Zika Virus in Brasil
The SUS response
Zika Virus in Brazil
The SUS response
Zika Virus in Brazil
The SUS response
Dedication

Two women in the Northeast region of Brazil have contributed to advance science. They gave samples of their amniotic fluid for the scientists to identify what caused microcephaly in babies. This sympathetic attitude allowed the scientific community to identify the high risk posed by the Zika virus to pregnant women.

We acknowledge the greatness of Maria da Conceição Alcantara Oliveira Matias' and Géssica Eduardo dos Santos' gesture. Two women from the inlands of Paraíba who suffered with the diagnosis of their babies still in their wombs. This book is dedicated to these brave women. On their behalf we extend the homage to all women who expect to have healthy pregnancy.

Acknowledgments

This book tells the history of the Zika virus in Brazil, since the confirmation of its circulation in April 2015, passing by the discovery that it caused microcephaly in babies, to the finding that the disease was a nervous system syndrome with serious sequels.

In 12 months the Brazilian and the international scientific community worked hard to diagnose the disease, learn about its severity, build protocols on surveillance and care, and establish networks of support to mothers and their babies.

Thousands individuals were engaged in the process of knowledge-building and providing social support. The book *Zika: the role of SUS* depicts the efforts by scientists, civil servants, health professionals and communication professionals to provide the society with responses. The Health Surveillance Department of the Brazilian Ministry of Health thanks all these individuals.
## SUMMARY

<table>
<thead>
<tr>
<th>Page</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Presentation</td>
</tr>
<tr>
<td>7</td>
<td>Preamble</td>
</tr>
<tr>
<td>7</td>
<td>The SVS mission in face of the epidemics</td>
</tr>
<tr>
<td>9</td>
<td>The beginning of everything</td>
</tr>
<tr>
<td>11</td>
<td>The surprise and the cry</td>
</tr>
<tr>
<td>21</td>
<td>Investigation of an outbreak – lessons to the health care community and public health</td>
</tr>
<tr>
<td>34</td>
<td>Surveillance in communication</td>
</tr>
<tr>
<td>36</td>
<td>Microcephaly, Zika and information</td>
</tr>
<tr>
<td>40</td>
<td>Communication as strategy</td>
</tr>
<tr>
<td>43</td>
<td>The careful view of journalism in health</td>
</tr>
<tr>
<td>47</td>
<td>Strategy building</td>
</tr>
<tr>
<td>49</td>
<td>Management, coordination and mobilization</td>
</tr>
<tr>
<td>57</td>
<td>Work of the National Coordination Office</td>
</tr>
<tr>
<td>62</td>
<td>Scientific investigation</td>
</tr>
<tr>
<td>64</td>
<td>Fiocruz’s role in the fight</td>
</tr>
<tr>
<td>71</td>
<td>The Evandro Chagas Institute’s contribution</td>
</tr>
<tr>
<td>79</td>
<td>The experience of PAHO/WHO</td>
</tr>
<tr>
<td>84</td>
<td>The collaboration with the CDC</td>
</tr>
<tr>
<td>88</td>
<td>Coping with the epidemic</td>
</tr>
<tr>
<td>90</td>
<td>The lab action to cope with the epidemic</td>
</tr>
<tr>
<td>97</td>
<td>Actions in states and municipalities</td>
</tr>
<tr>
<td>99</td>
<td>The frontline municipalities</td>
</tr>
<tr>
<td>106</td>
<td>The work of states</td>
</tr>
<tr>
<td>112</td>
<td>Knowledge dissemination</td>
</tr>
<tr>
<td>114</td>
<td>Dissemination of knowledge, research and educational initiatives</td>
</tr>
</tbody>
</table>
PRESENTATION

In the beginning it was nothing but rumor. The year was 2015 and public health was dealing with its regular issues. But the rumor was taking off and became a hardly understood statistic. In October that year the Health Surveillance Department (Secretaria de Vigilância em Saúde or SVS) of the Ministry of Health of Brazil would move away from rumors to deal with the notification sent by the Health Office of Pernambuco: there was a significant change on the standard of babies born with microcephaly.

The first field investigations by the EpiSus/SVS team in partnership with PAHO/WHO, the state and municipality, showed we were facing a serious and unknown issue. In November that same year the Zika virus was identified in the amniotic fluid of pregnant women. There was no more doubt that this virus, then considered as non-aggressive, was responsible for the serious sequels in babies such as microcephaly and other diseases.

The time for investigation, the time for decision-making, the time of interventions and to combat the Aedes aegypti, the mosquito that carries the virus, are not the same time of responses and solutions so longed for pregnant women, by women with babies affected by the disease and by a network of friends and family members.

In one year of outbreak of microcephaly and other malformations attributed to the Zika virus, scientists in Brazil and all over the world have learned a lot. The knowledge acquired was equivalent to three or four decades of studies. There have never been so many publications.

Even so, we have no responses or solutions to the hundreds women who got pregnant and delivered babies with microcephaly. Neither to those who will still get pregnant and have no guarantee of healthy pregnancy and tranquil delivery.

We don’t have all responses.

Little more than one year after October 2015 we do not know yet why the Zika virus has been so cruel in Brazil, differently from other countries, even Latin American ones, which reported few cases of microcephaly associated with the Zika virus. The challenge remains. Probably there are other causes associated with the Zika virus that result in this unique scenario in Brazil. And, above all, in the Northeast Region inlands.

Brave Northeasterner people that once again overcame adversity. Living in a region historically marked by calamities, as well depicted by Graciliano Ramos, a Northeastern citizen who was the mayor of Palmeira dos Índios (Alagoas) before becoming a writer, the Northeastern women taught us a lesson of faith and hope, holding their babies in their arms and looking for assistance in public health services to ensure minimum comfort to their babies with microcephaly and other serious sequels.

Just like the characters of Graciliano Ramos’ book, Vidas Secas, these women fight the adversities of the sertão, the shortage of resources, long distances and still raise their children.

As a Northeastern citizen, as a son of Alagoas, I am most proud of these women. The Brazilian Unified Health System (SUS) still owes them an answer. And I am absolutely sure this answer will come.

Adeilson Cavalcante
Health Surveillance Department
Ministry of Health of Brazil
The SVS mission in face of the epidemic

Among others, the Health Surveillance Department of the Ministry of Health of Brazil (SVS/MS) has the mission of monitoring events of public health concern, and supporting the states, whenever requested, in the control of outbreaks and epidemics. In September 2015 some rumors about a likely increase in the number of congenital malformations in newborns in some regions of the Northeast of Brazil came about.

As it was likely to be an event of high public health concern, the SVS started several responses pursuing further information about the cases and the potential epidemiological associations.

The initial analyses found strong association with episodes of exanthema among these babies’ mothers in their first months of pregnancy. In the broad spectrum of malformations, microcephaly was a prominent feature found in many cases. This suggested the arisal of a congenital syndrome that varies in severity and symptoms such as arthrogryposis, backbone malformation, ventriculomegaly, microcalcifications in the brain neurological tissue, cortical atrophy and eye malformations. This new syndrome became nationally and internationally known for its main characteristic: the microcephaly.

The SVS promptly mobilized the Brazilian scientific community, and a repertoire of information was quickly assembled. A likely association with an infection recently detected in the Brazilian territory was then suggested: the infection with Zika virus. That temporal association between the detection of the first cases of Zika in the Northeast region and the gestation period of those newborns’ mothers caused the Health Surveillance Department technical team and the surveillance teams in the affected states and municipalities, as well as the Brazilian scientific community, to adopt the infectious etiology as investigation line.

The Zika infection is an old acquainted of scientific communities, with cases reported in other countries at least 60 years ago. It is transmitted by the same vector of the dengue virus, the *Aedes aegypti*, of benign behavior, extremely low virulence and lethality. However, little was known about some likely teratogenicity related to the Zika virus, which then started being investigated in the Brazilian cases.

The possible association between the Zika virus and the microcephaly cases was strengthened after the necroscopic finding of strong concentrations of viral matter in the nervous tissue of stillborn children with microcephaly in the affected regions.

The SVS recommended declaring Public Health Emergency of National Concern considering the potential dissemination of cases and the need to intensify the investigation, and promote national mobilization and prevention of new cases. The World Health Organization (WHO) adhered to it and soon after declared emergency of international concern because of the spread of Zika cases to other American countries.

Brazil has undergone several seasonal dengue epidemics. The repetition of epidemics in the country with severity varying from year to year and from region to region, made Brazil call for task forces to fight the vector mosquito. The country also allotted more resources to research on the Zika virus, new technologies to fight that vector and the arboviruses, in addition to the required support to the families and children affect by microcephaly probably related to the Zika virus.

A huge intersectoral effort was organized, counting on the participation of several departments at different government levels, the academic community, the industry and the civil society.

PREAMBLE
The improved knowledge about this important event leveraged surveys and allowed to better understand this phenomenon. Brazil then got ready for a potential occurrence of new microcephaly cases in other regions caused by the expected spread of the Zika epidemics over the country.

Despite the strong temporal association and etiological suspicious of the Zika virus infection and the cases of microcephaly in the Brazilian Northeast, some knowledge gaps still remain up to now, such as the concentration of cases in some regions of the country and the possibility of other factors intervening in the infection and causing microcephaly.

The main legacies of this episode were:

- The strengthening of the role played by Brazil in the scientific community as regards epidemiological investigation and knowledge production.

- Opportunity to review the technologies to combat the mosquito such as the use of the Wolbachia bacteria to sterilize the mosquitoes, use of bio-larvicides and the increased intersectoral engagement.

- Leadership in the development of a vaccine against the Zika virus in a partnership between Brazilian and foreign scientists.

Finally, despite the advances the effort to fight the *Aedes aegypti* must go on, such as the survey on the etiology, cases monitoring, support to the affected families and the investigation of what has happened in Brazil since late 2015.

Antônio Nardi  
Executive Department of the Ministry of Health of Brazil / MoH
The beginning of everything
Façade of the Ministry of Health of Brazil
Photo by: Rondon Vellozo/MS
The surprise and the cry

An accident can change or even put an end to a person’s life. It may affect a group, cause a big shock. Cataclysms, revolutions, wars, coups tamper with nations, countries, large populations.

Some rare events affect everybody and demand changes in the society to overcome them. If only the poor population is affected, responses are typically slow, but assume significance as it threatens the segments that have voice and influence on governmental actions.

While I am writing this text, the World Health Organization (WHO) decided to suspend the condition of Public Health Emergency of International Concern declared on February 1, 2016 by its Emergency Committee. The declaration aimed to cope with the Zika virus infection considering the larger number of cases of neurological syndromes and birth of children with microcephaly related to the virus.

THE SURPRISE AND THE CRY

The impact of social catastrophes is usually enough for the media to spread the news in a speed that competes with the government’s capacity of reacting, thus increasing the perception of urgency.

And that was exactly what happened.

Pediatricians and neurologists lighted up the yellow light. They texted to their fellow specialists, obstetricians, sanitarian physicians, and the network expanded jointly with the figures and colors of suffering.

This time the social networks and the professionals’ sensitiveness made the government beat the reporters.

In October 2015, the birth of children with microcephaly motivated a federal health inspection mission to Recife, jointly with the Pan-American Health Organization (PAHO) that joined the teams of the Health Departments of Pernambuco and of the municipality.

There were no figures, but a large number of clinical reports, fearful individuals, doubts, disorientation. Images that impregnate memory: children, photos, tomography and ultrasound exams. Many professionals brought detailed and organized clinical histories of children and women under their care.

Although the causes and extent of the consequences were unknown we could affirm those children would face huge obstacles. Their brains had been deeply affected by some disease that impaired the expected development. The technical denomination as microcephaly means the skull and the brain sizes are much shorter than the expected for their ages. As observed in many babies, difficulties would worsen over time and would probably be serious. It goes without saying the deep suffering waiting for the mothers and family members in the future.

The report I heard from a young pediatric infectious disease specialist was very exemplary. Used to the hard task of taking care of mothers whose babies had acquired the AIDS virus during gestation, she said that in those cases she explained the situation, provided guidance.
on the required care and medications, explained how serious the situation was but that some therapies provided positive perspectives to the children’s health. But now, with microcephaly, as far too little is known, there was no encouraging message to give out.

The situation’s seriousness demanded very quick responses from health authorities. There was an increasing commotion. More children would surely be born with microcephaly on the following weeks and months and nothing could be done to prevent it since, regardless the cause, it had already affected other pregnant women. The society urged explanations, but the adoption of measures to avoid risks to the conception of other babies was even more urgent.

In such situations, two things are extremely helpful: sincerity and method. I could mention many others, but it would be redundant because they are part of the job.

The scientific investigation is the method to be followed. In our role this is translated into epidemiological research. First step of field investigation: description, listing the attributes of the population affected by a disease, the geographic distribution and occurrence of cases over time. The following stages, in addition to detailing the description, are: survey information published about similar situations; identify coinciding factors that could be of risk; and, hypothesize about the likely causes. The range of tasks expands proportionally to the complexity of the problem, as this paper describes. Fortunately, the teams of the Ministry of Health and of the involved states and municipalities were made up by competent and devoted professionals. This added with the crucial and prompt support provided by the Pan-American Health Organization and researchers of several institutions.

**A BIT OF SCIENCE, LOTS OF SENSE**

According to the initial information, physicians in many hospitals noticed the birth of different children. Even those experienced in neurological conditions were amazed with the quantity in such short time. Many traits coincided such as short forehead and reduced space between the skull bones. Imaging exams showed brain development failures, huge cavities (expanded brain ventricles) and several calcifications. Soon after birth, children usually presented normal behavior, moved the members, nursed spontaneously, cried like any other child. Experts in the subject pointed out that the condition resembled that observed in other congenital infections such as those caused by the cytomegalovirus or German measles.

The first field investigations confirmed the initial information. They also added that children were from different regions of the state, and many mothers recalled having a mild illness at the beginning of the pregnancy, with skin spots and itch. Many also reported fever, which had been mentioned by the health care professionals.

When we try to find the causes and risk conditions that may have triggered a disease outbreak we investigate the habits, background and any likely exposure such as intake of medications, food, illegal or legal drugs, environmental contaminants, i.e., potential coincident facts among the individuals affected by the problem. By that time, there was no suspicion except for the fact that families lived in the state of Pernambuco and were exposed to the regional conditions.

The initial alert increased the diseases surveillance system sensitiveness. Other states in the Northeast Region also observed higher number of children born with microcephaly, and reported features similar to those described in Pernambuco.

The first question was if that increase could be casual, a figure fluctuation that simulated an epidemic due only to coincidences. However, the first search on the Life Births Information System (Sinasc) confirmed that the figures found for October 2016, in Pernambuco, were much higher than the usual figures. The number of initial notifications, of 26 children born with microcephaly only

---

1This system is maintained by the Ministry of Health that receives data on births based on the statements of children born alive.
in that month, was more than double the prevalence at birth for every previous year, from January to December.

After confirming the increase, the standard of cases occurrence – one stage of the epidemiological analysis – was observed. Outbreaks can be determined by exposures of different nature, notably biological (infections) or toxic agents. The location and chronology of spread are of great usefulness to identify likely causes.

The virtually simultaneous occurrence of cases in different regions ruled out the possibility of diseases directly transmitted from a person to another or the exposure to a common environmental source. After refining possibilities, the exposure to products locally traded in the places concerned, or the spread by vectors existing in those sites were left aside.

Interviews could not identify suspected products – notably medications – to be blamed. At the same time, the circulation of vector-borne diseases potentially related to the cases was already known. Dengue, as annual epidemics for decades in Brazil, was not a strong candidate. Apparently, the chikungunya had not broadly circulated yet. Therefore, the Zika virus, recently present and of explosive spread in the Northeast Region, became the main bet.

In face of the impacts of this situation, questions genuinely became a cry for explanations and measures. In such occasions, there are few options to the so-called principle of precaution, i.e., assume the ignorance and promote the most far-reaching actions possible. This was the context that made me the core player of a polemic, when I said to journalist that women in the Northeast Region should postpone any planned pregnancy until we could learn more about what was happening. This kind of recommendation is surely awkward to the institutions involved, but seemed to be the only prompt measure capable of reducing the risk, although in the individual dimension.

Antonio Carlos Nardi – the by-then Health Surveillance secretary – followed the same principle when he proposed the Minister of Health, Marcelo Castro, to declare Public Health Emergency of National Concern (PHENC) since, although the cause of malformations had not yet been found, the situation fit into the criteria set forth in the International Health Regulation. Recently vested as minister, he enacted the PHENC and warned the President of the Republic, Dilma Roussef. The notification to the World Health Organization suggested it could consider the possibility of extending the measure to the international scope because of the indications of likely spread to other countries.

The Health Emergency Operations Center (Coes) was established at the Ministry of Health. This mechanism is provided for in the Public Health Emergency Response Plan to organize, coordinate and monitor the activities of all areas engaged in the work.

**RECENT HISTORY: THE ZIKA VIRUS INFLOW**

The epidemiological evaluation findings require us to go back in time a little. Late in 2014, professionals from several states of the Northeast Region noticed the emergence of cases of a seemingly light disease that caused itch, skin spot, could cause fever and, in four or five days, disappeared with no therapy. Early in February 2015, the situation appeared in the pages of local newspapers in Maranhão and Sergipe, making reference to a likely outbreak of German measles – a disease that had been vanished in Brazil.

The field investigation team of the Ministry of Health was then mobilized to several cities, and the surveillance services were instructed to officially report the occurrence of outbreaks and their characteristics. Cases notifications quickly increased in the region, including the states of Bahia, Maranhão, Pernambuco, Rio Grande do Norte, Sergipe and Paraíba.

The disease was consistently mild, self-limited, affecting individuals of 4 months to 98 years old, mostly in the 20-40 age group.

Considering the clinical characteristics reported, investigations were mainly focused on dengue, German measles, parvovirus B19, measles, enterovirus and
several arboviruses, notably the chikungunya that had come to Brazil about one year earlier. The Zika virus (ZIKAV) was included in investigations and repeatedly tested negative in reference labs.

There were so many notifications that we started investigating the outbreaks as “undetermined exanthematous syndrome”. Some samples were reagent to dengue, suggesting it could be the agent involved.

In April 2015 a researcher from the Federal University of Bahia identified the Zika virus in samples of individuals with exanthematous disease assisted in Camaçari. Later on, the reference labs of the Oswaldo Cruz Foundation (Fiocruz), Evandro Chagas Institute and Adolfo Lutz Institute have also identified the circulation of that agent.

Based on the few global previous reports about Zika infection outbreaks, it seemed to have no reasons for great concern because no severe or lethal case had been reported. Few studies showed an unlike possibility of association with increased cases of the Guillain-Barré syndrome (GBS) that causes paralysis and sometimes damage breathing, and that could result from different viral or bacterial infections.

By mid-July this calmness was interrupted when some bigger hospitals in Pernambuco, Bahia, Rio Grande do Norte and Maranhão observed significant increase in the number of hospitalizations of individuals with neurological symptoms. The hypothesis of association with Zika infection was reinforced by the testimonial of many victims who said to have suffered from an exanthematous disease shortly before. Once again, after several attempts the Zika virus was identified in blood samples collected from some patients and a liquor sample.

The teams could not devote long time to investigate the increase in the number of GBS cases because they were still in the field concluding the collection of data and blood when the alarm bells sounded in Recife.

**STRIKING EVIDENCES**

The preliminary conclusion of the investigation pointed out potential links between microcephaly cases and Zika infection during pregnancy. Brazil, as well as the world, was quite skeptical about it because such association had never been observed. More than that, the very occurrence of microcephaly epidemic was very controversial.

The suspicion was continuously strengthened by the detection of the virus genetic material in biological matters, and by surveys developed by several labs that expanded knowledge about the circulating agent in Brazil.

A physician and researcher from Campina Grande, state of Paraíba, collected amniotic fluid from pregnant women under her care. She had observed alterations in ultrasound exams and got the laboratorial support from Fiocruz. The Zika virus genetic material was identified in two cases.

Soon after, the Evandro Chagas Institute’s lab in Pará found positive results in the analysis of materials (blood and other tissues taken from the brain, spleen, kidney, etc.) collected from a newborn that deceased shortly after birth in Ceará. The baby suffered from microcephaly and relevant joint alterations.

Moreover, the Fiocruz/Paraná lab identified the Zika virus in samples of placentas collected after abortion, in the state of Rio Grande do Norte, submitted by a physician and researcher from the Federal University of that state. Other samples sent by him to the US Centers for Disease Control and Prevention (CDC) also tested positive (samples obtained after two abortions and two post-delivery deaths).

These results increased even more the confidence to affirm that microcephaly was surely caused by the Zika virus infection during pregnancy. Naturally, the controversy persisted among researchers, professionals and the society as a whole. In the following months the suggested relationship was strengthened by new surveys.
An article published in the famous New England Journal of Medicine reported that a European woman, who presented symptoms that suggested acute Zika infection when she was in Brazil, was informed that her baby had malformations and decided to interrupt the pregnancy in a Slovene hospital. The case was carefully analyzed and described by scientists from the University of Ljubljana. The malformations were quite similar to those observed in babies with microcephaly identified by that time in the Northeast region of Brazil. It contained Zika virus genetic material; tissue samples examined through indirect immunofluorescence also confirmed the presence of the agent in the nervous systems and some affected cells containing viral particles were photographed using electron microscopy. A more detailed study allowed describing the virus genetic sequence, which was identical to that in circulation in Brazil. This detailed study allowed inferring the relation between both things.

After the disclosure of what was happening in Brazil, academics reviewed information about the epidemic three years before in the French Polynesia, and the birth certificates. They also reported the association between Zika virus and the birth of children with microcephaly.

Other lab evidence was found in the following months, such as the identification of specific antibodies against the Zika virus in cerebrospinal fluid collected from 12 babies born with microcephaly in Pernambuco. The sample was collected by scientists of the Federal University of Rio de Janeiro, and the group also confirmed the presence of the virus in six cases in Paraiba.

Research groups from several institutions showed, both in tissues culture and lab animals, that the Zika virus damages the nervous tissue development, thus experimentally confirming the infection effect.

The identification in many countries of children with microcephaly whose mothers had been infected during their trips to Brazil or other places affected by the transmission provided additional evidence. Colombia – which was affected by the epidemic after Brazil – observed the birth of children with microcephaly associated with the Zika.

Finally, the conclusion of an epidemiological study with case-control, coordinated by the team of Aggeu Magalhães Institute, Fiocruz/PE, clarified any eventually existing doubt about the link between the infection of pregnant women and the occurrence of malformations.

On this path, the belief among world health experts and authorities on the cause and effect relation was gradually strengthened. This caused the World Health Organization to declare the situation as a Public Health Emergency of International Concern (PHENC).

Rumors
As could be expected, many alternative hypotheses were elaborated to explain what was happening. Some were based on scientific knowledge like the initial search for other potential infectious agents that could cause the infection during pregnancy and be transmitted to the fetus. Others came about from common sense. These should be distinguished. When dealing with science, the principle is that truths are provisory. In principle, there are no truths since all of them should be argued and replaced as different and deeper knowledge is produced. It may take days, months, years, centuries, but our understanding about all we know will change. Explanations are put down and responses arise thanks to research, investments, sweat and dedication.

Things are different when the starting point is some kind of dogma, prejudice or idea not produced with the due care demanded by science to question all that is being built. The indications of the second attitude become clearer when, in a scenario of democratic and institutional normality, the questioning (always required, I insist) is firstly made by the mainstream media, as a
denouncement, rather than in an environment that allows confronting ideas based on the accumulated knowledge.

The dissemination of ungrounded explanations by the media and social networks can result in two problems. First, they could damage or void efforts aimed to fight the most likely cause of the problem. Moreover, they could give rise to other negative outcomes encouraging measures and behaviors that could entail new risks.

This is what happened.

As the states of Pernambuco (in 2013) and Ceará (in 2014 and 2015) had undergone measles epidemics, in those years the immunization against the disease was intensified both in health units’ routine and through campaigns. The apparent temporal coincidence gave rise to rumors that there could be something wrong with the vaccines that could have caused the malformations.

When this kind of idea circulates, it is amplified by individuals and groups that, for strange philosophical beliefs or ignorance, are against any kind of vaccination. If the population believed in this theory, the coverage of vaccines against measles, mumps and German measles – which are prevented with the triple viral vaccine (or tetra viral which also combats chickenpox) – would be reduced and, thus, the population would be vulnerable to the reintroduction of these viruses. It is worth mentioning that mumps is one of the diseases long-related to congenital anomalies. In brief, the result could be an increase in the number of newborns with medical conditions. Other vaccines were also blamed to a lesser extent through messages circulated in the social networks.

The history of use of those vaccines and of distribution of vaccine batches in Brazil demonstrated, in a quite simple way, that such relation was totally fake.

Another wave, now so strong that has also involved groups of public health experts and went beyond the Brazilian borders, linked the epidemics to larvicides used to reduce the procreation of the *Aedes aegypti*. The message attributed teratogenic properties (i.e., causes congenital malformations) to the Pyriproxyfen. The impact on networks and on the media was so intensive that the Rio Grande do Sul state government even prohibited the use of that product.

As the Ministry of Health supplied the Pyriproxyfen to states, the echoing of this news could increase even more the transmission of this and other diseases because, besides suggesting the wrong cause, the message could deprive the public health services from a tool to fight the mosquito.

Likewise, this suspicion could be easily ruled out. The Pyriproxyfen – a well-known product with safety certified by the WHO experts committee – was used in most of the country with no problems. However, in Recife – where many of the affected children were born – the product was not used because the municipality had been using bacteria-based larvicides (biological larvicides) for years. Recently, to put an end to this issue, an epidemiological study ruled out the relation.

There were some rumors about the application of agrochemicals, water contamination, use of medications, but none of them were followed by any reasonable justification.

According to a balance recently published, of the ten articles about Zika virus more shared in the Facebook in Brazil, three contain humor or rumors. From May to August 2016, the data from the Brazilian office of Facebook show that almost 10% of all posts related to the epidemics in the country were not confirmed.

Some rumors brought about questionings from authorities of other countries, international organizations and the media, always answered based on the state-of-the-art information by the moment and, obviously, the resulting concepts and attitudes.

This movement increased even more the heavy workload and expenses with social communication. On the other hand, it brought the opportunity of exploring new dissemination and dialogue channels and mechanisms, notably the social networks. This topic deserves one
full chapter or maybe even a book. Putting it in an extremely brief way, it provided great lessons about the importance of listening to the population through a direct channel, and set an open relationship with the medial professionals and their vehicles. In opposition to what many times happens and scares even the most responsible public authorities, the media understood the seriousness of the crisis and fulfilled its role of informing, warning and instructing the community that consumes news.

When crises are no longer novelty, they lose the charm and the headlines. Regarding the Zika, there is a huge risk of repeating what happens for decades with dengue: trivialization, down turning of the sense of urgency, of social mobilization and of the crucial pressure on governments.

**THE COUNTRY REACTS**

The declaration of PHENC by the Minister of Health was not a merely formal act or instrument to relax administrative measures. The then president of the Republic, Dilma Roussef, placed the government’s political crisis in the background, and got personally engaged in the cause, heading the emergency response. She urged the Ministry of Health team to assist the governor and the Health Secretary of Pernambuco, and got acquainted with the information and seriousness of the problem.

Then, a huge political and institutional mobilization started in November 2015, when there were large information gaps and uncertainties about the nature of the epidemics.

The National Congress convened specific hearings to get information and to discuss the microcephaly.

The president met with all governors to call them to action. Governors welcomed the call and got engaged. A similar dynamic was used with representatives of the Brazilian municipalities’ mayors.

