PAHO/WHO Regional Research Agenda related to Zika virus infection

Development of a research agenda for characterizing the Zika virus outbreak and its public health implications in the Americas

Pan American Health Organization

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Acronyms and Abbreviations

AMRO	Americas Regional Office (of the World Health Organization)
CDC	Centers for Disease Control and Prevention
CHIKV	chikungunya virus
DENV	dengue virus
FIOCRUZ	Fundação Oswaldo Cruz
GBS	Guillain-Barré Syndrome
GOARN	Global Outbreak Alert and Response Network
LLINs	long-lasting insecticidal nets
NIH	National Institutes of Health
PAHO	Pan American Health Organization
RT-PCR	reverse transcription polymerase chain reaction
WHO	World Health Organization
YFV	yellow fever virus
ZIKV	Zika virus

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EXECUTIVE SUMMARY

Background

Since its first detection in Brazil in 2015, the Zika virus (ZIKV) has spread rapidly to most of the subregions of the Americas. As of April 6, 2016, ZIKV autochthonous transmission has been confirmed in 35 countries and territories of South America, Central America and the Caribbean. The Emergency Committee of the World Health Organization (WHO) advised that the clusters of microcephaly cases and other neurological disorders in endemic areas constitute a public health emergency of international concern.

The global prevention and control strategy launched by WHO/PAHO as a strategic response framework encompasses surveillance, response activities, and research. There is an urgent need for additional research to better characterize the ZIKV outbreak and respond to this public health emergency, especially those issues related to means of transmission and infection during pregnancy and Guillain-Barré syndrome (GBS).

Goals and objectives

The goal of the research agenda is to support the development of evidence needed to strengthen public health guidance and actions essential for limiting the impact of the ZIKV outbreak. By identifying areas of high priority research, results from this report will assist in creating a coordinated research agenda for the Region.

Methods

We used a modified Delphi process, an iterative and systematic method of developing consensus within a group. An initial literature review was conducted to locate gaps of research and institutional research agendas related to the ZIKV. Information was systematically extracted and recorded to create a preliminary Delphi survey. A face-to-face meeting consultation was conducted at the PAHO on March 1-2, 2016, which highlighted additional gaps of research and difficulties in coordination. Results from the Delphi survey 1 and gaps of research presented at the face-to-face meeting formed the lines of research of the final Delphi survey. Experts evaluated their agreement to the proposed research line using a 5-point Likert scale and indicated the need for short, medium and long-term implementation.

Results

52 experts representing 28 international public health and research institutions participated in the final Delphi consensus activity to set the final PAHO/WHO Regional research priorities. Gaps of research identified as critical and very important and need to be implemented in the short-term were identified in each of the six subtopics including: virus, vectors and reservoirs (3); epidemiology (6); disease pathogenesis and consequences of infection (3); public health interventions and clinical management (3); health systems and services (3), and research and development of products (4). Results of the critical and very important areas of research are displayed in Table 1.

Coordination

To improve research activities and implement a coordinated research agenda, it is imperative that the response of partners across sectors and services be coordinated at the global, regional and national levels. Virtual and face-to-face meeting consultations identified current difficulties in coordination that, if not addressed, will impede carrying out the research agenda. The complexity and scale of the emergency and the potential spread of ZIKV means that it is crucial for the various organizations to coordinate their activities to create a coherent, consistent response. Coordination of leaders, roles and resources is necessary to reduce, mitigate and respond to the ZIKV epidemic.

Table 1: Identification of Regional Research Priorities

Relevance and implementation by subtopic:	Delphi Classification	Time of implementation
Virus vectors and reservoirs		
Effectiveness of vector control measures on the transmission of ZIKV	Critical	Short-term
Effectiveness of dengue, urban yellow fever and CHIKV vector control	Very important	Short-term
What vectors are responsible for most human transmission (Culex, Mansonia and Anopheles genuses)?	Very important	Short-term
Epidemiology		
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 ZIKVIgM	Critical	Short-term
Disease pathogenesis and consequences of ZIKV infection		
ZIKV infection teratogenic effect in function of the gestational age	Critical	Short-term
What types of samples are needed and how should they be collected and transported?	Critical	Short-term
Zika infection pathogenesis to the fetus	Critical	Short-term
Public health interventions and clinical management		
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
Health systems and services response		
Efficient financing mechanisms for addressing ZIKV outbreaks	Critical	Short-term
Mechanisms to ensure the provision of health services for patients with complications from ZIKV infection	Critical	Short-term
Mechanisims to ensure the availiabilty of trained human resources in the clinical management and complications of ZIKV	Critical	Short-term
Research and development of products		
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; to be used as reference in the standardization of laboratory methodologies	Critical	Short-term
Assurance of reliable, accurate, and standardized testing	Critical	Short-term

BACKGROUND

Since it was first detected in Brazil in 2015, the Zika virus (ZIKV) has spread rapidly to most of the subregions of the Americas. As of April 6, 2016, ZIKV autochthonous (acquired locally, in-country) transmission has been confirmed in 35 countries and territories of South America, Central America and the Caribbean. A total of 52 countries and territories have reported autochthonous transmission or indication of transmission between January 1, 2007 and March 3, 2016 (41 countries since January 1, 2015). Despite its first clinical and epidemiological descriptions in the 1950s and 1960s, ZIKV was not identified as having a serious public health impact until 2014-15. However, following the reporting of Guillain-Barre syndrome (GBS) outbreaks concomitant with ZIKV outbreaks in the French Territories of the Pacific region during 2013-14; the temporal/spatial association between large ZIKV outbreaks and a dramatic increase of microcephaly cases in Brazil beginning in the last quarter of 2015, the ZIKV implications for public health appears to have been underestimated and are still not sufficiently characterized. While the increases in microcephaly cases and other neonatal malformations have only been reported in Brazil and French Polynesia, two cases linked to a stay in Brazil were detected in the United States and Slovenia[1].

ZIKV is a flavivirus that was first identified in Uganda in 1947.[3] Prior to 2007, only sporadic outbreaks were reported in parts of Africa and Southeast Asia. In 2007, the first documented outbreak of ZIKV was reported in Yap State, Federated States of Micronesia; 73% of the population aged ≥3 years is estimated to have been

infected.[4] In 2013, following the first reported case in French Polynesia, ZIKV spread rapidly in the Pacific area. Approximately 11% of the population was infected, and an estimated 28,000 people sought medical care. [5-6]

ZIKV is transmitted primarily by the *Aedes aegypti* (Ae. aegypti) mosquito. Experimental evidence suggests that *Aedes albopictus* (Ae. albopictus) may also transmit the virus. Ae. aegypti and Ae. albopictus mosquitoes are found throughout much of the Americas, including parts of the United States, and also transmit dengue virus (DENV) and chikungunya viruses (CHIKV).[7] ZIKV infections have also been documented through intrauterine transmission resulting in congenital infection and intrapartum transmission from a viremic mother to her newborn.[8] As of February 2, 2015, the first case was reported in the United States, via sexual transmission.[9]

An estimated 60-80% of people infected with ZIKV are asymptomatic.[10] Disease symptoms are usually mild, characterized by acute onset of fever, maculopapular rash, arthralgia, or nonpurulent conjunctivitis; symptoms rarely result in severe disease or fatality.[11] Severe clinical manifestations of autoimmune illness, GBS, and congenital neurological malformations are under investigation.[12] Of particular concern is the potential association between ZIKV and microcephaly. Brazil has reported a sudden increase in microcephaly and the detection of ZIKV RNA in the amniotic fluid of affected newborns.[13] As of January 2, 2015, the Ministry of Health of Brazil reported 4,222 suspected cases of microcephaly, which are spread across 684 municipalities in 22 federal units of Brazil.[14] A 20-fold annual increase in microcephaly cases was observed after ZIKV emerged in Brazil. The causal relationship between ZIKV and microcephaly is not yet established but is strongly suspected.

The global prevention and control strategy launched by WHO/PAHO as a Strategic Response Framework encompasses surveillance, response activities, and research. There is an urgent need for additional research and coordination of such research to better characterize to the ZIKV outbreak and respond to public health, as well as issues related to means of transmission and infection during pregnancy and GBS.

GOAL AND OBJECTIVES

The goal of the research agenda is to assist in developing evidence needed to improve public health guidance and actions for limiting the impact of the ZIKV outbreak By identifying gaps in research that are a high priority, this report will help create a coordinated research agenda for the Region.

