

ZIKA VIRUS RESEARCH AGENDA

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THE WHO ZIKA VIRUS RESEARCH AGENDA

BACKGROUND

Zika virus is a growing concern – it is endemic in parts of Africa, has been reported in South East Asia and is becoming established in the Americas and Caribbean. Since its detection in Brazil in 2015, it has emerged as a major public health challenge in the Americas. As of 16 June 2016¹, 60 countries and territories report continuing mosquito-borne transmission of which:

- 46 countries are experiencing a first outbreak of Zika virus since 2015, with no previous evidence of circulation, and with ongoing transmission by mosquitos.
- 14 countries have reported evidence of Zika virus transmission between 2007 and 2014, with ongoing transmission.

While the virus is known to cause mild illness (characterized by conjunctivitis, fever, rash and joint pain) many of the countries affected by Zika virus are also reporting potential neurological and auto-immune complications related to Zika virus infection with increased reports of Guillain-Barré syndrome, and birth defects including microcephaly.

In December 2015 the WHO's *R&D Blueprint for Action to Prevent Epidemics*² classified Zika virus-related neurological diseases as "serious" on its list of disease priorities needing urgent R&D attention.

The wide geographical range of the mosquito vector of the virus and the emerging complications of infection call for a global response. Based on the advice of the Emergency Committee of the World Health Organization (WHO), the WHO Director-General declared the clusters of microcephaly cases and the other neurological disorders in endemic areas as constituting a public health emergency of international concern on 1 February 2016.

Further to this declaration, WHO activated an emergency Incident Management System to coordinate the international response. This has included the development of a global *Zika Strategic Response Plan*³ encompassing surveillance, response activities and emphasising the urgent need for research to better characterize Zika virus infection to respond to this public health emergency.

GOALS

The goal of the WHO *Zika Virus Research Agenda* is to support the generation of evidence needed to strengthen essential public health guidance and actions to prevent and limit the impact of Zika virus and its complications.

The Research Agenda identifies critical areas of research where WHO is uniquely placed to implement or coordinate global activities. Research and evidence are the foundation for sound health policies. WHO is recognized for its access to decision-makers, public health experts, scientists and data, and for its ability to coordinate actors at national, regional and global levels. As the United Nations' specialized agency for health, WHO plays a pivotal role in leveraging its ability to convene experts and partners at the highest level to collaboratively address global health challenges. The WHO *R&D Blueprint* is an action plan to accelerate research and development for emerging pathogens likely to cause severe outbreaks in the near future, and for which few or no medical countermeasures exist.

The *Zika Virus Research Agenda* also acknowledges that management and support are needed to enable scientific research. The Research Agenda

¹ Situation Report: Zika virus Microcephaly Guillain-Barré Syndrome. Geneva: World Health Organization; 16 June 2016. Available at <http://apps.who.int/iris/bitstream/10665/242439/1/zikasitrep-16Jun2016-eng.pdf>.

² About R&D Blueprint (webpage). Geneva: World Health Organization. Available at <http://www.who.int/csr/research-and-development/blueprint/en/>

³ Zika Strategic Response Plan: revised for July 2016 - December 2017. Geneva: World Health Organization; 2016. Available at <http://apps.who.int/iris/bitstream/10665/246091/1/WHO-ZIKV-SRF-16.3-eng.pdf>.

outlines support activities and functions that will be required to ensure research coordination, management, capacity building and quality assurance. The Research Agenda is also intended to serve as a catalyst to align and mobilize partners to address core scientific questions about Zika virus. In doing so, it will strengthen relationships between healthcare professionals, researchers, response partners, donors and other stakeholders to advance our understanding of Zika virus and our response to the threats that it poses.

NEEDS ANALYSIS

RESEARCH GAPS

Gaps in research related to Zika virus were identified by a process initiated from the WHO Region of the Americas – the region at the centre of the current crisis. At regional level, this process identified priority research and development needs in:

- characterizing Zika virus infection including investigating public health and clinical implications;
- describing the dynamics of arbovirus epidemics in the Americas region and characterizing arbovirus vectors; and
- developing and enhancing laboratory platforms to support surveillance
- piloting new vector control tools

This process was complemented by consultative meetings convened by WHO at global level to expand on the identified areas. Meetings were convened to discuss research and product development (as part of the WHO *R&D Blueprint* process), vector control and the management of complications associated with Zika virus infection. These highlighted additional global research needs including:

- developing diagnostic products and increasing access to common standards, methods and reference materials to facilitate development;
- developing a vaccine, with a focus on protecting women of child-bearing age, pregnant women and their babies;
- developing effective therapeutics for both Zika virus and complications;
- holding cohort studies of pregnant women (infected and not infected with Zika virus) to better understand the outcomes of Zika virus infection on pregnancy;
- developing a causality framework to evaluate the association between Zika virus and neurological disorders; and
- understanding the natural history of Zika virus infection and identifying risk factors for severe complications.