All ministers, heads of the Armed Forces and leadership of federal companies and bodies were summoned. Brazil multiplied its efforts to combat the *Aedes aegypti* mosquito, believed to be the main vector of the Zika virus. A mobilization never achieved in the 30 years of dengue epidemics was organized in little over a month, with the set up of a national coordination office to coordinate a network of similar, multi-sector initiatives in all states and many municipalities. The civil defense organizations were fully engaged in the collective effort that rushed to inhibit the rising in the infestation indexes typical to the summer seasons.

The screens of the federal governments’ computers were infested with virtual mosquitoes that called the civil servants to fight the mosquito. Schools, health units, social assistance, cultural and sports centers, and even public banks opened their doors and invited the population to engage in the campaign.

Today, my deep sorrow is the same as that I shared with the president, and that can be summarized in two sentences: 1 – the situation is serious and its late consequences may be even more serious; 2 – the problem is not transitory and demands endurance to cope with it. The concern is justified by the perception that efforts to combat the mosquito weakened after the last fall and, mainly, during the electoral campaigns in the Brazilian municipalities. The inter-epidemics period, when rainfalls diminish and temperature drops, is crucial to reduce the level of *Aedes aegypti* infestation in the next season.

At the same time, despite the belief that all the valid tools to fight the vectors were being used, the ministry – the minister personally – brought to Brasilia a large number of researchers from the public and private sectors, jointly with businesspersons with innovative proposals that could generate better results than the traditional approach. They were carefully heard, presented ideas, experiences, figures, and unfortunately confirmed that novelties needed more research and improvement.
In my view, the intervention was effective. There were no figures to compare the incidence of Zika infection in 2015 and that of 2016, since notification became mandatory only in 2016. However, dengue incidence can be compared.

The peak of incidence of annual epidemics is in April. The curves consistently tend to ascend between the end of the previous year and the beginning of the second quarter. In 2015 we recorded the largest dengue epidemics ever in the history of Brazil. The number of cases in the turn of the year of 2015 to 2016 was much higher than one year ago, forecasting even greater epidemic. However, before the end of the summer the incidences started dropping, much earlier than all over the dengue historical series. Maybe, the huge national effort to fight the mosquito caused the change on the 2016 epidemic curve. The same effort may have postponed a predicted disaster: great epidemics in the other parties of Brazil, including the areas of higher population concentration like the state of São Paulo, where half of the cases of dengue were notified in 2015.

**IT IS A GLOBAL SCARE!**

These events were informed to the international correspondents of the World Health Organization (WHO) and of the Pan-American Health Organization (PAHO), as provided for in the International Health Regulation. Much more important than the official statements was the engagement of institutions and individuals that work in those organizations.

Leaders and experts of the PAHO representation in Brazil have monitored the activities of the ministry, having also participated in the investigation stages. The international support network was activated and facilitated bringing experts from abroad to support the work. The epidemics immediately spread. Very recently another epidemic disease had come into scene: the chikungunya, transmitted by the same vector, and with hundreds of thousands cases in the Central America, in the Caribbean and in South America.

News that foreign travelers had being infected here by the Zika virus was frequent. Cases of newborns with microcephaly whose mothers had been in Brazil during the pregnancy period started being identified. In this scenario, the WHO declared the Public Health Emergency of International Concern (PHEIC), urged the countries to adopt preventive measures and address efforts and resources to the required actions.

Motivated by the identification of the virus in neighboring countries and the great likelihood of overseas expansion of the epidemics, the WHO General Director, Margareth Chan, visited Brazil. Here she held long meetings with the president by then and, jointly with the Health Minister, the PAHO Director and the respective advisors, travelled to Pernambuco where she saw some of the children born with microcephaly, and talked to local health professionals and authorities.

About one month later, the WHO affirmed there was no doubt in the scientific community about the relation between Zika infection and microcephaly. During the visit of the General Director this was the topic of many talks during the activities and trips of the delegations.

The virus dissemination, which became faster in South America in 2015, followed to the Central America and the Caribbean, got to North America, Africa and Asia, following the end of winter in the North hemisphere. This year, the virus circulation has been officially recorded in 65 countries up to now, some with important epidemics. And figures continue to grow. The United States, recently traumatized by another arbovirus, the West Nile, has monitoring the Zika dissemination in its continent-sized territory.

The Brazilian Zika epidemic and microcephaly cases concerned many countries where these were not present since, with the Olympic and Paralympic Games, athletes, their relatives and tourists from all corners of the world were expected to visit Brazil. Thus, the European Community office in Brazil invited the Minister of Health for a meeting, where ambassadors of virtually all European countries expressed their fears. The meeting was a highlight in the international news as well.
The history of invariably low incidences of dengue in the second half of the years let us convey a calming message. Nonetheless, the PHEIC caused the cancelling of travels and was bad highlight in the media. There were no surprises. The intensified work at the Game venues may have contributed, but basically happened what happens every year from July to October, when the dengue vector mosquito virtually disappears in its adult form and resumes its cycle by the end of the year. During and after competitions, not even the few figures estimated to the event were recorded.

On November 18, 2016 the WHO declared the end of the international emergency situation. The justifications for the Emergency Committee’s position were not peaceful. The decision considered that the relation between Zika infection and microcephaly was defined and that the disease was not transitory, demanding robust and permanent mechanisms to cope with it. Therefore, I fear the problem can be undervalued and lose funding in the political agenda of the institution and of health all over the world.

**SCIENCE AND SOLIDARITY**

Today, many of the initial questions brought about by the emergency have been clarified. Others have not and each response clearly produces a plethora of new questions.

New knowledge started being generated in the investigation of the exanthematous disease epidemics, followed by the identification of the agent, associated neurological syndrome and, later, of microcephaly. A new disease was identified and many of its characteristics were described in less than a year. Unknown forms of arbovirus transmission were identified. Important things resulting from the infection of individuals, tissues and human cells with the Zika virus have been deeply studied.

Countless subject matters are engaged in studies ranging from the molecular characteristics of the virus and the cells with which it interacts, to the development of public policies on prevention and care. While news arises in a fast pace, each previous discovery is reviewed and gone through dozens times.

I withstand with the temptation of expatiating on any detail of what has been studied. However, I would like to draw attention to the speed with which surveys are made and information arises. The dynamic of research related to microcephaly from Zika in Brazil and globally, since October 2015, is extraordinary.

I was lucky to be tasked with the duty of inciting many of the engaged scientists. Much more than being welcome I was treated with affection and interest by all. Long telephone calls through the night, weekends and holidays; e-mails, WhatsApp, Facebook and Twitter continuously used helped building and expanding informal networks and connecting with the official ones. Times of great learning, when the concern with human suffering was paradoxically mixed with the enthusiasm of scientific search.

I do not know any other time in our history when so many brains, in a record time, have worked together towards a shared goal. All working in an open way, generously disclosing their data without waiting for their publication, sharing samples, materials, structures and ideas. Some celebrated Christmas in the lab, bringing the gift of a successful viral culture.

Countless experts attended the many technical meetings held. There was a need to set positions that could unfold in documents, guidance and rules about the disease; the criteria to notify and classify cases; investigation protocols; risk conditions; preventive measures; technologies to combat the vector; working processes, among many other urgent issues. Decisions were made to be immediately applied, with consequences that would affect the lives of many and mobilize important financial and social resources.

The mobilization in Brazil echoed all over the world and gained momentum with the WHO appeals. Thus, research institutions of different countries were open to cooperation; governments mobilized resources; scientific journals hastened the publication of articles.
related to the emergency and provided their contents on the internet, for free. Just like the meetings organized in Brazil, others were held in different countries to establish cooperation and provide inputs to the decision-making by authorities all over the world.

Many groups around the world are working to discover a vaccine, including with the participation of Brazilian institutions. It is too early to say if the vaccine will be as efficacious as that to prevent the yellow fever, or if results will be nothing but acceptable such as those for the vaccine against dengue, both diseases caused by viruses similar to the Zika virus.

**AND SO?**

As I have said, there is strong commitment, some financial investment and many people engaged in the challenge posed by the pandemics. I resisted the temptation of expressing my admiration and acknowledgment, did not mention the name of the main players that have participated in this history – a list of devoted and competent people making immeasurable efforts. I would need more pages.

Many uncertainties remain. Every week the scientific journals provide information about previously unknown manifestations of the Zika infection. We already know that most cases have mild symptoms or the disease goes unnoticed. Neurological disorders, such as the Guillain-Barré syndrome, may follow the acute infection. Deaths have been recorded. Microcephaly is well-documented; changes on eyes and hearing are being described. There is a suspicion that some effects of the disease acquired during pregnancy can only be perceived when the child grows a little. The tendency is that the term ‘congenital Zika syndrome’, just like that used for congenital German measles, becomes the official term.

Even greater are the uncertainties about the disease’s epidemiological behavior. The explosive behavior of the epidemic in the Northeast region early in 2015, if spread to other parts of Brazil, could lead to the quick natural elimination, since in short time everyone would be immune and the virus would no longer circulate.

However, some combination of people circulation, climate cycle and the vector’s behavior changed the speed of spread, worsening the fear that it could persist in an endemic way, with epidemics that move from a place to another.

The Brazilian public health authorities must keep sight on two priorities. Keep, expand and adopt new technologies to reduce the infestation from *Aedes aegypti* is the first one. The second one is to ensure the concerned mothers’ and families’ with full access to care and therapy.

In times of general institutional crises in the three powers, we can hardly be optimistic and imagine that the Unified Health System (SUS) will be granted priority and the technical, administrative and financial resources required to cope with the crisis. The SUS has ride out many storms. It is the largest asset of the Brazilian population: to keep alive the hope that the Zika, as happened with many other diseases, does not come to be a long-lasting threat. The national mobilization experience triggered by the head of the Executive Power in the initial stage of the crisis was a priceless lesson learned. We are talking about a disease, a health condition and not only a problem of Health. Nice expectations depend on the efforts of all governmental sectors and the society’s commitment.
In little less than a year Brazil managed outbreaks of Zika virus-related diseases that stroke the community.

In the first quarter, a great outbreak of a new ‘exanthematous acute disease’ affected hundreds of thousands individual, overloading the health units.

When the cause of the first epidemics was found, a second outbreak of neurological cases related to the infection was identified in the second quarter of 2015. Although less concerning if compared to the classic form, this second outbreak affected hundreds individuals in different states, with severe clinical conditions, some fatal outcomes and others that left permanent motor sequels.

When everything seemed to have been clarified, and the likely complications caused by this arbovirus seemed to have ended, the microcephaly epidemics arose. This was a new page in the history of medicine that shocked the world with the repercussions of this infection on the embryo, leading to major scale international mobilization.

This chapter does not focus on the scientific evidence on the topic, which is available in many indexed journals search websites. Some will be mentioned only to contextualize facts in time. This paper aims to report the experience and history of the epidemics in the light of a physician. It aims to report how, based on clinical and epidemiological data, the hypotheses that supported the final knowledge production were built.

The Zika epidemic that befell Brazil in 2015 should be described under different viewpoints: that of the clinical community, of ‘pure science’ researchers, of epidemiological surveillance and of different public health actors. This enables an analysis focused on the lessons learned in the process of investigating a new disease.

That episode, which will be part of the Public Health history, brings a unique opportunity that goes beyond the important papers published in notorious journals. In fact, it allows to learn with mistakes, identify successes, reassess the strategies of investigation, integration and coordination among the actors engaged, learn and teach new concepts in epidemiology and, above all, lead to recommendations to cope with new outbreaks of new diseases, or of old diseases that will emerge again.

AN OUTBREAK OF EXANTHEMATOUS DISEASE – JANUARY TO APRIL 2015

IDENTIFICATION OF A NEW OUTBREAK

In the history of medicine, many outbreaks are identified based on the health care’s perception, when Health professionals observe an unusual increase in the number of cases, or atypical manifestation of a clinical presentation, and alert the public health authorities that, in turn, start an investigation process until the case is concluded. The history of Zika in Brazil was not different.
THE ONSET OF THE NEW EPIDEMICS IN BRAZIL

In the last two months of 2015, cases of an exanthematous disease drew the attention of health professionals in the Northeast of Brazil. It took on an epidemical standard in the first quarter of the year and reached its peak in March. The outbreak had high attack rate, with thousands diseased individuals overcrowding the public and private urgency health services (FOLHA PE, 2015), although it had not been measured by the official notification system. The notification of this disease was not mandatory yet and health surveillances instructed that cases should be reported as dengue, even when physician suspected of Zika (PERNAMBUCO, 2015a).

An outbreak investigation demands systematization, including some important issues such as: 1) establish case definition (clinical-epidemiological x laboratorial; suspected x likely x confirmed); 2) confirm if cases are “real” (deeply discussed with physicians); 3) define the frequency (incidence rate per area); 4) analyze the epidemiological characteristics that describe the cases; 6) generate hypotheses; 7) test the hypotheses.

The following description of the facts in the first stage of the epidemics makes clear that all those processes were undertaken, but not in a systematized and coordinated way, sometimes even biased (factor of confusion). Valuable lessons were learned in this first stage, perceived in the different systematic conductions regarding the microcephaly outbreak late in 2015.

CASE DEFINITION

First, physicians from there states of the Northeast, Dr. Kleber Luz (Natal/RN), Dr. Celso Tavares (Maceió/AL) and Dr. Carlos Brito of Recife/PE (author of this chapter) reported a large number of patients with acute disease characterized by: a) exanthema as the main and many times the first symptom, with craniocaudal patterns, itchy; b) most cases had no fever or had mild and short-duration fever; c) some cases reported joint pain, hand edema, foot edema and ankle edema. We had a clinical-epidemiological definition to the new outbreak that coincided for all the different states affected. There was not diagnostic suspicion yet, but the clinical-epidemiological description deeply discussed by the health care experts excluded many likely etiological agents, narrowing the investigation process scope (DINIZ, 2016).

CLINICAL-EPIDEMIOLOGICAL DESCRIPTION – A DIFFERENT PATTERN

Cases description made the physicians conclude that it was a new pattern of arboviral disease and that clinical characteristics were different from the dengue, endemic in the Northeast, and of the chikungunya (CHIKV) epidemics that stroke Bahia in 2014.

THE FIRST NETWORK OF ARBOVIRUS EXPERTS – CONTRIBUTIONS

From November 12 to 15 the Health Care Department (SAS) of the Ministry of Health visited Feira de Santana (BA) with a team of multi-professional experts from different states, made up by members of the dengue committee, physicians, physiotherapists, sanitary physicians and managers to assess the recent chikungunya outbreak. On November 19 Rodrigo Said, of the SAS, set up a WhatsApp group (the “CHIK a missão”) made up by those experts to monitor the CHIKV outbreak, but which provided great inputs to expand the debate bout the Zika epidemics and shorten the regional and temporal distances (Carlois – PAHO; Jesuina Castro-BH; Kleber Luz-RN; Rivaldo Venâncio-MoH; Rodrigo Said-Brasilia/MG; Lúcia Silveira/RJ; Theresa Cardoso/ES; Eduardo Carneiro/GO; Leandro Coelho/GO; Elizabeth França/BH). The debate was intensified in the group with images of cases, exams results, opinions and suggestions in a consensual perception that it was a new epidemic caused by a new etiological agent (FRONTLINE, 2016).

HYPOTHESIZING

RESISTANCE TO THE NEW – PART OF THE LEARNING PROCESS

In the first quarter official authorities, municipal and State Health Departments and the Ministry of Health did not welcome the hypothesis of a new virus. The epidemiological investigation needs some skepticism, precipitation may lead to mistakes, the challenge is to balance the intensity, and resistance must be
based on strong reasons. The hypothesis advocated by the official authorities and supported by some infectious disease specialists was that we were facing an epidemic likely to be related to a change in the dengue standard caused by a 4-serotype or the mutation of other serotypes, the so-called ‘mild dengue’ (NE10, 2015; FOLHA PE, 2015). However, over months the contrary opinions advocated by care professionals bulged.

The arguments against this hypothesis were built, discussed by e-mail and in many meetings and teleconferences promoted by the official institutions.

BUILDING ARGUMENTS: CONTRARY TO THE ‘MILD DENGUE’

The arguments against the hypothesis of dengue as the cause of the outbreak and that we were facing a new disease were built based on a clinical-epidemiological observation. In principle, hypotheses were based on exclusion – a procedure part of any epidemiological investigation of outbreaks.

1. Pattern quite different from that described to dengue:

- In dengue, rash happens from the 4th day of the disease on and in 30% of the patients, differently from the epidemics that affected virtually 100% of those seeking urgency care in the early days of symptoms. Moreover, it started on the face and was gradually expanded to the body (craniocaudal), differently from dengue, where it is simultaneous.

- Fever is a symptom for almost 100% of the cases of dengue, and is even a required criterion to notify suspect cases. It is high, occurs many times a day and lasts up to 4-7 days, completely different from what health care was observing for the ‘new outbreak’ in which most cases had no fever and, when they had fever it was mild, one single episode and did not last longer than 48 hours.

- Conjunctivitis. Cases frequently reported non-purulent conjunctivitis, which was barely observed – although described – for dengue.

2. A serotype mutation could be responsible for the ‘new outbreak’; another argument was that a population previously exposed to many epidemics could, after decades, develop milder forms of the disease in a second infection (partial crossed protection). Arguments against this were based on evidence found in literature:

- There were cases of dengue but in lesser proportion in comparison to the huge ‘exanthematous disease outbreak’. The theory of dengue virus mutation was weak, based on the fact that dengue serotypes circulating in the Northeast region that summer were not the same.

Viral mutation capable of changing the pattern of a disease is a rare event, and we should consider that many viruses should have mutated simultaneously, since the same clinical pattern was found in different states, with different types of circulating dengue serotypes. Other Asian countries suffered epidemics caused by the four serotypes and no change of pattern was reported for mild forms of dengue after several epidemics, and thus did not support the suggested ‘partial crossed protection’.

3. Testing hypotheses (study design/planning biases and factor of confusion)

One of the arguments that advocated for the ‘mild dengue’ to explain molecular tests and serology that consistently tested negative for dengue in many cases of the outbreak could be related to the moment of collection or low sensitiveness of the techniques. Based on that, the Ministry of Health designed a research
protocol to be implemented in the Northeastern states, pursuing late samples of patients affected by the disease in the acute stage. This could allow detecting the seroconversion and confirm the dengue epidemics. The SSE/PE technical committee drafted guidelines on the search for other etiologies, but the design now attached priority to the search for dengue cases. According to it, the negative cases of IgM for dengue in samples of acute stage should undergo a second sample to search IgG for dengue. Moreover, it instructed the adoption of new methodologies to perform the PCR and NS1, and apply techniques of plaque reduction neutralization test (PRNT) (PERNAMBUCO, 2015b). This introduced some biases to the proposed studies. The health care group that opposite to hypothesis of ‘mild dengue’ insisted in the investigation of other causes, presenting strong arguments:

3.1 Despite being likely cases of dengue many IgM serology tested negative. The argument suggested by authorities and some experts was that in a second infection the number of cases with negative IgM serology increases, due to a change of immunoglobulin isotypes from IgM to IgG, leading the MoH to prepare the aforementioned study design to find late samples to detect seroconversion for dengue.

- This is a likely phenomenon, but according to literature it happens in less than 20% of the cases of secondary infection. We sustain that in the dengue cohort in Pernambuco only 16% of the secondary infections reported negative IgM and were confirmed by increased IgG or by PCR. This frequency was quite different from that described in Pernambuco, for example, presented in national teleconference and technical note (SSE/PE), according to which of 2,109 serologies for suspected cases, 1,160 tested negative for IgM.

4. Patients with positive IgM serology for dengue with patterns of the ‘new exanthematous disease’ were found in Recife.

In April, another factor of confusion that came about and made the SSE/PE reinforce the hypothesis of ‘atypical and mild dengue’ was a study carried out by the Recife city hall based on the identification in the database of the Central Public Health Lab (Lacen) of 167 samples of positive IgM serology for dengue. The patients’ claims were further checked by phone. The technical note suggested that 23% of the patients had no fever, 70% had arthralgia and 50% had edemas, which is compatible with the ‘new exanthematous disease outbreak’ (RECIFE, 2015).

- No case proved the virus presence (by PCR or virus isolation). In the same record, from January to April, only 16 cases tested positive in molecular tests for dengue. The group of experts that disagreed with this current suggested these data in fact reinforced another etiology that tested negative in molecular tests, and that the serology was likely to be a crossed reaction.

- The positive results for molecular tests for dengue, when timely performed, exceeds to 50% in different studies. The state reference labs used the internally recommended standard molecular techniques and, more than three months after the investigation, the viral survey performed by reference labs was consistently negative for dengue.

Mainly based on the clinical-epidemiological arguments complemented by lab data, the health care professionals of the CHIKV group (aforementioned) and others like Dr. Celso Tavares believed, based on these data, these were not cases of dengue and, thus, efforts to search another infectious agent were required.

BUILDING ARGUMENTS: IT’S ARBOVIRUS, IT’S ZIKA

The perception that it was a new infectious agent related to arbovirus came about in the first two months of the year, and in March the range of hypothesis was narrowed, leading to the suspect of Zika (suggested by Dr. Kleber Luz).
IT’S AN ARBOVIRAL DISEASE!
Although the investigation for measles, parvovirus and German measles as likely agents was expanded in many states (PERNAMBUCO, 2015b), the epidemiological clinical data suggested these agents were unlikely, despite some rumors in the media that some of them had been confirmed. A disease with large number of cases (epidemics), affecting different regions of the Northeast in a short time span, characterized a disease with high dispersion rate, which is unlikely for infectious diseases transmitted by inhalation. We pointed out that the dispersion pattern was of arthropods-borne diseases. There was some consensus about it between the health care and surveillance, considering that the last advocate for dengue and health care groups were seeking for another arbovirus.

- The discussion in the CHIKV group focused on the identification of some arbovirus. The article by Nayara Lopes named Características gerais e epidemia dos arbovírus emergentes no Brasil, published in 2014, was incorporated to some presentations.

- The article did not refer to the chikungunya, but it was the first agent that came into the mind of the CHIKV group that visited Feira de Santana in 2014 and expected a huge epidemic of the disease that did not happen that year. However, a posting in the group showed that clinical data were not compatible with the idea: “An outbreak of exanthema characterized by few or no fever, with hand and ankles edema, joint pains, but totally different from the intensity of fever and pain caused by the chikungunya”. It seemed to have been ruled out based on clinical data and subsequent negative lab tests.

- It is Zika. The hypothesis of Zika was suggested for the first time in March, when Dr. Kleber Luz (Natal/RN), in his studies and review of literature, started seeking for an arboviral disease with a pattern of exanthematous disease and arthritogenic component, and concluded it was the Zika. He posted on the WhatsApp group: “I guess this is the Zika virus. You see, everybody is sick here... it must be Zika. I think we’ll have the results next week”. All the group members supported the suggestion based on the clinical data and epidemiology, and started advocating for the hypothesis raised by Dr. Kleber Luz. The physician had submitted samples to be tested at the Oswaldo Cruz Foundation (Fiocruz) of Paraná. The hypothesis was presented in teleconferences promoted by the MoH with state departments, but the search for dengue persisted.

After the dissemination of the hypothesis of Zika, early in May two researchers of the University of Bahia, Gubio Soares and Silvia Sardi, identified the virus in samples of cases from Bahia (CAMPOS; BANDEIRA; SARDI, 2015) and few days later the Fiocruz/PR researchers, Dr. Claudia Santos and Dr. Camila Zanluca, informed that samples from Rio Grande do Norte tested positive for ZIKV (ZANLUCA et al., 2015).

The lab diagnosis put an end to the long-lasting investigation and debates. In May the Ministry of Health recognized that the epidemic in the Northeast of Brazil was caused by the Zika arbovirus.

The suspicion of that etiological agent as cause of the epidemic was extremely hard. Although Zika had been identified in 1947 in Uganda, Africa, the occurrences of human infection were isolate and sporadic, and most individuals were asymptomatic. The epidemical potential was not perceived until 2007, in Micronesia; however, it was only in 2013, mainly in the French Polynesia, that pattern changed, with high attack rates, estimated to have affected 11% of the population (BRITO, 2016). In fact, information about the disease was limited, but the crossing of clinical-epidemiological data, use of exclusion criteria and an additional dose of persistence led to the suspicion and to the solution of the investigation.

A publication in the New England Journal of Medicine (NEJM) of 2009 reports the outbreak on Yap Island. We highlight a piece that seems to have been extracted from the recent history of the epidemic reported herein:
In April and May 2007, physicians on Yap Island, Federated States of Micronesia, noted an outbreak of illness characterized by rash, conjunctivitis, subjective fever, arthralgia and arthritis. Although three patients tested positive with a commercially available dengue IgM kit, the physicians had the impression that this illness was clinically distinct from dengue… (DUFFY, 2009).

One of the lessons learned with this first outbreak is that clinical communities and public health should share more data and debate more intensively; clinical and epidemiological data are crucial to guide investigations; lab diagnosis play an important role to confirm clinical suspicions, but should not inverse the logic of a clinical-epidemiological-laboratorial investigation.

The lessons learned with the outbreak of the exanthematous disease caused by the Zika virus, early in 2015, hastened the responses to and investigation of the Zika microcephaly outbreak in October, carried out by the Ministry of Health and State Health Departments, in a more organized and coordinated way. This effort became a reference to the world.

**CASES NOTIFICATION – LESSON STILL TO BE LEARNED**

When the viral circulation was confirmed in April/May and the ongoing epidemic was identified as resulting from the Zika, we failed to get in 2015 an actual scenario of the epidemic dimension. The Ministry of Health made estimates based on the attack rates envisaged for other countries (BRASIL, 2015).

In some states, the suspected Zika cases were notified as dengue, reducing the cases estimates (PERNAMBUCO, 2015a). Pernambuco allowed the notification of suspected Zika cases since December 2015 (PERNAMBUCO, 2015b). Only in February 2016 the Ministry of Health published an administrative order making Zika a disease of compulsory notification (BRASIL, 2016).

Even after the Zika epidemic was recognized, it continued being notified as dengue, thus distorting the future analyses by the scientific community about those arboviral diseases such as attack rate, lethality, frequency of symptoms, etc.

During the meetings of the technical committee on arboviral diseases we insisted in the need for reviewing the 2015 cases and suggest an estimate. However, the impression of the SSE/PE and Health Surveillance Department (SVS/MS) leadership was that the cases could not be reviewed, neither estimates could be made.

Still in 2015 we performed a hospital-based study, retrospectively analyzing suspected cases of arboviral diseases in a private hospital in Recife, which is reference for urgency care, to evaluate the frequency of arboviral diseases. Of the 1,046 cases, 895 (86%) were classified as cases of Zika and only 151 (14%) as cases of dengue, based on clinical-epidemiological data (BRITO et al., 2016). Results showed that health care effectively understood that the 2015 epidemic was mainly caused by Zika. Late in 2015, the state of Pernambuco officially notified 1,386 cases of Zika and 146,089 suspected cases of dengue, but most of these cases should be Zika but notified as dengue (PERNAMBUCO, 2016c).

Brazil became a global reference in surveillance and notifications of cases of dengue; however, with the emergence of new arboviruses such as the chikungunya in 2014 and Zika in 2015 the surveillance model demanded urgent changes so that notification data could reflect the reality.

