial *Orthoflavivirus* infection or vaccination.¹²³ Sustaining cohorts can be expensive and traditional grant methods are often siloed to address specific pathogens or research questions. However, the value of longitudinal cohorts, including pregnancy cohorts, has been consistently demonstrated, as these projects support research for multiple health threats and rapidly pivot to address new and emerging pathogens. Engagement of funders is needed to identify novel ways to support cohorts, such as integrated arbovirus research, leveraging shared resources for studies of medical countermeasures, and investigating interactions of multiple circulating pathogens, vectors, and animal reservoirs.

Country engagement and regulatory approvals

Country leadership, engagement, and coordination are essential elements of research and development throughout the research process, including involvement and investment in national governments, researchers, public health agencies, regulatory authorities, and community representatives. Social science research is needed to better understand community acceptance, participation in research, and approaches to communications related to uptake of medical countermeasures, particularly in pregnancy.^{124,125}

Approval of new medical countermeasures will require input from various national regulatory authorities. Different national and regional regulatory authorities might have distinct approaches and requirements, particularly if using non-traditional approval pathways, as discussed further in Series paper 2.²² Early and ongoing communication between product developers and regulatory agencies will help inform clinical trial design and regulatory pathways.

Research priorities to improve vector surveillance and control

In recent decades, the distribution and intensity of Aedes-borne diseases has escalated worldwide, fuelled by a convergence of multiple factors, including climate

change, urbanisation, migration, poverty, land use, deficiencies in water storage and sanitation, and mosquito adaptations to more temperate and urban environments.^{126–129} The expansion and severity of new and existing Aedes-borne pathogens highlight the crucial need to address vector surveillance and control as an essential component of a research agenda for Zika virus and other arboviruses.¹³⁰

Evaluation of current vector control strategies

The global distribution and density of Aedes mosquitoes reflects the insufficient impact of current vector control programmes and highlights the need for quality studies that evaluate traditional methods.^{131–133}

Multiple traditional strategies are currently in use, including reduction of breeding sites (removal of trash and open water containers), ovitraps and larvicides, residual spraying, household curtains and screens, and personal protective sprays and clothing.^{134,135} Systematic reviews and meta-analyses have revealed that these strategies have often failed to identify a substantial effect on disease transmission^{131,136} and concerns remain regarding the ecological effect of pesticides and pesticide resistance in vectors.¹³⁵ Extensive and sustained community engagement is essential and requires long-term commitment, political support, and behavioural change; research is needed to monitor quality of implementation, adherence, and outcomes.^{135,136} A stronger evidence base is needed to guide vector control programmes and investment.^{135–137}

Research priorities for novel vector control strategies

Innovation in vector control has accelerated, but still lags behind the urgent need for scalable solutions. The release of *Aedes aegypti* infected with *Wolbachia* has shown promising results and has emerged as a leading candidate for preventing arboviral diseases.^{138–140} Researchers are exploring many techniques, such as spatial repellents, sterile insect technique, and population suppression by *Wolbachia* to reduce mosquito populations or their capacity to transmit viruses.¹⁴¹ Additional examples include sex-determined mosquitoes (M factor), release of insects carrying a dominant lethal gene (*RIDL*), and gene drive.¹⁴¹ A comprehensive research agenda is needed to advance these novel techniques, including randomised trials, and pathways for regulatory approval warrant further delineation. Systems are needed to accelerate scale up and sustainability, coupled with long-term studies to monitor potential adverse effects on ecological disruption, viral evolution, resistance, or replacement with new mosquito vectors.^{142,143}

Increase capacity to monitor vector ecology, virus transmission, and vector-host-pathogen interactions

Global capacity and investment in vector surveillance and research is grossly inadequate worldwide. The number of trained entomologists is small and

Panel: Priorities for Zika virus research for preparedness and response

Priorities to advance research and development for Zika virus medical countermeasures