Most importantly, the research needs to address Zika virus have been focused by the unfolding human cost of the epidemic. At the fore are the stories of families of infants born with microcephaly and other congenital syndromes, whose conditions are now being linked to maternal infection with Zika virus during pregnancy. Many of these infants will develop learning and motor disabilities as they grow older, and will require life-long care and social support. As of June 2016, the overwhelming majority of these infants have been born in Brazil where a Zika virus outbreak began in late 2015. However more cases are projected from other countries that have experienced outbreaks of Zika virus in 2016 as women who were infected in these areas during their pregnancies come to full term.

See Annex 1 for further details of the WHO Region for the Americas Zika virus research prioritisation process.

See Annex 2 for further details of the WHO global consultative meetings.

In addition to identifying priority research gaps, a need was also identified to align the activities of partners at all levels in order to implement effective and coordinated international research, and to provide supportive functions to enable robust research to take place.

Coordination and management support will be critical to address the research priorities identified and to harmonise the efforts of partners across countries, regions and institutions. Key actors will need to collaborate on scientific research projects and will also need to work with responders to translate research findings into improved public health responses.

The following key research coordination and management functions have been identified to support the *Zika Virus Research Agenda*.

Research and partner coordination

Close partner coordination and collaboration is required to ensure that research and response activities are aligned to agreed global priorities within the Research Agenda. This will require strengthening mechanisms to implement collaborative international research, share and access data, and disseminate preliminary research findings.

Towards this goal, WHO is working with Chatham House and Wellcome Trust as part of the *WHO R&D Blueprint* effort to develop a global coordination mechanism to improve global capacity for coordination and consensus about key actors supporting research and development before and during emergencies.

Common platform for standardised processes, protocols and tools, and for sharing specimens, data and information

Global, regional and national actors will require clear and standardized protocols to effectively detect, track and monitor Zika virus infection and associated complications. Standardization is required to assure the accuracy of data collection, to increase the power of research and to improve both quality assurance and quality control. Standardized protocols will be required for biological sampling, sample storage, shipment and transport, testing, record taking and data entry. Shared platforms will include common repositories for data, research outcomes and findings, and dissemination strategies will be put in place to enable the sharing of preliminary research findings and data.

Training and capacity building for research and public health response

The execution of new and harmonized tools, standards, processes and protocols requires enhanced training of users including laboratory technicians, public health workers, clinicians and others. Training is also required at local level for public health responders working on clinical management of Zika virus and its complications, vector control and risk communications.

Financing, implementation monitoring and management

Financing will be sought to initiate and maintain work in the Research Agenda over an anticipated timeframe of June 2016 to December 2018. Support will be sought from key funding partners and donors, and robust mechanisms established to ensure transparent monitoring, management, reporting, and accountability of funds and activities.

Ethics, regulatory support and quality assurance

The potential impact of Zika virus infection on pregnant women and their

babies raises additional ethical and regulatory complexities for research in this field. Public health decisions may have to be made on an urgent basis and in the context of scientific uncertainty. Establishing a sound basis of ethics, regulatory support and quality assurance for the Research Agenda will be key to enabling researchers and decision-makers to lead an evidence-based and robust response to the challenges posed by Zika virus.

WHO has recently published Ethics guidance⁴ for infectious disease outbreaks to focus on the cross cutting ethical issues that apply to infectious disease outbreaks generally, and examines how these principles can be adapted to different epidemiological and social circumstances.

IMPLEMENTATION FRAMEWORK

The coordination and management elements described above form the key support structure for the overall implementation of the WHO *Zika Virus Research Agenda*. The proposed research areas and the coordination and management functions that enable them are shown in the Implementation Framework below (Figure 1).

The Implementation Framework identifies three prioritised research areas: 1) Characterisation, 2) Prevention and Control, and 3) Women, Communities and Health Systems. These are coordinated by an overall research and partner coordination function. The research areas are supported by common platforms for standardised processes, protocol and tools, and specimen, data and information sharing. These platforms allow needs from the public health response to flow up to and inform research activities, and will also enable research findings to guide and improve the international response.

Training and capacity building for research and public health response forms the foundation of the Implementation Framework. Developing these skills in the key workforce involved in implementing the Research Agenda – laboratory technicians, clinicians, responders and others – is fundamental to making the Research Agenda operational and achieving its goals.