Other countries have fit into the new reality. Zika epidemic in Brazil has the potential to raise among managers the need to review the existing guidelines for the surveillance system. The French Polynesia used the definition of suspect cases based on clinical data to estimate cases all over the country. To that, it selected 40 to 50 health units of the network, located on 25 islands of five archipelagos, 40% of which were private clinics and 50% were public hospitals and
From October 2013 to February 7, 2014, this syndromic sentinel surveillance network reported 8,262 suspected cases of Zika infection (POLYNÉSIE FRANÇAISE, 2014). Only 746 blood samples were submitted to laboratory confirmation and 396 (53.1%) tested positive by RT-PCR. The cases notified based on clinical criteria were extrapolated to the whole territory, and the number of patients receiving care for Zika was estimated to exceed 29 thousand (about 11.5% of the French Polynesia population). The total number of cases could be even greater because many diseased individuals do not seek for medical care (POLYNÉSIE FRANÇAISE, 2014).

The medical care continued and continues stating that the official surveillance data for arboviral diseases in 2015 and 2016 are different from those perceived by professionals working at health units, recently worsened by the presence of triple epidemic with the arisal of chikungunya. The Reunion Island is another good example to be followed. When authorities noted that the number of cases exceeded the traditional surveillance system’s capacity and they could no longer monitor the tendencies of the epidemics, they started an active search that employed the perception of physicians external to sentinel network, hospital records, public and private labs reports, data from health insurance funds and self-reports of the population on a toll-free number. With this new information, the number of cases of arboviral diseases reached 244 thousand (RENAUT et al., 2007).

The official data on arboviral diseases not only failed in reflecting the reality of the Zika epidemic, but also distorted the analysis of the behavior of other epidemic arboviral diseases in the country. Re-write this epidemiological history of Zika in 2015, and rethink the strategies for future epidemics estimating in a more realistic way the disease frequency and behavior, is a need but also a challenge. The selection of the methodology to be applied must be exhaustively discussed, base on the experience in 2015, and if the best technique is not possible, the most feasible and applicable to our reality should be the choice.

**AN OUTBREAK OF NEUROLOGICAL MANIFESTATIONS – APRIL TO JULY 2015**

The emergence of neurological cases potentially associated with ZIKV was firstly described in 2013 in the French Polynesia, with reports of 41 SGB cases after the epidemics. But the virus was not isolated. After the Zika outbreak in the Northeast of Brazil was confirmed, in April 2015, number of neurological cases in Bahia, Pernambuco and Rio Grande do Norte increased.

In Pernambuco I have sent WhatsApp messages to groups of neurologists informing the risk of the increased number of neurological cases, and asking them to inform if they noticed any change in the pattern (BECKER, 2016). In May, Dr. Iris Machado and Dr. Lúcia Brito from the Restauração hospital, reference in neurology, informed an increase in the number of neurological cases with history of viral disease, firstly reported as likely to be dengue.

We scheduled a visit to the hospital with the application of a form for clinical-epidemiological investigation of inpatients. When we interviewed the first patients with clinical background of viral disease previous to the neurological conditions, which some patients called dengue, I was amazed with the report of conditions suggesting Zika – the typical standard we had recently observed in the epidemic started in January and still under way. The patients’ testimonials were recorded (authorized in writing) and made up the historical register of the first cases associated with the Zika virus further confirmed in Brazil. Blood and liquor samples were collected and sent to the Lab of Virology and Experimental Therapy (Lavite) of the Aggeu Magalhães Research Center (CPqAM/Fiocruz) in Recife.

Through her records, from January to May Dr. Lúcia Brito observed about 120 neurological cases potentially associated with viral diseases and for which no specific etiological agent had been identified. The average for the previous years was 25 cases in the same period. It was a 500% increase in the number of cases.

In the following weeks the Lavite endeavored to standardize the molecular tests for Zika and, on June
14, 2015, Dr. Ernesto Marques, Dr. Marli Tenório and Dr. Lindomar Pena informed that the PCR and isolation were positive for Zika in blood and liquor sample of six patients. The virus detection in neurological cases was then confirmed by the very first time.

Polynesia had hypothesized the association based on clinical-epidemiological data, and Pernambuco confirmed the molecular lab diagnosis for the first time. Later on, the first 41 neurological cases described in 2013 with SGB in the French Polynesia had serological confirmation in stocked serum samples (CAO-LORMEAU et al., 2016). A recent publication challenged the interpretation of the serological tests performed in the study, arguing that results do not allow concluding for Zika because of the potential crossed reaction with dengue (SMITH; MACKENZIE, 2016).

The SSE/PE and the Ministry of Health were informed, and the cases were notified on the official record of the Pan-American Health Organization (PAHO) in October 2015. The Ministry of Health designed a national protocol for investigation of neurological cases when the cases reported were confirmed.

Surprisingly the first six cases have not yet been published in indexed journals, and were reported only on the PAHO record. This is a profile of many physicians mainly in health care, where priority is to inform the fact to the clinical community. Late communication hinders the group from publishing the cases further. A lesson to the future, reinforcing that health care and research reports can take place in parallel and quickly.

Studies advanced, international partnerships have been established and other cases are being investigated, of which nearly 400 are related to arboviruses and are not limited to SGB, with confirmed cases of acute disseminated encephalomyelitis (ADEM), optical neuritis, encephalitis, meningitis, etc.

**A MICROCEPHALY OUTBREAK – OCTOBER TO DECEMBER 2015**

On October 19, 2015 Dr. Vanessa Van der Linden and Dr. Adélia Henriques asked me to evaluate an atypical situation characterized by larger number of microcephaly cases. Dr. Vanessa Van der Linden reported the presentation pattern that, based on clinical and imaging findings, suggested congenital infection typically related to infections with CMV, toxoplasmosis, German measles, etc., but now more severe and more frequent. As suggested by Dr. Adélia Henriques, the neurologist asked my opinion due to my experience with previous epidemics such as cholera in 1992 and dengue throughout the last 20 years. The hypothesis was that a congenital infection was causing an increase of cases, probably by infectious agents known to neuropediatricians, but whose pattern had changed (BRITO, 2015; EXPRESSO, 2016; DINIZ, 2016).

By the time we got in touch with Dr. Jucille Menezes, the neonatologist responsible for the maternity of the Mother-Child Institute of Pernambuco which is reference in high-risk pregnancy. By phone, the physician said she had never seen so many cases of microcephaly all over her professional life.

In a joint effort on October 19, 2015 we interviewed the 16 pregnant women with children with microcephaly hospitalized in the unit. We applied a questionnaire with clinical-epidemiological data seeking information common to the pregnant women, since our goal was to identify congenital infections known to cause microcephaly (e.g., toxoplasmosis, German measles, CMV, etc.). The picture taken that day with the team of resident physicians, physicians, mothers and their children is impressive for the number of cases. The photo became the historical record of the first standardized investigation for microcephaly cases (DINIZ, 2016).

The number of cases was the first alert about the severity. We have identified an article published in the IMIP, which surveyed all the central nervous system malformations that received the institution’s care from 2000 and 2004, and only 11 cases were reported in five years (PACHECO et al., 2006).
Despite being scared by this fact, the investigation should be built and deepened to search for the likely etiology to duly avoid the eventual exposure.

The first awkward information that day was that mothers came from different cities in the state, which ruled out the possibility of infection with some known agents transmitted by respiratory inhalators, such as German measles, or transmission routes such as toxoplasmosis as the causers of the outbreak, since they were not in direct contact and these outbreaks are limited to small communities. These infections do not follow a quick dispersion pattern. In addition, Dr. Jucille Menezes had been informed that some of the pregnant women had undergone serologic tests during the prenatal care, as well as when hospitalized, and tested negative for usual causes.

When I interviewed some mothers I had a big surprise, just like when I interviewed the first neurological cases. When I heard mothers describing a viral condition in the early stage of gestation, which some patients refer to as allergy or virus disease, I noted this condition was an indication of Zika – the typical pattern we had recently experienced during the epidemic in the first quarter of 2015.

Some other initiatives were fostered. While Dr. Jucille Menezes and her team recorded the cases that described microcephaly pattern, on the next two days I visited and personally applied the questionnaire to other pregnant women in three maternities: of the Barão de Lucena hospital, the Cisam maternity and the maternity of the D’Ávila private hospital. On October 22 we had information on 26 pregnant women whose children had microcephaly.

In that same period we contacted George Dimech, the executive officer of Control of Diseases and Illnesses of the SSE/PE, reporting the effort and seeking information from the National System of Live Births regarding microcephaly. There were five cases in 2011, nine in 2012, 10 in 2013, and 12 in 2014, with average rate of 0.5 per 10 thousand Live Births.

He also referred to other 20 cases, mainly from August on, with International Disease Classification (CID) of microcephaly recorded on the certificate of Live Births. However, the system had no clinical information about these cases. In fact, the notification of 20 cases in the system accounted for an increase of almost 100% in the number of cases against the previous years. These data served as second conclusion and a lesson learned with the epidemic we experienced, suggesting that the official notifications systems, despite recording cases, are not ready to notice anomalies, identify outliers in real time, and warn authorities.

With one case a month on average, we had 16 cases in one single hospital, totaling 26 cases in one week. This would be enough to characterize an outbreak.

The puzzle started to be put together. Primary (genetic) and secondary causes were suggested, but the initial investigation of these cases made me hypothesize that the increase in microcephaly cases could be associated with the ZikaV infection (BRITO, 2015; TEIXEIRA et al., 2016), based on the following clinical-epidemiological aspects and the differential diagnosis:

- Arisal of many cases in short time span, occurring simultaneously in different cities and states, characterizes disease with high attack rates and quick dispersion – a phenomenon associated with arthropod-borne disease.

- In addition to microcephaly, the imaging exams shared some characteristics: periventricular and cortical microcalcifications; hypoplasia of the cerebellar vermis and some cases of lissencephaly compatible with congenital infections pattern.

- Diseases associated with toxoplasmosis, German measles, cytomegalovirus, syphilis, HIV, parvovirus B19, etc. (TORCH) due to the transmission means that is not associated with large outbreaks.

- Investigations in prenatal and perinatal tested negative for those TORCH infections.
Most mothers (70%) reported viral disease compatible with the Zika in the first quarter of pregnancy, when The ZikaV outbreak occurred in the region.

Neurotropism is higher in Zika than in other arboviral diseases.

Other arboviral diseases such as dengue, endemic and epidemic in the region, which are not associated with congenital malformations, or chikungunya that, despite being associated with perinatal disease lacks evidence of malformations, and in the beginning of that year the ChikV had not yet been detected in many Northeastern states.

As a member of the Technical Committee on Dengue of the Ministry of Health I informed the facts to Dr. Giovanini Evelin Coelho, coordinator of the National Programme on Dengue Control (PNCD), and to Dr. Cláudio Maierovitch, executive officer of the Ministry of Health’s department of communicable diseases, and George Dimech.

The Ministry of Health had not yet been formally informed about the increased number of microcephaly cases. On October 22 we drafted a document that has also comprised the larger number of microcephaly cases but, considering the earliness of the investigation on the hypothesis of Zika, we decided to inform only the suspicion about congenital infections. The communication was officially published in a technical note by the SSE/PE (PERNAMBUCO, 2016). In compliance with the international health treaties the Ministry of Health reported the fact to the PAHO.

In that same week I sought the Regional Council of Medicine of Pernambuco (Cremepe) and, jointly with the President, Council Members and Vice-President, we decided to establish a technical chamber to follow-up and support the investigation outcomes. On October 26 a meeting was held with several experts and representatives of the state and municipal Health Departments to speak out about the cases. By that time, I introduced the hypothesis related to the Zika virus. The meeting was attended by Dr. Giovanini Evelin, Dr. Cláudio Maierovitch and Dr. Enrique Vazquez (PAHO).

The increasing number of cases and the evidence available made the Brazilian Ministry of Health to declare health emergency state more or less 25 days after the investigation started.

On November 17 a fetal medicine expert (Dr. Adriana Melo) from another state, identified by RT-PCR the infection with ZikaV in amniotic fluid of a pregnant woman in the fifth month of pregnancy, whose baby had microcephaly. On November 28 a virologist (Dr. Pedro Vasconcelos) detected the presence of the virus in blood and tissue tests of two stillborn children with microcephaly, reinforcing and confirming the association between congenital malformation and the Zika virus (PAHO, 2015). The Ministry of Health then acknowledged the association.

After the Brazilian alert, the French Polynesia recognized 17 cases of microcephaly in that region after the Zika outbreak. The previous average ranged from 0 to 2 cases of microcephaly a year (PAHO, 2015; CAUCHEMEZ et al., 2016). In December 2015, samples of tissues of two stillborn babies with microcephaly and two abortions in Rio Grande do Norte tested positive to Zika by RT-PCR and immunohistochemistry (MARTINES et al., 2016).

The clinical findings of imaging and lab tests of the first cases in Pernambuco started being quoted in different publications, and many other papers are being drafted, thus contributing to better understand the disease (HAZIN et al., 2016; MERG, 2016; CORDEIRO, 2016).

In addition to microcephaly, other anomalies started being identified such as musculoskeletal malformations, vision and hearing alterations. These could be related to the moment when the infection occurred, and reinforces the need to expand the investigation. Jointly with a group of infectious diseases experts (Dr. Rivaldo Venâncio, Dr. Kleber Luz), as early as in November 2015 we started using the term ‘syndrome associated with congenital infection with Zika’ or just ‘congenital
Zika’ (BRITO, 2015), like the congenital infections with defined patterns.

Countless papers were published in the following months, definitely confirming the association that, nonetheless, was not recognized by the WHO until 2016.

The evidence that Zika virus causes microcephaly wrote a new chapter in the history of medicine. New concepts and risks related to congenital infections, inexistent up to then, came about. An etiological agent that causes malformations communicable by mosquito, a vector with no perspective to be eliminated in the medium and short terms in most countries where the Aedes circulates. This brings uncertainty to women in fertile period, changing family planning, when the ideal period for conception is decided based on the epidemiological surveillance information and circulation of the vector, and is likely to impact birth rates in the short term.

Brazil – notably the Ministry of Health as coordinator – proved to the world its capacity of investigation. Few days after being informed by the health system that something was going wrong, it recognized and informed the world about a change on the patterns; clearly disclosed the Zika-related hypotheses to the scientific community; supported and expanded investigations in many Northeastern states; took less than 30 days after the investigation to declare national health emergency situation and confirmed the association in two months.

THE FUTURE

There is a lot yet to be studied about the Zika virus and its interactions with the vector, human beings and the environment. The lessons learned with this epidemic through some mistakes and lots of successes surely increased coordination among different players in the public health scenario, including care professionals, researchers, sanitary physicians, managers, the media and the community, providing them with the maturity required to cope with and prevent future epidemics. Actions now should be focused on combating the vector that will only be eradicated with the population’s better living conditions, investing in basic sanitation and piped water continuously supplied. In the short term it should keep on supporting strategies to eliminate the vector and then reduce the vector density, consequently reducing the transmissibility and number of cases. Medium and long term investments towards the development of antiviral therapies in the event of pregnant woman’s exposure and, above all, efforts to develop a vaccine are urgent and necessary.

REFERENCES


Zika Virus in Brazil: The SUS response


ZIKA VIRUS IN BRAZIL: THE SUS RESPONSE
Surveillance in communication
Press Conference and Workshops: press conference about the microcephaly record on 11/30/2015
Photo by: Rondon Vellozo/MS
The arrival of Zika in Brazil was announced late in the morning of May 14, 2015. The then Minister of Health, Arthur Chioro, called journalists in an auditorium and disclosed the result of exams performed at the Evandro Chagas Institute of Pará. The tests pointed out the infection in samples from 16 patients. Just after the notice, Chioro said: “The Zika virus is nor worrisome [...] We are concerned about dengue, because dengue is lethal”.

Six months later the successor of Chioro, Marcelo Castro, convened another press conference. This time it was to declare Public Health Emergency of National Concern due to a condition likely to be related to the same virus: the microcephaly.

This change from the image of “virus cousin of dengue” with no huge offensive potential towards the main suspect of the increased cases of babies born with neurological problems was quick and surprising, but not unexpected.

The first sign that Zika was not as inoffensive as believed came up in an interview on a Sunday with the then Executive Officer of Communicable Diseases of the Ministry of Health, Cláudio Maierovitch. The number of cases of Guillain-Barré syndrome, which causes gradual paralysis, was above the standard levels. It was suspected to be related to the Zika. Similar association had been made in Micronesia, but in much reduced proportions. Considering this, surveillance teams were assigned to visit the cities where patients were receiving care.

And this just strengthened the belief about the need for visiting Pernambuco when the first indications of increase in the number of notified microcephaly cases arose. Some physicians hypothesized that the phenomenon could also be related to Zika. If the infection was suspect of causing neurological damages among adults, why not among babies?

In the Pernambuco Health Department the data, disclosed with caution, suggest something was going wrong. The professor at the Federal University of Pernambuco, Carlos Brito, was convinced of the relation between the rising number of cases and the likely transmission of Zika from the pregnant woman to the fetus. He considered the distribution of cases in the state, the coincident period of birth – six months after a suspect of Zika epidemic in the region – as important signs.

It was during the visit to the Barão de Lucena hospital, where the neuropediatrician Vanessa Van der Linden works, that doubts about the relevance of the issue were clarified. Vanessa and her mother Ana Van der Linden, who is also a neuropediatrician, were the very first ones to note that the number of babies born with the malformation, considered rare up to then, was drastically increasing. Talking with her daughter at night, Ana said to have had, in one single day, seven patients with problems. Vanessa, in turn, had met five. Mother and daughter called a fellow, Adélia Souza, who confirmed the tendency.

During the interview with the neuropediatrician in a small room she shared with her team, we were
interrupted once to be informed that one more case of microcephaly had been confirmed.

When I contacted Vanessa I thought I would have some difficulty to find a child with the problem. I even imagined I would have to go visit several homes before finding family members wanting to tell a little about their and their babies’ histories. But at the hospital, as soon as my interview with Vanessa ended, I met Cláudio’s parents. I had just started interviewing the young couple still shocked with the confirmation of the malformation diagnosis on the previous day, and another patient, who had delivered in that hospital, drew near. She looked at the baby and promptly recognized: “Does he have microcephaly? I know it”, she said. “My sister-in-law has just delivered a baby with the same problem”.

Her easiness astonished me. Up to then I had never seen a baby with this malformation. I had just heard histories that microcephaly could occur in cases of congenital syphilis. But I always believed this was a rare condition. And it was. But things were changing. At least for the families served by that hospital.

Since the beginning, the main doubt was how to approach the subject. There was an undeniable increase in the number of cases, but nothing but suspicions about the reasons that caused the phenomenon never seen before. Inform about the suspicions without causing panic – this was the major challenge. Physicians and researchers were facing a totally new situation, and most of the answers given to journalist included “I don’t know”, “maybe”, “unlikely”.

The only certainty was there was a flaw: the emergence of Zika in Brazil had been undervalued. The executive director of the Evandro Chagas Institute, Pedro Vasconcelos, admitted in an interview this month that this was a lesson that all researchers learned with the Zika: no infectious agent can be considered of little importance beforehand.

Another difficulty was how to report the history of those babies’ mothers. Daniele, the sister-in-law of that girl I met in the Barão de Lucena hospital, was the first to show off the difficulties. David’s mother, she told her routine in the first weeks she stayed at the hospital, until the diagnosis of microcephaly. She spent 20 days far from her older children, dealing with the unknown, a mix of outrage and happiness for having a new baby. After that period she went home. She noted her baby’s difficulties to sleep, the constant cry, quite different from her other children. Her love for her son increased, but also did the uncertainty about the future and, above all, about how the society would deal with him.

Few weeks after the declaration of national emergency, the waiting room of the pediatric infectious disease care at the Oswaldo Cruz Teaching Hospital was always crowded. To avoid curiosity, despite the intense heat of Pernambuco, the parents covered their son’s head with a cap and the daughter’s head with enormous ribbons.

Physicians showed signs of exhaustion because of the overload. Mothers left their homes still at dawn, sometimes in cars rented by the city halls, to take their children to be examined by physicians in Recife. Although crowded, rooms were filled with silence. Fear was evident. Parents and even the health professionals were not sure about what they were dealing with. And, above all, about the consequences to the babies. Would they get proper therapies? If the path before diagnosis was so long, how about the future path?

Three main discussions came about in the first months of increase in microcephaly cases. Birth control, abortion and, less prominently, the poor health situation in Brazil. This problem is associated not only with Zika, but with the other two Aedes aegypti-related diseases: dengue and chikungunya.

The uncertainty about the disease increased the anxiety of those planning to have a baby and of pregnant women. Could a woman with Zika transmit it to the fetus during pregnancy? If 80% of the cases of the disease are asymptomatic, how could the pregnant woman know if she was infected or not? No one knew the answers. One day after the declaration of emergency situation, I asked Mairéovitch his recommendation for the women. “Don’t get pregnant by now. This is the most rational advice”.

ZIKA VIRUS IN BRAZIL: THE SUS RESPONSE
The statement reinforced the debate about the limits between warning the population and the risk of panic, the disservice. By that moment, the causes of increased microcephaly cases in the region were obscure. To the critics this statement reinforced the disquieting feeling among pregnant women. Would the council’s concealment avoid this reaction? No one knows. The truth is that Maierovitch’s opinion could be an additional element to be considered by those wanting to get pregnant by that time. The more elements to subsidize the decision so the better. The more information about what physicians and sanitary authorities really knew by the moment and what they did not know, the better.

The debate about the right to abortion gained impetus in January when the anthropologist of the Anis Bioethics Institute announced that the entity would submit a proposal to the Federal Supreme Court (STF) to allow the interruption of pregnancy in the event of fetuses diagnosed with microcephaly. One of the arguments was that the Brazilian government was negligent when it did not eradicate the disease vector, the Aedes aegypti. Since the 1980s Brazil contends with problems caused by the mosquito. Over the last three decades successive dengue epidemics were recorded with at least 5,800 deaths. And although the campaigns have emphasized the relevance of the mosquito breeding sites such as plant pots, gutters, water tanks or tires, little was done to reduce the sites associated with lack of water supply and the irregular waste collection. In the Northeast in 2015, 82.5% of the mosquito breeding sites were found in water storage places. In that same year, garbage-associated hotspots were the most relevant in the North Region. The combat to both breeding sites goes far beyond the ‘cleaning’ recommended by the advertisement campaigns released every year by the federal government. They depend on investments in works to prevent shortage and in proper garbage collection systems. Actions under the government’s responsibility.

One year later, the core role played by welfare physicians was clear as regards the quick association between Zika and microcephaly, namely Ana, Vanessa and César in Pernambuco, the Federal University of Rio Grande do Norte’s Professor, Kleber Luz. Responsive, they quickly set out a network that used instant messaging applications to communicate.

Thanks to the physician Adriana Melo, from Campina Grande, the link between Zika and microcephaly was proved. With the agreement of two pregnant women and the support of the Municipal Health Department of Campina Grande, she collected samples from the fetuses, submitted the material for analysis at the Oswaldo Cruz Foundation in Rio. Few days later the babies’ contamination with Zika was confirmed. The straightforward logic took many by surprise. “I wanted to provide an explanation to my patients”, she said.

The devotion and confidence of professionals were crucial to the investigation. Adriana, for example, is supported by the Campina Grande Health Department up to now. Members of the Federal University of Rio de Janeiro and of the Federal University of São Paulo cooperated with some institutes, but there was no direct funding for research.

Doubts about microcephaly still abound. The connection with Zika was proved, but are there any other factors that could protect or increase the risk for babies to born with malformation? Why is the disease more severe in some children than in others?

Research networks were assembled with Brazilian professionals to clarify these doubts. The collaboration with other countries was intensified, but there is a long way to run, and quickly. However, after the kickoff the Brazilian surveys lost room to those carried out abroad. That was not because of shortage of capacity, but because of shortage of resources to the studies.

The knowledge gaps, challenges posed to care to patients – mostly from more disadvantaged social classes, of little educated mothers – remain. Some children have convulsive fits, difficulty in swallowing. Added with the lack of access to health care, many families do not even have the baby’s microcephaly confirmed. In November 2016, 30% of the notified
microcephaly cases remained undefined. It is still not clear if the problem exists and is effectively related to the infection with Zika.

The episode clearly demonstrated the professionals’ competence, made the difficulties faced to have access to health even more evident and, above all, the social inequalities. It unveils how the omission of government’s involvement left women and children even more exposed to the potential aggression of a mosquito and of a virus.
Communication as strategy

There was willingness to cope with the situation, providing visibility to the problem and transparency to information so we could prevent a crisis. But managers were also cautious, and delayed making this decision. And it was in this dialectical way that we dealt with an up-to-then unknown condition: the microcephaly attributed to the Zika virus.

The books *A Era do Escândalo – Lições, Relatos e Bastidores de Quem Viveu as Grandes Crises de Imagem* (Geração Editorial) by the journalist Mário Rosa, and *Gestão de Crises e Comunicação* (Atlas) by the journalist João José Forni are references that support the decision of disclosing a little known fact whose impacts on the society and media, nonetheless, are known through previous professional experiences.

And these authors and countless bibliographic references on crisis management and risk communication came to our minds in October 2015, soon after the Health Surveillance Department (SVS) of the Ministry of Health received the notification from the Pernambuco State Health Department (SES/PE) about a change of pattern in the occurrence of microcephaly. It was on October 22.

On that day, Wanderson Kleber de Oliveira, Head of the General Coordination of Surveillance and Response to Public Health Emergencies entered the SVS Communication Unit (Nucom) and convened a private meeting. Some technicians have also attended the meeting to analyze the data submitted by the SES/PE.

We were facing new facts on which we should work a lot in the forthcoming months.

It was a hard, serious and sensitive work. To the Nucom/SVS it started with the planning of strategic communication actions to approach the subject with media professionals, in an initiative aligned with the Communication Department (Ascom) of the Ministry of Health and, some time later, also in line with the Communications Department of the Presidency of the Republic (Secom/PR).

We were working on communication of risk to the society. The goal was to inform risks the best way as possible, in an objective way and without causing panic. On November 25, in Brasilia, a seminar gathered representatives of the communication departments of all State Health Departments to familiarize them with what could be the first chikungunya case in Brazil, according to the media report and a resident of Amapá, and the first case of Zika as informed by the media in Rio Grande do Norte.

The workshop held in Brasilia allowed the formulation of hypotheses, analysis of the regional media behavior – which was disclosing many cases of chikungunya and Zika in Brazil – and of the national media that said almost nothing about the subject, except for the *O Estado de S. Paulo* newspaper.

Only Cinthya Leite, reporter of the *Jornal do Commercio* newspaper of Pernambuco, published news and interviews about microcephaly cases in Recife, did not
identify the cause but raised assumptions. Cinthya was a pioneer in the debate about this issue.

On November 12, considering the increasing number of microcephaly cases, the Ministry of Health declared Public Health Emergency situation. On the day before, the O Estado de S. Paulo newspaper sent its health sector columnist Lígia Formenti to cover the subject. She was the first journalist of the national media to publish news about the likely relation between Zika and microcephaly, mentioning the name of babies and mothers that we knew just as statistics.

Cynthia and Lígia presented to us the history of Géssica, mother of João Guilherme who died, and of Conceição, mother of Catarina, and of Alessandra, mother of Samuel, and of the patient that science named ‘zero’: he is twin with other boy, but his twin brother was not affected by the Zika virus their mother acquired during pregnancy. The media showed us hundreds women who contracted the Zika during pregnancy and delivered children with microcephaly or central nervous system malformations.

Soon after, on November 28, the Evandro Chagas Institute (IEC), a body of the Ministry of Health, established the causal relation between the Zika virus and the cases of microcephaly when it analyzed tissues of a baby born with the disease and then died. The tissues were sent from Ceará for analysis.