- Advance availability of sensitive and specific Zika virus diagnostics
 - Conduct a landscape review of diagnostics that are commercially available or in the development pipeline, including multiplex platforms and point-of-care tests
 - Conduct standardised assessments of commercially available and investigational diagnostics using well characterised panels, including samples from diverse populations and with serial infections with other arboviruses
- Advance research in Zika virus infection, immunology, and pathogenesis
 - Investigate mechanistic studies of Zika virus host receptors, replication, immunology, and pathogenesis, including immunological interactions with other orthoflaviviruses
 - Advance research strategies to block infection or mitigate pathogenesis in the developing fetus
 - Accelerate use of animal models, in-vitro methods, and controlled human infection model studies to drive research and development during times of low Zika virus transmission
- Define the full spectrum of disease associated with congenital Zika virus infection
 - Conduct well characterised, long-term studies of sequelae of congenital Zika virus infection, compared with unexposed pregnancies, using standardised diagnostic, clinical, and imaging studies and controlling for confounding variables
- Strengthen global capacity to monitor Zika virus transmission for early detection and response
 - Evaluate and disseminate current standardised clinical case definitions, in connection with strengthening laboratory diagnostics and testing algorithms, and modify as needed
 - Build national and regional laboratory capacity for Zika virus and other arboviruses for surveillance, clinical diagnosis, and research
 - Strengthen national and regional surveillance systems, including studies of genomic epidemiology
 - Develop systems for sharing sequence data to track global Zika virus transmission, linked with epidemiological, clinical, and vector data, including information for risk mapping and forecasting models
 - Develop methods for active case finding of Zika virus lineages circulating in Africa and Asia, to advance an

understanding of transmission, pathogenicity, and immune response

- Improve coordination of research sites to accelerate research and development
 - Develop and implement standardised protocols and coordination among research sites, to accelerate research and development, strengthen sample size, and improve comparability of results
- Develop global research sites for clinical trials and cohorts
 - Identify strategies for building integrated, long-term, sustainable research infrastructure for investigations of Zika virus and cocirculating arboviruses, including capacity for clinical trials in pregnancy

Research priorities for vector surveillance and control

- Evaluate efficacy of currently available vector-control strategies
 - Conduct well designed investigations of currently available vector control strategies to guide public health programmes and investment
- Accelerate research in novel vector control methods
 - Investigate novel methods for vector control, including *Wolbachia*, genetic modification, and other tools, including research related to implementation, sustainability, health effects, and potential adverse ecological impacts
- Advance research in vector ecology and vector competence
 - Build local and national human, laboratory, surveillance, and research capacity for investigations of vector ecology, transmission drivers, dynamics of vector competence, and interactions of pathogens in vectors, hosts, and animal reservoirs

Policy and investment

- Build investment and political will essential for Zika virus research and development and vector control
 - Improve coordination among governments and funding organisations to advance integration of research, surveillance, and laboratory capacity related to multiple pathogens and vectors, to improve efficiencies, reduce costs, and diminish duplication of effort
 - Increase sustained funding for Zika virus research and development through strengthened advocacy and visibility among governments, funders, and the general public
 - Identify incentives to improve engagement and reduce risk for developers of Zika virus countermeasures and novel vector control methods

diminishing, even in high-income settings.¹⁴⁴ A broad research agenda is needed to address knowledge gaps related to vector ecology, transmission drivers, and spatiotemporal spread; dynamics of vector competence; and interactions and evolution of pathogens in vectors,

hosts, and animal reservoirs, as well as advancements in epidemiological, molecular, genomic, and serological surveillance. Visibility and investment are inadequate to advance research and programmes that are urgently needed to prevent the expansion of arboviral diseases.

New approaches to funding are needed to improve coordination, efficiency, and sustainability of mosquito surveillance, such as co-funding mosquito trapping for research in arboviruses, malaria, and other mosquito-borne pathogens. Implementation of a unified, global strategy is needed to accelerate progress in basic and applied research and programme evaluation.¹⁴⁵

Policy and investment

The primary constraints to advancing Zika virus research and development are insufficient funding and political will. Without increased investment, research in Zika virus medical countermeasures and vector control will continue to be inadequate, leaving the world unprepared to address ongoing transmission and future epidemics.