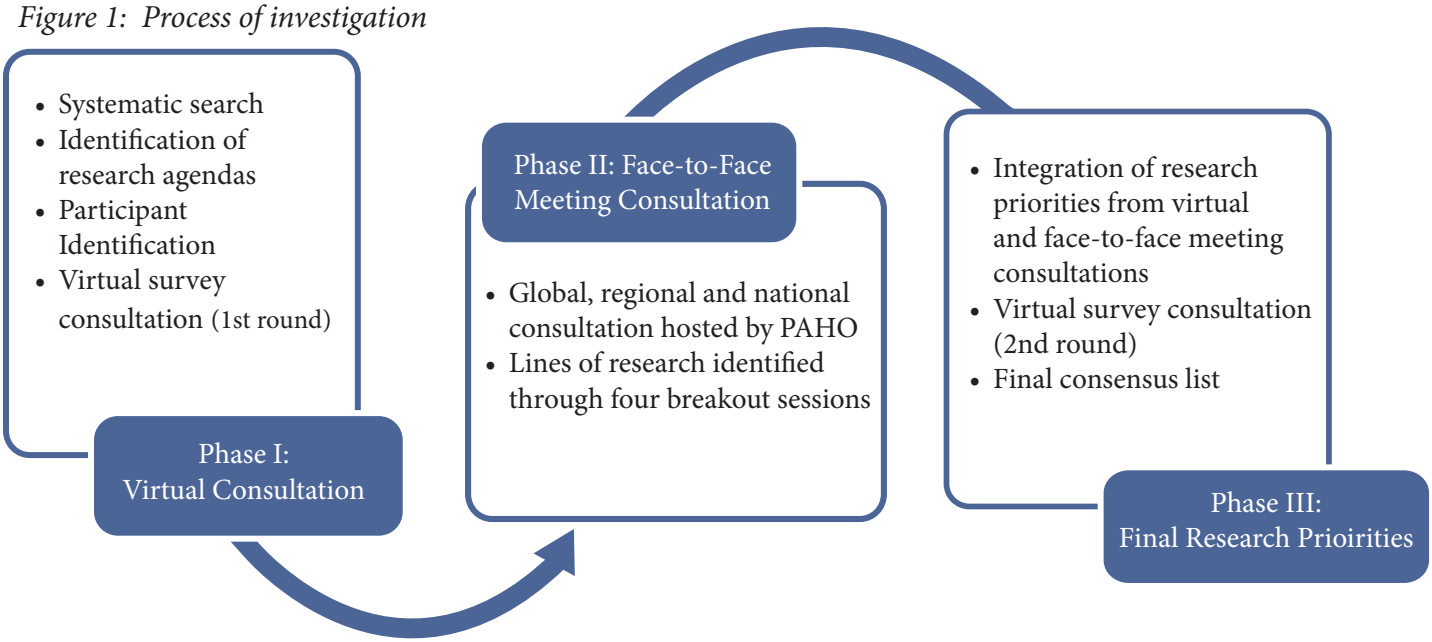
This report intends to meet these objectives:

1. Provide a framework that reflects public health research priorities for the ZIKV outbreak.
2. Identify priority research lines/topics for addressing and bridging existing knowledge gaps and prioritize their importance to meet short- and long-term public health needs.
3. Help to coordinate and articulate research activities.
4. Serve as a catalyst for strengthening the relationships between research networks and response partners.
5. Help mobilize resources to respond appropriately to the ZIKV.

METHODS

The objective of this report is to create a list of critical research priorities related to the ZIKV to assist in creating a coordinated response to the epidemic. Critical research priorities were developed through three phases: 1) virtual consultation; 2.) face-to-face meeting consultation; and, 3.) compelling new lines of research into a final prioritization exercise.

Figure 1: Process of investigation



PHASE I: VIRTUAL CONSULTATION

Aim and objectives

Phase I included the development of investigative agenda on ZIKV based on a review of the literature and needs analysis.

The following objectives were completed:

- Systematically searched the literature to identify and characterize ZIKV research gaps.
- Identified ongoing research and surveillance efforts in the Region.
- Identified both published and ongoing research studies, available at www.paho.org/zika-research.
- Identified and classified the gaps in knowledge about the virus, its clinical and public health implications, and the dynamics of the epidemic in the Americas.
- Developed a map of themes, sub-themes and research questions that serves as the basis for consultation with experts and key players.
- Developed a virtual survey aimed at decision-makers, researchers, academics, managers, implementers, international organizations and sub-regional, civil society and medical associations, among others, in selected countries; identified themes, sub-themes and questions of unidentified research and prioritized each for combatting ZIKV at the global level.
- Compiled findings to be used in PAHO and WHO face-to-face meetings to establish and implement a research agenda.

Literature review

First methodological approach: We conducted a systematic search of the literature of the following databases: PubMed, EMBASE, Cochrane Library, and Lilacs, and used search engines such as Google scholar to locate articles related to the proposed research lines/topics (last search was January 31, 2016). Because there are no validated strategies for this topic, we identified search keywords and synonyms using the PubMed search engine.

Second methodological approach: We identified priority research lines/topics for research on ZIKV, based on the information of available institutions. We revised the websites of ministries of health and institutions of each of the countries of the Americas. We also searched other sources, such as press releases and statements from key institutions. We identified and compiled research agendas of ZIKV published by other institutions, as well as research meeting reports that described research priorities and called for research (grants) of key institutions and organizations.

Results of the systematic search

The search strategy identified 626 citations, five research priority documents and three webpages with relevant information. We evaluated all documents to identify priority research lines/topics for research on ZIKV.

Delphi Round 1

Survey creation

Based on the findings of the literature review, an initial survey was created through Survey Monkey on the research priority lines/topics for ZIKV. Experts working in the Region also reviewed the research lines/topics to ensure that they were short and specific, and that each item was consistent and measurable. Given the short timeframe for responding to the epidemic, it was not feasible to conduct a broader consultation and validation process. These lines were classified into six subcategories:

1. Virology, entomology and reservoirs
2. Epidemiology
3. Pathogenesis and consequences of ZIKV infection
4. Public health interventions and clinical management
5. Health systems and services response
6. Research and development of products

The survey consisted of three sections: the first section included the demographic description of participants (sex, age, occupation, country) and their area of work; the second section consisted of proposed research lines/topics; the third section included an open-ended section for identifying additional research needs (additional lines/topics) not previously listed. The survey was drafted in English; two reminders were sent.

Criteria for prioritization

Each question was prioritized according to its relevance using the following criteria:

- Impact: The topic contributes to the social welfare and has the potential to reduce the burden of disease, reduce the infection rate, and create an equitable health systems response.
- Temporality: The timeframe for implementing the topic addressing ZIKV: short-term (less than six months), medium-term (6 months to 2 years), and long-term (more than 2 years).
- Feasibility: The line of action can be proposed and implemented within a technological, cultural, political, and socioeconomic context, taking into account available resources.

Selection of participants

The survey included key actors working in the research lines/topics of ZIKV and other arboviruses. They included clinicians, epidemiologists, virologists, entomologists, obstetricians, neurologists, pathologists, public health and global health specialists, and decision-makers in health systems that are currently working on ZIKV or a related discipline.

Participants in the first prioritization exercise were identified through the systematic search described previously, through national information sources, and by individuals working with institutions such as PAHO, WHO, CDC, NIH, Instituto Nacional de Salud in Colombia, Fundação Oswaldo Cruz (FIOCRUZ), among others.

Collection, handling and data analysis

Data was collected through the Survey Monkey and was exported and cleaned in Excel to be used in the statistical analysis. A descriptive analysis of the characteristics of the participants was conducted. A priority analysis was conducted on the research lines/topics in relation to the classification "critical," "very important," "important," "less important," and "not important" and a time analysis was conducted to determine if implementation should be "short-term," "medium-term" or "long-term." Measures of central tendency (mean/median) and level of dispersion (standard deviation) were presented concerning the collective judgments on the relevance of research lines/topics of respondents. Implementation time of research lines/topics required 70% or more of agreement. All comparative analysis was carried out under the statistical significance of $P < 0.05$. Statistical analysis was conducted using the statistical software STATA.

Ethical aspects

The study was reviewed by PAHO Ethics Committee (PAHO-ERC). Participants agreed to participate through a survey consent form. In the analysis of responses, participants' identities were anonymous.

Results

The first Delphi round began on February 24 and ended March 16, 2016. Of the 134 experts solicited to participate in the survey, 62 completed the questionnaire. Of those, 66.1% were men; respondents' average age was 49. The average research experience on ZIKV was 2.42 years. Respondents' main areas of expertise were virology (13.33%), public health (20%), and epidemiology (28.89%). Respondents represented 20 different countries, although their home institutions were primarily Brazil (16.67%), Colombia (8.33%), and the USA (31.25%). In all, 81% of respondents answered questions on virus vectors and reservoirs; 84% on epidemiology; 68% on disease pathogenesis; 47% on clinical management; 80% on public health interventions; 61% on health systems and services; and 85% on research and development of products.

Several research lines/topics were identified as critical priorities to be implemented in the short-term.

In the subtopic of **epidemiology**, 12 topics were identified as critical research priorities for short-term implementation: perinatal transmission and trans-placental transmission; sexual transmission; development of an epidemic curve; establishment of causality; microcephaly and other congenital malformations; flavivirus effects (including viral persistence and viral load); diagnostic tools; sensitivity/specificity/predictive value of serum Zika IgM; potential of individuals with previous history of infection from other flaviviruses; data sharing, and frequency and risk factors for complications of ZIKV.