This important finding was crucial to associate microcephaly and the Zika virus. It was supported by the results of the exam performed by Fiocruz/Rio which confirmed the presence of the Zika in the amniotic fluid of pregnant women in Paraíba, on November 17. We had strong elements to establish some link between the virus and microcephaly, and ethical reasons to bring this fact into light, communicating the risk to mitigate damages.

What should be communicated? How could we mitigate damage? What should we say to women and the population at large? Here started the search for the best message and the intensification of dialogue with managers to have the strategy implemented. The argument was straightforward: we will be demanded and must be prepared; if we have no message to the media and to the society, press will resort to other sources of information and we will lose room and opportunity.

The manifestations to the press started with formal notes and a ‘Questions and Answers’ published on the Ministry of Health portal. On December 1, the first press conference was organized, followed by many others, and a spokesperson was selected for this topic. The focus was defined: eliminate the mosquito breeding sites; protect mainly pregnant women and those in fertile age; wear clothes that cover most of the body; and, avoid areas with infestation of the Aedes aegypti mosquito that transmits dengue, chikungunya and Zika.

Still in November we started preparing a new campaign about the Aedes aegypti, warning about the Zika virus transmission. On December 13 the first TV campaign exclusively for pregnant women was aired.

Risk communication was outlined and information transparency was established. Through the SVS, the Ministry of Health became national and international reference on the issue. A journalist of the Nucom/SVS was assigned to work at the Situation Room set up in the same way as the Pan-American Health Organization (PAHO) room. The Nucom/SVS also started following the videoconferences with states organized by the National Coordination and Control Office to fight against the Aedes aegypti and its Consequences (SNCC) to share information. This was also done during the summer break.

The more the researchers from several institutions in Brazil and abroad and the technical areas of the Ministry of Health investigated and advanced the responses about the microcephaly epidemic in Brazil, the more the communication departments of all ministries, in Brasília, under the leadership of the Ministry of Health Ascom and in full interaction with the Secom/PR, could produce guidance to the society.

Other ministries – such as the Ministries of Education, Integration and Social Development, among others – were more deeply engaged in the strategies to combat the
mosquito that transmits the diseases. The Ascom quickly disseminated the information of each ministry, and worked on it, shared it and disseminated to the society.

There were dozens interviews about the combat to the *Aedes aegypti* and the fight against the Zika virus and microcephaly not only to the national media, but also to international correspondents and news agencies from several countries, mainly the United States, Canada, England and France.

The material was made available on the hotsite <www.combateaedes.saude.gov.br>, face-to-face interviews were held to answer the questions submitted by users, and the content was customized to be publicized on social networks. Moreover, the Ministry of Health technical area was available to respond requests for lectures and training courses.

The Health Ombudsman Office was prepared to answer the population’s questions by phone and electronic messages. WhatsApp groups were set up everyday, with different focuses, to service the areas of research, lab, communication, etc. Never so much has been done in such short time.

And all that was planned and carried out during the sharpest political crisis ever faced by Brazil since the military coup in 1964. The country was facing a likely impeachment of the President of the Republic – the second in 24 years. Because of that, the federal government negotiated with the political parties to expand its base of support, and ended up promoting changes in many ministries, including the Ministry of Health.

The minister who started the fight against the Zika virus, when the disease was still known as ‘benign’, made room to this successor who, missing managerial experience in Health, took office on October 6, 2015 and few days later faced the Zika and microcephaly epidemic. And he stood up well. Surrounded by a competent team of experts from different areas, including communication, he adopted impacting actions. When the impeachment was confirmed and the President of the Republic was ousted, the Ministry of Health again underwent changes that, nonetheless, did not damage the development of the actions defined to cope with the epidemic, and even rushed the adoption of new practices.

And what about the crisis we mentioned in the beginning of the text? It did not come true. We faced hard times, but no crisis. Crisis could be defined as the moment when the reputation of a person or institution is challenged. This did not happen. Throughout the process, the Ministry of Health served as a source of reference to the national and international media. Its spokesperson was always available to everyone, providing information and recommendations, and clearly talking about the little we knew every time findings came up.
It was a Friday early afternoon (October 23, 2015 to be more exact) when I saw on my cell the alert of a message from the Cities editor of the Jornal do Commercio, André Galvão, asking us to investigate something very sensitive. “Are you near the newsroom?” he asked. I said I would be there in 15 minutes. He briefly said that Flávia de Gusmão, another editor of Jornal do Commercio, had been informed that many babies were born in Pernambuco with microcephaly, and some physicians were instructed, on the WhatsApp, about the best way to notify the cases and investigate why many maternities in the state were observing an unusual increase in the number of newborns with heads shorter than the expected. Up to then, the only thing I knew about microcephaly was that it was a condition characterized by a change on the brain growth. Nothing else. I could not even imagine the damages this malformation could cause.

On that afternoon of October 23, 2015 the information provided by Flávia de Gusmão already linked the unexpected increase in the microcephaly cases and the hypothesis that during pregnancy mothers had been infected with dengue, chikungunya or Zika. I still remember that when I got to the newsroom I called the State Health Department (SES) to confirm (or not) the information. While I was waiting for their return call, I got in contact with the infantile neurologist Adélia Henriques Souza (a physician I had met due to previous articles about epilepsy). I remember how carefully she was when she provided me the information and the instructions to write the article. When talking about the change on the microcephaly occurrence pattern, she emphasized that, by that time, one could not relate the rising of cases and the infection with dengue, chikungunya and Zika during pregnancy. “The problem is that since early this year we are facing a dengue epidemic that coincides with the period of gestation of women who recently delivered babies with microcephaly. But it is too early to draw any conclusion, because we are only starting the work”, Adélia Henriques Souza said, and also informed about the investigations in other states like Rio Grande do Norte, where cases were also reported. And, to better understand the microcephaly observed by that time, I recall asking lots of questions to Adélia, always followed by the answer: “for us, up to now, it is nothing about a small head, although we know that microcephaly can also be caused by congenital infections associated with toxoplasmosis, German measles and the cytomegalovirus”.

During the interview, Adélia mentioned that the practitioner Carlos Brito would also be aware about the increased number of newborns with the disease. He was talking to some mothers of babies with microcephaly and, in the academic halls, suggested associating the increased cases and the Zika, as early as in October 2015. Before getting in touch with Carlos Brito I got the SES response that – in a note – confirmed to have been informed in October about the occurrence of cases of microcephaly in newborns in the state. “Supported by the teams of the concerned public and private health units, the SES is consolidating the information about these patients, including imaging exams of the newborns, blood samples of the mothers and general data of the

The careful view of journalism in health

Cinthya Leite
Journalist of the Jornal do Commercio Communication System. Master's Degree in Human Communication Health from the Federal University of Pernambuco
prenatal care. The SES is investigating all cases with the Ministry of Health to set strategies to explain the factors associated with this congenital alteration. The records of the National System of Live Births (SISNAC) show that, as of September this year, 20 occurrences of this event were notified, of which 70% in the months of August and September (partial data subject to updating). The records for the same period in the previous years were of 10 cases in 2013 and 12 in 2014”.

When I interviewed Carlos Brito I learned that, in addition to these figures, there was an extra-official scenario perceived in the last 15 days prior to our talk (i.e., in the first week of October) that had not yet been inputted in the SINASC. “In two weeks we observed 26 new cases of microcephaly in newborns. These data include only babies born in public maternities. Those born in private units are still to be included in the investigation” Carlos Brito, a member of the Committee on Arboviral Diseases of the Ministry of Health, said.

After checking, I talked to André Galvão and we decided we needed a clean page to announce this unprecedented fact in the world. That day I made a search using the key word "microcephaly" in the PubMed (US virtual medicine library that stores scientific articles from all over the world) and found just a few papers. And when I refined the search, crossing the key words ‘microcephaly’, ‘dengue’, ‘chikungunya’ and ‘Zika’, results were even fewer. This evidenced how new the connection between malformation and arboviral diseases was.

To write the article, I need some minutes to connect ideas, the respondents’ testimonials and the positioning of the state government. I was supported by Bianca Bion, a reporter of the Jornal do Commercio, to gather data on cases of dengue, chikungunya and Zika and, thus, set up an infographic to support the article edited by André Galvão and by the journalist Ciara Carvalho.

That day I left the newsroom around 10:30pm and went to bed with a feeling that this first article about the change on microcephaly occurrence pattern still needed many other efforts to explain what was really happening. It did not take too long for new articles to be published. On the blog Casa Saudável of the NE10 (portal of the Jornal do Commercio Communication System), where I am the editor, few days after the publication of the article on Jornal do Commercio and on the blog, families experiencing uncertainties after the birth of babies with microcephaly started posting comments. This encouraged me to advance the investigations.

On the 27th, the Casa Saudável announced beforehand that the Ministry of Health had already sent a team to Pernambuco to investigate and actively search for cases. On the same day the JC advertised the set up of the Thematic Chamber of Microcephaly at the Pernambuco Regional Council of Medicine (Cremepe), under the leadership of Carlos Brito.

I remember a calm All Soul’s Day when I was on duty at the newsroom, and decided to intensively search articles about microcephaly on the internet. This subject was always coming into my mind since October 23. After intensive search, I had the flash of an idea that the Center of Strategic Health Inspection Center of Pernambuco (Cievs/PE) website could have some information about it. And there I found the information that from August to October 2015, 90 microcephaly cases were reported in Pernambuco (ten times more than the average registered between 2011 and 2014 in that state). Because of that, the SES established the prompt compulsory notification of malformations. This scenario was the topic of a new article published on Jornal do Commercio on November 4, 2015. There I told the history of a mother who had just delivered a girl with microcephaly. The suspicion of microcephaly appeared during the ultrasound in the 22nd week of gestation. Just like many other mothers facing the same situation, she was scared with so few responses to so much doubts and fears.

This feeling of insecurity that took the families, researchers and health authorities made me go to the Oswaldo Cruz Teaching Hospital (HUOC) in the district of Santo Amaro, central area of Recife, on November 10, 2015. There I met the pediatricians specialized in infectious diseases, Regina Coeli Ramos and Angela
Rocha. By that time, the HUOC Pediatric Infectious Disease outpatient care service was receiving from six to 10 newborns a day with suspected microcephaly. “We are committed to carefully investigate the likely causes of the change on the microcephaly occurrence pattern in the state. The imaging exams of the babies monitored show lesions that do not match the patterns of genetic microcephaly. We found calcifications on the brain of these children, suggesting an anomaly of infectious nature”, Regina Coeli explained in the article published on November 11 on the Jornal do Commercio.

In the afternoon of that day, the then minister of health, Marcelo Castro, convened a press conference in Brasilia to declare Public Health Emergency because of that situation. “We are analyzing all hypotheses”, the minister said. By that time, representatives of the Ministry of Health said it was too early to attribute the event to the Zika virus, which had been confirmed in 14 Brazilian states since April 2015.

The point is that only in Pernambuco nearly 80% of the 110 thousand records of dengue notified until November 2015 were estimated to be (in fact) cases of Zika, since the notification for this last arboviral disease was not mandatory in the state by that time. The four cases confirmed in Pernambuco in June 2015 were evidenced by the Evandro Chagas Institute (IEC) which is a national reference lab in Belém do Pará. “As there is no national protocol specific to the surveillance and therapy of the Zika virus in Brazil, our instruction to the physicians is to keep on notifying the suspected cases as dengue”, the SES informed in a press release on June 22, 2015.

In all of our interviews about the rising numbers of microcephaly cases, Carlos Brito always made clear that Pernambuco had a Zika epidemic in the first half of 2015 that peaked in March. “We performed a hospital-based study in Pernambuco that comprised 1.1 thousand patients who received care in the first five months this year in the emergency room of a private hospital in Recife. Of these, 81% met the clinical criteria for Zika. Most of the women who delivered a baby with microcephaly, mainly in October 2015, reported many of those symptoms in the first quarter of gestation, which coincides with the epidemic of Zika – a virus that mainly attacks the central nervous system. This was the new agent we were observing for this rising number of cases”, Carlos Brito said in an interview published on the Jornal do Commercio on November 29, 2015, one day after the Ministry of Health confirmed the relation between the Zika virus and microcephaly. He emphasized the need by that time to increasingly understand the virus behaviors and complications. “I’m absolutely sure we are now opening a new chapter in the history of medicine”.

In fact, this scenario launched the Zika age in sciences. This brought about several questions to physicians, researchers, journalists and families of children with microcephaly, mainly because the world had never recorded in such a short time thousands newborns with a congenital malformation that still challenges science. In the article dated November 24, 2016, one year after the Jornal do Commercio firstly publicized the rising number of microcephaly cases associated with the Zika virus, the housewife Raphaella Oliveira dos Santos, 21 years old, mother of Luiz Felipe (1 year old) who was born with microcephaly stated: “Sometimes I just don’t know how to answer many questions”.

She is not the only one. And questions are not limited to the families of children impacted by a virus that used to be known as cousin of dengue, which caused nothing but a mild viral disease including where it had already left traces. Even the experts that warned the health authorities one year before still have some uncertainties. “We now ask: which complications can we expect in the future? Some babies are moving towards hydrocephaly, for example. And more: why between twins, sometimes one child is affected and the other not? Would there be any factor in the individual that makes him/her resistant to the infection with Zika? We still miss answers to these kinds of questions”, the neuropediatrician Ana Van der Linden emphasized in that article of October 24, 2016. She was one of the first physicians to warn about the above-average births of babies with microcephaly.

It is worth mentioning that, over little more than a year, the families were hit by a huge volume of information
about a condition that has deeply shaken the society. On one hand, physicians witnessed the emergence of an unprecedented problem in the world, and even felt powerless due to the limitations imposed by a virus that causes different degrees of brain lesion. On the other hand, mothers accumulated anxiety thanks to the challenge of taking care of a baby whose malformation challenges the public health. Concurrently with this scenario the families of babies with microcephaly got together to find answers to the questions and feelings that raise more suffering and uncertainties. Hands in hands, fathers and mothers became strong in to take care of the development of their children who bear the consequences of a virus capable of putting the world in state of alert. And as the families member of the União de Mães de Anjos (UMA) – an entity that provides support to children born with the congenital malformation in Pernambuco – use to say “microcephaly is not the end”. This motto brings us some hope about the future.
Strategy building
Managers: Meeting of the inter-ministerial microcephaly group, 12/04/2015
Photo by: Rondon Vellozo/M5
Management, coordination and mobilization

NATIONAL CONTEXT

In the last 12 months Brazil has increasingly lived (and still lives) troubled, uncertain and conflicting moments in both political and economic scenarios, with deep and distressing social results to the society as a whole, which culminated in an impeachment suit against the President of the Republic. Amidst this turbulence, Brazil experienced a severe public health situation, represented by the emergence and quick spread of a new virus with different consequences. This unexpected situation deserved declarations of Public Health Emergency of National and International Concern, declared by the Brazilian government and the World Health Organization (WHO), respectively. These declarations resulted from the severe epidemic that arose in Brazil and soon became a threat in many countries all over the world, represented by the Zika virus and the severe anomalies it causes, notably the microcephaly.

Therefore, this alarming picture encouraged and challenged authorities and researchers to promptly adopt some measures and seek new knowledge to subsidize the definition of a robust coping strategy. In Brazil, it enabled the deployment and implementation of a response plan in which the research agenda plays a core role, and little importance is attached to management/coordination.

This has quickly and significantly expanded the scientific production with countless important and enlightening papers that gave rise to a wide range of new information, although many aspects remain unknown. This encourages other studies mainly related to epidemiology and clinics, medications and immunobiologics, demanding quick development and technological innovation.

In this context, the increasingly relevant studies and different types of investigation and research resulted in scientific papers published on the most notorious specialized magazines and journals, mainly because it was a new microorganism in the country with severe implications for pregnant women and children.

A general survey and bibliographic review found in the PubMed database, as of June 15, 2016, about 830 articles (686 only in 2016), in some national and international journals considered to be the most important, crowded and hard to have a paper accepted for publication. While in 2014 we found 17 articles and 42 articles in 2015 on this topic, in 2016 (as of September) we found 1,277 publications, i.e., an average of 270 papers published a week.

However the focus of those papers in the epidemiological field, clinical field, diagnosis field and therapy seems to be weakly or absolutely not related to the measures of coordination, mobilization and/or management. This chapter describes the main strategies of management, coordination and mobilization (political and social) adopted by Brazil in this scenario. Moreover, it discusses the relevance of some of these actions as core components for the coping and success to overcome the Zika and microcephaly epidemic in Brazil. These actions are also required and crucial to cope with any Public Health Emergency of National Concern.
First of all, it is worth emphasizing the benchmarks that should ground the responses: health care integrality and the intersectoral nature of the actions, making decisions that consider the innovative aspects of implementation and the development of initiatives, as well as that systematize the many findings, strategies and lessons learned so these serve as grounds and contribution to other countries coping with similar threats.

Finally, another seemly simple fact, but extremely symbolic in mobilization terms, deserves special attention. The *National Plan to Fight Microcephaly* with its three development axes was quickly renamed to and became (properly) known as National Plan to Fight the *Aedes aegypti* and its consequences, which assigned core and guiding role to the axis of coordination/mobilization/management aimed at broad social participation.

**ANOTHER TIMELINE: THAT OF MANAGEMENT/MOBILIZATION**

Several parameters and/or dimensions could serve as baseline to define a timeline. Even this book is likely to present different timelines, but I would like to emphasize ‘another’ timeline, due to its special parameter. It is the mobilization/management timeline crucial to the success of any process aimed at coping with public health threats anywhere in the world, whose importance is increasingly recognized but that remains ‘hidden’ in most sets of scientific publications.

**YEAR OF 2015**

**1/27**
Launching of the pre-campaign Zero Zika at the Education network – 1 million managers and teachers of the *TV Escola* network and 1.6 million managers and teachers of the basic education network engaged in actions to combat the mosquito.

**1/27**
Broadcasting of the radio soap opera about the combat to the mosquito, focusing the low-income population.

**1/29**
Visit of the President of the Republic to the National Coordination and Control Office.

**1/29**
Beginning of the mobilization of the federal government bodies and companies towards preventing and eliminating the mosquito developing sites.

**2/3**
Coordination with the National Health Council and State Health Councils to mobilize the civil society.

**2/4**
Meeting with managers of the Unified Health System (SUS) Network to prepare the activities to be developed by the municipalities on the National Mobilization Days (Saturday of Cleaning) and to eliminate the *Aedes* breeding sites at health units (hospitals, UPA, UBS, etc.).

**2/13**
Mobilization of 220 thousand troops to instruct about how to combat the mosquito in 428 municipalities, with the participation of federal government authorities, including the President of the Republic, in educational activities and visits to homes to check and eliminate mosquito developing sites. On that day, information materials were distributed to the population, and 2.8 million properties were visited. The action was fully supported by local governments, with great synergy among the federal, state and municipal Armed Forces.

**2/15 to 2/18**
Task force with 50 thousand troops and teams of community agents of combat to endemics (ACE) and community health agents (ACS) to eliminate mosquito developing sites in priority municipalities (115 with highest incidence of dengue + capitals)

**2/15 to 3/4**
Journeys to mobilize high school students, daycare and pre-school and extension pro-rectors (3 cycles).
2/19
Z Day in Education – mobilization at schools, supported by the Armed Forces, and mobilization activities with vulnerable communities developed by the 7,300 Reference and Social Assistance Centers (CRAS) and 2,300 Specialized Social Assistance Centers (CREAS). Recorded as the largest mobilization of the Brazilian education under the coordination of the Ministry of Education, the action counted on the participation of 11.3 thousand schools all over the country, mobilizing 4.2 million students and 198 thousand education professionals.

3/11
Mobilization Day to Combat the Aedes aegypti in federal public buildings, reinforcing the society’s attention, mainly of federal civil servants, in the combat to the mosquito and ensuring that all federal civil servants, service providers and contractors are informed and permanently engaged in the elimination of breeding sites. This action trained 9.4 thousand civil servants, and 6.3 thousand inspections were performed in public buildings of 223 municipalities.

3/16
Health Command on highways – action planned by the Ministry of Justice and developed by the Federal Highway Patrol to provide professional drivers with health care information. In that year the action provided guidance on the need to reinforce prevention and expand professional drivers’ awareness to prevent the proliferation of the Aedes aegypti and the diseases it transmits. With an educational focus, the action informed and explained to drivers how they can prevent the accumulation of still waters in vehicles, thus eliminating all potential breeding sites for the Aedes.

4/4 to 4/9
Family’s and Community’s Mobilization at School to Combat the Aedes aegypti and the Zika, coordinated by the Ministry of Education in partnership with the Ministry of Health. The action was developed considering that the debate at school can include the political dimension and the perspective of seeking solutions to situations such as the combat to the Aedes, basic care to avoid mosquito developing sites in residences, public spaces and urban areas, as well as foster the adoption of behaviors to promote healthy environments. This was a far-reaching action attended by 16.1 thousand schools, 262.1 thousand teachers and 5.8 million students.

These are some of the episodes and initiatives at national level that have enabled thousands other initiatives at local and/or regional level. They were crucial to increase awareness about the epidemic severity and to understand that coping with it demands moving away from the traditional view of only promoting “campaigns” towards building a complex, permanent, continued and intensive process.

In my view, although the formalization/standardization/officialization is important and necessary, efficient coordination and mobilizations are neither achieved nor promoted by decree. Rather, to be successful they need a set of different strategies, sometimes of complex and giant dimensions like some of the aforementioned examples. However, most of the times they are simple and easy to carry out, like the weekly and coordinated ‘alignment meetings’ that bring together the different sectors involved and promote several common tasks such as data and measures communication, and the production of clear information to be provided to different groups of strategic partners.

In line with this view, several internal forums were organized, but one stands out for its simplicity and broad dialogue: the “weekly alignment meeting of the Executive Department/Ministry of Health”. In those meetings the different areas of the MoH and the multiple aspects (from surveillance, care, research and training until communication) were dynamically coordinated, integrated and monitored, gradually reinforcing the replication of information and mobilizations in and between institutions and sectors. All these brought about new initiatives and optimized resources, time and work.

Following are some flowcharts and diagrams on some of the main initiatives and measures developed in the dimension of Management/Coordination/Mobilization in the National Plan to Combat the Aedes aegypti and its Consequences:
COORDINATION AND DEBATE FORUMS

Meetings convened by the Presidential Staff
- Inter-ministerial coordination to respond the crisis
- Focus on federal actions to fight the virus

Convened by others Ministries (e.g., MI, MEC)

Meetings convened by the SE/MS
- Inter-ministerial (e.g., MEC, MDS) and inter-sectoral (e.g., BB, CEF) coordination and outcomes of the actions at inter-ministerial level
- Ensure the operation of decisions made at the existing forums
- Make decisions and streamline the pending decisions in the different areas of the ministry

SVS Meetings (focus on Combat)
SAS Meetings (focus on CerA)
SCTIE Meetings (focus on R&D)
Other departments of the MoH (e.g., SGEP, ASCOM)

SNCC Meetings
- Focus on combat to the Aedes
- Inter-ministerial and inter-federative coordination under the leadership of the MoH and integration of the CC

COES
- Focus on all actions related to the Aedes
- Intra-ministerial coordination under the leadership of the SVS/MS
- Role of the scientific intelligence in the effort against the virus
COORDINATION AND MANAGEMENT STRATEGY TO COMBAT THE ZIKA AND MICROCEPHALY

1. Governance
   - Strategic objectives
   - Response coordination
   - Strategic planning budget

2. Combat
   - Visitation strategy
   - Inputs management to combat the carrier
   - Society’s participation

3. Care and Welcoming
   - Prevention
   - Diagnosis
   - Therapy
   - Welcoming families

4. Science, Technology and Innovation
   - Understand the pathology
   - Alignment of the efforts by (inter)national R&D institutes
   - Evaluation, engagement and organization of (inter)national events
   - Facilitate access to international funding sources

5. Control and monitoring
   - Monitoring of indicators
   - Dissemination of reports and records
   - Processes of data collection and analysis

6. Communication
   - Events calendar; daily press services; agenda of press conferences; dissemination of reports

7. Partnerships
   - Programme of collaboration with international bodies (WHO/PAHO) and other affected countries
   - Partnerships with private sector entities

COORDINATION/ENGAGEMENT OF GOVERNMENT AND POPULATION

- Government
  - Institutions and Associations of Community Leaders
  - Community Leaders
    - Population
COORDINATION / MOBILIZATION OF FEDERAL STATE-OWNED COMPANIES

Considering the huge potential of mobilization and repercussion of actions, mainly those aimed at dissemination and education, special attention was attached to the mobilization and coordination of the Federal State-owned Companies, firstly in a broad meeting held on 01/22/2016 to introduce the national, epidemiological and political/social context. In this meeting, the severity of this threat to national and global public health was strongly emphasized and the potential engagement of the many Brazilian state-owned companies was discussed. In this aspect, the Ministry of Health has also disclosed the real and serious situation of microcephaly, as well as the existing actions: establishment of the National Coordination and Control Office at the Cenad/MI and State Offices in all Brazilian states, in addition to hundreds Municipal Coordination and Control Offices; coordination with the Ministry of Education and Ministry of Tourism; active participation of many other ministries such as those of Integration, Education, Labor and Social Development, among others.

Based on the reports and on the debates held that brought about countless proposals of actions to be developed in each company, as well as on the consolidation of the suggestions defined, each company outlined a specific action plan comprising actions of mobilization and combat to the Aedes aegypti focusing on the following axes:

- Social Mobilization
- Communication
- Information
- Education
- Prevention
- Technologies
- Integration (with other state-owned companies, bodies and institutions).

Coordinated by the Ministry of Planning, Ministry of Health and the Presidential Staff, in one week most of the state-owned companies had prepared their proposals and e-mailed them to the Ministry of Planning, Budget and Management (MPGO), identifying the target audience (quantitative and qualitative); activities time schedule (short-term until February/2016, medium-term until May/2016 and long term from May/2016 on); definition of the venue and the officer in charge of each action. This helped us to quickly organize and align a set of measures to be developed. Some of these are listed below:
<table>
<thead>
<tr>
<th>Company</th>
<th>Suggestions / Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infraero</td>
<td>Many actions, including: banner on the website, integration with bodies (MoH, Ceará state, Brazilian Association of Airlines – Abear), intervention/mobilization at airports, actions among employees and users. Presents the achievements.</td>
</tr>
<tr>
<td>Banco do Brasil</td>
<td>Coordinated with the MoH and sent the content to be disseminated in its branches all over the country; it will adhere to the State Coordination and Control Offices, but needs the MoH Advisory. Makes the Banco do Brasil Foundation available for cooperation and dissemination.</td>
</tr>
<tr>
<td>Caixa Econômica Federal</td>
<td>Suggests immediate and far-reaching actions such as: provide information on the bank statements, social networks, banner on its website, at the Agência Caixa de Notícias, on the launching of developments under the “Minha casa, minha vida” housing programme. Provide guidance to employees through the newsletter available at the intranet, text messaging, wallpaper of computers, internal mail marketing, internal health programmes. Actions with sponsored events (Carnival, Soccer, Street Races, etc.). Movies on Caixa theater and movie rooms. It also needs the MoH advisory and support to become a member of the State Coordination and Control Offices.</td>
</tr>
<tr>
<td>BNDES</td>
<td>Said to be able to develop actions with about 2 million corporations, sponsorship of sports, and increase research funding.</td>
</tr>
<tr>
<td>EBC</td>
<td>Suggested to set up a mail and a WhatsApp group. It works on state and public communication. (Production and broadcasting of interview and general and/or specific releases)</td>
</tr>
<tr>
<td>EBSERH</td>
<td>Since November 2015 it develops actions on the following axes: knowledge promotion (research lines) and actions on prevention, care, education, technological incorporation and capillarity (37 hospitals). It standardized the service protocols. It participates in the MoH’s Coes.</td>
</tr>
<tr>
<td>Biomanguinhos</td>
<td>It works on the development of a diagnosis kit to the three diseases, and participates in the development of vaccines (long term). It emphasized the need for mass and strong communication but not ‘starling’ information.</td>
</tr>
<tr>
<td>Correios</td>
<td>It can develop actions among its nearly 120 thousand employees and their family members (directly reaching about 500 thousand individuals). Use the offices and units to disseminate information to clients. It can deliver information at the residences. (Training mailmen to identify sites of risk).</td>
</tr>
<tr>
<td>Eletrobras</td>
<td>It suggested using social networks and empowering employees. It asked access to the network of professionals who could come to the companies to inform employees that would then replicate the information to the society. The company could perform more comprehensive actions involving the riparian populations. Dissemination of information and messages on the electricity bill. The Ministry of Mines and Energy will try to engage the private energy companies/SPE.</td>
</tr>
<tr>
<td>HCPA</td>
<td>It suggested the creation of a logo/seal of “partner company in the fight against the mosquito”. It believes this could contribute to mobilize the society and facilitate the dissemination of information.</td>
</tr>
<tr>
<td>Hemobrás</td>
<td>It suggested two focuses of action: mobilization and prevention among direct and indirect employees, and development of engagement actions to encourage changes of attitudes. It suggested that companies should work together in local events.</td>
</tr>
<tr>
<td>Embrapa</td>
<td>It suggested that companies could mobilize their maintenance teams and work jointly with the internal and external communication areas, as well as with partners and personal actions.</td>
</tr>
</tbody>
</table>
Therefore, hundreds new initiatives and strategies started being developed and spread in the Brazilian regions and states. This greatly contributed to consolidate an intersectoral planning and work of great visibility, encouraging many other business organizations to schedule specific actions and be attentive and committed to the replication of information and sector-specific and local mobilizations. Many of such mobilizations could follow national mobilizations, but with a large set of initiatives by their own, including possibility/opportunity to develop medium and long-term sustainable health practices.