Developing, testing, and implementing Zika virus medical countermeasures and vector control will require long-term investment, extending well beyond the model of outbreak-driven funding.¹⁴⁶ The waning of the 2015–16 epidemic created uncertain markets for Zika virus medical countermeasures and undermined continued investment.¹⁴⁷ For example, the US Biomedical Advanced Research and Development Authority (BARDA) supported Zika virus vaccine research and development, but when funding expired, prominent industry developers discontinued Zika virus vaccine research programmes.^{148,149}

A plan to achieve sustained investment for Zika virus research and development is needed, including funding from government agencies, philanthropic organisations, and public–private partnerships.¹⁴⁷ Full public health value propositions and detailed cost–benefit analyses would help guide investment and increase political will, including assessment of long-term care costs for children and families that are affected by Zika-related disease.^{150,151} Push incentives, such as grants from philanthropic,

multilateral, and governmental organisations, would advance research and development based on public health need, even if not profitable. Pull incentives, such as advanced market agreements, would create more stable and predictable markets, with a focus on global access. Global support for manufacturing of vaccines and other countermeasures would alleviate the cost and risk of manufacturing otherwise borne by the developer and could help drive equitable global distribution for future epidemics.¹⁵² Funding during this inter-epidemic period, including of researchers and infrastructure in low-income and middle-income countries, would advance research and development capacity that could support clinical trials during future outbreaks. Novel approaches to funding that would support laboratories, cohorts, and other country research infrastructure for multiple pathogens would build on current investments, improve efficiencies, reduce costs, and enhance preparedness.

In addition to financial barriers, researchers and developers have long avoided research in pregnancy, primarily due to liability concerns. The unintended consequence is that safety and efficacy data are rarely available to guide clinical management in pregnancy. Special projects and workshops have been conducted to identify and reduce barriers to research in pregnancy; these initiatives serve as models that could be applied to advancing pregnancy research at the global level.^{153,154}

Conclusion

This Series paper summarises a comprehensive research agenda to advance research and development of Zika virus medical countermeasures and vector control, developed with input from a group of global experts (panel). Implementation of this strategy will require formation of research coalitions, standardisation of research methods, and coordination between governments, researchers, regulators, funders, and multilateral organisations to monitor progress and address priorities strategically. Most importantly, this agenda cannot be realised without sustained investment, engagement, and leadership of governments, foundations, and international and national health organisations. Complacency during this period of low Zika virus transmission is the primary barrier to progress. Building awareness and advocacy will be essential to drive change. Advancing research now is crucial to prepare the world to detect and respond to Zika virus epidemics in the future.

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Search strategy and selection criteria

References for this Series paper were identified through searches of PubMed for articles published from Jan 1, 2015, to Nov 5, 2024, using a broad range of search terms: “Zika” and “epidemiology”, “diagnostics”, (including searches of NAAT, IgM, IgG, IgA, and rapid tests), “pathogenesis”, “congenital infection”, “congenital Zika syndrome”, “treatment guidelines”, “cohorts”, “vaccines”, “monoclonal antibodies”, “therapeutics”, “transmission”, “prevention”, “wastewater”, “Aedes”, “vector control”, “controlled human infection models”, “pregnancy complications”, “adverse outcomes”, “funding”, “policy”, “surveillance”, “Wolbachia”, “case definitions”, “sexual transmission”, “vector surveillance”, and “animal reservoirs”. Search criteria included review articles and did not have any language restrictions. Information on Zika epidemiology, guidelines, arbovirus and vector control initiatives, and emergency use authorisations were identified through searches of the websites of WHO, Pan American Health Organization (WHO Region of the Americas), US Centers for Disease Control and Prevention, European Centre for Disease Prevention and Control, US Food and Drug Administration, Brazilian Health Regulatory Agency, and European Medicines Agency. Articles resulting from these searches and relevant references cited in those articles were reviewed.

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Contributors

EML was the overall project lead for all aspects of this project, including project design, literature reviews, writing of the initial manuscript draft, and editing and updating all subsequent drafts. TL, NMM, and L-CN contributed to literature reviews and writing initial manuscript drafts. AJM, JTO, and AKU contributed to conceptualisation, research and literature reviews, project coordination, and reviewing manuscript drafts. ADTB, DWCB, NB, AC, PCF, JPG, KAM, and MTO contributed to conceptualisation, project coordination, discussions of content, and critical review of manuscript drafts. ACB, EH, AIK, ETAM, JAM-R, IBR, JES, RV, and AW-S contributed to discussions of content, critically reviewed the content, and edited multiple drafts of the manuscript.

Declaration of interests

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