In the subtopic of **public health interventions**, 5 line items fit this criteria. They include prevention strategies and risk communication; strategies to prevent congenital infections; interventions in endemic areas for protection from mosquito bites; registries to understand complications of congenital birth defects; and cohort studies in areas of high infection.

In the subtopic of **health systems and services**, 3 topics were identified as critical research priorities for short-term implementation: efficient financing mechanisms to ensure the provision of health services for patients with complications from ZIKV infection; mechanisms for addressing outbreaks ZIKV; and effective mechanisms to ensure availability of trained human resources in the clinical management and complications of ZIKV.

In the subcategory of **research and development** of products, 3 research lines/topics were identified as being critical priorities to be implemented in the short-term: development of serologic, blood, and urine tests; development and validation of rapid test for ZIKV infection; and assurance of reliable, accurate, and standardized testing, safety, efficacy, and cost-effectiveness of ZIKV screening.

No topics in **virus, vector and reservoirs** were listed as critical for implementation.

Additional information regarding the research priorities from the first Delphi prioritization exercise is available in Annex 4.

PHASE II: FACE-TO-FACE MEETING CONSULTATION

On March 1-2, 2016, PAHO hosted a meeting "Towards the development of a research agenda for characterizing the Zika virus outbreak and its public health implications in the Americas." The meeting was carried under the auspices of the Global Outbreak Alert and Response Network (GOARN); PAHO/WHO served as secretariat, and key stakeholders and experts from around the globe participated. The meeting involved participation from key experts from the CDC and the National Institutes of Health (NIH) in the United States; the Oswaldo Cruz Foundation and the Evandro Chagas Institute in Brazil; the London School of Hygiene and Tropical Medicine in the United Kingdom; Institute Pasteur in France, Senegal, and French Polynesia; and the Institute Pedro Kouri in Cuba. Additional key researchers and experts with relevant expertise attended from different institutions of affected countries of the Region. The two-day meeting involved experts from an array of different backgrounds, including medicine, public health, epidemiology, virology, biology, and entomology, among others.

Objectives

Discuss knowledge gaps and research needs and priorities that will inform future interventions and public health practices and that can be applied under real-world settings in Latin America and the Caribbean.

Consultation Process

The first day focused on the regional situation and the response to the ZIKV outbreak. Country presentations were made from representatives of Brazil, Colombia and the United States. Panel presentations highlighted gaps in research and prevention strategies associated with the emergence of the ZIKV in the Americas. Specifically highlighted during the sessions were gaps in research regarding epidemiological characteristics; reservoirs and vectors; disease pathogenesis, clinical management and public health interventions; health systems and services, and prevention strategies associated with the emergence of ZIKV in the Americas.

Identified Gaps in Research from the Face-to-Face Meeting Consultation

During the workshop, participants were assigned to sessions in three key areas:

1) laboratory platforms for supporting surveillance, including the situation, limitations, and challenges;
2) characterization of the disease, causality studies of risk factors, and public health and clinical implications; and
3) dynamics of the arbovirus epidemics in the Americas and characterization of the vector. Priority research lines were identified for addressing and bridging gaps in existing knowledge about ZIKV.

Participants identified and discussed key factors to reduce the likelihood of local transmission of ZIKV in the Americas. Areas of insufficient knowledge related to strategies for addressing the epidemic, and the need to generate research questions of specific concern.

Session 1: Laboratory platforms for supporting ZIKV surveillance

The first breakout discussion centered on the limitations and challenges of laboratory platforms for the surveillance of ZIKV in the Americas. During this discussion, several high-priority gaps in research were identified; particular attention was given to diagnostic testing and methods of sample collection. The CDC has determined that testing conducted through reverse transcription polymerase chain reaction (RT-PCR) should be prioritized due to the sensitivity and specificity of the test. On the other hand, antibody testing utilizing ELISA or plaque reduction neutralizing tests (PRNT) is limited and should be carefully interpreted; cross-reactivity and co-detection of antibodies against related flaviviruses (including dengue and yellow fever) is common, and confirmation may be difficult to establish. Therefore, submission of an acute serum specimen collected within 7 days of the onset of symptoms and, ideally, between 3 and 7 days after onset for RT-PCR is particularly encouraged. Because viremia decreases over time, a negative RT-PCR collected 5-7 days after the onset of symptoms does not necessarily exclude the possibility of a ZIKV infection. In such cases, serologic testing should be performed. Due to these constraints, high-priority areas of research were determined to focus on laboratory diagnosis due to the difficulties in the detection of viremia and cross-reactivity of ZIKV antibodies with other flaviviruses. Interim guidelines exist for evaluating and testing infants with microcephaly or intracranial calcifications whose mothers have traveled to or resided in an area with ZIKV transmission during their pregnancy. Due to the challenges of the current available tests, a high-priority area of research was identified as the need for developing specific tests and platforms that can confirm the diagnosis of ZIKV, especially when association to GBS, microcephaly and other congenital abnormalities are suspected. Furthermore, this breakout session identified a high-priority area of research on the development and guidelines available for collecting and transporting samples.

Session 2: Characterizations of the disease, including public health and clinical implications

The second breakout discussion centered on the characterizations of ZIKV, including risk factors, causality studies, and public health and clinical implications of the disease. Several high-priority gaps in research were identified. Participants of the group noted that as the infection from ZIKV has reached epidemic proportions, it has become urgent that we understand the characterization of the disease and the potential causal relationship with microcephaly. Although there is strong supporting evidence that ZIKV infection during pregnancy is associated with adverse fetal outcomes, the magnitude of the association and the mechanisms and overall

effects are not well understood. The group identified that determining the absolute risk of congenital malformation by gestational week was a high-priority area of research. The group also identified a high-priority area of research through the clinical and subclinical presence of ZIKV in pregnant women through the development of cohort studies. Additional emphasis was placed on the follow-up of infants with microcephaly and other abnormalities. Because much is still unknown about the epidemiological competencies of the disease, modeling to understand the infection rate and the role of natural immunity (particularly in regions with previous outbreaks) was identified as a high-priority area. Finally, the group emphasized the need for developing standard operating procedures for ZIKV screening and for disseminating information about such processes through a common core protocol.

Session 3: Dynamics of the arbovirus epidemic in the Americas and characterization of the vector

The third session centered on the dynamics of the arbovirus epidemics in the Americans and characterization of the vector. Several high-priority gaps in research were identified. The group focused on the need for human-vector contact protection, particularly for pregnant women. One high-priority area of research: evaluating current prevention and vector control activities. The group discussed the need to understand women's daily activities at home and work in order to evaluate strategies for prevention. A second high-priority area of research: strategies that improve the implementation and evaluation of vector control strategies and diminish the risk of human-vector contact. A third high-priority area of research: understanding the effects of selective indoor residual insecticide spraying. This research should be conducted in or around the homes of pregnant women. A fourth high-priority area of research: evaluating the effectiveness of supplying personal protection kits that include repellents, long-lasting insecticidal nets (LLINs), treated curtains, condoms, and flyers with recommendations for the eliminating breeding sites in the houses and working places. A fifth and final high-priority area of research: implementing systematic insecticide resistance surveillance for Aedes aegypti for insecticides used in each country. These results must be used for judicious management of insecticides and decision-making at the local level.

PHASE III: FINAL PRIORITIZATION EXERCISE AND PRESENTATION OF PAHO/WHO REGIONAL PRIORITIES

Delphi Round 2

In order to develop PAHO/WHO Regional research priorities, we conducted an international Delphi survey among experts to determine which lines/topics of research were the most critical to implement in the short-term, medium-term and long-term, respectively. Using the same methodology in the Phase 1 consultation, respondents were asked to prioritize each topic according to its relevance using the criteria of (1) impact, (2) temporality and (3) feasibility, taking into account the national and regional context. The final modified Delphi survey included respondents from the first Delphi prioritization exercise and participants from the PAHO/WHO face-to-face meeting consultation.

Results

The second Delphi round began March 17 and ended March 30, 2016. Of the 134 experts solicited for participation, 50 completed the second round. The study committee stopped the Delphi process at the second round, estimating that additional rounds were unlikely to substantially change the final results. The average age of respondents was 45; 54.35% were men. The average research experience on ZIKV was 2.30 years. Respondents' main areas of expertise were in virology (13.33%), public health (20%), and epidemiology (28.89%). Respondents represented 20 different countries although their home institutions were primarily Colombia (8.33%), Brazil (16.67%), and the USA (31.25%).

Critical areas of research were identified in each of the six subtopic areas.

In the subtopic of ***virus vectors and reservoirs***, the effectiveness of vector control measures on ZIKV transmission was considered a critical area of research in the short-term.