**FINAL REMARKS**

Without attempting to exhaustively discuss this subject/consideration about the relevant role of management/coordination/mobilization in situations of public health emergency, we should highlight the core role played by communication both in the epidemiological-welfare sense and (mainly) in the aspect of political and social mobilization and coordination. And, although each institution had their own communication department, all of which extremely individualized and fragmented in the action, it was the determination of the MoH management/coordination with the Communication Department of the Presidency of the Republic (Secom/PR) and many sector-specific ASCOMS that enabled more collaborative and agile action on information/cooperation.

Moreover, in a governmental effort that provided important support to the recording and dissemination of our strategies, an external consultancy sponsored by the Presidential Staff and carried out by the McKinsey & Company/Brazil, coordinated by the Executive Department/MoH, has largely contributed to the production of different instruments and forums of debate and coordination/integration. These were further organized and consolidated in a paper called *Estratégia de resposta ao vírus Zika e o combate ao mosquito transmissor* (http://www.casacivil.gov.br/arquivos/estrategia-de-resposta-ao-virus-zika.pdf). This brief document has surely expanded the visibility of our efforts and achievements, and also served as reference to other coping initiatives in other countries also affected by the presence of the *Aedes aegypti* and the spread of the Zika virus.

In the same line, the United States Agency for International Development (USAID) launched a challenge to gather innovative ideas to combat the Zika, boosting the Open IDEO platform – an amazing space and opportunity for Brazil to participate in international debates (http://us2.campaign-archive2.com/?u=ea27d4a8fa8ca350b13e5fa43&aid=b490f8d40c&e=399d660508), what is still quite unusual for most countries in times of emergency of international concern.
Dengue is the viral mosquito-borne disease most widely spread in the world. In the last 50 years the incidence raised 30-fold due to the increased geographic expansion to new countries and, in this decade, from urban to rural areas. It is estimated that 50 million infections with dengue occur a year and almost 2.5 billion individuals live in countries endemic of dengue (WHO, © 2016).

Brazil has recorded dengue cases since 1986, with severe cases and death from the disease.

The fast-paced urbanization of Brazil precluded suitable basic sanitation structures that, added to the increasing traffic of people and cargo, made up the perfect set to maintain and spread the *Aedes aegypti* all over the Brazilian territory (MENDONÇA; SOUZA; DUTRA, 2009).

This evidence reinforces the fact that the Health sector alone cannot solve the complexity of factors that favor the vector proliferation and, thus, the spread of diseases it transmits: dengue, chikungunya and Zika.

All national efforts to control the *Aedes aegypti* since the 1990s (FUNASA, 1996; 2001) focus on the need for intersectoral effort to cope with the vector, considering the vector control as a collective responsibility. More recently the Ministry of Health reinforced this principle (FUNASA, 2002; BRASIL, 2009).

The Pan-American Health Organization (PAHO), in the paper called “Prevention and Control of Dengue in the Americas: integrated focus and lessons learned” (CONFERÊNCIA SANITÁRIA PANAMERICANA, 2007) highlights the need to organize and structure the countries’ dengue control programmes focused on integrated management of the many relevant components (COELHO, 2008).

Despite the efforts by the three SUS spheres to keep low vector infection indexes, Brazil suffers with the high dengue load in the last few years and with the introduction of chikungunya in 2014 and Zika virus fever in 2015.

In October 2015 was detected a change on the microcephaly occurrence pattern in the country (BRASIL, 2015a); in November that year, the Public Health Emergency of National Concern (PHENC) was declared (BRASIL, 2015b).

The further confirmation of the relation between Zika virus and the outbreak of microcephaly caused the Inter-ministerial Executive Group of Public Health Emergencies of National and International Concern (GEI-ESPIII) to outline a National Plan to Combat Microcephaly (PNEM), currently known as National Plan to Combat the *Aedes* and its consequences. This is a three-front plan: Axis 1 – “Mobilization and Combat against the mosquito”; Axis 2 – “Health Care and Assistance to People”; and, Axis 3 – “Technological Development, Education and Research”.

The National Coordination and Control Office (SNCC) was set up to plan and execute the actions scheduled in Axis 1. The office is coordinated by the Ministry of Health and
also made up by the Ministries of Integration, Defense, Social and Land Development, Education, the Presidential Staff and the Government Department of the Presidency of the Republic, in addition to other guest organizations.

The SNCC main principle is to strengthen the policy based on intersectoral efforts, aiming to minimize the impact of diseases transmitted by the *Aedes aegypti* on the population, through direct actions of the federal government and the mobilization of states and municipalities to set up local offices. The SNCC became operational in December 2015.

Four guidelines were outlined for the SNCC actions:

- General Guideline that defined the Coordination and Control System, the structure, duties and work of the Coordination and Control Office at the three governmental levels, and the relationship among them (BRASIL, 2015c).

- SNCC Guideline # 1 – Actions to Combat the *Aedes aegypti* with instructions for states and municipalities to strengthen actions to combat the *Aedes aegypti* mosquito during the PHENC (BRASIL, 2015d).

- SNCC Guideline # 2 – Armed Forces’ Support providing for the Armed Forces’ work with municipalities (BRASIL, 2015e).

- SNCC Guideline # 3 – Basic Sanitation, aimed to promote permanent and emergency basic sanitation actions that contribute to eliminate the *Aedes aegypti* breeding sites (BRASIL, 2015f).

After setting forth the aforementioned guidelines, the SNCC put in practice several activities, always considering the specificities of each Ministry that makes it up.

The political support of the Presidential Staff and the Government Department of the Presidency of the Republic played a core role in the setting up of the State Coordination ad Control Offices (SECC). Late in January 2016 all the SECC were operational and integrated to the SNCC.

With its expertise in emergency situations, the Ministry of Integration assisted the organization of actions planning, and contributed granting the physical infrastructure, thus enabling several weekly videoconferences with the SECC to enhance mobilization and integrate actions, and also optimize time and reduce eventual expenses with displacement to states and municipalities.

The Ministry of Health agreed to intensify the number of visits to all urban properties and public infrastructures to provide guidance in health to the population, inspect potential breeding sites and treat containers that cannot be mechanically eliminated by endemic control agents (ACE). In March and April 2016, period of more intensive circulation of dengue, chikungunya and Zika in Brazil, the interval between home visits was shortened from bimonthly to monthly. Moreover, in the first four months of the year the entomological surveys performed by municipalities were suspended, and focus was on the elimination of breeding sites and consequent reduction of infestation indexes.

The Ministry of Defense strongly performed in actions aimed to mobilize the population, notably a great effort on February 13, with the participation of about 220 thousand troops in municipalities with highest incidence of the disease. The troops have also worked in other municipalities, in partnership with the Health professionals, from January to June 2016, visiting properties to combat the vector proliferation sites, and performing activities in health education.

The Ministry of Education promoted important actions such as the “National Day of Education Mobilization”, early in the academic year, broadly mobilizing the Brazilian education institutions from elementary school to higher education to raise the school community’s awareness about the importance of eliminating the mosquito breeding sites and preventing related diseases.
On February 4, 2016 the Ministry of Education celebrated the Brazilian Education Act against the Zika with 20 entities to urge 60 million individuals directly related to school education such as students, teachers and supporting staff, to engage in the fight against the proliferation of the Aedes aegypti vector; develop a culture of health promotion, respect to environment and prevention; production of knowledge through research and innovation; and, specialized care and monitoring of affected people seeking medical care in teaching hospitals.

The SNCC monitored and followed up the national action with the school network, held on February 19. The action included visits of federal authorities and state and municipal education secretaries, school managers, rectors, teachers and technical-administrative staff from federal universities and leaders of public and private education entities. Altogether, the mobilization reached 188,673 Basic Education (97.1%) schools; 63 federal universities – 341 university campuses (100%); 40 Federal Higher Education Institutes and Federal Centers of Technological Training – 532 campuses (95.2%) (BRASIL, 2016a).

The Ministry of Social and Agrarian Development works in partnership with the Ministry of Health in the care and assistance to families, mainly to mothers and children with microcephaly. In March the Interministerial Ordinance MS/MDS 405 (BRASIL, 2016b) was issued. It established the Strategy of Quick Action to Strengthen Health Care and Social Protection to Children with Microcephaly in the scope of the Unified Health System (SUS) and the Unified Social Assistance System (SUAS). This ordinance, like other regulations and operational instructions jointly prepared by both areas, aims to hasten the active search and diagnosis of the disease, and the provision of health care and the Social Assistance Continued Allowance (BPC) for children that fit the eligibility criteria (BRAZIL, 2016b).

In addition to the Ministries that make up the SNCC, the following cross-sector partnerships are crucial: Funasa, Ministry of Transports, Ministry of Cities, Ministry of Environment, Banco do Brasil, Caixa Econômica Federal, Correios, Eletrobrás, UNICEF, PAHO, the Red Cross, Reciclanip, Federal Highway Patrol, among others.

In order to expand the actions to eliminate solid residues with high likelihood to serve as breeding site to the Aedes aegypti mosquito, the Ministry of Environment and the Reciclanip (programme to collect and dispose unserviceable tires of the National Association of Pneumatics Industry – ANIP) coordinated a “National Mobilization of Tire Collection” in many Brazilian states.

The SNCC and the SECC worked to set up Municipal Coordination and Control Offices (SMCC). The implementation of these offices/committees effectively contributes to intensify actions aimed to combat the vector, to the population’s mobilization and to strengthen the intersectoral work at local level.

All that effort resulted in the set up of 1,796 Municipal Coordination and Control Departments distributed as follows:

- 106 SMCC in the North Region.
- 237 SMCC in the Northeast Region.
- 721 SMCC in the Southeast Region.
- 476 SMCC in the South Region.
- 256 SMCC in the Mid-West Region.

Moreover, the government of the Federal District and of Goiás set up an interstate department to develop, in collaboration, actions to fight the Aedes aegypti at municipalities in the vicinities of Brasília. A Binational department that works between the municipality of Tabatinga, in the state of Amazonas, and Letícia, in Colombia, has also been established.

As of October 28, 2016, 274,333,376 visits were made to properties to identify and eliminate the mosquito developing sites, provide mechanical or chemical treatment to breeding sites, and instruct the population about the ways to combat the Aedes aegypti mosquito.
Visits resulted in 230,198,650 (83.91%) properties inspected or worked on.

Another comprehensive action developed in partnership between the Ministry of Education and the Ministry of Health was the Week of Family and Community Mobilization at School to fight the Aedes aegypti, from April 4 to 9, 2016. The action mobilized the 32 thousand Basic Health teams of Brazil to enhance the actions developed by the Health at School Programme, and involved more than 77 thousand schools (39.6%) in 4,787 municipalities.

The efforts shortened the duration of the dengue cases notification peak in comparison to the years of 2015 and 2014. Although 2016 started with higher number of cases than the previous years, after the set up of municipal and state departments (Epidemiological Week – SE 4: 1/24 to 1/30/2016) the number of weeks of the disease peak (six weeks) was reduced. The SE 4 enabled enhancing the control actions, and 584,361 likely dengue cases were recorded, a 22.2% reduction of cases against the peak in 2015 that lasted eight weeks and recorded 751,558 potential cases.

The aforementioned clearly shows the need to work to fight the Aedes aegypti and its consequence, sustaining a state policy that engages different sectors of the society, strengthening collective responsibility and institutionalizing initiatives taken during the emergency, ensuring the sustainability and expansion of those actions.

REFERENCES


Scientific investigation
Organization of the Lab Networks LAB: Fiocruz
Photo by: Vinicius Marinho
Fiocruz’s role in the fight

By mid-October 2014, an outbreak of exanthematous disease of unknown origin was observed in Rio Grande do Norte, followed by other cities in the Northeast region of Brazil. The symptoms associated with the skin rash were mild or low fever, arthralgia, member edema, maculopapular rash for four to seven days, with no critical evolution (EDITORIAL..., 2016). These symptoms and transmission dynamic led experts to suggest a likely epidemic of arboviral infection to be investigated. In May 2015 the Zika virus (ZIKV) was identified in lab by RT-PCR as the etiological agent of the epidemic in the Northeast of Brazil (CAMPOS; BANDEIRA; SARDI, 2015).

Nearly one year after the outbreak emergence a significant increase in the number of microcephaly cases was observed in the states of Pernambuco and Paraiba. The cases coincided with the arisal of the same symptoms of the exanthematous outbreak caused by ZIKV. The state of Pernambuco was the first one to note that the increased number of microcephaly cases could be related with the congenital infection with ZIKV.

On November 12, 2016 the Brazilian government, through the Ministry of Health (MoH) declared Public Health Emergency of National Concern (PHENC) (BRASIL, 2015) because of the increase – yet to be investigated – in the number of microcephaly cases in babies, mainly in the Northeast region. Likewise, after the notification of ZIKV epidemic in 24 countries, the gradual increase on the number of microcephaly cases and other central nervous disorders in newborns and adults, such as the Guillain-Barré syndrome in Brazil, the World Health Organization (WHO) declared Health Emergency of International Concern on February 1, 2016 (WHO, ©2016).

After the declarations of national and international emergencies, the global scientific community mobilized to understand the ZIKV-caused epidemic and its effects.

Since the first reports of the epidemic in Paraiba, the Oswaldo Cruz Foundation (Fiocruz) has actively worked on the topic through its scientific technical staff in different areas, mainly health care, health surveillance and the sentinel labs. Fiocruz was the one to affirm, based on the molecular diagnosis performed by the regional sentinel lab of the Carlos Chagas Institute, Fiocruz Paraná, that the exanthematous outbreak in the Brazilian Northeast, more specifically in Rio Grande do Norte in May 2015, was caused by ZIKV. Evidence came about when results were confirmed by the Evandro Chagas Institute (IEC), a national reference lab in the disease.

This was the starting point to the mobilization of several experts and collaborators of Fiocruz to understand the epidemic. One week before the declaration of PHENC, Fiocruz had already promoted the seminar Vigilância em Saúde das Doenças Virais Chikungunya, Zika e Dengue: desafios para o controle e a atenção à saúde (FIOCRUZ, 2015a). The seminar aimed to mobilize experts and the society to expand and strengthen knowledge about the triple epidemics (dengue, chikungunya and Zika).

After the Ministry of Health declared the PHENC, on December 18, 2015 (FIOCRUZ, 2015b) the Oswaldo
Cruz Foundation set up the Office to Fight Public Health Emergency of National Concern to unify the institutional actions and get quick responses to the Brazilian population in the scope of the Unified Health System (SUS).

WHY STUDY THE ZIKA VIRUS THROUGH COORDINATED AND ACCURATE ACTION?

The ZIKV was discovered in 1947, at the Zika forest, Uganda, Africa by the blood analysis of rhesus sentinelas monkeys to monitor the yellow fever (DICK; KITCHEN; HADDOW, 1952). In the next year the ZIKV was isolated in the Aedes africanus mosquito (FAUCI; MORENS, 2016) suggesting a likely transmission route of the virus. After that, antibodies against ZIKV in humans were reported in Africa, Asia and India (KOKERNOT et al., 1965; SMITHBURN, 1952). Despite the presence of antibodies, the virus had never been associated with clinical symptoms that could draw the international surveillance’s attention to the ZIKV (LESSLER et al., 2016). It was not before 1957 that the virus was isolated from human body in Nigeria, Africa (MACNAMARA, 1954). In 1956, the vector transmission capacity was confirmed by experiments with volunteer human (BEARCROFT, 1956).

The history of infection with ZIKV of no epidemiological relevance dates back to the 1950s to 2013 (WHO, 2016a) with reports of ZIKV epidemics in the French Polynesia, where about 67% of the residents were infected with the ZIKV. For the first time the ZIKV was associated with neurological disorders, with 42 cases of Guillain-Barré described and correlated to the infection of adults with ZIKV (CAO-LORMEAU et al., 2014; 2016; CAUCHEMEZ et al., 2016). Based on the scientific information about the Brazilian epidemic in 2015, the French Polynesia – in a retrospective study – also reported rising numbers of microcephaly cases associated with the infection with congenital ZIKV (CAUCHEMEZ et al., 2016).

However, the greater ZIKV epidemic was in Brazil, probably starting in 2014. It explosively spread over the Americas and reached worldwide proportions in 2016. Today more than 73 countries in the five continents report infection with ZIKV (WHO, 2016b).

Since it is an arbovirus it did not raise epidemiological interest, there is too little information about the etiopathogenesis of the ZIKV, thus bringing up the need for quick mobilization of the scientific force to understand the ZIKV complex behavior in human beings and its complications.

Fiocruz, aware about its role as strategic institution to Brazil, started permanent mobilization by setting up an Office to cope with the PHENC.

In February 2016 Fiocruz delivered to the MoH the “Fiocruz Plan” to cope with the PHENC and assist the MoH to combat the epidemic.

FIOCRUCZ PLAN TO COPE WITH THE HEALTH EMERGENCY OF NATIONAL AND INTERNATIONAL CONCERN

The infection with ZIKAV, and mainly the related neurological manifestation, builds a complex picture and still misses accumulated scientific knowledge. The precise understanding of many factors required to cope with the Epidemic demands broad, sympathetic, collective and continued effort of scientific investigation to explain many aspects of the infection with virus, its transmission, entry, dispersion and interaction with human beings, as well as the resulting impacts on the SUS.

The Fiocruz Plan (FIOCRUCZ, [2015]) systematized the Foundation’s actions and proposals. The Plan was produced in short-time and is encompassing, since it gathers different areas. It was outlined based on works and research the Foundation already developed in the extensive range of factors involved in the emergency caused by the ZIKV, and its association with microcephaly and other conditions.

Thanks to its set of installed institutional competences, as those listed below, Fiocruz successfully worked on
different fronts of the fight against the ZIKV epidemic and its clinical association.

- Network of reference labs for infectious and parasitic diseases;
- Participation in the national network of reference labs in public health (SNLSP);
- Production of immunobiologics comprised by the National Immunization Programme (PNI);
- Strategic role in the health quality control;
- Training program in health surveillance;
- Cutting-edge research on neglected and emerging diseases;
- Many study centers, observatories and labs handling with a wide range of health conditions, risks and vulnerabilities;
- Centers of Collaborators of the World Health Organization / Pan-American Health Organization (WHO/PAHO) on health topics and problems of global concern.

Here, the overall goal of the plan was to produce integrated actions to significantly contribute with the National Health Policy to cope with the PHENC. It was designed in fronts of action. It is worth mentioning that the Fiocruz Plan to cope with the PHENC remains in force and is being reviewed and improved by the network of experts, part of the Fiocruz Coping Office.

The research agenda defined in the Plan fronts was published on the *Lancet* journal (BARRETO et al., 2016) and served as base to launch the axis III – Technological Development, Education and Research of the National Plan to fight the *Aedes aegypti* mosquito and the Microcephaly, in March 2016 (BRASIL, 2016b).

The Plan fronts systematically approach the actions on: (a) technological development and reference labs; (b) scientific knowledge; (c) health care; (d) education; (e) social mobilization; (f) information and social communication; (g) international cooperation.

One year after the PHENC coping, the Fiocruz Plan advanced. It is worth mentioning that Fiocruz was the first Brazilian institution to present a structured plan to the MoH and that published more documents about the ZIKV in the scientific field, significantly contributing to build knowledge about the epidemic, thus enabling the outline of a strategy to combat the virus.

Only in 2016, more than 56 ZIKV-related articles were published on the most notorious international journals in terms of scientific knowledge dissemination. When one analyzes the publication considering the DENV, ZIKV and CKIKV triple epidemic, more than 120 articles have been published.

Some articles were crucial to understand the ZIKV physiopathology in relation to the diseases caused in the congenital form. For example, the first ZIKV genetic sequencing in amniotic fluid of a mother whose child had microcephaly (CALVET et al., 2016) with result disclosed to the Health Surveillance Department (SVS/MS) one month after the PHENC declaration; presence of ZIKV in the brain tissue of a baby with microcephaly (NORONHA et al., 2016; CORDEIRO et al., 2016); congenital ZIKV can cause brain damage in any gestation period (BRASIL et al., 2016); presence of ZIKV with potential risk of infection in the urine and saliva (BONAL et al., 2016); *Culex quinquefasciatus* collected in regions of Rio de Janeiro is not competent in the ZIKV transmission (FERNANDES et al., 2016); and one of the most relevant assays, the case-control study that seals the correlation between the ZIKV congenital infection and the increased number of microcephaly cases in the Northeast of Brazil, developed by the Aggeu Magalhães Institute, Fiocruz Pernambuco (ARAÚJO et al., 2016).

Despite all advances made by the world science, there is still a lot to be studied, fostering the engagement of national research development agents, the Brazilian government and international agencies. The immuno-physiopathological knowledge about the infection
with ZIKV and its relation with the infection with different DENV serotypes and cousin infected by CHIKV, for example, is still very poor. These are pieces of information crucial to develop immunotherapeutic approach and prevention by vaccines, for example.

In the field of diagnostic surveillance Fiocruz, through three sentinel reference labs, has worked on the diagnosis of ZIKV in three different macroregions of Brazil: (i) Virology Lab of the Aggeu Magalhães Institute, Fiocruz Pernambuco, in charge of the differential diagnosis to the states of Rio Grande do Norte, Pernambuco and Paraíba; (ii) Virology Lab of the Carlos Chagas Institute, Fiocruz Paraná, in charge of the differential diagnosis to the states of Paraná, Santa Catarina and Rio Grande do Sul; and, (iii) Flavivirus Lab of the Oswaldo Cruz Institute (IOC) in Rio de Janeiro, in charge of the differential diagnosis to the states of Rio de Janeiro, Espírito Santo and Minas Gerais. The Fiocruz sentinel labs were the first ones to find positive results for the ZIKV presence in Brazil. In addition, during the PHENC these labs performed more than 20 thousand molecular analyses of samples of potentially infected individuals all over Brazil.

In the field of health care, Fiocruz has worked on the elaboration of protocols to the clinical management of the CHIKV and ZIKV. Since Health professionals are less familiar with both diseases, Fiocruz also designed professional training in many fronts, including the course on clinical management delivered in collaboration with the SUS Open University (UNA-SUS) which now has more than 30 thousand professionals enrolled in the distance training.

The multiprofessional approach for pregnant women and children with congenital syndrome from the ZIKV, carried out by the National Institute of Health of Women, Children and Adolescents (IFF), Fiocruz/RJ, evidenced the relevance of a prenatal exam to ensure accurate diagnosis of virus-related diseases and, at the same time, to provide guidance on protection of pregnant women and further protocol care for babies identified with any alteration of the central nervous system, such as early global essential stimulation to reduce the impact of these changes on these children’s growth and development. These essays developed by the IFF were recommended to be incorporated in the health care and assistance handbook of the Ministry of Health.

Still in the field of care and assistance, many studies of cohorts coordinated by Fiocruz could provide relevant information about the required actions in the cases, and the most suitable clinical measures to assist those patients, considering the severest consequences of CNS alterations, which can be diagnosed at birth but many of which can only be perceived later, and cannot avoid integral therapeutic approaches.

In the dimension of technological development Fiocruz has worked on three main fronts: (i) development of methods and technology to control the A. aegypti mosquito; (ii) development of molecular and serological diagnosis kit; (iii) studies to develop vaccine against the ZIKV.

In vector control Fiocruz has worked on the development of control processes by Pyriproxyfen Larvicide Disperser. The research is performed by the Leônidas e Maria Deane Institute, Fiocruz Amazonas. The work was recommended as practice of control, incorporating the method to the recommendations of the epidemiological report of the SVS/MS (BRASIL, 2016a). It is the official control practice recommended by the Department of Vector Control and Surveillance of the SVS/MS.

Still in the field of vector control, Fiocruz has proposals of research on vector control through biologically modified mosquitoes. One of the actions is part of the international collaboration Eliminate Dengue. Our Challenge, coordinated by the Monash University (Australia). Fiocruz is part of this collaborative action that in Brazil is named Eliminate Dengue Project: Brazil Challenge. It aims to implement in Brazil, in large-scale, the A. aegypti mosquitoes with Wolbachia pipientis, a bacteria that naturally occurs in the environment. Pilot experiments were successful reporting inhibition of transmission of the three important arboviruses transmitted by that vector, DENV, ZIKV (DUTRA et al., 2016) and CHIKV in two regions of Rio de Janeiro.
In partnership with the Ministry of Health, the project is negotiating the expansion of the technology for the coverage and release of mosquitoes with Wolbachia all over the Rio de Janeiro municipality.

Regarding the study to the technological development of vaccines, Fiocruz has approached several strategies from the ZIKV inactive lineage and heterologous recombining proteins with advanced achievements. At least two institutes, namely the Institute of Technology in Immunobiologicals/RH (Bio-manguinhos) and the Aggeu Magalhães Institute/PE are working on this issue. The studies are expected to enter experimentation with non-human primates (NHP) until March 2017.

In the field of diagnostic development Bio-manguinhos developed a molecular kit of simultaneous identification of the three viruses, DENV, CHIKV and ZIKV, and a kit of quick serological detection of IgM/IgG antibodies. The last is developed in cooperation with the American ChemBio. The two kits are in final process of registration at the Brazilian Sanitary Surveillance Agency (ANVISA) (processes ANVISA 25351.349394/2016-07, 25351.025582/2016-12 and 25351.339309/2016-08).

The explosive epidemic of ZIKV and its consequences fostered the gathering of global scientists around scientific cooperation works.