The management and administration of the Research Agenda is supported by two cross-cutting functions encompassing financing, implementation monitoring and management as well as ethics and quality assurance. These functions will provide the necessary organizational support required to run this major international project, as mechanisms to ensure that the highest levels of quality and accountability are maintained.

⁴ http://www.who.int/csr/research-and-development/guidance_for_managing_ethical_issues.pdf?ua=1

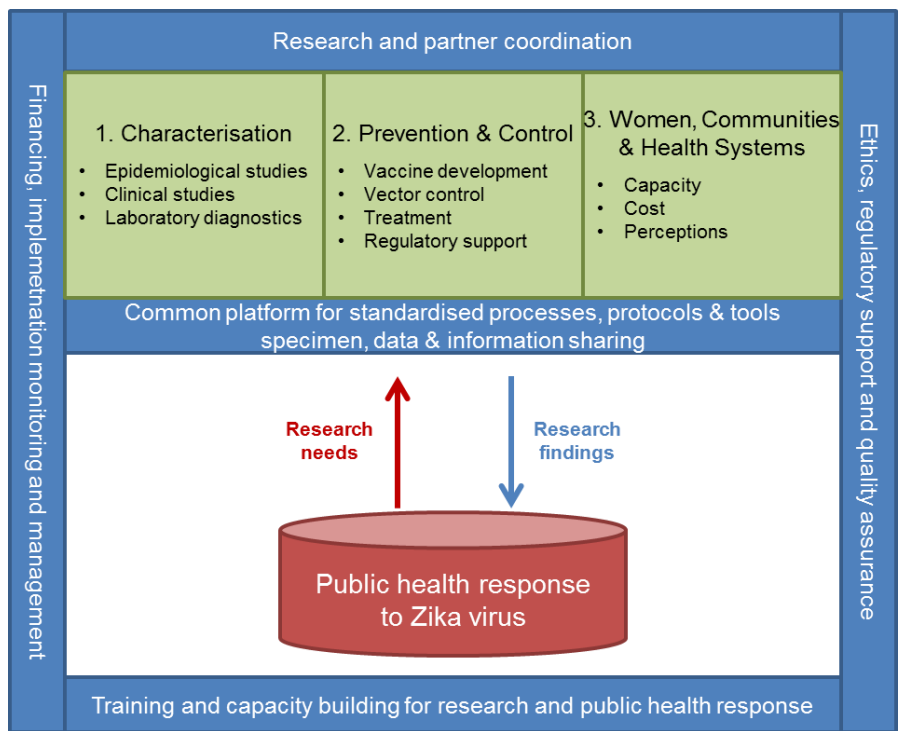


Figure 1. WHO Zika Virus Research Agenda Implementation Framework

RESEARCH AGENDA

As part of the WHO *Zika Virus Research Agenda* and within the WHO's *R&D Blueprint for Action to Prevent Epidemics*⁵, WHO has identified research activities in three key areas where the Organization is best placed to provide international leadership and to leverage its convening power. Activities under the WHO *R&D Blueprint* related in particular to activities 1.3 and 2 below.

1. CHARACTERIZATION

There is an urgent need to better understand and characterize Zika virus infection and its complications. This including investigating the association between Zika virus infection and complications and understanding the natural history of Zika virus disease and pathology.

Key research areas include: epidemiological studies to strengthen global epidemiological data on Zika virus infection and to support modelling and future projections of presumed congenital Zika virus syndrome; clinical studies to determine causality and characterization of complications; and laboratory diagnostics.

1.1 Epidemiological studies

- 1.1.1 Retrospective seroprevalence survey of Zika virus infection in frozen sera bio-banked from other studies, such as clinical trials for vaccine.
- 1.1.2 Support to prevalence survey in populations or communities representative of general populations, using PCR and IgG.
- 1.1.3 Characterization and risk of infection in other countries (baseline of epidemiology of Zika virus, sentinel surveillance activities).

1.2 Clinical studies

- 1.2.1 Support for development and implementation of cohort studies that will be selected:
 - i. To explore the risk of adverse outcomes of pregnancy (including all congenital abnormalities) in pregnant women infected with Zika virus compared with non-infected women; early pregnancy initiated cohort study of pregnancy outcomes in the context of Zika virus.
 - ii. Follow-up for at least two years of babies and infants born to infected mother and non-infected mothers.
 - iii. To study complications of Zika virus infection in adult men and women (autoimmune-mediated disorders such as GBS).
- 1.2.2 Persistence of Zika virus in body fluids of patients with acute infection or convalescents. Research on viral persistence in a cohort of men and women and regular testing of their body fluids (e.g. blood, semen, vaginal fluids, urine, saliva, breast milk) to explore risk of onwards transmission.