In the subtopic of *epidemiology,* three research lines/topics were considered critical areas for short-term implementation: understanding the absolute risk of congenital malformation by gestational week of infection; perinatal transmission and trans-placental transmission; and characterization of clinical and subclinical presence of ZIKV in pregnant women.

In the subtopic of ***disease pathogenesis and consequences,*** two were identified as critical areas of research for the short-term: understanding ZIKV's teratogenic effect in relation to gestational age, and understanding the types of samples needed and the best way to collect and transport them.

In the subtopic of ***public health interventions,*** three research areas were considered critical in the short-term: strategies for prevention and risk communication; strategies for preventing congenital infections; and interventions in endemic areas for protecting people against mosquito bites.

In the subtopic of ***health systems and services,*** three research areas were considered critical in the short-term: efficient financing mechanisms; mechanisms to ensure the provision of health services for patients with complications; and effective mechanisms to ensure the availability of trained human resources in the clinical management and complications of ZIKV.

In the subtopic of ***research and development of products,*** four research areas were considered critical in the short-term: development of serologic, blood, and urine tests; validation and field testing of kits for the serological diagnosis of ZIKV; 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; and assurance of reliable, accurate, and standardized testing.

Final Delphi survey results: classification of Regional research priorities

Relevance and implementation by subtopic:	Delphi Classification	Time of implementation
Virus vectors and reservoirs		
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	Very important	Medium-term
Epidemiology		
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 processes and platforms for serology, antigenic and molecular detection	Critical	Short-term
Sensitivity/specificity/predictive value of serum ZIKVIgM	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 ZIKVRNA 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 modeling to understand the rate of infection and to understand the role of natural immunity, particularly in regions with previous ZIKV outbreaks	Less important	Medium-term
Spatial distribution of ZIKV, dengue and chikungunya: Are there clusters?	Less important	Medium-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

Relevance and implementation by subtopic:	Delphi Classification	Time of implementation
Epidemiology		
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 and clinical management		
Prevention strategies and risk communication	Critical	Short-term
Strategies to prevent congenital infections	Critical	Short-term
Interventions for protection from mosquito bites in endemic areas (including the application of selective indoor residual insecticide spraying in and around houses, source reduction, and application of larviciding, with corresponding evaluation)	Critical	Short-term
Description of clinical manifestations 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
Implementation of 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
Assessment and evaluation of women's routine activities at home and at work to understand their priorities and how to intervene to avoid human-vector contact	Not important	Medium-term
Health systems and services response		
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 children and adults with complications and disabilities	Less important	Medium-term

Relevance and implementation by subtopic:	Delphi Classification	Time of implementation
Research and development of products		
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
Use of Wolbachia as replacement strategy for controlling mosquito population	Less important	Long-term

IMPLEMENTATION OF THE RESEARCH AGENDA

Coordination

Key actors should work to create a coordinated response to 1) improve surveillance and detection of infections, congenital malformations, and neurological complications; 2) improve control of mosquito populations; and 3) expedite the development of diagnostic tests and vaccines to protect people who are at risk. Implementation of a research agenda will require improvements in coordinating and financing research, networks and collaboration between academic institutions and public health agencies.

This process allowed us to identity key areas in which coordination can be improved. Participants of the PAHO/WHO meeting expressed a need for coordination among laboratories. Laboratories already play an important role in helping to understand the outbreak. However, validated and broadly available testing diagnostics are urgently needed to step up research, clinical management, and surveillance. The use of these tools requires enhanced training in diagnostics for laboratory technicians. Additionally, training is required at the local level for vector control and the clinical management of ZIKV.

Furthermore, actors at the global, regional and national level should develop a clear and uniform protocol to standardize case definitions for surveillance. And in order to effectively detect, track and monitor ZIKV, public health, laboratory and individual diagnosis are necessary. Standardization is also necessary to assure the accuracy of data collection for improving quality assurance and quality control. A standardized protocol is also needed for biological sampling, sample storage, shipment and transport, record-taking, data entry, and other functions related to collecting and storing samples.

Close coordination and collaboration among partners is required to address this crisis. To ensure that response activities are supported to the fullest extent possible requires stronger mechanisms for implementing a collaborative international research response, and for disseminating preliminary research findings and access to the data that is generated.

Financing

WHO has reported that $56 million is necessary to implement the Strategic Response Framework and Joint Operations Plan. Over $25 million will be funded by WHO/AMRO/PAHO; key partners will provide an additional $31 million. To finance its initial operations, WHO has recently established an emergency contingency fund. However, to ensure the longevity of a research agenda and help fund prioritized research areas, long-term financing is needed.

CONCLUSION

A robust and multidisciplinary scientific knowledge base is an essential element in making the global health system more resilient and responsive to the current ZIKV epidemic and the threat of future pandemics. In this report, our team consolidates the proposed research agendas surrounding the epidemic and aims to articulate in a clear manner the gaps in research as identified by the main contributors. However, research priority setting involves a continuous process which requires coordination and re-evaluation to address emerging and shifting research priorities. We encourage periodic review and updating to ensure relevancy.

This report has been directed toward key institutions interested in conducting research related to the ZIKV. A comprehensive Regional research agenda will help funding organizations make informed choices between competing research options. Funders should consider how to best use their research dollars to seek the maximum utility and focus on areas of high interest and priority.

The Regional research priorities were produced through a consensus-based tool for achieving these results. This report should facilitate discussion and interaction among researchers, donors and public health professionals, and serve as a guide for future research activities in critical areas while encouraging opportunity for networking and south-south collaboration.

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ANNEX 2. List of identified research agendas, call for research (grants), and meeting reports identified

1. Johns Hopkins Bloomberg School of Public Health Zika: the Current Epidemic, Research Agenda, & Public Health Response. http://www.hopkinsglobalhealth.org/news-events/events/zika-the-current-epidemiology-research-agenda-public-health-response/

2) National Academies of Sciences, Engineering, and Medicine. Research Priorities to Inform Public Health and Medical Practice for Domestic Zika Virus: A Workshop http://iom.nationalacademies.org/Reports/2016/Zika-Research-WIB.aspx

3) SC1-PM-XX–2016: Addressing the urgent research gaps against the Zika virus and other emerging threats in Latin America.

4) WHO. Outline for a causality framework for the associations between Zika virus infections and congenital brain abnormalities (including microcephaly) and Guillain-Barré syndrome

5) Potential Research Priorities to Inform Public Health and Medical Practice for Domestic Zika Virus - See more at: http://iom.nationalacademies.org/activities/publichealth/zikaresearch/workshop-in-brief#sthash.0ptDdwNa.dpuf

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7) Ministerio de Salud y Protección Social – Colombia

8) National Institutes of Health: high-priority Zika virus research areas

9) European Commission. Key Research Areas: Zika. http://ec.europa.eu/research/health/index.cfm?pg=area&areaname=zika

10) Medical Research Council (MRC) rapid response funding initiative

ANNEX 3. List of all identified ongoing studies (April 8, 2016)

#	Original Project Title	Title	Institution
1	A eficácia da hidrocinesioterapia e do exercício de Frenkel em paciente com Síndrome de Guillain Barrè (SGB): Estudo de Caso.	Effectiveness of hydrotherapy and Frenkel exercise in patients with Guillain Barre Syndrome (GBS): Case Study	Faculdades Cathedral de Ensino Superior, Boa Vista
2	A Epidemia de Zika virus no Estado do Espírito Santo: Estudo do Impacto da Infecção Sobre o Feto em uma Coorte de Gestantes, com Sintomas da Doença e Confirmação Virológica da Infecção.	Zika outbreak in Espirito Santo state: Study of infection impact on Fetus in a pregnant women cohort with disease symptoms and virologic confirmation.	Hospital Universitário Cassiano Antônio de Moraes
3	Achados tomográficos em pacientes recém-nascidos com microcefalia em surto epidêmico do estado de Pernambuco no ano de 2015.	Tomographic findings in newborn with microcephaly in the outbreak of Pernambuco state in 2015	Secretaria de Saude, Recife
4	Análise da independência funcional mediante a aplicação protocolar equoterápica em um caso de microcefalia.	Analysis of functional independence by applying equitherapy protocol in a case of microcephaly	UNISEP-UNIAO de Ensino do Sudoeste do Parana S/C Ltda
5	Análise genômica e funcional para a compreensão dos efeitos teratogênicos do virus Zika	Genomics and functional analysis for understanding of teratogenic effects of Zika virus	Instituto de Biociências da Universidade de São Paulo - IBUSP
6	Anticorpos anti-Zika	Antibodies anti- ZIKV	Universidade de São Paulo
7	Associação entre infecção viral por zika na gravidez e infecção congênita em campina grande Paraíba	Association between ZIKV infection during pregnancy and congenital infection in Campina Grande Paraíba	IPESQ - Instituto Professor Joaquim Amorim Neto de Desenvolvimento, Fomento, Campina Grande
8	Avaliação audiológica de crianças com suspeita infecção congênita por Zika vírus	Audiological evaluation of children with suspected congenital infection of Zika virus	Hospital Agamenon Magalhães - HAM
9	Avaliação da imunidade inata e resposta humoral autoimune na infecção por vírus Zika em pacientes com e sem síndrome Guíllan-Barré (SGB)	Evaluation of innate immunity and humoral autoimmune response in Zika virus infection in patients with and without Guillain-Barré syndrome (GBS)	Hospital das Clinicas da Faculdade de Medicina da USP
10	Avaliação da imunidade inata e resposta humoral autoimune na infecção por vírus Zika em pacientes grávidas com fetos diagnosticados com e sem microcefalia	Evaluation of innate immunity and humoral autoimmune response in Zika virus infection in pregnant women with fetuses diagnosed with and without microcephaly	Hospital das Clinicas da Faculdade De Medicina da USP