Fiocruz is the global leader in several international cooperation works with scientific institutions in Europe, such as in the United Kingdom and France, and in the United States and Africa. It is worth mentioning that Fiocruz, jointly with the National Institutes of American Public Health (NIH) – one of the main institutions in health science and technology in the world –, coordinates a study of international multicentric cohort in three Latin American countries (Brazil, Bolivia and Colombia) to review the natural history of infections with ZIKV among pregnant women. Brazil established three study sites, two of which in Fiocruz institutes: Aggeu Magalhães Institute, Fiocruz/PE and National Institute of Health of Women, Children and Adolescents, Fernandes Figueira (IFF/RJ).

**FINAL REMARKS**

This brief report depicts the significant work of Fiocruz in the search for answers and mechanisms of intervention to combat microcephaly and diseases related to and transmitted by the A. aegypti mosquito, in line with the declaration of PHENC and the Brazilian government’s National Plan of Combat to Microcephaly and to the Aedes mosquito.

However, there is a lot yet to be done in all fronts of the Fiocruz action and axes of action of the governmental national plan. This is mainly true in the field of scientific investigation. Even with the PHENC declaration and the innovation in legal aspects to the Brazilian science since the enactment of the set of laws that rule the national code of ST&I, in January this year, Brazil has not yet created quick funding means to dynamically foster emergency knowledge production. One year has gone since the PHENC declaration, and the main Brazilian science and technology funding agencies have not released funds. This shows that Brazil should be more dynamically prepared to cope with new health emergencies likely to occur due to the globalized world’s dynamic.

Despite the unfavorable context and the bureaucratic obstacles, the corpus of Brazilian scientists, through their research units, have quickly reacted and brought about crucial responses to cope with the epidemic. Brazil proved it has well-prepared and skilled scientists to answer crucial questions to cope with emergency problems in the field of Health and to the development of the country. The situation unveiled the lack of required technology and infrastructure, as well as underfunding, which slowed down the discovery process in Brazil.

Finally, Fiocruz believes that a plan to cope with a health emergency of national concern should not attach priority to this or that action. In the case of the triple epidemic that reached Brazil, actions should be jointly developed in the light of surveillance, vector control, assistance, social mobilization, information and communication with the society and, above all, in the development of scientific knowledge, solutions and practices based on the national ST&I.
Brazil came up with a quick response when it was challenged with the PHENC declaration, but is far from success in the combat to the triple epidemic DENV, CHIKV, ZIKV caused by the A. aegypti mosquito.

Therefore, the governmental mobilization must be intensive and dynamic, just like by the time of declaration of PHENC on November 12, 2015, paying special attention to the advances of the CHIKV epidemic all over the country, and the consequences that the morbidity from the infection of this virus brings to those affect.

REFERENCES


MACNAMARA, F. N. Zika virus: A report on three cases of human infection during an epidemic of jaundice in Nigeria.


The Evandro Chagas Institute’s contribution

THE INTRODUCTION OF ZIKA VIRUS IN BRAZIL

Late in January 2015 I received calls and exchanged e-mails with Prof. Kleber Luz, clinical infectious disease physician of the Federal University of Rio Grande do Norte (UFRN) about suspected cases that consistently tested negative in the tests performed at the Central Public Health Lab of Rio Grande do Norte (Lacen/RN), and that he wanted to be tested at the Evandro Chagas Institute (IEC), since the clinic picture was compatible with dengue. I told him we could test the serums for dengue and chikungunya, which few months before had been confirmed by the IEC in Brazil as responsible for epidemics of exanthematous febrile and acute disease and followed with severe arthralgia. The epidemics were reported in the states of Amapá and Bahia (TEIXEIRA et al., 2015; NUNES et al., 2015).

We in the IEC received the samples of serums tested to dengue and chikungunya, both by serology and molecular biology, and attempts of virus isolation in cellular culture. Most of the samples tested negative, and few cases were confirmed as dengue. In face if that, Prof. Kleber requested us to re-test the serums, because those negative for dengue presented symptoms very similar to the chikungunya fever. Samples were re-tested and nothing changed. In face of that, Prof. Kleber Luz, still in February 2015, hypothesized that cases could be caused by the Zika virus (ZIKV). Thus, we requested the production of the inputs to be able to diagnose the ZIKV and said that as soon as we got the reagents we would process the serums for testing against the ZIKV. We received the reagents by the end of April. However, this happened about one week after Prof. Gubio Campos, of the Federal University of Bahia (UFBA), had reported the Ministry of Health that similar cases to those described by Prof. Kleber Luz, but coming from Bahia, were caused by the ZIKV, resulting in the first identification of ZIKV cases in Brazil (CAMPOS; BANDEIRA; SARDI, 2015).

Still in April, the Health Surveillance Department (SVS) of the Ministry of Health (MoH) requested us the confirmation of Bahia’s cases. It was done in the last day of the month and then, by the end of April, we confirmed that the cases of Natal were equally caused by the ZIKV. Early in April the IEC isolated the ZIKV in culture of C6/36 cells. In May the virus was isolated for the first time in Brazil. In May Fiocruz groups of Paraná and UFRN informed that cases in Rio Grande do Norte were caused by ZIKV, and published an article reporting the cases in the state in the June edition of the Memórias do Instituto Oswaldo Cruz (ZANLUCA et al., 2015), which was the first article on ZIKV published in Brazil. Table 1 shows a chronological summary of these events.
## TABLE 1
RATE OF CASES OF MICROCEPHALY PER 100 THOUSAND BORN ALIVE IN BRAZIL 2010-2014 AND 2015

<table>
<thead>
<tr>
<th>States</th>
<th>Average cases of microcephaly per 100 thousand born alive from 2010-14</th>
<th>Average cases of microcephaly per 100 thousand Born alive in 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MID-WEST REGION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distrito Federal</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Goiás</td>
<td>3.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Mato Grosso do Sul</td>
<td>1.9</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>NORTHEAST REGION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alagoas</td>
<td>6.2</td>
<td>112.4</td>
</tr>
<tr>
<td>Bahia</td>
<td>5.2</td>
<td>18.2</td>
</tr>
<tr>
<td>Ceará</td>
<td>5.3</td>
<td>20</td>
</tr>
<tr>
<td>Maranhão</td>
<td>2.6</td>
<td>10.4</td>
</tr>
<tr>
<td>Paraíba</td>
<td>7.4</td>
<td>436.2</td>
</tr>
<tr>
<td>Pernambuco</td>
<td>6.1</td>
<td>456.7</td>
</tr>
<tr>
<td>Piauí</td>
<td>6.5</td>
<td>77.6</td>
</tr>
<tr>
<td>Rio Grande do Norte</td>
<td>3.8</td>
<td>168.8</td>
</tr>
<tr>
<td>Sergipe</td>
<td>4.7</td>
<td>225.0</td>
</tr>
<tr>
<td><strong>NORTH REGION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tocantins</td>
<td>5.0</td>
<td>49.8</td>
</tr>
<tr>
<td><strong>SOUTHEAST REGION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rio de Janeiro</td>
<td>5.5</td>
<td>5.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4.9</td>
<td>99.7</td>
</tr>
</tbody>
</table>

Source: SVS/MS.
**MICROCEPHALY AND THE ZIKA VIRUS**

In September and October 2015 the number of microcephaly cases detected by neonatologists increased in Pernambuco, and then in many states of the Northeast of Brazil. The number of detections was many times higher than the historical average of microcephaly to those states (Figure 1). Between October and November, the Ministry of Health (MoH) convened several meetings in Brasilia to debate the likely causes of those events. The main suspicion was that these would be congenital complications caused by infections with ZIKV in women that, when pregnant, presented conditions similar to allergy, with or without fever, conjunctiva hyperemia and painful or painless edema of joints. The media raised many other hypotheses that lacked scientific grounds, including the use of organophosphate insecticides or expired vaccines, which were nothing but rumors, some extremely nasty, which pressed the MoH to search the actual etiology of such drastic conditions.

Although there was not causal (etiological) determination that could associate the microcephaly cases followed by many congenital malformations with the ZIKV, the suspicion was enhanced with the ZIKV epidemic in the Northeast region some months before, with a large number of cases in Pernambuco, Paraíba, Alagoas, Rio Grande do Norte, Ceará etc. Thus, there was a temporal association, but no final exam unequivocally demonstrating the causal association of the ZIKV as agent of the microcephaly cases.

Many physicians, neonatologists, infectious diseases physicians, radiologists presented non-conclusive evidence about the likely temporal association of the ZIKV epidemic some months after the outbreaks of microcephaly that occurred in states of the Northeast. Images of microcephaly diagnosed by brain ultrasound imaging were disclosed by Dr. Adriana Melo, from Campina Grande (PB), describing many alterations, including reduced skull, multiple calcifications in the encephalon, changes on the shape and size of lateral ventricles, their asymmetry, etc. in pregnant women with conditions compatible with ZIKV, but with no specific exams.

On November 11 Dr. Ana Bispo from Oswaldo Cruz Foundation (Fiocruz) in Rio de Janeiro notified the MoH that she found the RNA of the ZIKV in the amniotic fluid of two children whose brain ultrasound exams showed the aforementioned alterations. This increased the suspicion, but was also an indirect evidence of the presence of ZIKV in the pregnant woman that did not mean yet a causal link, because the ZIKV was found in the amniotic fluid and not in the tissues or blood of the fetuses.

**THE IEC IRREFUTABLY AND UNEQUIVOCALLY EVIDENCES THE CAUSAL LINK BETWEEN THE ZIKA VIRUS AND MICROCEPHALY AND OTHER CONGENITAL MALFORMATIONS**

On November 28 the Evandro Chagas Institute reported to the MoH it had found the ribonucleic acid (RNA) of ZIKV in the blood, brain and viscera (heart, lung, liver, kidney and spleen) of a newborn who died five minutes after a cesarean section in Fortaleza, Ceará. In the same materials the IEC isolated the ZIKV in cell culture. This ZIKV sample was obtained in C6/36 cells cultivated with suspensions of those biological specimens (the ZIKV was isolated from blood, brain and pool of viscera). Later one, virus antigens were detected by immunohistochemistry in all tissues analyzed of that child, except the spleen. In this way, it was unequivocally demonstrated that the ZIKV was responsible for the congenital malformations of the child. The IEC was responsible for demonstrating the cases. That was how we have unequivocally and irrefutably demonstrated the causal relation between the ZIKV and the cases of microcephaly and other congenital malformations in mothers diseased with conditions that suggested the ZIKV and who delivered children with congenital malformations. In the following days, the IEC and other institutions confirmed many other cases. Chart 3 summarizes the events until the confirmation of causality of the ZIKV as responsible for the microcephaly cases.
FIGURE 1
CHRONOLOGICAL SUMMARY OF THE ZIKA VIRUS IN BRAZIL

First records of exanthematic syndrome in Rio Grande do Norte

CIEVS – Monitoring of the rising number of cases of exanthematic syndrome in the Northeast
  - Low or no fever
  - Maculopapular exanthema
  - Itch
  - Arthralgia
  - Members edema

SVS/MS Investigation Team Inquiry in MA, RN, PB

Exams performed at the UFBA* positive for Zika Virus (8/25) in Camaçari/BA

Positive Zika by RT-qPCR at ICC*** in samples from Natal/RN (8/21)

2014 2015

October February April May

* Federal University of Bahia
** Evandro Chagas Institute
*** Carlos Chagas Institute (Fiocruz-PR)

Source: Adapted from SVS/MoH.

Note: The IEC further demonstrated that the ZIKV was introduced in Brazil in 2013 (FARIA JUNIOR et al., 2016).

FIGURE 2
CHRONOLOGICAL SUMMARY OF THE OCCURRENCE, INVESTIGATION UNTIL THE CONFIRMATION OF THE CAUSALITY BETWEEN MICROCEPHALY AND ZIKV IN BRAZIL

2015

Aug-Sept October Nov. 11 Nov. 28

Perceived increased number of born alive with microcephaly

The SES/PE1 receives the notification from practitioner physicians

Clinical situation suggests congenital infection

The SES/PE1, SVS/MoH2 and PAHO3 start the investigation

The MoH declares Public Health Emergency of National Concern

The IEC4 diagnoses the ZIKV in a case of microcephaly and describes it for the first time associating ZIKV and microcephaly

1 Pernambuco State Health Secretariat
2 Health Inspection Secretariat of the Ministry of Health
3 Pan-American Health Organization
4 Evandro Chagas Institute

Source: Adapted from the SVS/MS.
THE IEC DEMONSTRATES FOR THE FIRST TIME IN THE WORLD THAT THE ZIKV CAN CAUSE DEATH IN PEOPLE WITH AUTOIMMUNE DISEASES AND IMMUNE DISORDERS

In the same day, the IEC also notified the MoH about the occurrence of two cases of death caused by the ZIKV in an adult with systemic lupus erythematosus and one adolescent with Evans syndrome. These are both autoimmune conditions that, in some yet unknown situations, seem to favor severe forms of the ZIKV-caused disease. These deaths have also stood for the first descriptions of severe and lethal cases caused by the ZIKV whose etiology was the ZIKV. The lupus erythematosus case was in Maranhão, and the patient developed an extreme severe condition with insufficiency of multiple organs, and died more or less one week after symptoms started. The IEC isolated the ZIKV from brain tissues, blood and batches of viscera. Likewise, it showed the presence of ZIKV antigens in the tissues of the brain, liver, heart, lung and kidneys and the presence of the ZIKV RNA in blood, brain and tissues of the same viscera. The Evans syndrome case was in Benevides, Pará, in a 15 years old youngster, who died about 30 days after the febrile disease started, and whose exams demonstrated the presence of the ZIKV RNA in the patient’s serum with seven days of the disease. There was no necropsy and, thus, tissues were not collected for lab exams.


The three deaths confirmed by the IEC as caused by the ZIKV were the first official records of deaths caused by the ZIKV in the world. This made the Pan-American Health Organization (PAHO) and the World Health Organization (WHO) publish a special edition of the Epidemiological Alert on December 1, 2015, on their causal relation, including that between microcephaly and the ZIKV (PAHO, 2015). This fact globally demonstrated the relevant contribution of the IEC to clarify the causal link between microcephaly and other congenital malformations caused by the ZIKV, but also went beyond by demonstrating the first deaths attributed to the ZIKV based on the cases of Maranhão and Pará.

THE WHO ESTABLISHES THE ADVISORY EMERGENCY COMMITTEE FOR MICROCEPHALY AND ZIKA

On February 1st, 2016 the WHO declared the epidemic of ZIKV with cases of microcephaly as a Public Health Emergency of International Concern, and created the WHO emergency advisory committee for microcephaly and ZIka, made up by 12 teachers, doctors and epidemiologists from different parts of the world. Dr. Pedro Fernando da Costa Vasconcelos, virologist and the IEC Executive Officer, was the only representative of Brazil in the committee. The group’s report was published on February 15 on The Lancet (HEYMANN et al., 2016).

ZIKA WAS INTRODUCED IN BRAZIL IN 2013

On February 23, 2016 our IEC group, supported by many other institutions, published on the Science journal the first article on the spread and phylogenetic origin of the ZIKV in Brazil, with seven isolates of the virus. In the same article, using molecular tools and bio-informatics, we have proven that the ZIKV was introduced in Brazil between May and December 2013, probably in the months of July and August, by the time of the Confederations Cup – one year before the 2014 World Cup. The time the virus remained unnoticed played a core role in the spread over the Northeast region, mainly because 80% of the infections are asymptomatic or oligosymptomatic (FARIA JUNIOR et al., 2016). The article also depicted how hard is to isolate the ZIKV.

THE IEC DISTRIBUTES THE ZIKV TO SEVERAL SCIENTIFIC INSTITUTIONS IN BRAZIL AND ABROAD

The IEC has also contributed with the Brazilian research institutions and universities. I decided we should give ZIKV samples for research. Thus, USP, Fiocruz (RJ and MG), UFRJ, the Brain Institute (RN), Federal University of Minas Gerais (UFMG) etc., and scientific institutions
of many countries such as Australia, Korea, the USA and Singapore, have received the ZIKV. This enabled research works that provided input to publications that contributed to advance the scientific knowledge about the ZIKV, including the development of vaccination candidates by the Harvard University (LAROCCA et al., 2016) and in experimental models at the University of São Paulo (USP) (CUGOLA et al., 2016) that used the ZIKV isolates obtained from the IEC to develop those studies.

Finally, my participation heading a group of IEC’s researchers was and has been crucial to the development of scientific research with the ZIKV. Today we are carrying out research to develop a vaccine against the ZIKV (in cooperation with the University of Texas Medical Branch (UTMB), Galveston, USA) under a project fully funded by the MoH; development of experimental models in non-human primates from the New World and from the Old World to get scientific information about the pathogenic and physiopathology of the infection with ZIKV in those primates that, in evolution terms, are closest to the human beings and, therefore, are expected to generate information closer or similar to what happens in human beings. These projects are funded with resources from the MoH (SVS), CNPq, Capes and Finep.

IEC IS IN THE RACE TO DEVELOP A VACCINE AGAINST THE ZIKA

After the boom of ZIKV-related disease cases, notably the unprecedented rising in the number of cases of microcephaly and other malformations of the CNS, the MoH asked me about the possibility of developing a vaccine against the ZIKV. I said no Brazilian institution could develop alone a vaccine with the required speed and safety to meet the demands of the emergency caused by the events resulting from the epidemic of microcephaly caused by the ZIKV.

The minister of Health by the time – Marcelo Castro – and the then Executive Secretary of the MoH, Agenor Alvarens, asked me about the possibility of heading an initiative of the MoH to develop the vaccine. When we talked on the phone, I was in Manaus attending a seminar about arboviral diseases, coordinated by the US National Institutes of Health (NIH) and Fiocruz, where I participated in the scientific commission. That was when I presented to the participants (and for the first time to the scientific world) the first cases of microcephaly proven to have been caused by the ZIKV and of the deaths of adults from autoimmune diseases. Prof. Robert Tesh from the University of Texas Medical Branch (UTMB), Galveston, was attending the seminar. He has partnered with me in my research works for many years, and the UTMB was where I held my year during the Doctoral course, where I was visitor scientist and took my post-Doctor’s degree. I talked to Prof. Tesh about the issue and we concluded that the IEC and the UTMB could co-develop the vaccine the MoH wanted.

On the following weeks the MoH and the UTMB, facilitated by the PAHO and exchanging e-mails with the UTMB leadership, decided that I and two IEC fellows (Dr. Daniele Barbosa Medeiros and Dr. Bruno Tardelli Nunes) would visit the UTMB in Galveston for one week, early in February 2016. During the visit, we agreed that in the UTMB professor Pei-Yong Shi would be the main researcher of the vaccine project in the USA and I would take on this role in Brazil. The agreement also provided that two IEC researchers would actively participate in the project on the vaccine development in the USA. In April 2016, Dr. Bruno Tardelli and Dr. Daniele Medeiros went to the UTMB where they still work (October 2016). Their participation has been crucial to develop the vaccine, and the mutant obtained with the best vaccination approach was that developed by the IEC researchers.

The MoH’s vaccine approach, fruit of that partnership, is a vaccine of attenuated living virus. Several mutations have been inserted in the ZIKV genome, reducing its virulence without losing the immunogenic capacity. The vaccination candidates developed were assessed regarding innocuity, antigenicity and genicity in mouse, with 100% of protection to vaccinated animals that received lethal dose of ZIKV. Attempts of infection from Aedes aegypti mosquitoes showed that vaccination candidates lost the capacity of infecting these ZIKV vectors, pointing out the required safety to the testing on non-human primate (NHP) and humans in clinical
assays. Today, we are concluding the negotiations with the Brazilian Technical Commission on Biosafety (CTNBio) and the National Sanitary Surveillance Agency (ANVISA) to import the vaccination candidates, which are expected to be important before the end of this year (still in November). The clinical assays on NHP are expected to be started by that time and then, early in 2017, the Phase 1 clinical assays in adult humans should be started.

**ARTICLES PUBLISHED ABOUT THE ZIKA**


   This article approaches a proposal by the authors to a positive agenda of research with the Zika virus in Brazil. It resulted from scientific meetings held at the Ministry of Science, Technology and Innovation late in the 2015 and in the first months of 2016.


   This was the first article to systematically analyze the ZIKV spread in Brazil and showed that, differently from the common belief, the Zika had not been introduced in 2015, but in 2013 and, considering that nearly 80% of the infections with ZIKV are asymptomatic, the virus had time to spread over the Northeast region. Moreover, the article is the first one to mention the potential association between the ZIKV and microcephaly, based on the finding of the virus in the brain tissues of a newborn in Ceará who died soon after birth. Finally, the article also reports the analysis, for the very first time, of seven full genomes of the ZIKV, the Asian genotype that circulates in Brazil and was (and continues being) the responsible for the epidemic of Zika and microcephaly in the New World.


   This article describes the main points of the first meeting of the WHO Advisory Committee in Zika and Microcephaly, evaluating the situation in Brazil and in the Americas, as well as the risks of dissemination all over the world.


   This article describes the first three cases of death caused by the ZIKV in adults in Brazil. It is important since it represents the description of cases where changes on autoimmunity and the immune system disorders may result in deaths during the ZIKV-related disease.

This article describes measures to prospect antiviral drugs and Zika antivirus vaccines that could be used to heal cases and prevent infection, respectively.


This is an editorial about the likely risks of the Zika epidemic in the Americas and the consequences of eventual spread of the virus over the world.

REFERENCES


INTRODUCTION AND BACKGROUND

Although the first cases of an exanthematous disease had been reported in Rio Grande do Norte in October 2014, the Zika virus probably started circulating in Brazil still in 2013. In the first months of 2015 the Ministry of Health (MoH) reported to the Pan-American Health Organization / World Health Organization (PAHO/WHO) cases of exanthematous diseases that tested negative for dengue, chikungunya, German measles, measles, B19 parvovirus and enterovirus in the states of Northeast. By that time the prevailing instruction was that such cases should be recorded as dengue due to the similarity with this disease. On April 29, researchers from the Federal University of Bahia have identified the Zika virus by RT-PCR, confirmed by the Evandro Chagas Institute of Belém one week later.

The virus was identified and the origin of the exanthematous disease that behaved like a mild dengue was clarified and only seven days after the PAHO/WHO launched a regional alert: “The PAHO/WHO recommends its state-members to establish and maintain the capacity to detect and confirm cases of infection with Zika, treat patients, implement effective communication strategy with the population to reduce the presence of the virus-carrier mosquito, mainly in areas with the presence of the vector”. This was followed by other alerts; protocols for the surveillance of Zika and Guillain-Barré syndrome (GBS) were prepared based on the experience of the outbreak in the French Polynesia. By mid-July, the Zika virus was found in 20 Brazilian states, and 49 cases of GBS associated with the Zika virus were reported. From May 7, 2015 to October 20, 2016, PAHO/WHO issued to its state-members 35 alerts and updates about the Zika virus and its consequences.

Although the response to the circulation of a virus not previously identified in the region was agile and timely, it happened in a context of relative calmness because the infection was mild, there were no severe sequels except for the GBS, and the authorities were facing bigger challenges such as the chikungunya or even the dengue that caused disabilities and whose lethality could not be neglected. Thus, three months elapsed and on October 22, 2015 the MoH is warned by the Pernambuco State Health Department about an unusual increase of cases of microcephaly in newborns in Pernambuco and some other states in the Brazilian Northeast.

On October 26 a delegation of the MoH, jointly with PAHO/WHO representatives, attended meetings with authorities and experts in the state of Pernambuco, Recife, in which the seriousness of the situation was disclosed, and priorities were established such as care to affected children, characterization of the cases and the urgent implementation of a case-control study.

On November 11 the MoH declared the outbreak as a Public Health Emergency of National Concern (PHENC) for the first time in history, in a preview of what was about to come. The sequence of events triggered by that moment was vertiginous: declarations, experts meetings, support by the Global Outbreak Alert and Response Network (GOARN) – made up by the PAHO and the CDC professionals – which visited Recife and
Brasilia in the first week of November; debates among professionals who did not believe in the implication of the Zika virus on microcephaly, and were even skeptic about the outbreak of this manifestation, with others who believed in the relation based on the epidemiological link and lack of other likely explanation. A true convulsion.

Upon the agreement by the Health Surveillance Department (SVS) of the MoH, the PAHO/WHO promoted, since the beginning of the microcephaly outbreak, a case-control study in Recife to support the search for evidences on the causes of the microcephaly outbreak (SONJA et al., 2016). The prospective entry of cases started in February 2016 and, in September the preliminary results were published (ARAÚJO et al., 2016), which was the first study of this kind, laying another brick on the constructing of evidence that the infection of pregnant women by the Zika virus can cause microcephaly on the fetus, in addition to other neurological alterations.

On February 1, 2016 the WHO declared the global emergency due to the infection with Zika Virus (PHEIC) and the directors of WHO, Dr. Margaret Chan, and of PAHO, Dr. Carissa Etienne, visited Brasilia and Recife from February 21 to 24 to demonstrate their personal and the organization’s support to the preventive and control measures the Brazilian government was promoting since the emergence of the first cases.

Until February 1, 2016, when the WHO declared global emergency due to the infection with the Zika virus, the response of the PAHO/WHO Office in Brazil was being channeled through the regular structure of the different areas of work. That quickly changed with the aforementioned declaration, which strongly increased the demands on the PAHO/WHO Representation and enabled the installation of a “situation room” to improve the coordination of information and the interaction with the national counterparts and other instances of the PAHO/WHO. The room opened its doors on February 15, 2016 initially scheduled to be operational until the end of the year.

GOAL AND PURPOSE OF THE SITUATION ROOM

The initial goal of the room was to systematize and analyze the information about the most relevant topics related to the infection with the Zika virus and its consequences. However, after some weeks of work, data and information about dengue and chikungunya were incorporated, making it a true situation room of the main arboviral diseases in Brazil.

The goals of the room were to receive, systematize, analyze and disseminate evidence-based information to assist the PAHO/WHO to make decisions, support the Ministry of Health and the State Departments, meet the internal demands of the UN agencies, embassies and other actors interested in the issue, as well as other representations and organizational levels of PAHO and WHO.

The situation room intended to help answering some questions that did not have or still do not have clear answers, such as the magnitude and tendency of the problem, the likely future scenarios, the most vulnerable population, the most effective measures to control the infection, how the logistical aspects were being developed and the response by the organization, and how information was being disseminated to the population, among others.

INFORMATION SOURCES

The situation room used secondary data sources and information. In other words, generally and except for some few exceptions where it produced its own information, it recompiled information from several official and extra-official sources:

THE MINISTRY OF HEALTH INFORMATION SYSTEMS:

- Registry of Public Health Events (Resp): online form to record public health emergencies all over Brazil. It allows supporting the surveillance actions. Since the declaration of PHENC due to the increased number of microcephaly cases and the need to promptly notify suspected cases of microcephaly, the Resp-Microcefalias was made available. (http://portalsinan.saude.gov.br/resp).
Information System of Diseases of Compulsory Notification (Sinan): it is the set of tools and processes that supports the epidemiological surveillance of diseases of compulsory notification at the three governmental levels, such as: dengue, chikungunya, Zika, malaria, among others.

Sinan Net: it is a Sinan platform to be used by the typing-points with unstable internet connection so they can record the forms and monitor the progress of the installation process.

Information System on Live Births (Sinasc): it is the set of tools and processes that allow collecting information on live births all over the country. It provides data on birth, congenital malformations and some morphological alterations of the newborns.

Information System on Mortality (SIM): it is the system that facilitates gathering information about fetal and non-fetal deaths. It allows the generation of mortality indicators for several diseases and injuries.

Hospital Information System (SIH): it is the information system about hospitalization by the Unified Health System (SUS) for payment purposes. Because of its quality, scope and timeliness, it is also used for epidemiological purposes, like the occurrence of cases of Guillain-Barré syndrome.