1.3 Laboratory diagnostics

- 1.3.1 Conduct and maintain a landscape analysis of commercially available tests.
- 1.3.2 Establish a consultative process to develop a target product profile for Zika virus diagnostics to detect active infection and

⁵ About R&D Blueprint (webpage). Geneva: World Health Organization. Available at <http://www.who.int/csr/research-and-development/blueprint/en/>

evidence of prior infection.

- 1.3.3 Implement an Emergency Assessment procedure for timely availability of quality assured diagnostics for Zika virus.
 - 1.3.4 Develop WHO biological standards.
-

2. PREVENTION AND CONTROL

2.1 Vaccine development

- 2.1.1 Conduct and update a landscape analysis of approaches taken by commercial, governmental, academic and any other known entities towards the development of Zika virus vaccine candidates.
 - 2.1.2 Develop a target product profile for a Zika virus vaccine for use in the emergency context and future outbreaks, targeted at the protection of women of child-bearing age and pregnant women.
 - 2.1.3 Develop regulatory considerations for Zika virus vaccines.
 - 2.1.4 Identify barriers to expedite and support the development of prioritised vaccine candidates, and collaborate with partners on the development and provision of reference materials.
 - 2.1.5 Provide technical advice for clinical trials of prioritised candidates.
-

2.2 Vector control

The vector control research priorities aim at evaluating community directed interventions and establishing vector control surveillance systems.

- 2.2.1 Conduct and update a landscape analysis of commercially available tests.
 - 2.2.2 Maintain landscape and support development of intervention options until sufficient development is achieved for deployment.
 - 2.2.3 Identify operational considerations for comparative and multi-centre controls for vector control trials.
 - 2.2.4 Research on the impact of insecticide resistance on vector control efficacy.
 - 2.2.5 Research on new indicators for entomological surveillance.
 - 2.2.6 Investigations on community-based vector control approaches, taking into account social and cultural differences.
 - 2.2.7 Identification of secondary vectors that may play a role in Zika virus dynamics.
 - 2.2.8 Support pilot implementation of new vector control tools for Zika virus (e.g. Wolbachia, transgenic mosquitoes).
 - 2.2.9 Evaluation of a prioritized selective vector control approach with existing tools targeting pregnant women.
-

2.3 Treatment

- 2.3.1 Conduct and update a landscape analysis of potential therapeutics and small molecule prophylaxis.
 - 2.3.2 Maintain landscape and promote development of intervention options until sufficient regulatory approval.
 - 2.3.3 Establish a Consultative Working Group to prioritize therapeutic and prophylactic candidates.
-

2.4 Regulatory support

- 2.4.1 Establish regulatory support for vaccines, diagnostics and therapeutics and prepare and characterize reference reagents.
-

3. WOMEN, COMMUNITIES AND HEALTH SYSTEMS

3.1 Perceptions and behaviours

- 3.1.1 Qualitative studies to explore the needs, attitudes and practices of women, men and healthcare service providers related to pregnancy prevention, abortion care, pregnancy care, and care for affected children.
- 3.1.2 Coordinate and synthesise community-level operational research (qualitative and quantitative) conducted by partners, including Knowledge, Attitudes and Perceptions (KAP) surveys on Zika virus, prevention, treatment, sexual reproductive health, vector control and other topics as identified during the response.

3.2 Health system capacity

Research activities will build on country assessments undertaken by the WHO Regional Office for the Americas and WHO guidance on Guillain-Barré syndrome, pregnancy management, microcephaly, infant feeding and others.

- 3.2.1 Bottleneck analysis to determine key barriers, potential drivers and priority issues for improving compliance with the issued guidance and ensuring successful uptake/implementation of the guidance.
- 3.2.2 Rapid assessment of the barriers to access, availability, utilization and readiness of contraception and abortion/post-abortion services in Zika virus affected areas.
- 3.2.3 Establish networks of sentinel sites in Zika virus affected countries to track changes in demand, provision and utilization of sexual reproductive health services.