#	Original Project Title	Title	Institution
11	Avaliação da prevalência de viremia por Zika virus em doadores de sangue	Prevalence of ZIKV viremia in blood donors	Hospital Israelita Albert Einstein-SP
12	Avaliação da síndrome de Guillain-Barré em pacientes atendidos pela 10ª Regional de Saúde do Estado do Paraná	Evaluation of Guillain-Barré syndrome in patients treated for the 10th Health Regional of Paraná State	Faculdade Assis Gurgacz/PR
13	Avaliação das sorologias de Flavivírus e perfil imunológico em pacientes portadores de Síndrome de Guillain-Barré na epidemia de vírus Zika no Brasil	Evaluation of Flavivirus Serology and immunological profile in patients with Guillain-Barré syndrome during Zika outbreak in Brazil.	Escola Paulista de Medicina
14	Avaliação laboratorial em pacientes com suspeita de infecção congênita por Zika vírus	Laboratory evaluation of patients with suspected congenital infection by Zika virus	Universidade Federal de São Paulo - UNIFESP/EPM
15	Avaliação oftalmológica de pacientes com microcefalia expostos ao Zika vírus durante a gestação	Ophthalmologic evaluation of patients with microcephaly exposed to Zika virus during pregnancy	Universidade Federal de São Paulo - UNIFESP/EPM
16	Avaliação ultrassonográfica e por ressonância magnética de fetos com microcefalia e alterações estruturais provavelmente relacionados ao Zika vírus	Ultrasonography and magnetic resonance evaluation of fetuses with microcephaly and structural changes probably related to Zika virus	Maternidade Escola Assis Chateaubriand / MEAC/ UFC, Fortaleza
17	Características clínicas, epidemiológicas, desenlace fetal y neonatal en mujeres embarazadas expuestas al virus del Zika con diagnóstico clínico y laboratorio	Clinical and epidemiological characteristics and fetal and neonatal outcomes in pregnant women exposed to Zika virus with clinical and laboratory diagnosis	Universidad libre de Cali Colombia.
18	Casos de microcefalia possivelmente associados a infecção por arbovírus no Brasil: Um estudo de caso-controle	Cases of microcephaly possibly associated with arbovirus infection in Brazil: A case-control study	Secretaria de Vigilância em Saúde, Brasília
19	Casos de Síndrome de Guillain-Barré possivelmente associados a infecções por arbovírus no Brasil: um estudo de caso-controle.	Guillain-Barré syndrome cases possibly associated with arbovirus infection in Brazil: A case-control study	Secretaria de Vigilância em Saúde
20	Cohort of Patients Infected by an Arbovirus (CARBO)	Cohort of Patients Infected by an Arbovirus (CARBO)	Centre Hospitalier Universitaire de Fort-de-France
21	Concept note on Zika virus disease: a proposal for a case control study in Zambia	Concept note on Zika virus disease: a proposal for a case control study in Zambia	The University of Zambia School of Veterinary Medicine Laboratory

#	Original Project Title	Title	Institution
22	Conhecimento das gestantes de um serviço de saúde do Recife em relação à microcefalia e à infecção congênita pelo Zika vírus.	Knowledge of pregnant women from a Recife health service in relation to microcephaly and congenital infection for Zika virus.	Centro Integrado de Saúde Amaury de Medeiros - CISAM/UPE.
23	Coorte clínica de crianças com microcefalia em Pernambuco	Clinical cohort of children presenting microcephaly in Pernambuco	MERG Microcephaly Epidemic Resarch Group Universidade Federal de Pernambuco and Centro de Pesquisas Aggeu Magalhães-Fiocruz-PE
24	Coorte de gestantes com exantema no estado de Pernambuco	Cohort of pregnant women with rash in the state of Pernambuco	MERG Microcephaly Epidemic Resarch Group Universidade Federal de Pernambuco and Centro de Pesquisas Aggeu Magalhães-Fiocruz-PE
25	Costos de tratamiento en Unidad de Cuidado Intensivo a pacientes afectados por Síndrome de Guillain Barré asociado a la infección por virus de Zika	Treatment costs in Intensive Care Unit patients affected by Guillain Barre syndrome associated with Zika virus infection	Instituto de Evaluación Tecnológica en Salud - IETS
26	Criação de um painel de soro humano para validação inicial de teste sorológico para Zika Vírus	Creating a human serum panel for initial validation of ZIKV serologic tests	Instituto de Pesquisa Clínica Evandro Chagas - IPEC / FIOCRUZ
27	Descrição clinica e epidemiológica de pacientes com exantema e infecção pelo virus Zika no estado da Bahia	Clinical and epidemiological description of patients with rash and Zika virus infection from Bahia State	Hospital Couto Maia/SES/BA
28	Descrição de resultados do exame de RT-qPCR para detecção simultânea dos vírus zika, dengue e chikungunya: um estudo observacional baseado na análise do banco de dados laboratorial.	Description of RT-PCR results for simultaneous detection of Zika, Dengue and Chikungunya viruses: an observational study based on the analysis of laboratory database.	Laboratorio Sabin de Analises Clinicas LTDA.
29	Diagnóstico de arboviroses brasileiras e emergentes em pacientes e mosquitos em duas regiões distintas do Brasil	Diagnosis of Brazilian and emerging arboviral infections in patients and mosquitoes in two regions from Brasil	Faculdade de Medicina de São José do Rio Preto (FAMERP). Secretaria de Desenvolvimento Econômico, Ciência e Tecnologia (São Paulo - Estado). São José do Rio Preto, SP, Brasil

#	Original Project Title	Title	Institution
30	Efeito da Fisioterapia na Funcionalidade de Paciente Com a Síndrome De Guillain Barré Estudo de Caso	Physiotherapy effect on functionality of patient with Guillain Barré syndrome case study	Associacao Piripiriense de Ensino Superior, PIRIPIPI
31	Eliminar el dengue - Colombia (ED – Colombia): Estrategia de Control Biológico basada en el uso de Wolbachia para eliminar Dengue, Zika y Chikungunya. Estudio piloto en Bello (Antioquia, Colombia)	Eliminate Dengue - Colombia (ED - Colombia): Biological Control Strategy based on the use of Wolbachia to eliminate Dengue, Chikungunya and Zika. Pilot study in Bello (Antioquia, Colombia)	PECET-Universidad de Antioquia, Universidad Nacional (Sede Medellín), Universidad de Monash (Australia), Universidad de Wisconsin (EU
32	Epidemia de microcefalia na Bahia e a descrição dos achados da tomografia computadorizada de crânio de 23 recém nascidos.	Microcephaly epidemic in Bahia and description of computed tomography findings of 23 newborns.	Hospital Geral Roberto Santos - BA
33	Estudo caso-controle para investigação dos casos de microcefalia	Case-control study to investigate microcephaly cases	Fundacao Oswaldo Cruz, Recife
34	Estudo caso-controle sobre exantema máculopapular pruriginoso acompanhado de outros sintomas dengue-símile durante a gravidez e microcefalia	Case-control study on maculopapular pruritic rash accompanied by other dengue-like symptoms during pregnancy and microcephaly	Laboratorio Sabin De Analises Clinicas LTDA, Brasília
35	Estudo Clinicopatológico e Epidemiológico da microcefalia no Estado do Rio Grande do Norte: potenciais fatores causais	Clinical-Pathological and Epidemiological study of microcephaly in Rio Grande do Norte State: potential causal factors	Universidade Federal do Rio Grande do Norte - UFRN
36	Estudo da infecção pelo vírus Zika (ZIKV) na epidemia emergente em recém-nascidos com microcefalia em Salvador-BA: um estudo de prevalência em gestantes e neonatos.	Study of Zika virus (ZIKV) infection in the emerging epidemic in infants with microcephaly from Salvador, Bahia: a prevalence study in pregnant women and newborns	Hospital Geral Roberto Santos - BA
37	Estudo epidemiológico, clínico e imunológico nas infecções pelos vírus Zika, Chikungunya e Dengue na patogênese de anomalias fetais e em doenças de indivíduos adultos	Epidemiological, clinical and immunological study of Zika, Chikungunya and Dengue infections in the pathogenesis of fetal malformation and diseases of adults	Fundação Universidade Federal de Sergipe.
38	Estudo longitudinal clínico e virológico em pacientes sintomáticos com Zika virus (ZIKV) em São Paulo, Brasil	Clinical and virological longitudinal study in symptomatic patients with Zika virus (ZIKV) in São Paulo, Brazil	Faculdade de Medicina da Universidade de São Paulo - FMUSP.
39	Evolução pré-natal e pós-natal das gestantes atendidas com rash cutâneo e com microcefalia fetal	Prenatal and postnatal evolution of pregnant women with rash and fetal microcephaly	Instituto de Medicina Integral Professor Fernando Figueira - IMIP/PE