Lab Environment Managerial System (GAL): it is a tool that manages the processes and activities of lab analysis of public health concern, of samples of human, animal and environmental origin to be collected in the lab or by third parties. This system works on the state networks of public health labs, comprising local labs (LL), network labs (LR), Central Public Health Labs (Lacen) and External Labs (LE).

FormSUS: it is a platform to create online forms to gather data, and which can be used for different purposes such as to support the epidemiological surveillance.

Moreover, it uses information from several research works underway (case-control study, cohorts studies, among others), publications by official authorities from other countries (CDC, WHO and PAHO), publications on journals (more than 300 full articles about Zika and its consequences), reports by groups of national and foreign experts, news websites and social networks, in addition to the internal managerial systems of PAHO/WHO.

TOOLS – TABLEAU, STATA, MICROSOFT OFFICE AND ENDNOTE

The Technical Unit of Health Services developed a tool for the “Evaluation of Essential Conditions of the Health Services Network to respond to Outbreaks and Epidemics of the Zika virus and other arboviral diseases”, which has been applied on the Pernambuco and Alagoas State Health Departments, and on the Recife and Florianópolis Municipal Health Departments, providing useful information about the basic health care conditions, response at hospital level and integration of health services networks, epidemiological surveillance system, governance and knowledge management. This is a managerial tool to identify opportunities to improve and define medium and long terms actions and strategies.

STRUCTURE

In principle, the room was structured on 11 areas and one timeline, on which the main events related to the Zika virus were recorded, as well as their consequences and the other relevant arboviral diseases in Brazil. Later, and to better coordinate the structure and operation of the room and improve the effort avoiding duplicities, the 11 areas were regrouped in four, plus the timeline.

Following are the areas:

INTERNATIONAL AND INTERAGENCY COOPERATION

Interagency cooperation: description of the main strategic actions of the area of International Cooperation and the UN Agencies, in an
effort to improve the coherence, integration, harmonization and complementarity of the joint actions, offering timely and efficacious response in support to the Brazilian government during the emergency situation. It assisted strengthening the interagency relations without interfering on the cooperation inherent to the specificities of each agency.

- South-South Cooperation: collection and systematization of supporting experiences among countries, considering that Brazil was the global focus for the novelty and impact of the International Public Health Emergency. The International Health Regulation (IHR) proved to be a core tool as the milestone of technical cooperation between the countries.
- Technical visits of the PAHO/WHO authorities.
- The UN Country Action Plan.

Monitor and organize the demand of request for information/support to other institutions to ensure proper response.

COMMUNICATION AND INFORMATION AND KNOWLEDGE MANAGEMENT

- Inform about the PAHO/WHO initiatives on the infection with Zika virus and the related health situations.
- Track research works being developed in Brazil.
- Systematize information (scientific articles, newsletters, guidelines, handbooks) to support knowledge management.
- Follow-up on the training courses supported by PAHO through the Technical Cooperation.
- Monitor fake information (rumors) that could damage the population’s understanding about the infection with Zika virus and the likely consequences.

LOGISTICAL SUPPORT

- Support events and the participation of experts at national and international level.
- Monitor the procurement of strategic inputs aimed to the lab diagnosis and vector control.

EPIDEMIOLOGICAL ANALYSIS

- Monitor and evaluate the magnitude and tendencies of the infection with Zika virus in Brazil and the main consequences.
- Define the most vulnerable areas and likely future scenarios of the infection with Zika virus and the main consequences.
- Monitor other arboviral diseases.
- Monitor the activity of labs.
- Monitor the vector control outcomes.

NORTHEAST PROJECT

The Northeast Nucleus of the decentralized technical cooperation on Zika was an initiative by the Technical Unit of Communicable Diseases and Health Situation Analysis to provide technical cooperation to some states in the Northeast Region (Paraíba, Pernambuco, Sergipe, Alagoas and Rio Grande do Norte). To facilitate the technical cooperation process, a provisory technical cooperation center to the Northeast Region was assembled, based in the Aggeu Magalhães Research Center of Fiocruz, in the city of Recife, in coordination with the Ministry of Health of Brazil and the health departments of the five states. Depending on the institutions involved, the proposal attached priority on strengthening the epidemiological surveillance of Zika and other arboviral diseases, health care to pregnant women, mothers and babies with microcephaly and/or other malformations associated with the infection, prepare simplified models of analysis for decision-making using data available at the different care levels, and identify and disseminate the lessons learned as subsidy to strengthen South-South cooperation in health in the Americas.
Activities started on July 1, 2016 and the tracking of the states’ needs involved six areas of work:

- Quality and timeliness of the information available – confirmation of microcephaly cases and monitoring of pregnant women with exanthema.
- Access to and decentralization of health care to children with microcephaly.
- Increase the number of experts in the SUS to provide care to children with microcephaly.
- Health care to the pregnant woman and to the family.
- Qualification of the basic health care and its devices (Nasf).
- Integration of the health services networks.

The activities performed aimed to meet the initial needs found by the states, and followed the prioritization and appropriate political moment of each state to execute the actions. In addition, it prioritized the improvement of the state labs’ (Lacen) capacity of response and the define the enhancement needed at the individual level and as a whole. The project was firstly scheduled to end on December 31, 2016 but should to be continued throughout 2017 due to the new needs and challenges posed, such as support the structuring of surveillance of of Guillain-Barré syndrome cases; deepen the upgrading of the diagnostic capacity of public health labs; and, surveillance and outcomes of the cases of death from arbovirus, among others.

**FINAL COMMENT**

Since the beginning of the outbreak Brazil was, and keeps on being, a core player to assist other countries in the response preparation. The strong and traditional partnership between the Ministry of Health and the PAHO/WHO helped taking the Brazilian experience to other countries in the region. The generosity of the government, researchers and health professionals of Brazil who shared their discoveries and allowed other countries to access the information about Zika and microcephaly was a great example of international cooperation.

**REFERENCES**


Partnership with the Health Surveillance Department (SVS/MS) to implement case studies about the association between infection with the Zika virus and the neurological manifestations.

The Brazilian Office of the US Centers for Communicable Disease Control and Prevention (CDC) is the only in the world where all staff members are locals. This model favors the relationship with the government and the civil society organizations, besides fostering the capacity of designing, monitoring and evaluating programs that could be locally developed. Evidencing this successful partnership, the CDC/Brazil Office is located in the Ministry of Health’s facilities, ensuring the integration of teams and promoting efficacious dialogue about the national goals of combat to diseases.

In 2015, upon request by the Ministry of Health, the CDC started supporting studies related to Zika virus infection and the neurological manifestations associated with the virus, including microcephaly and the Guillain-Barré syndrome.

In 2016 and 2017 the CDC and the government of Brazil will work together to refrain the proliferation of the Aedes aegypti, strengthen health surveillance, increase the labs’ capacity to detect the infection and support epidemiological and surveillance studies about the Zika virus behavior and its impact on human health. The field works (interviews, collection of epidemiological data and samples) were implemented in strong collaboration with the Health Surveillance Department (SVS/MS), and carried out by the teams of graduated from the classes of Field Epidemiology of the EpiSUS (Brazil) and scientists from the Epidemic Intelligence Service – EIS of the US CDC.

**CASE STUDIES IN THE STATES OF BAHIA AND PARAÍBA**

**CONCENTRATIONS OF THE GUILLAIN-BARRÉ SYNDROME AND LIKELY ASSOCIATION WITH INFECTIONS WITH ARBOVIRUS IN BRAZIL: A CASE-CONTROL INVESTIGATION IN BAHIA**

Early in 2015 the recent introduction and spread of the Zika Virus in Brazil was identified for the first time. This event happened simultaneously to the circulation of the dengue virus (already endemic in Brazil) and of the chikungunya virus – a mosquito-borne alphavirus in the Central and South Americas (COELHO, 2016a; 2016b). The Zika virus emergence in Brazil was abrupt and explosive with many cases reported mainly in Bahia and Pernambuco.

Around the second quarter of 2015 many concentrations of the Guillain-Barré syndrome (GBS) were identified mainly in two Brazilian states: Pernambuco and Bahia (BRASIL, 2016c; 2016d; GOARN, 2015; PAHO, 2015). The GBS is a peripheral nerve disorder in which an antecedent antigenic stimulus leads to the development of autoantibodies with crossed reactivity and T cells that cross-react with the myelin and/or axonal proteins of the peripheral nerve. The resulting damage leads to clinical results typical to acute/sub-acute manifestation of ascending symmetric muscle weakness with reduction or absence of deep reflections of tendons.
In severe cases it may cause neuromuscular respiratory failure, demanding mechanical ventilation. The antecedent antigenic stimulus is usually an infections disease. Around 70% of the GBS patients report febrile, respiratory or gastrointestinal illness, usually from two to six weeks before the muscle weakness starts (ECDC, 2016; MELO et al., 2016; MARTIN et al., 2000; BEATY; CALISHER; SHOPE, 1995). Many viruses and bacteria have been associated with the GBS development although the actual causality is hard to prove. In Brazil, the two states in which concentrations of GBS were observed were among the most strongly affected by the Zika virus. Based on this, the public health authorities began suspecting that these GBS cases could be attributed to the Zika virus or to a combination of the Zika virus with the co-circulation of other arboviruses, causing the development of the GBS in susceptible individuals (COELHO, 2016b; GOARN, 2015; PAHO, 2015).

In Bahia, the rising number of registered cases of GBS was firstly observed by mid-July 2015. The FETP/MS program made another investigation from August 17 to September 23, 2015. Eight cities, including Salvador (the capital of Bahia) and Feira de Santana, reported most of the cases according to the analysis of the medical records of inpatients in the Metropolitan Region of Salvador and Feira de Santana. The investigation comprised patients with neurological disorders such as encephalitis, meningoencephalitis, myelitis, optic neuritis and Guillain-Barré syndrome, all of them with history of viral infection (dengue, chikungunya or Zika) started between March and August, 2015. The Oswaldo Cruz Foundation (Fiocruz) was responsible for the reverse transcription polimerase chain reaction (RT-PCR) exams for dengue, Zika and chikungunya at the Radiological Sciences Lab (LCR), serum and urine of 138 patients. Of these patients, 58 cases presented suspected GBS, of which 32 cases had lab confirmation of viral infection with RT-PCR: 22 diagnosed with infection with Zika virus and 10 diagnosed with infection with the dengue virus (COELHO, 2016a; 2016b; BRASIL, 2016c; GOARN, 2015; PAHO, 2015).

The fact of considering the existence of an outbreak or concentration of GBS cases in different areas of Brazil, in the context of the recent introduction of the Zika virus in the country, similarly to other situations that arose in other areas of the world, is very concerning. Therefore, a quick evaluation of the current situation in Brazil could enable carrying out preventive and intervention measures to assess the suspected association between the Zika virus or other arboviral diseases and those GBS concentrations (COELHO, 2016b; BRASIL, 2016c; GOARN, 2015). Upon request by the Brazilian Program on Dengue Control, the CDC Brazil, in coordination with the SVS/MS and graduates from the EpiSUS, supported the implementation of a case-control study about the association of Zika virus and cases of Guillain-Barré syndrome in the metropolitan region of Salvador and in Feira de Santana, state of Bahia. The study recruited 41 cases and 85 paired controls, four multidisciplinary teams of field epidemiologists (each team made up by one graduate from the EpiSUS and one field epidemiologist of the epidemic intelligence program (EIS, CDC/USA)), in addition to phlebotomists and representatives of the Bahia State Health Department in February 2016.

**CASE-CONTROL STUDY IN PARAÍBA**

From May 2015 onwards the autochthon circulation of the Zika virus was detected in Brazil. In October 2015, physicians warned the Pernambuco State Health Department about a likely rise in the number of cases of microcephaly. Then, an investigation was started. On October 22, the Pernambuco State Health Department confirmed the finding and warned the national authorities. The Ministry of Health issued an alert about the occurrence of 26 cases of microcephaly in Pernambuco, through the International Health Regulation.

On November 11, Brazil declared National Public Health Emergency State and started conversations with international partners. As of January 16, twenty-one states had reported 3,893 cases of microcephaly to the national authorities (COELHO, 2016a; BRASIL, 2016c). Most of the cases (86% or 3,402) were registered in the Northeast Region (BRASIL, 2016c; GOARN, 2015; PAHO, 2015). Until November 2016, twenty-one states had confirmed the autochthon transmission of the Zika virus.
virus (COELHO, 2016a; 2016b; BRASIL, 2016c; GOARN, 2015). Once again in response to a request by the Brazilian Program on Dengue Control and in partnership with the SVS and EpiSUS, the CDC Brazil supported the implementation of a case-control study about the association of Zika virus and microcephaly in 66 municipalities of Paraíba, including the capital João Pessoa. The study recruited 170 cases (mothers and babies) and 477 paired controls, eight multidisciplinary teams of field epidemiologists – just like in the case-control study of Zika and GBS (Feb. 2016) – made up by one graduated from the EpiSUS and one epidemiologist of the EIS/CDC USA, in addition to phlebotomists and representatives of the Paraíba State Health Department. The study was performed from March to May 2016 and aimed to: (i) estimate the ratio of newborns with microcephaly presenting evidence of congenital infection with the Zika virus; (ii) estimate the relative risk of microcephaly associated with the infection with the Zika virus; (iii) estimate the attributable risk of microcephaly explained by the Zika virus infection; and, (iv) describe the clinical characteristics and current outcomes of children with microcephaly who had been exposed to the virus.

**METHODOLOGY OF ANALYSIS OF THE CASE-CONTROL STUDIES**

Although the crossed serologic reactivity between the several flaviviruses is many times quite complicate, such crossed reactivity can vary between the many flaviviruses (BRASIL, 2016c; GOARN, 2015; PAHO, 2015) and, so, the serological tests, mainly to identify IgM antibodies specific to the virus are useful tools in the diagnosis tests to the Zika virus (GOARN, 2015; PAHO, 2015; BRASIL, 2016d; ECDC, 2016) and other flaviviruses (MELO et al., 2016; MARTIN et al., 2000; BEATY; CALISHER; SHOPE, 1995; LANCIOtTI et al., 2008; HENNESSEY; FISHER; STAPLES, 2016). Complementarily, the plaque reduction neutralization test (PRNT) provides higher degree of specificity to the serologic tests, mainly among cases of arboviral infection testing positive (BEATY; CALISHER; SHOPE, 1995; LANCIOtTI et al., 2008). The exams of the biological samples resulting from this investigation were performed at the labs of the CDC Vector-Borne Division, in Fort Collins, Colorado, USA, and included PCR, serology and PRNT. The whole documentation and agreements required between the Brazilian Ministry of Health and the CDC, such as agreements on transfer of materials and customs documents, were concluded and agreed on by the institutions before starting the investigations. In the long term, the CDC is also expected to assist the technology transfer and lab capacity-building of the labs in Brazil skilled to perform these exams in an independent way (COELHO, 2016a; 2016b).

Since 2012 the Ministry of Health partners with the CDC for cooperation on health issues. In addition to the agreement to develop a vaccine against the Zika virus which includes the Evandro Chagas Institute (IEC), the Butantã Institute, the US National Institutes of Health (NIH) and the Texas University Medical Branch, there is a partnership between the Brazilian Program on Dengue Control (PNCD) and the CDC aimed at studies to monitor congenital malformations in babies exposed to the Zika virus infection (BEATY; CALISHER; SHOPE, 1995; LANCIOtTI et al., 2008; HENNESSEY; FISHER; STAPLES, 2016; BRASIL, 2016a; 2016b).

The recent case studies presented herein are some few examples of the successful technical cooperation and of the sound working partnership between the CDC and the Health Surveillance Department of the Brazilian Ministry of Health. These studies illustrate the cooperation involving Brazil and the United States. Today the CDC participates in the investment in new technologies which is one of the axes of the National Plan to Combat the *Aedes aegypti* and the microcephaly being executed by the federal government (BRASIL, 2016a; 2016b).
REFERENCES


Coping with the epidemic
Role of the EpiSUS-CDC. State Seminar on Microcephaly
Photo by: Tereza Santa Cruz
The lab action to cope with the epidemic

**CONTEXT**

The General Coordination of Public Health Labs (CGLAB) of the Health Surveillance Department (SVS), Ministry of Health, coordinates actions and activities at national level aimed to control diseases and conditions through the offer of inputs, technical training and implementation of the network to optimize the lab diagnosis of conditions of public health concern in Brazil.

The Central Public Health Lab (Lacen) was established in 1935 and, throughout these years, has been one of the main diagnosis instruments in the units that provide health care to the population. In 1971 it was incorporated to the Network of Public Health Labs established by the Ministry of Health. However, it was not before 2004, upon the publication of the GM Order # 2031 on September 23, 2004, that the National System of Public Health Labs (Sislab) was created.

In the recent restructuring of the Sislab the four national lab networks were corroborated, namely: National Network of Epidemiological Surveillance Lab, National Network of Environmental Surveillance Lab, National Network of Sanitary Surveillance Lab and National Network of High-Complexity Medical Care. The networks were structured in sub-networks specified by conditions or programs, with the following classification of lab units: Collaborator Centers (CC); National Reference Lab (LRN), Regional Reference Lab (LRR); State Reference Lab (LRE) or Central Public Health Lab (Lacen); Municipal Reference Lab (LRM), Local Labs (LL) and Frontier Labs (LF).

The Lacens report to the State Health Departments and hold the strategic mission of performing accurate and timely lab diagnosis to the epidemiological, environmental and sanitary surveillance systems. Its main actions are grounded on epidemiological criteria in the field of clinical analysis and in the solution of public health problems. It plays a core role to the health surveillance because it subsidizes actions aimed to the population’s health.

Just like the Public Health Lab, the Lacen’s profile is different from the other labs because it carries out technical activities of research and prevention and promotion of collective health. It works mainly on the lab diagnosis of mandatory notification conditions, i.e., of concern to the Epidemiological Surveillance.

To fulfill with its tasks, the Lacen makes clinical and epidemiological diagnoses with samples from patients suspected of diseases of health concern. Moreover, it meets the analytical demand of products related to sanitary surveillance such as food, medications and home sanitizers.

The Lacens determine the etiology of the diseases that affect the community, identify the direct and indirect causes, and provide accurate and reliable information to medical-sanitary care professionals to adopt proper measures on diseases prevention and control.

According to the Ordinance # 2031 of September 23, 2004, the General Coordination of Public Health Labs (CGLAB) is responsible for the coordination,
standardization and supervision of the sub-networks of labs belonging to the National System of Public Health Labs in the activities of Epidemiological Surveillance and Environmental Surveillance.

Within the SVS scope, the CGLAB is tasked, among others, with the duty of fostering the labs network structuring and acquisition of inputs for the methodologies ELISA, Immunochromatography, RT-qPCR, Kato-Katz parasitological method and Immunofluorescence for the laboratorial diagnosis of measles, German measles, parvovirus, respiratory virus, bacterial meningitis, dengue, Zika, chikungunya, tuberculosis, human and canine leishmaniasis, Chagas’ disease, schistosomiasis, Hansen’s disease, hantavirus, rabies, rotavirus and cholinesterase dosage.

The progress in the diagnosis of diseases of public health concern in the last few years demanded the implementation of more advanced techniques, and the molecular biology is largely used in several areas of research. The biggest impact is on the diagnosis of infectious diseases, mainly those caused by non-cultivable microorganisms, of slow growth or which demand highly-specialized culture medium, such as virus, some bacteria, fungi and protozoa.

The technique is mandatory since 2002 – according to the Ordinance # 262 of February 5, 2002, issued by the Ministry of Health – with the inclusion of tests of amplification and detection of nucleic acids in all blood samples of donators.

Since 2009 the CGLAB has worked to implement on the 26 Lacens of the Brazilian states and the Federal District the molecular biology methodology based on the PCR (Polymerase Chain Reaction) technique for the laboratorial diagnosis of infectious-contagious diseases.

To that, the CGLAB is funding the purchase of diagnostic reagents and training professionals in those labs to perform the RT-qPCR technique, mainly to employ the technique to the diagnosis of influenza, meningitis, dengue, chikungunya and Zika.

The Molecular Diagnosis is an area of the molecular biology that employs techniques based on the principles of nucleic acid hybridization to detect and characterize the infectious agents or relevant genetic characteristics.

The use of these techniques, mainly the PCR and today the real-time qPCR – Quantitative Polymerase Chain Reaction, has promoted great advances in the regular clinical lab analyses because of the method accuracy and short testing time.

The items and methodologies acquired by the CGLAB are standardized by strategies, recommendations and technical protocols validated and adopted by the technical areas in Health Surveillance to cope with communicable diseases, as provided for in Ordinance # 204 of February 17, 2016 which defines the National List of Compulsory Notification of Diseases, Conditions and Public Health Events.

The CGLAB provides inputs to the labs belonging to the National Network of Public Health Labs for the laboratorial diagnosis of diseases and conditions of notification and concern to health surveillance, according to the Ordinance # 1378 of July 9, 2013, which are crucial to monitor the circulation of emerging and re-emerging diseases all over the national territory.

The centralized purchase of inputs aims to standardize the laboratorial diagnosis in the Network; supply quality inputs validated by the National Reference Labs to each condition; ensure quality and, thus, reduce analytical biases in the exams.

**ZIKA VIRUS**

When the Zika virus circulation in the national territory was confirmed, only the IEC, LRN for arboviral diseases and the Oswaldo Cruz Foundation (Fiocruz/RJ) performed the diagnosis of suspected cases. After the declaration of Public Health Emergency of National Concern (PHENC) in November 2015, the network of Sentinel Labs was defined. It was made up by the IEC, Fiocruz/RJ, Fiocruz/PE, Fiocruz/PR and the Adolfo Lutz
Institute (IAL), in charge of performing the Zika virus diagnosis to the other labs.

Later on, with the increased demand and the need to structure a diagnosis network, the Sentinel Labs became part of the Zika Reference Labs.

By that time, the molecular biology (Reverse Transcriptase Quantitative Polymerase Chain Reaction – RT-qPCR) was the methodology recommended as gold-standard test by the Reference Labs and advocated in the network of laboratorial diagnosis for the Zika virus fever in Brazil was through the molecular biology.

Usually, the CGLAB plans the purchase of diagnosis inputs at least one year in advance. However, because of the Public Health Emergency of International Concern (PHEIC) declared in February 2016, and considering the required monitoring of likely cases of congenital disease associated with the Zika virus, the purchase of reagents for the Zika virus diagnosis was of emergency nature, to follow-up likely cases of congenital disease associated with this virus, whose occurrence pattern changed in 2015.

The initial amount of inputs agreed on by the SVS to purchase the reagents for diagnosis by molecular biology, through the CGLAB, was of 2 million reactions a year.

The first acquisition for the Zika virus diagnosis was through bid, as emergency and in record time of three months, through the Evandro Chagas Institute (IEC/PA), in quantity enough to perform 500 thousand reactions. Deliveries were divided in two parcels of 50% each.

The first distribution of the 250 thousand reactions was in February 2016 to 23 labs, as follows: 18 Lacens and 5 LRs (Figure 1). By that time the labs had the equipment, had been trained and skilled in the RT-qPCR technique, and provided 69% of the network with implemented routine. The first distribution phase aimed to supply the labs skilled in the technique.
The second distribution phase started in April 2016 and the remaining 250 thousand reactions were distributed to 20 Lacens and five Reference Labs. The goal for the second distribution phase was to meet the demand of each lab based on the production of exams performed by each Lacen.
Today, 24 Lacens account for 88% of the network of labs structured with equipment and skilled experts to perform the RT-qPCR technique. The CGLAB gathers efforts – in addition to the consistent concern in permanently supplying inputs and training to its technical staff and labs technicians and managers – to ensure the modernization of the Sislab labs. It is common sense that the implementation of totally automated methodologies is crucial to provide labs with the required conditions to timely meet the increasing demand for more complex exams, with traceability and the required quality (Figure 3).
It is worth mentioning that there was no shortage of inputs for this methodology in that period. However, the need to monitor the likely cases of congenital diseases associated with the Zika virus demanded a new diagnosis strategy to screen the likely cases and ensure the proper care to mitigate damages caused by the Zika virus to the affected children.

Also worthy of notice is that the first record by the Brazilian Health Surveillance Agency (ANVISA) of IgM/IgG immunochromatographic assay (quick test) and an IgM anti-Zika enzyme immunoassay test (ELISA) was in February and April 2016, respectively. In order to ensure the reliability and safety of tests to be implemented in the network, the CGLAB asked the National Institute of Quality Control (INCQS) and the Brazilian Health Surveillance Agency to evaluate the performance of those tests. The first assays performed by the INCQS show low sensitiveness and specificity in the tests, making them unfeasible considering the standards established by the Ministry of Health to purchase tests by that time. It was only by mid-September that products presented satisfactory results regarding the efficacy of the quick tests and ELISA IgM for acquisition through the Logistic Department of the Ministry of Health (DLOG/MS).

Therefore, the purchase of 3.5 million units of quick test is scheduled with waiver of bid by technology transfer to the Baiana Foundation (BahiaFarma), and 1 million
ELISA IgM anti-Zika tests, through bid, scheduled to be delivered early in 2017.

The quick test aims to investigate the immune condition of the health service user by the time of the medical appointment, either during prenatal or in any other situation the physician deems to be necessary. This test used for screening will not be provided to the Lacens, but to the health services of all states, after tracking the state health units – a work being performed by the Health Care Department (SAS). To be supplied with the quick tests the health unit must have proper facilities to store the kits and a minimum lab infrastructure with collector, needles and syringes, dry pipes, disposers and centrifuge. The ELISA IgM anti-Zika tests, in turn, will be used as confirmatory tests of recent infection whenever the quick test is reagent, and will be performed at the Lacens of each state.
Actions in states and municipalities
Actions of Prevention and Control on the street on February 12 and 19, 2016: Ministry of Health and Cufa promote cleaning actions at Rocinha
Photo by: Thamyres Ferreira
The frontline municipalities

By the end of last year six Brazilian states declared emergency state and made news in the international media. By that time, the country was starting to face what was evidenced to be the biggest public health issue in the last few years: the Zika virus and its association with the high number of cases of babies born with microcephaly. The virus, transmitted by the Aedes aegypti mosquito, quickly spread over all regions and reached other countries in America before being considered an international emergency by the World Health Organization.

The expression ‘triple epidemic’ refers to the incidence of dengue, chikungunya and Zika – three types of virus transmitted by the same species of mosquito. In 2016, until March, 500 thousand likely cases of dengue were notified in Brazil, while 14 thousand cases of chikungunya were notified. The Zika virus, in turn, started being detected in Brazil in April 2015, and spread all over the states. However, in the epidemiological light the Zika virus is a serious threat if it is found in assays performed in pregnant women because of the likely association with congenital microcephaly.

Pernambuco was the state with more cases of infection with Zika virus and microcephaly, followed by Bahia, Paraíba, Rio Grande do Norte and Ceará. Health has always been a hard reality in the Northeast municipalities. And the Zika virus came to worsen the situation even more. In Jaboatão dos Guararapes, Metropolitan Region of Recife, only 10% of the municipality is serviced with basic sanitation and the epidemic proliferation was drastic, according to Gessyanne Vale, the municipal health secretary of Jaboatão dos Guararapes and Head of the Pernambuco Council of Municipal Health Departments (Cosems/PE).

This is one of the main problems in the municipality, with drastic impacts on health. We have always had many cases of dengue because of the areas where the mosquito grows. Lately, in addition to dengue we have started notifying countless cases of Zika.

Besides the lack of basic sanitation there is an even worse situation: lack of water.

In municipalities close to ours, located in the Northeast arid region (sertão) residents have no drinkable water, the water tank truck supplies twice or three times a month. So, they have to store water and these reservoirs become mosquito breeding sites, the secretary said.