4. COORDINATION AND MANAGEMENT

4.1 Common platform for standardized processes, protocols and tools, and for sharing specimens, data and information

- 4.1.1 Develop case definitions for surveillance, public health, laboratory and individual diagnosis.
- 4.1.2 Define full spectrum of complications in neonatal clinical data collection and evaluation of surveillance reports to define 'presumed congenital Zika virus syndrome'. Data collection training to describe the broad range of clinical manifestations and abnormalities being observed.
- 4.1.3 Develop and implement standardized protocols for biological sampling, storage, shipment and transport, and other relevant topics. Support the development of bio-banking.
- 4.1.4 Develop generic protocols for six types of study that will be implemented by countries to address key research priorities:
 - cross sectional prevalence survey
 - cohort studies of pregnant women
 - cohort studies of neonates and infants
 - case control studies for risk factors of microcephaly
 - case control studies of GBS
 - persistence of Zika virus in body fluids of patients with acute infection.
- 4.1.5 Generic protocol on natural history/clinical characterization studies, including biological sampling and follow up of patients with Zika virus infection to understand full spectrum of the infection, risk factors and evolution of complications. The study is also expected to provide insights for the timing and means

for potential clinical and therapeutic interventions, and to contribute to revised case definition for surveillance.

- 4.1.6 Inventory of ongoing of research projects and activities on Zika virus and observed complications.
- 4.1.7 Individual patient data (IPD) meta-analysis of pregnant women and adult and infant cohorts in areas with Zika virus transmission.
- 4.1.8 Develop data sharing platforms to support ongoing systematic reviews of available evidence to contribute to the Zika virus causality framework. Systems should be developed for continuous and efficient updates of the evidence that can be adapted for future outbreaks of new and emerging communicable diseases.

4.2 Training and capacity building for research and public health response

- 4.2.1 Evaluate health workforce strategies related to vector control in and around surrounding areas of health facilities.
- 4.2.2 Call for grants to support countries to address their own research priorities (published by the Special Programme of Research, Development and Research Training in Human Reproduction (HRP)⁶ and Special Programme for Research and Training in Tropical Diseases (TDR)⁷).
- 4.2.3 Coordinate planning and implementation of strengthened laboratory capacity and infrastructure in Zika virus endemic regions.

5. RESEARCH SUPPORT ACTIVITIES

5.1 Ethics

- 5.1.1 Establish an ethics working group to develop guidance on ethics and Zika virus for public health professionals and researchers that will support surveillance and public health research activities, including for the governance of bio-banks.
- 5.1.2 Conduct scoping reviews on ethics and Zika virus, including the outcome of relevant ongoing research on ethical issues raised by the Zika virus epidemic.
- 5.1.3 Support accelerated ethics review at global and regional levels to assure a rapid and timely turnover for all Zika virus related activities (both research and surveillance) that require ethics approval.
- 5.1.4 Strengthen national research ethics committees to conduct timely and efficient ethics review of Zika virus related research protocols, and national bioethics commissions to provide ethics related advice to their governments.

⁶ Special Programme of Research, Development and Research Training in Human Reproduction (webpage). Geneva: World Health Organization. Available at http://www.who.int/reproductivehealth/about_us/hrp/en/.

⁷ Special Programme for Research and Training in Tropical Diseases (webpage). Geneva: World Health Organization. Available at <http://www.who.int/tdr/en/>.

IMPLEMENTATION

BUDGET

A total budget of **USD 13,841,000** is sought from financing partners and donors to support the Research Agenda.

Characterisation	\$ 5,356,000
Prevention and Control	\$ 3,220,000
Women, Communities and Health Systems	\$ 2,700,000
Coordination and Management	\$ 1,985,000
Research Support Activities	\$ 580,000
Total	\$13,841,000

See Annex 3 for a detailed budget and description of activities.

TIMEFRAME

Activities will be implemented over a period of 24 months, from June 2016 to December 2018.

NEXT STEPS – TRANSLATING KNOWLEDGE INTO ACTION

The *WHO Zika Virus Research Agenda* aims to find answers to core scientific questions underlying our understanding of Zika virus and the public health measures used in our global response.

As research findings are produced, there will be further needs for partnerships and collaborations to translate research into policy, and into adapted and effective public health measures implemented on the ground. WHO will work with national health authorities and implementing partners to translate research knowledge into action, in order to strengthen essential public health actions and limit the impact of Zika virus and its complications on the people and communities affected.

CONTACTS

For further information on the Zika Virus Research Agenda and WHO's international response, please contact:

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ANNEX 1: DEVELOPMENT OF REGIONAL RESEARCH PRIORITIES

The WHO Regional Office for the Americas identified regional research priorities through a three-phase process, as depicted in Figure 2 below.