#	Original Project Title	Title	Institution
40	Exposição Vertical ao Zika Virus e suas conseqüências no neurodesenvolvimento da criança	Vertical exposure to Zika virus and its consequences on the neurodevelopment of child	Instituto Fernandes Figueira - IFF/ FIOCRUZ - RJ/ MS
41	Fatores de risco e proteção para microcefalia em área de ocorrência do Zika vírus: estudo caso-controle no Estado do Ceará, Brasil	Risk and protective factors for microcephaly in ZIKV outbreak area: case-control study in Ceará state, Brazil	Instituto para o Desenvolvimento da Educação Ltda-IPADE/ Faculdade Christus, Fortaleza
42	Fluxo de notificação de dengue, chikungunya e zika vírus em feira de Santana-BA: um relato de experiência	Notification flow of dengue, Chikungunya and Zika in Santana-BA Feira: an experience report	Universidade Estadual de Feira de Santana
43	Follow-up of pregnancy women in a Caribbean private clinics, Colombia	Follow-up of pregnancy women in a Caribbean private clinics, Colombia	Institute for Tropical Biological Research, School of Veterinary Medicine, University of Cordoba, Colombia
44	Fortalecimiento de la prevención, diagnóstico temprano y adecuado manejo de síndrome febril viral pediátrico dentro de un modelo de atención primaria en salud	Strengthening prevention, early diagnosis and appropriate management of pediatric viral febrile syndrome in a primary health care model	Universidad Surcolombiana - Neiva
45	Frequência de Infecções por Flavivírus (Dengue, Chikungunya e Zika) em Habitantes em Salvador-Bahia.	Frequency of Flavivirus infection (Dengue, Chikungunya and Zika) in inhabitants from Salvador, Bahia	Fundação Bahiana de Infectologia
46	Infecção congênita pelo zika virus: delimitação do fenótipo	Congenital infection by Zika virus: phenotype definition	Instituto Fernandes Figueira - IFF/ FIOCRUZ - RJ/ MS
47	Infecção Vertical pelo vírus ZIKA e suas repercussões na área materno-infantil	Vertical infection by ZIKA virus and its effects on maternal-child health service	Faculdade de Medicina de Jundiaí
48	Inquérito epidemiológico da dengue, zika vírus e chikungunya em uma instituição de ensino superior na cidade de Salvador Bahia	Epidemiological survey of dengue, chikungunya and zika viruses in an University of Salvador Bahia	Instituto Mantenedor de Ensino Superior da Bahia - IMES
49	Investigação da prevalência de vírus emergentes entre doadores de sangue da Fundação Hemominas: vírus da Dengue, Zika e Chikungunya	Investigation of emerging virus prevalence among blood donors from Hemominas Foundation: Dengue, Chikungunya and Zika viruses.	Fund Centro Hematologia e Hemoterapia de Minas Gerais
50	Investigação de Síndrome Infecciosa Exantemática Indeterminada em Pediatria, Possivelmente Relacionada com Infecção por Zika Virus, Vírus da Dengue ou Chikungunya	Research of infectious exanthematous indefinite syndrome in Pediatrics, possibly related with ZIKV, DENV or CHIKV infection	Hospital das Clinicas da Faculdade de Medicina da USP

#	Original Project Title	Title	Institution
51	Investigação do papel da infecção pelo vírus Zika na epidemia de recém-nascidos com microcefalia em Salvador-BA: um estudo de prevalência em gestantes e neonatos	Investigation about the role of Zika virus infection in the microcephaly epidemic in Salvador, Bahia: a prevalence study in pregnant women and newborns	Centro de Pesquisas Gonçalo Moniz - CPqGM/ FIOCRUZ/ BA
52	Investigação dos casos de microcefalia: estudo caso-controle	Investigation of cases of microcephaly - Case control study	MERG Microcephaly Epidemic Resarch Group Universidade Federal de Pernambuco and Centro de Pesquisas Aggeu Magalhães-Fiocruz-PE
53	Investigação dos casos de microcefalia: estudo caso-controle – Fase I.	Research of microcephaly cases : case-control study - Phase I	Fundação para o Desenvolvimento Científico e Tecnológico em Saúde - Fiotec
54	Investigação sobre as infecções causadas pelo vírus Zika.	Research about Zika virus infections	Universidade de Sao Paulo, Ribeirão Preto
55	Manifestaciones neurológicas en infecciones por virus Zika diferentes a microcefalia. Respuesta durante la epidemia en Colombia	Neurological manifestations in Zika virus infections other than microcephaly. Response during the epidemic in Colombia	MINSALUD, Instituto Nacional de Salud, CDC
56	Manifestações neurológicas associados a infecção por Zika vírus	Neurological manifestations associated with Zika virus infection	Fundacao Oswaldo Cruz, Recife
57	Manifestações oftalmológicas em pacientes com microcefalia expostos ao zika vírus na gravidez no Brasil	Ocular manifestations in patients with microcephaly exposed to Zika virus during pregnancy in Brazil	Fundacao Altino Ventura
58	Medidas de combate à dengue, à febre de Chikungunya e ao Zika Vírus	Control measures to dengue, chikungunya and zika fever	Instituto Federal de Educacao, Ciencia e Tecnologia de Goias, Goiânia
59	Metagenômica viral de Dengue, Chikungunya e Zika vírus: Acompanhar, explicar e prever a transmissão e distribuição espaço-temporal no Brasil.	Viral metagenomics of Dengue, Chikungunya and Zika viruses: Accompanying, explaining and predicting the transmission and space-temporal distribution in Brazil	Faculdade de Medicina da Universidade de São Paulo
60	Monitoramento da microcefalia em recém-nascidos e acompanhamento clínico e de crescimento e desenvolvimento de uma coorte de crianças com provável infecção congênita pelo virus da Zika	Monitoring of microcephaly in newborns and clinical follow-up, growth and development of a cohort of children with probable congenital Zika virus infection	Hospital Universitário da Universidade Federal do Maranhão/HU/UFMA

#	Original Project Title	Title	Institution
61	Outbreak of Zika virus infection in Chiapas State, Mexico	Outbreak of Zika virus infection in Chiapas State, Mexico	Instituto Nacional de Salud Pública, Centro Regional de Salud Pública, Tapachula, Chiapas, México; University of Texas Medical Branch
62	Paraíba: Aplicação do modelo de rede LEGOS no enfrentamento da microcefalia	Paraíba: Application of LEGOS Network Model in confrontation of microcephaly	Secretaria de Estado da Saude - SES
63	Percepção dos estudantes de Odontologia da UFPB a respeito do aborto em casos de microcefalia.	Perception of dental students from UFPB on abortion in microcephaly cases	Associacao de Apoio A Pesquisa em Saude Bucal
64	Perfil dos pacientes internados por síndrome de Guillain-Barré no Hospital Nossa Senhora da Conceição e identificação de fatores prognósticos	Profile of inpatients for Guillain-Barré syndrome in the Hospital Nossa Senhora da Conceição and identification of prognostic factors	Hospital Nossa Senhora Da Conceicao SA, Porto Alegre
65	Perfil epidemiológico dos nascidos vivos acometidos por microcefalia no estado da paraíba	Epidemiologic profile of newborns with microcephaly in Paraiba State	Secretaria de Estado da Saude - SES
66	Perfil epidemiológico e clínico de neonatos com microcefalia nascidos durante epidemia do Agravo no Brasil	Clinical and epidemiological profile of newborn with microcephaly born during the epidemic of Agravo in Brazil	Instituto de Medicina Integral Professor Fernando Figueira - IMIP/PE
67	Persistence of Zika Virus in Semen After Acute Infection	Persistence of Zika Virus in Semen After Acute Infection	Institute of Tropical Medicine, Belgium
68	Pregnant Women Cohort for evaluation of absolute and relative risk of congenital malformations after Zika Virus Infection – developmental milestones of children born to women exposed to Zika Virus during pregnancy	Pregnant Women Cohort for evaluation of absolute and relative risk of congenital malformations after Zika Virus Infection – developmental milestones of children born to women exposed to Zika Virus during pregnancy	University of Carabobo, Valencia in Venezuela University of Ceara, Fortaleza; FIOCRUZ in Recife FIOCRUZ in Rio de Janeiro).
69	Prevalência de microcefalia em recém-nascidos a termo: pequenos, adequados e grandes para a idade gestacional	Prevalence of Microcephaly in term newborn:	Universidade Federal de Pernambuco - UFPE
70	Prevalência, Evolução Temporal e Fatores Associados à Microcefalia em Pacientes de Terapia Intensiva Neonatal.	Prevalence, temporal evolution and associated factors with microcephaly in Patients of Neonatal Intensive Care Unit	Hospital Copa Dor, Rio de Janeiro
71	Proporcion de casos asintomaticos de infeccion por virus Zika en gestantes residentes de area endemica	Proportion of asymptomatic cases of Zika virus infection in pregnant from endemic area	MINSALUD Instituto Nacional de Salud