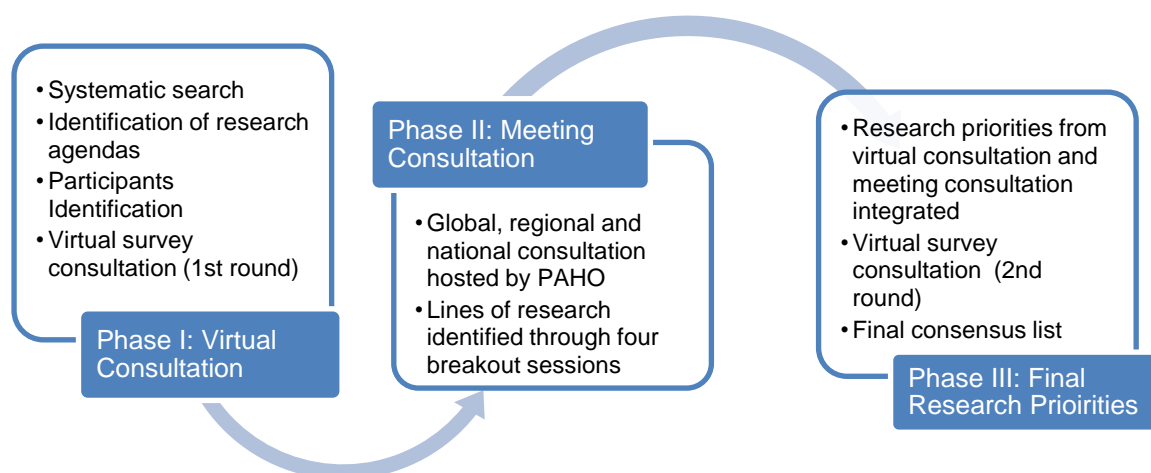


Figure 2: Process of development of the priority research agenda

PHASE I: VIRTUAL CONSULTATION

Phase I was managed and implemented through virtual consultation focused on the identification of research priorities through literature review, needs analysis, and definition of opportunities and threats to implementation. The literature review was conducted through a systematic database literature search, and searching information available on institutional websites. The systematic search yielded 626 citations, five research priority documents and three webpages with relevant information. These were evaluated and used to identify priority research lines/topics on Zika virus. Based on these topics, an initial survey using the Delphi method (Delphi Round 1) was conducted, which generated the first list of priority research needs/gaps.

PHASE II: MEETING CONSULTATION

The WHO Regional Office for the Americas held the ‘Towards the development of a research agenda for characterizing the Zika virus outbreak and its public health implications in the Americas’ meeting from 1–2 March 2016. The meeting brought together key stakeholders and experts to discuss Zika virus research priorities, and integrated new lines of research into a final prioritization exercise resulting in defined regional and global research priorities. The meeting sessions comprised of 1) Laboratory platform for supporting Zika virus surveillance; 2) characterization of the disease including public health and clinical implications; and 3) dynamics of the arbovirus epidemic in the Americas region and characterization of the vector.

PHASE III: FINAL RESEARCH PRIORITIES

During this phase, an International Delphi Round 2 survey was conducted among experts between 17–30 March 2016 to determine research lines/topics that were the most critical for implementation in the short-, medium-, and long-term. A list of high priority research needs was identified and categorized into three broad groups:

1. Laboratory platforms for supporting the surveillance: situation, limitations, challenges;
2. Characterizations of the disease, risk factors, causality studies, public health and clinical implications and complications;

3. Dynamics of the arbovirus epidemics in the American region and characterization of the vector / Zika virus relationships.

These critical areas of research identified were then presented to the WHO Regional Office for the Americas for endorsement. The complete results of the prioritization exercise are in Table 1 below. .