#	Original Project Title	Title	Institution
72	Relato de série de casos de alterações auditivas relacionadas a infecção por Zika vírus	Case series of hearing alterations related to Zika virus infection	Santa Casa de Misericordia da Bahia
73	Síndrome de Guillain-Barré após infecção por Zika Vírus: relato de caso	Guillain-Barré syndrome after Zika virus infection: a case report	Santa Casa De Misericordia Da Bahia
74	Síndrome do Zika Vírus: nutrição materno-fetal e perfil imune-inflamatório do binômio gestante/recém-nascido	Zika virus syndrome: maternal-fetal nutrition and immuno-inflammatory profile of pregnant binomial/newborn	Universidade Federal de Pernambuco - UFPE
75	Testing of re-purposed drugs for anti-Zika activity	Testing of re-purposed drugs for anti-Zika activity	Atheric Pharmaceutical LLC
76	The University of California Zika Virus Project	The University of California Zika Virus Project	The University of California (California National Primate Research Center, UC Davis and UC San Francisco & Blood Systems Research Institute (BSRI))
77	Triagem molecular para zika virus de unidades de sangue destinadas a transfusões intraútero e pacientes grávidas	Molecular screening for Zika virus in blood units intended for intrauterine transfusions and pregnant patients	Fundacao Pro-Sangue Hemocentro de Sao Paulo
78	Vigilancia intensificada de gestantes y sus hijos luego de infección por el virus del Zika y desenlaces desfavorables del embarazo, Colombia	Intensified surveillance of pregnant women and their children after Zika virus infection and unfavorable pregnancy outcomes, Colombia	MINSALUD, Instituto Nacional de Salud, CDC
79	Zika experimental science team (ZEST)	Zika experimental science team (ZEST)	University of Wisconsin–Madison

ANNEX 4. Priorities of Delphi Survey, Round 1

Critical relevance and short-term implementation	Delphi Classification	Time of implementation
Virus vectors and reservoirs		
Molecular epidemiology to establish evolutionary patterns, distribution and molecular changes involved in virulence of ZIKV	Very important	Short-term
Role of asymptomatically infected individuals	Very important	Short-term
Vertical transmission in Aedes spp. Vectors	Very important	Short-term
Detection of specific antibodies in various animal species (large mammals) and rodents (potential vectors and potential reservoirs)	Very important	Medium-term
Assess the possible establishment of sylvatic cycles of ZIKV in new world reservoirs (potential vectors and potential reservoirs)	Very important	Medium-term
Epidemiology		
Perinatal transmission and trans-placental transmission	Critical	Short-term
Sexual transmission	Critical	Short-term
Including incident cases, birth defects, development of an epidemic curve	Critical	Short-term
Establish causality	Critical	Short-term
Biological plausibility for maternal-fetal transmission	Critical	Short-term
Microcephaly and other congenital malformations	Critical	Short-term
Flavivirus effects (including viral persistence and viral load) on neural tissues, placental barrier transfer and teratogenic	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 Zika IgM	Critical	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	Critical	Short-term

Critical relevance and short-term implementation	Delphi Classification	Time of implementation
Epidemiology		
Data sharing	Critical	Short-term
Frequency and risk factors for complications of ZIKV	Critical	Short-term
Disease pathogenesis		
ZIKV infection pathogenesis to the fetus	Critical	Short-term
Association/risk factors between ZIKV infection and autoimmune syndromes GBS	Critical	Short-term
ZIKV infection teratogenic effect in function of the gestational age	Critical	Short-term
Effect of infection by the ZIKV (with and without microcephaly) in the neurological, cognitive and motor development of the child	Critical	Short-term
Including incident cases, birth defects, development of an epidemic curve	Very important	Short-term
Public health interventions and clinical management		
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	Critical	Short-term
Registries to understand complications of congenital birth defects	Critical	Short-term
Knowledge/attitudes and beliefs about the use of repellents in pregnancy	Critical	Short-term
Epidemiological behavior of the ZIKV in order to determine future disease outbreaks	Very important	Medium-term
Cohort studies in high transmission areas	Less important	Short-term

Critical relevance and short-term implementation	Delphi Classification	Time of implementation
Health systems and services		
Efficient financing mechanisms for addressing outbreaks ZIKVt	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	Short-term
Research and development of products		
Development of serologic, blood, and urine tests	Critical	Short-term
Develop and validate of rapid test for ZIKV infection	Critical	Short-term
Assurance of reliable, accurate, and standardize testing	Critical	Short-term
Safety, efficacy, and cost effectiveness of screening test for ZIKV	Critical	Short-term

ANNEX 5: Research priorities identified through face-to-face meeting consultation

Breakout session: Laboratory platforms for supporting ZIKV surveillance

High-priority gaps in research
Validation and field testing of commercial kits for the serological diagnosis of Zika and standardization of evaluation protocols
Construction of a panel of samples from arbovirus endemic areas for validation of commercial kits and to be used as reference in the standardization of laboratory methodologies
Diagnostic tests to confirm the infection of Zika linked with diagnosis of microcephaly and identification of abnormalities in the brain
Understanding the mechanism that makes IgM antibodies against Zika virus, dengue viruses, and other flaviviruses have strong cross-reactivity that may generate false positive results in serological tests
Understanding the detection of ZIKV RNA in an infant or child who had ZIKV infection in utero after the period of viremia has passed
Additional gaps in research
Understanding virus-specific IgM and neutralizing antibodies and cross-reaction with related flaviviruses
Guideline development and standardization in Regional sample collection
Quality control of serological assay
Strategies for effective surveillance
Evaluation of the sensitivity and positive predictive value in clinical cases
Development of diagnostic tests that confirm microcephaly and other congenital malformations
Development of RT-PCR proficiency panels including both positive and negative
Ability to detect ZIKV in greater quantity in one area of the human body as opposed to other flaviviruses
Presence of vitro markers and assays that are reliable surrogates of protection in vivo
Persistence in other bodily fluids (urine, amniotic fluid, semen, saliva, breast milk)
Understanding the molecular variability of the virus

Breakout session: Characterizations of the disease, including public health and clinical implications

High-priority gaps in research
What is the absolute risk of congenital malformation by gestational week of infection?
Clinical and subclinical presence of the ZIKV in pregnant women through the use of cohorts, and follow-up of infants with microcephaly and other abnormalities
Use of modeling to understand the rate of infection and to understand the role of natural immunity, particularly in the regions with previous outbreaks
Development of SOPs regarding screening for the ZIKV and perhaps the dissemination of such through a common core protocol
Additional gaps in research
Development of qualitative and quantitative studies
Characterization of the natural history of disease, ratio of clinical to subclinical
Guidance of public health measures and the impact and evaluation of such measures
Characterization of the role of sexual transmission in the dynamics of the outbreak
Understanding equity in the risk of disease and in accessing reproductive health services
Development of support structures for disabled children
Natural immunity in endemic regions
Ratio of clinical to sub-clinical cases, incidence of microcephaly and other neurological malformations
Need for standardization of procedures in collecting samples
Equal access to health services

Breakout session: Dynamics of the arbovirus epidemic in the Americas region and characterization of the vector

High-priority gaps in research
Evaluation of the current prevention and vector control activities in countries endemic for dengue and chikungunya
Enhance communication strategies that focus on pregnant women in order to reduce the risk of human-vector contact
Understanding the application of selective indoor residual insecticide spraying targeting adult mosquitoes, mainly in and around houses where pregnant women reside
Assessing the effectiveness of personal protection kits, including repellents, LLINs, treated curtains, condoms and flyers with recommendations for the elimination of breeding sites
Monitoring insecticide resistance of Aedes aegypti, for evaluating insecticides used in public health
Additional gaps in research
Cohort studies to evaluate prevention strategies
Assessing indicators that relate entomological variables with epidemiology to verify the impact of the vector control strategies applied
Inform the development of an integrated surveillance system for arborviruses
Molecular testing of infected mosquitoes
Measuring the entomological and epidemiological impact of new vector-control alternatives, including genetically modified mosquitoes, sterile mosquito males, Wolbachia, lethal traps, aerial insecticide spraying, toxic sugar baits, and others, for adults and larvae control, particularly in large urban environments
To determine the role in transmission of other mosquitoes species as ZIKV and the possibility of invasion of sylvatic ecosystems
Modeling to understand the epidemics and the impact of the control measures
Improvement of available resources in vector control and prevention of infection in pregnant women