Table 1. WHO Regional Office for the Americas Zika Virus Research Priorities

Virus vectors and reservoirs	Relevance	Timeframe
Effectiveness of vector control measures on the transmission of ZIKV	Critical	Short-term
Effectiveness of Dengue, urban yellow fever and Chikungunya vector control	Very important	Short-term
What vectors are responsible for most human transmission (Culex, Mansonia and Anopheles genuses)?	Very important	Short-term
Screening of viral strains in mosquito vectors		Medium-term
Epidemiology	Relevance	Timeframe
What is the absolute risk of congenital malformation by gestational week	Critical	Short-term
Perinatal transmission and trans-placental transmission	Critical	Short-term
Characterization of clinical and subclinical ZIKV infections in pregnant women	Critical	Short-term
Diagnostic tools: Effective methodologies and validation of new process and platforms for serology, antigenic and molecular detection	Critical	Short-term
Sensitivity/specificity/predictive value of serum ZIKV IgM	Critical	Short-term
Biological plausibility for maternal-fetal transmission	Very important	Short-term
Including incident cases, birth defects, development of an epidemic curve	Less important	Short-term
Is it possible to detect ZIKV RNA in an infant or child who had the ZIKV infection in utero if the period of viremia has passed?	Less important	Short-term
Potential of individuals with previous history of infection from other flaviviruses (especially dengue, yellow fever and West Nile) to cross-react in tests	Less important	Short-term
Performance of ultrasound and other imaging tests to detect brain abnormalities in prenatal and postnatal period	Less important	Short-term
Influence of co-infections and super-infections of ZIKV and other co-circulating (CHIKV, DENV, YFV) arboviruses as well as pre-existing immunity / vaccination against other Flaviviruses	Less important	Medium-term
Use of modelling to understand the rate of infection and to understand what is the role of natural immunity particularly in the regions with previous ZIKV outbreaks	Less important	Medium-term
Spatial distribution of ZIKV, dengue and Chikungunya Are there clusters?	Less important	Medium-term
Characterization of the natural history of disease; ratio clinical to subclinical incidence SGB and others neurological complications; rare severe complications; mortality, dynamics of immune response	Less important	Medium-term
Identify clinical, laboratory and virological parameters among patients infected with ZIKV associated with complications or that can predict the progression to more severe disease.	Less important	Medium-term

Disease Pathogenesis and Consequences of ZIKV infection	Relevance	Timeframe
What types of samples are needed and how should they be collected and transported?	Critical	Short-term
ZIKV Infection teratogenic effect in function of the gestational age	Critical	Short-term
ZIKV infection pathogenesis to the fetus	Very important	Short-term
Association / risk factors between ZIKV infection and autoimmune syndromes	Less important	Short-term
Sexual and body fluids transmission	Less important	Short-term
Effect of infection by the ZIKV (with and without microcephaly) in the neurological, cognitive and motor development child mother with infection	Less important	Medium-term
What is the mechanism that makes IgM antibodies against ZIKV, dengue viruses, and other flaviviruses have strong cross-reactivity which may generate false positive results in serological tests? May this cross reactivity be involved in some kind of pathogenesis mediated by immune enhancement?	Less important	Medium-term
Flavivirus effects (including viral persistence and viral load) on neural tissues, placental barrier transfer and teratogenic	Less important	Medium-term
Animal models of teratogenic infection	Not important	Medium-term
Public health interventions	Relevance	Timeframe
Prevention strategies and risk communication	Critical	Short-term
Strategies to prevent congenital infections	Critical	Short-term
Interventions for the protection from mosquito bites in endemic areas (including the application of selective indoor residual insecticide spraying, in houses and around them, source reduction and larviciding application, with their corresponding evaluation)	Critical	Short-term
To describe clinical manifestation across a broad age of age and countries of ZIKV infection with a common standardized protocol	Less important	Short-term
Registries to understand complications of congenital birth defects	Less important	Medium-term
Evaluation of the impact of public health recommendations	Less important	Medium-term
To implement the systematic insecticide resistance surveillance for Aedes aegypti, for insecticides used in each country. These results must be used for the judicious management of insecticides and decision making at local level.	Less important	Medium-term
Evaluation of the current prevention and vector control activities by the countries, including the impact of countries current prevention strategies	Less important	Medium-term
Need to understand the routinely activities women do at home and at working places, which are their priorities and how to intervene to avoid human-vector contact	Not important	Medium-term
Health Systems and Services response	Relevance	Timeframe
Efficient financing mechanisms for addressing outbreaks ZIKV	Critical	Short-term
Mechanisms to ensure the provision of health services for patients with complications from ZIKV infection	Critical	Short-term
Effective mechanisms to ensure the availability of trained human resources in the clinical management and complications of ZIKV	Critical	Medium-term
Equity in risk of disease and in access to contraception, access for managing	Less important	Medium-term

children and adults with complications and disabilities		
Research and Development of Products	Relevance	Timeframe
Development of serologic, blood, and urine tests	Critical	Short-term
Validation and field testing of kits for the serological diagnosis of ZIKV	Critical	Short-term
Construction of a panel (of samples) from arbovirus endemic areas for validation of kits and to be used as reference in the standardization of laboratory methodologies	Critical	Short-term
Assurance of reliable, accurate, and standardized testing	Critical	Short-term
Vaccine development	Very important	Medium-term
Development of critical reagents: ZIKV Monoclonal antibodies, usefulness of NS1 antigen, recombinant antigen and antigenic peptides	Less important	Short-term
Safety, efficacy, and cost effectiveness of screening test for ZIKV	Less important	Medium-term
Using Wolbachia as mosquito population replacement strategy	Less important	Long-term

ANNEX 2: GLOBAL CONSULTATIVE MEETINGS

WHO GLOBAL CONSULTATION ON RESEARCH RELATED TO ZIKA VIRUS INFECTION

(GENEVA, 7–9 MARCH 2016)

With regard to research and development, research on following areas, was considered priority:

Diagnostics products: Development of Multiplex tests for Zika, Dengue and Chikungunya viruses, in addition to more traditional tests is essential, and evaluation in field conditions, on all fluids and not just blood, should be ongoing. In this context, there is an urgent need increased access to standards and reference materials and methods to facilitate product development

1. **Vaccines:** the development of a vaccine that can, above all, protect pregnant women and their babies remains an imperative for countries where the epidemic is expected to arrive in the foreseeable future. All current vaccine projects are in their early stages, but experience with other flaviviruses suggests that the end goal should be technically feasible. A target product profile for an emergency use vaccine, focuses on approaches using non-live vaccine, such as inactivated vaccines; should assist in reaching consensus on regulatory requirements for evaluating prospective Zika vaccines, and provide orientation to vaccine developers. Identification of correlates of protection against ZIKV will be important to help with vaccine development. In addition, animal models are needed to elucidate Zika's pathogenesis and complications, especially to help scientists assess the possible reproductive toxicity of candidate vaccines;
2. **Therapeutics:** known antivirals and immune-based interventions are being examined for their suitability for use as treatment, and similarities between the Zika and dengue viruses raise the possibility of repurposing existing molecule. However, there is a pressing need for relevant animal models to complement various ongoing questions and studies.

With regard to public health priority, the group highlighted the importance of developing

3. Causality framework to evaluate the association between Zika virus and neurological disorders.
4. Develop and implement cohort studies of pregnant women (infected and non-infected w Zika virus) to understand better the outcomes of pregnancy

VECTOR CONTROL ADVISORY GROUP MEETING

(GENEVA, 14-15 MARCH 2016)

On 14–15 March 2016, the WHO Vector Control Advisory Group (VCAG) reviewed five potential vector control tools and existing tools for use in the context of the response to the Zika virus outbreak, including: (1) mosquito control of human pathogens in adult vectors (Wolbachia); (2) mosquito control through genetic manipulation (OX513A); (3) sterile insect technique; (4) vector traps; and (5) attractive toxic sugar baits.

The main conclusions and recommendations of the meeting are as follows:

1. Well implemented vector control programmes using existing tools and strategies are effective in reducing the transmission of Aedes-borne diseases, including Zika virus. These tools should be promoted and used to control the Zika virus. They include: (i) targeted residual spraying; (ii) space spraying; (iii) larval control; and (iv) personal protection measures.
2. Full-scale programmatic deployment is not currently recommended for any of the five new potential tools reviewed by VCAG. However, the

VCAG recommended the carefully planned pilot deployment under operational conditions of two tools (Wolbachia-based biocontrol and OX513A transgenic mosquitoes) accompanied by rigorous independent monitoring and evaluation.

3. The VCAG concluded that more evidence is required before consideration of the pilot deployment of the three additional tools reviewed (sterile insect technique, vector traps and attractive toxic sugar baits).

MANAGEMENT OF COMPLICATIONS AND DEVELOPMENT OF THE ZIKA VIRUS CAUSALITY FRAMEWORK MEETING

(GENEVA, 17-19 MARCH 2016)

Management of Complications of Zika Virus

The group identified implications for surveillance, health systems, and research. The research priorities were mainly for the area of public health namely: finalization of the causality framework; supporting case-control and cohort studies with appropriate control groups to better understand the natural history of the disease and characterization of clinical outcomes; improving laboratory diagnostics with particular reference to serological tests; and carrying out social science research on impact and behavioural and care seeking choices in the context of Zika virus transmission. The group also agreed on the need to understand the full spectrum of fetal, newborn and adult neurological complications presumably associated with Zika virus infection.

Development of the ZIKV Causality framework

Against the background of emerging evidence suggestive of the linkage between ZIKV infection and potential neurological syndromes including adverse pregnancy outcomes, WHO developed a framework for systematic assessment of the evidence for causal associations with specified clinical outcomes that include three main categories: autoimmune disorders including GBS; acute central nervous system disorders, including myelitis; congenital anomalies, including microcephaly.

The causality framework was developed based on the list of dimensions of causality published by Bradford Hill: temporality, biological plausibility; exclusion of alternative explanations; strength of association; consistency of associations; cessation/reversibility; experimental evidence; analogy with other diseases; and specificity of effect at both individual and population levels.