ANNEX 6. PAHO Meeting Agenda "Towards the development of a research agenda for characterizing the Zika virus outbreak and its public health implications in the Americas"

Day 1

08:30-09:00 **Registration**

09:00-09:30 **Opening**

09:00 Welcome and opening remarks: Marcos Espinal, Director CHA, PAHO

09:10 Remarks from WHO: Sylvie Briand, Director PED, WHO Geneva

09:20 Objectives of the meeting: Ray Arthur, GOARN Chair

09:30 10:30 **Global and regional situation**

09:30 Global situation: Sylvie Briand, Director PED, WHO Geneva

09:45 Country situation Brazil: Giovanini Evelim Coelho, SVS, Brasilia, Brazil

10:00 Country situation Colombia: Marta Ospina, Director, National Institute of Health, Colombia, (via WEBEX)

10:15 Country situation USA: Lyle Petersen, CDC

10:30 Regional situation and response: Sylvain Aldighieri, Incident Manager, PAHO

10:45-11:00 **Coffee**

11:00-12:45 **Laboratory platforms for supporting the surveillance: situation, limitations, challenges**

Chair of the session: Delia Enria, Director, INEVH, Pergamino, Argentina

- Introduction by the chair of the session
- Panel: what we have, existing challenges, what we need to develop
  - * ZIKV Laboratory network in Brazil: Pedro Vasconcelos, Evandro Chagas Institute, Belem, Brazil
  - * ZIKV Molecular characterization: Dominique Rousset, Institut Pasteur, Cayenne, French Guiana
  - * ZIKV serology techniques: Amadou Sall, Institut Pasteur, Dakar, Sénégal
- New generation of tests and diagnostic strategies: Julie Villanueva, CDC, USA
- Open discussion: main research priorities topics; key actors; timeline; resources Wrapup by the chair

12:45-14:00 **Light lunch** (meeting rooms will be available for bilateral and multilateral discussions)

14:00-15:45 **Characterization of the disease, risk factors, causality studies and public health and clinical implications**

Chair of the session: Laura Rodrigues, London School of Hygiene and Tropical Medicine, UK

- Introduction by the session's chair
- Panel: studies in place in the region and globally, scope of the studies
  - *MERG studies in Brazil: Ricardo Ximenes, MERG consortium, Pernambuco, Brazil
  - *ZIKV, GBS and neurological malformations studies in Fr. Polynesia: Henri-Pierre Mallet, Public Health Department, Papeete, French Polynesia
  - *Ongoing epidemiological studies in pregnant women: Bruno Hoen, University of the French West Indies, Guadeloupe
  - *How to quantify the risk of the ZIKV tropism on fetus, what we can learn from the investigation of other infections: Susan Reef, CDC, USA
- Open discussion: main research priorities topics; key actors; timeline; resources
- Wrapup by the Chair

Day 1

15:45-16:00 **Coffee**

16:00-17:45 **Dynamics of the arbovirus epidemics in the American region and characterization of the vector/ZIKV relationships**

Chair of the session: Lyle Petersen, Director, CDC Ft Collins, USA

- Introduction by the chair of the session
- Panel: what we know, scope of new studies
  - *What do we know about Aedes spp. competency for ZIKV and the potential role of other vectors: Ricardo Lourenco, FioCruz, Rio de Janeiro, Brazil
  - *Subsequent arboviral infections, what we have learned from outbreaks in the Americas: Scott Weaver, UTMB, Galveston Texas, USA
  - *Modeling resources for characterizing the ZIKV epidemics: Mark Miller, NIH, USA
  - *Vector control, what tools are working, what new tools may be helpful: Janet McAllister, CDC, USA

Open discussion: main research priorities topics; key actors; timeline; resources

- Wrap up by the chair

17:45 **Adjourn**

18:00-18:30 **Meeting of Chair, session's chairs and rapporteurs**

18:30 **Reception**

Day 2

08:30-08:45 **Main points from Day 1, Chair and session's chair**

08:45-09:45 **Breakout Discussion**

Objectives: Identify critical research questions (shortlist) and discuss implementation issues, facilitators and challenges, based on results from sessions on Day 1

(1) Laboratory platforms for supporting the surveillance: situation, limitations, challenges

Facilitator: Delia Enria, Jairo Mendez Rico

(2) Characterizations of the disease, risk factors, causality studies and public health and clinical implications.

Facilitator: Laura Rodrigues, Pilar Ramon-Pardo

(3) Dynamics of the arbovirus epidemics in the American region and characterization of the vector/ZIKV relationships.

Facilitator: Lyle Petersen, Marco Fidel Suarez

09:45-10:00 **Main points from Breakout sessions, Chair and session's chair**

10:00-10:30 **Coffee**

10:30-12:00 **Prioritization of research lines for bridging the gaps in knowledge on ZIKV.**

Chair: Paulo Gadelha, President, FioCruz, Rio de Janeiro, Brazil

During this session, participants will discuss issues such as: Coordination and financing; Networks; Examples of transversal programs; Collaboration between academy and public health agencies.

- FioCruz
- IANPHI
- CDC
- Institut Pasteur International Network
- Others

Open discussion Wrapup

12:00-12:30 **Conclusion of the session Chair - Adjourn**

ANNEX 7: List of participants in the PAHO meeting March 1-2, 2016

Institution	Name
Centers for Disease Control and Prevention, Atlanta, GA, USA	Coleen Boyle Ray Arthur Susan Reef
Centers for Disease Control and Prevention, Ft Collins, CO, USA	Janet McAllister Julie Villanueva Lyle Petersen
Columbia University, New York, NY, US	Madeleine Thomson
Direction de la Santé, Papeete, Tahiti, French Polynésie	Henri-Pierre Mallet
French Army Medical Corps, Laveran Military Hospital, Marseille, France	Fabrice Simon
Fundação Oswaldo Cruz Foundation, Rio de Janeiro, Brazil	Manuel Barral Marcos Freire Maria Elizabeth Moreira Paulo Buss Paulo Gadelha Ricardo Lourenco Wim Degrave
Institute of Health Services and Policy Research, Montreal, Canada	Marc Ouellette
Institut Pasteur de Guyane, Cayenne, French Guiana	Dominique Rousset
Institut Pasteur, Dakar, Senegal	Amadou Sall
Institut Pasteur, Paris, France	Jean-Claude Manuguerra Maria Van Kerkhove
Instituto Evandro Chagas, Belem, Brazil	Pedro Vasconcelos
Instituto de Diagnóstico y Referencia Epidemiológicos, Mexico City, Mexico	Jose Alberto Diaz
Instituto Julio Maiztegui, Buenos Aires, Argentina	Delia Enria
Instituto Gorgas, Panama City, Panama	Juan Miguel Pascale
Instituto Nacional de Salud, Bogota, Colombia	Marta Ospina
Instituto Nacional de Salud Pública, Mexico City, Mexico	Mauricio Hernández-Avila
ISARIC, Oxford, UK	Gail Carson
London School Of Hygiene and Tropical Medicine, London, UK	Laura Rodrigues
Microcephaly Epidemic Research Group, Pernambuco, Recife, Brazil	Ricardo Ximenes
Ministry of Health, Brasilia, Brazil	Giovanini Evelim Coelho

Institution	Name
National Institutes of Health, Bethesda MD, USA	Cristina Casetti Mark Miller
Pan American Health Organization, Washington, DC, USA	Haroldo Bezerra Jairo Andres Mendez Rico Ludovic Reveiz Marco Fidel Suarez Marcos Espinal Maria Almiron Pilar Ramon-Pardo Sylvain Aldighieri Thais dos Santos Vanessa Elias Zaida Yadon
Public Health Agency Canada, Ottawa, Canada	David Safronetz John Topping Peter Buck
United Nations Children's Fund, New York, NY, US	Heather Papowitz
University of Texas Medical Branch, Galveston, TX, USA	Jim LeDuc Scott Weaver
University of Aix-Marseille, Marseille, France	Xavier de Lamballerie
University of the French West Indies and Guiana, Pointe-à-Pitre, Guadeloupe	Bruno Hoen
University of West Indies, Jamaica & Barbados	Angie Rose Peter Figueroa
World Health Organization, Geneva, Switzerland	Anthony Costello Asheena Kahlakdina Celine Gurry Joachim Hombach Nathalie Broutet Patrick Drury Sylvie Briand William Perea

www.paho.org/zikavirus

Pan American Health Organization

World Health Organization

REGIONAL OFFICE FOR THE Americas