In the Northeast nearly 80% of the mosquito larvae’s deposits were found in water reservoirs, most of which improvised to overcome water supply problems.

This situation is added with the underfunding of health with serious tendencies to worsen because of the Proposal of Amendment to the Constitution (PEC 241/CD and PEC 55/SF). The direct consequence of that PEC is the freezing of federal public expenditures in health for 20 years – an extremely serious threat to the Unified Health System (SUS). Based on studies, the National Council of Municipal Health Departments (Conasems)
evidenced this shortage and likely impact on the Brazilian public health.

In the heart of this problem in Brazil, the municipal health secretary of Recife, Jailson Correia, reported the difficulty faced by the municipality. According to him, the number of Zika cases increased very quickly, and this challenge was under the municipality’s responsibility.

The epidemic came in a critical moment of shortage of resources. We were over-stretched and experiencing the biggest public health crisis ever in the country. We developed actions such as the monitoring of Aedes developing sites at the Situation Rooms, which are also present in other Brazilian states and municipalities, in addition to educational and informational campaigns. We are betting on all forms to raise awareness, even the bread bags of most bakeries in the city bear information about how to eliminate the mosquito developing sites, the secretary said.

The Situation Room mentioned by Jailson is one of the 26 State Rooms spread all over Brazil, which were established after the declaration of Public Health Emergency of National Concern (PHENC).

On November 11, 2015 the Ordinance GM/MS # 1813 declares “Public Health Emergency of National Concern (PHENC) because of the change on the pattern of microcephaly occurrence in Brazil” and establishes the Public Health Emergency Operations Center (Coes) as a mechanism of coordinated national management of the response to the emergency at national level. The establishment of the National Coordination and Control Office of Combat to the Aedes (SNCC), where the Conasems has a seat, was followed by the installation of the State and Municipal Rooms.

The National Coordination and Control Office aims to coordinate the support to the other Rooms – State, of the Federal District and Municipal – to monitor and control the Aedes, and clarify doubts about the topic and foster actions through videoconferences. The State Rooms support the Municipal Rooms. Despite the instruction of assembling Rooms only in bigger municipalities, now there are more than 1,000 rooms in Brazil, made up by representatives of several departments to ensure the cross-sector nature of the control actions, and the Cosems that represent the municipal health departments at state level.

The Conasems is the national representative of the municipalities in the scope of the Unified Health System (SUS) tripartite management. The core role of this representation in the SNCC was crucial to facilitate the communication with municipalities aiming at mobilization and to combat the Aedes.

Special reference should be made to a core trait of the SNCC: the intersectoral approach. This approach enabled changing the form to combat the Aedes and broke the paradigm of the health sector’s exclusive responsibility. The intersectoral sharing of responsibilities in the combat to the vector is of utmost relevance, since this concept perceives and works on the interdependence of several factors, thus joining strengths and maximizing efforts to achieve results.

When the SNCC was created, the first guideline focused on actions to combat the Aedes aegypti to set directions to the organization and execute actions to intensify the combat to the mosquito in all municipalities to reduce the Aedes infestation index.

The main contribution of the Conasems was the coordination with the Cosems – which are the municipal representations at state level – towards the mobilization and engagement of the municipal leadership in the fight against the Aedes aegypti.

In this process featured by the Conasems, many strategies were proposed, discussed and passed in the meetings of the Conares – representation forum of the Conasems’ organizational structure.

Following we describe these strategies, emphasizing the importance of putting these in practice simultaneously. The order of description is not related to the importance of the action, since what really matters is the gathering of efforts.
The first one was the Conasems’ presence in the everyday work of the national room with the collaboration and contribution of the municipal vision in the process, as well as with the proposal of coping actions, being protagonist in this dialogue.

Another strategy that in our view was very appropriate to promote the municipal leadership engagement in the process was that of videoconferences regularly organized between the Conasems and the Cosems. These videoconferences were held in February and July 2016, on a weekly basis, to keep the Cosems updated about the strategies and decisions made at the SNCC and thus, in a quick and efficient way, keep municipalities motivated to execute and monitor the actions and also to get updated information and clarify doubts inherent to the process of building strategies to combat the vector. The Cosems have seat in the state rooms but, nonetheless, the Conasems’ strategy of also holding videoconferences was extremely efficient and profitable since the direct contact and frank dialogue provided reliability and efficiency to the communication.

Moreover, the Conasems produced and shared reports on the SNCC decisions to make them more understandable to the municipal leadership and provide feedback on the information. Municipalities had a direct channel opened by the Cosems and Conasems to criticize, make suggestions and propose changes to make the process more efficient.

The Conasems also disseminated – and still disseminates – in real time the epidemiological report prepared by the Health Surveillance Department (SVS).

Another communication front adopted was the direct dialogue between the Conasems’ technical advice with the institution’s leadership, generating quick and consistent information to subsidize the decision-making process.

All these actions have been presented, updated and discussed in all the Conares meetings in 2016, keeping the Conasems state representation informed and active in the process.

An innovative initiative was the creation of a blog with contents related to the epidemic, which integrated all pieces of information and newsletters, reports of successful experiences, guidance to managers, map of notified cases, protocols, among others. Thus, the municipal manager could find all the required and updated information in one single place.

This protagonism coordinated and concerted among the state representations in those spaces was extremely important and efficient, and ensured that all strategies proposed were well-grounded and validated by the municipal representation, depicting the municipalities’ reality.

We are now participating in the planning of actions for 2017, using the lessons learned in 2016 to improve the process and correct likely mistakes.

Jailson, Recife Municipal Health Secretary commented on the Ministry of Health support specifically to that municipality of Pernambuco.

“We designed a coping project and submitted it to the Ministry. They offered per capita transfer focused on the combat to the mosquito, but giving the municipality freedom to decide about investments.”

According to Josete Malheiros, head of the Cosems Ceará, despite missing resources the municipalities were responsible for providing care to people.

“The municipalities of Ceará are among those with the largest number of the mosquito developing sites, and we miss basic inputs, we are almost out of larvicides and the climate is totally favorable to the mosquito reproduction”, he said.

MICROCEPHALY: ONLY THE TIP OF THE ICEBERG

Everyday new cases came to hospitals in Recife – 18 on the peak of the crisis in November 2015, according to the Recife Health Secretary, Jailson Correia, who is also infectious disease specialist and pediatrician.
“In my whole professional life I saw children born with microcephaly and other congenital malformation diseases, but I’ve never seen anything like what I saw in the last months in the hospitals of Recife. I talked to many neurologists who work in the state and they said the same thing”, he said.

In 2015 the number of suspected cases of microcephaly was 400% bigger than the figures for the previous year, when 147 babies were born with the condition. The number of confirmed microcephaly cases in Brazil was as high as 1,113. Altogether, there were 7,015 notifications since the investigations started, from October 22, 2015 to April 9, 2016. Of the confirmed cases of microcephaly, 189 tested positive to the Zika virus.

Microcephaly was underreported and in the last months the notification became compulsory.

“This collaborates with the high numbers but cannot effectively explain what is happening. The situation is a quite complex challenge. We are literally writing a new chapter of the section of infections diseases, of congenital malformations. Never in our history the Zika has been associated with microcephaly”, Jailson stated.

According to him, the microcephaly cases are only the tip of the iceberg.

“Unfortunately we are finding problems in babies who were born normal, with no suspicion of microcephaly but whose mothers have surely got Zika during pregnancy. It means that we are following up the development of children born with the disease, but there are many other children apparently healthy who, in principle, would not need early stimulus and monitoring, but who have great chances of not having the proper development."

And he added:

“It is still a mystery for us which could be the disabilities, the degree of those disabilities, the standard of lesions, the repercussions on other areas of the organism and the whole development of these babies born from a pregnancy in which the mother had been infected by the Zika. These questions are being discovered and debated in an unprecedented way all over the world.”

Another important factor is the system’s difficulty regarding early diagnosis and monitoring during pregnancy and birth, due to late access to exams.

Throughout the epidemic we found that many microcephaly cases are not related only with the Zika virus. These could be related with other diseases during pregnancy such as syphilis and toxoplasmosis, for example, and could cause the same damages to the child. Usually these pathologies can be healed and should be identified in the prenatal exams.

The epidemic of dengue, Zika and chikungunya unveiled weaknesses in the prenatal actions delivered by the basic health care in the municipalities.

This process led the Tripartite Inter-managers Commission (CIT) to pass the Inter-ministerial Ordinance # 405/MS/MDSA, of March 15, 2016, which established in the scope of the Unified Health System (SUS) and the Unified Social Assistance System (SUAS) the Quick Action Strategy to Strengthen Health Care and Social Protection to Children with Microcephaly. This strategy is a set of measures focused on the health care and assistance to these children, such as guidance to families about early stimulation, with no need to wait for a specialized medical appointment. Evidence show that the earliest the child is stimulated, the less brain damages s/he may come to have.

Before these measures, the hard access to specialized clinical assistance (neurological follow-up and specialized exams) because of the slowness to get the results, book a visit, regulation of medical appointments and procedures, in addition to the vision that was focused on procedure as the main component to start the therapy, impaired many children from taking early therapy. With the new logic of diagnosis at the maternity and enhanced protagonism of the
basic health care, the Health Care Network had to be organized to respond to these needs.

The basic health care took on the health care management, providing guidance to families on early stimulation actions, childcare, greater coordination with the specialized care and identification of the families’ social risk, thus granting the Social Assistance Continued Allowance (BPC) to these children.

Once again the Conasems played an important role in the mobilization of the municipal health departments that, despite the scarce resources, endeavored to let us work to minimize the damages caused by microcephaly in children and to support the families.

However, what we observed is that municipalities are once again urgently called to take on executive responsibilities in the system that not always come jointly with the due funding or even the shared responsibility between the states. Although understanding the Basic Health Care role as coordinator of the network and of the care, many municipalities still miss the state’s and even the federal government’s technical and financial support.

The training of Health workers is another action front in which Conasems participate to qualify the support to municipalities and enhance the response to families of babies with microcephaly.

In partnership with Johnson & Johnson and the Institute of Research and Support to Social Development (IPADS) the Conasems participates in the coordination of the “ZikaLab” Project – Lab to Train Health Workers in the Context of Microcephaly. The project aims to implement a capacity-building program focused on Health workers, promoting intersectoral actions (Health, Education and Social Assistance) to improve the care and assistance to families in the combat to the Zika virus and microcephaly. The ZikaLab was developed to support Brazil through innovations in the Education in Health processes. It focuses on the mother-child cycle and works with the municipal health team, training the SUS workers to provide care to pregnant women and babies with Zika virus and microcephaly in the most affected territories in Brazil. The project intends to train teams to welcome the families and ensure line of care to babies with microcephaly. This is a 60-hour qualification offer and six municipalities participate in the project: Recife/PE, Campina Grande/PB, Salvador/BA, Juiz de Fora/MG, Araguaína/TO and Cuiabá/MT. The proposal is to train around 1,300 workers in 26 classes, who will further serve as multipliers in the health teams and other institutions in their territories.

In another partnership, the Conasems has supported, through mobilization and communication, the Inclusion Network Project – an initiative of the United Nations Children’s Fund (UNICEF), in partnership with the Brazilian Ministry of Health and the Pan-American Health Organization (PAHO/WHO). The goal of the initiative is to elaborate, implement and evaluate an intervention methodology for the integral, integrated and humanized care to pregnant women, families and caregivers of children with congenital ZIKAv syndrome (SCZv) and other disabilities. Still in the line of training, the project proposes expanding the audience and works on three training fronts: community, the health care worker and the municipal health system leadership worker. Here the work is limited to the two more affected municipalities in Brazil: Recife/PE and Campina Grande/PB.

The Conasems has also participated in the Work Group headed by the Pan-American Health Organization / World Health Organization in partnership with the Ministry of Health, the UN Children’s Fund (UNICEF), the United Nations Population Fund (UNFPA) and the United Nations Entity for Gender Equality and Women’s Empowerment (UN Women) to align and maximize strategic actions to strengthen health care and social protection to individuals affected by the Zika virus.

The increased number of cases of babies with microcephaly has surely caused surprise, but if we can say something we would surely say that everyone got mobilized, thought and put in practice many strategies.

Results are noticeable and positive. The first babies born with microcephaly associated with the presence of
the Zika virus are completing their first year of life and many, monitored since the beginning, show the results of the early and qualified intervention, against the most pessimistic forecasts.

The most affected municipalities, such as Recife and Campina Grande, got organized and provided the proper assistance and care to pregnant women, babies and families. There is a lot yet to be organized and improved, another summer is coming and the combat to the mosquito must be restless.

Is there a solution?

In face of the challenge of combating the mosquito vector of so many diseases, the Conasems suggests primordial changes and proposes approaches:

**STRENGTHEN** the SUS: provide proper funding to public health and promote intersectoral actions to combat the Aedes.

**FOCUS** on the enhancement of the Health Surveillance and Promotion processes, fostering changes on the current disease-focused model.

**INVEST** in basic sanitation, proper garbage collection and urban cleaning.

**PROMOTE** the integration of Health Surveillance actions with Basic Health Care.
In face of the challenge of combating the mosquito vector of so many diseases, the Conasems suggests primordial changes and proposes approaches:

- Strengthen the SUS: provide proper funding to public health and promote intersectoral actions to combat the Aedes.

- Focus on the enhancement of the Health Surveillance and Promotion processes, fostering changes on the current disease-focused model.

- Invest in basic sanitation, proper garbage collection and urban cleaning.

- Promote the integration of Health Surveillance actions with Basic Health Care.

- Qualify Health professionals or the early diagnosis during prenatal care through ultrasound imaging, followed by assistance to the mother and the child at birth, promptly acting on early stimulation, ophthalmological evaluation (red reflex test), hearing evaluation (OAE test) and other associated pathologies (neonatal heel prick) while waiting for the medical appointment and specialized exams.

- Organize the Regional Health Care Network for early actions on the management of care to children with microcephaly and pregnant women affected by the Zika virus to minimize further damages.
The work of states

Since the first notifications suggesting a rise in the number of microcephaly cases in the Northeast Region, the Brazilian public health started watching out.

The first State Health Department (SES) to identify a change on the occurrence pattern based on the communications by the network professionals was Pernambuco (PE) in the first weeks of October 2016 (CONASS, 2015; BRASIL, 2015b). In that same month the SES/PE notified the Ministry of Health; established an Emergency Operations Center (Coes) to discuss the cases; planned actions on care to mothers and their babies; and started – jointly with the municipal health departments – investigating the cases reviewing medical reports, interviewing family members and gathering lab exams (BRASIL, 2015b; DIMECH, 2016).

Early in November the SES/PE published the first version of a Clinical-Epidemiological Protocol with guidance to support the clinical and epidemiological investigation, criteria to detect and define cases, and the flow for care, diagnosis and assistance (DIMECH, 2016).

The Ministry of Health has also responded very quickly, providing technical support to the SES and municipal departments, and promptly activating the Team of Quick Response to Public Health Emergencies of the Ministry of Health (EpiSUS). On November 11 the situation was declared to be Public Health Emergency of National Concern (PHENC) (CONASS, 2015; BRASIL, 2015b; DIMECH, 2016).

Since the beginning it was hypothesized that the rising in the number of microcephaly cases, which some time later appeared as one of the likely manifestation of a congenital syndrome characterized by malformations of the central nervous system, could be associated with the congenital infection with the Zika virus. This correlation was first considered because of the temporal relation with the period of greater circulation of the Zika virus in the Northeast Region, and became more and more likely as new assays were performed (CONASS, 2015; BRASIL, 2015b).

In face of these events, the National Council of Health Secretaries (Conass) got mobilized and participated in the debates with the Ministry of Health teams, fostering the exchange of information among the experts from the state departments who participated in its Technical Chamber of Epidemiology.

Considering the seriousness of the situation, on November 20 the Conass organized in Salvador a meeting of the Northeast Region Health Secretaries (CONASS, 2015).

In a document prepared in that meeting and submitted to the then Minister of Health, Marcelo Castro, the secretaries “considering the significant increase of cases of dengue in 2015; the introduction, in 2014 and 2015, of the Aedes aegypti mosquito-borne chikungunya and Zika viruses in the Brazilian territory, concentrated in the Northeast Region; the increased neurological complications associated with the Zika virus like the Guillain-Barré syndrome, and the situation of Public
Health Emergency of National Concern” resulting from the change on the microcephaly occurrence pattern, with irreversible sequels that demand permanent care, “with consequent economic and social impact, and impact on the organization of the Health System as a whole”, urged “stronger engagement of the Brazilian State to cope with this national emergency” by “integrating the three government levels and through the effective participation of the civil society.” It also proposed the establishment of a “National Action Plan to Combat Arboviral Diseases and their complications” comprising “integrated and intersectoral actions on the vector control, surveillance and organization of the line of care to provide qualified assistance to suspected cases”; incentives and financial support to the “scientific institutions for the sustained development of research, studies and development of new methods and technologies to control the vector and cope with the complications associated with arboviral diseases” and the “effective and timely liability of the many governmental sectors involved in the combat to arboviral diseases including, in addition to Health, the areas of Environment, Infrastructure, Urban Development, Finances, Education, Communication, Social Assistance and the Armed Forces, among others.” Considering the “overriding need for new resources and investments” to cope with the problem, it also proposes the creation of the emergency fund for actions to combat arboviral diseases and control their complications (CONASS, 2015).

The Conass Chairperson, who was also the Rio Grande do Sul State Health Secretary, João Gabbardo dos Reis, in an interview to the Consensus magazine during the Conass Assembly held on November 25, highlighted that “although being not sure about the relation between the Zika virus and microcephaly” by then, managers could not waste time, assuming that such relation was true, taking the initiative and the required measures, enhancing actions of combat to the mosquito which should already be in place to control the dengue (CONASS, 2015).

The Assembly on November 25 was also attended by the then Minister of Health, Marcelo Castro, the then Health Surveillance Secretary, Antônio Carlos Nardi, and the then director of the Epidemiological Surveillance Department, Cláudio Maierovitch. Marcelo Castro expressed his support to the measures recommended in the Conass document and ensured these were in line with the Ministry of Health’s ideas. The minister explained that, despite the care required in face of the unexpected situation in the country and the lack of references in the global literature up to then, considering the evidence found, it was time to share decisions, execute the required actions and, above all, prevent the expansion of the Aedes aegypti population in the next summer (CONASS, 2015).

On November 28 the correlation between the Zika virus and the occurrence of microcephaly cases was formally recognized based on the results of epidemiological studies and the identification of the virus in the amniotic fluid of two pregnant women in Paraíba (who had exanthematous disease during pregnancy) and on tissues of a newborn with microcephaly who died in the state of Ceará. On November 29 the events were declared to be Public Health Emergency of International Concern (PHEIC) (BRASIL, 2015b).

In face of that confirmation the three managerial levels intensified the ongoing actions implementing the National Plan to Fight Microcephaly, launched on December 5. The highlights were the surveillance actions for microcephaly cases and Zika (which was included among the diseases of mandatory notification), vector control and organization of health care to assist and provide care to affected pregnant women and children, also attaching priority to the organization of the rehabilitation network and early stimulation of newborns (BRASIL, 2015a). Moreover the National Coordination and Control Office was established, with the participation of several ministries, the Conass and Conasems. State and municipal offices have also been implemented.

Still in the first Conass Assembly in February 2016, the state health secretaries sustained the topic as priority, promoting debate with the participation of four renowned infectious disease experts seasoned
in the fields of management, teaching and research. Professors Dr. Marcos Boulos, Pedro Tauil, Roberto Badaró and Wilson Alecrim presented and discussed the existing options and likely new technologies to cope with arboviral diseases. Based on an evaluation of the factors that determined the maintenance of the *Aedes aegypti* infestation levels, the triple epidemic of dengue, Zika and chikungunya, and the inexistence of vaccines and etiological therapies that were efficacious, effective and safe, it was evidenced that the *Aedes aegypti* is the only vulnerable link of the epidemiological chain to reduce the transmission of those diseases and, therefore, controlling that vector is crucial (CONASS, 2016b; TAUIL, 2016).

The debate clearly showed the need for associating different strategies, since there is no unique, magical or definitive solution (CONASS, 2016b; BADARÓ, 2016). As most of the developing sites are found in the domiciles, the population's engagement and actions of education in health to them must be enhanced considering that public authorities have difficulty to get into all the domiciles (CONASS, 2016b). Issues related to the accelerated urbanization process with unsuitable systems of housing, water supply and disposal of solid residues still demand priority and intersectoral work (CONASS, 2016b; TAUIL, 2016). Meanwhile, there is the need to improve the health inspection practices at domiciles and strategic areas such as tire shops, scrap yards, empty lands and cemeteries. To that, the teams of endemic disease agents should be qualified, and surveillance actions should be integrated with the primary health care actions (CONASS, 2016b).

In the same debate participants observed the need to expand the discussion on control of arboviral diseases towards more structuring actions, mainly regarding the environmental aspect. This motivated the re-insertion of the topic in the agenda for the next assembly on March 23. Representatives of the Health and Environment Group of the Brazilian Association of Collective Health (ABRASCO), the professors and researchers Marcelo Firpo Porto and Lia Giraldo da Silva Augusto were invited to attend the assembly (CONASS, 2016a).

The assembly showed that discussing a model focused not only on combating the mosquito, but also on the socio-environmental inequalities, their implications to health and on the strategies to promote health and eliminate breeding sites is crucial. Participants emphasized the need for a “positive agenda of transformation”, “favorable to collective health”, prioritizing basic sanitation, social and health inequalities, urban reform, the issue of garbage and access to quality water (CONASS, 2016a; PORTO, 2016). During the debate, the ABRASCO representatives emphasized their understanding that the model centered on chemical control (larvicides and insecticides) proved to be inefficient in the more than 30 years after their implementation (CONASS, 2016a; PORTO, 2016). In addition to “end the use of venoms” participants emphasized the need of “care with the new technologies that once again place the mosquito in the heart of the question, like in the case of poison bearer, transgenic and/or infected mosquitoes since these strategies are nothing but variations of the same model applied” (CONASS, 2016a; AUGUSTO, 2016).

In the occasion, the representatives of Pedra Branca (CE) Municipal Health Department, Ana Paula Albuquerque Vieira and Donizete Alves, reported the municipality’s experience with good vector control for over 10 years, using virtually no chemical control. The municipality work is focused on regular and periodic visits with actions on continuous education and inspection to remove breeding sites; monitoring the infestation using traps (known as *ovitrampas*) and using alternative methods such as plastered screens to protect the water deposits and larvivorous fish (CONASS, 2016a; ALBUQUERQUE; ALVES, 2016).

Prior to this assembly, on March 21 to 23, the Conass held a joint meeting of its technical chambers of Epidemiology and Environmental Health Surveillance, with the participation of the coordination of these areas in the SES and guest experts of the Health Surveillance Department of the Ministry of Health. The combat to arboviral diseases was the main topic of discussion. During the meeting the epidemiological situation was presented; the integration of dengue, chikungunya
and Zika surveillances was debated; the operational aspects to improve the Zika virus surveillance were detailed; the situation of the investigation of associated neurological complications was debated, including the presentation of the Bahia and Piauí SES’ experience in the investigation and monitoring of cases. Participants have also approached the Protocol of Surveillance and Response to the Occurrence of Microcephaly, occasion when the Pernambuco SES reported its experience in the investigation and monitoring of those cases.

The issue of vector control was deeply discussed, emphasizing the need for qualifying the field activities developed by agents of combat to endemics and the role of the state leadership to improve these agents’ training and supervision. The results of the international meeting held in February about new alternatives to control the *Aedes aegypti* were also presented.

Another issue approached referred to the environmental aspects related to the vector control such as safe use of insecticides, updating the recommendation to test workers for acetylcholinesterase, and safe use of larvicides mainly in water for human consumption. The SES/RS also reported its experience on this matter.

The environmental issue remained in evidence during the proceeding by the National Congress of the Provisional Remedy about emergency measures to control the *Aedes aegypti* that included a subparagraph allowing the incorporation of insecticide spraying by aircrafts for that purpose. When it participated in the Public Hearing about this matter at the House of Representatives, the Conass supported most of the proposals in the original text, but objected to this specific point. When the National Congress passed the Provisional Remedy, the Conass and Conasems prepared a joint note and formally requested the Ministry of Health to recommend the presidential veto to this proposal, because they considered that it not only posed risk to the environment and the population’s health, but was also of little efficacy in the combat to the *Aedes aegypti* that, in its adult stage, lives mainly in the domiciles.

Despite these initiatives and the contrary opinions of the technical areas of the Ministry of Health, when the Law 13.301 was enacted in June 2016 it maintained the subparagraph IV of the 3rd paragraph of article 1 which included the “permission for incorporating vector control mechanisms through the spraying by aircrafts upon approval of sanitary authorities and scientific evidence on the efficacy of the measure” (BRASIL, 2016). Since then, the Brazilian Health Council (CNS) and several state bipartite commissions (in charge of the Unified Health System – SUS governance in states), such as those from Amazonas, Ceará, Espírito Santo, Goiás, Paraná, Rio Grande do Sul and São Paulo, objected to the use of airway chemical control (CNS, 2016; AMAZONAS, 2016; CEARÁ, 2016; ESPÍRITO SANTO, 2016; GOIÁS, 2016; PARANÁ, 2016; RIO GRANDE DO SUL, 2016; SÃO PAULO, 2016).

The arboviral diseases, mainly the recent Zika virus epidemic and the unexpected arisal of the microcephaly outbreak, are one of the main public health issues in Brazil (and in the world). Much has been done in the light of building knowledge on the issue and organization of management towards the care, inspection and prevention of the problem. The Unified Health System and state managerial levels have mobilized strong efforts towards this coping.

In this sense, the Conass defined the maintenance and improvement of ongoing actions aimed to control arboviral diseases as one of the short-term priorities included in the proposed agenda of governability submitted to the Minister of Health, Ricardo Barros, in the beginning of his mandate.

Huge challenges persist. The intervention on determinant causes should be prioritized, and the responsibility over it cannot be restricted to the Health sector. The solution of problems such as uncontrolled occupation of urban spaces; poor basic sanitation; improper packaging, collection and disposal of garbage; the change of the populations’ attitude; and the maintenance of actions to control vectors should be managed through the implementation of integrated and continuous public policies, in an action jointly developed by the three government levels (CONASS, 2009).
The Health sector should get organized to fulfill its responsibilities before this challenge of efficiently working on: health (environmental, entomological, epidemiological and sanitary) surveillance; health care organization (from primary care to reference services); vector control; establishment of health promotion strategies that imply changes on the population’s attitude; and, permanent education of teams engaged in these activities (CONASS, 2009).

The National Council of Health Secretaries will keep on fulfilling its mission of promoting the coordination and political representation of the SUS state management, and provide technical support, disseminate information and promote the exchange of experiences. The development of specific project of support to the SES to combat arboviral diseases was incorporated to the operational planning of the Conass Executive Secretary for 2017.

REFERENCES


Knowledge dissemination
Minister of Health of Brazil meets the European Union ambassadors to discuss the Zika virus, 2/16/2016
Photo by: Rondon Vellozo/MS
Dissemination of knowledge, research and educational initiatives

INTRODUCTION

The team of the General Coordination of the Development of Epidemiology in Services, of the Health Surveillance Management Department, Health Surveillance Department, Brazilian Ministry of Health (CGDEP/SVS/MS), monitored the Zika virus epidemic since its early stages. Even before the detection of the Zika virus presence in Brazil, the editorial team of the SUS journal named Epidemiologia e Serviços de Saúde (Ress), edited by the coordination, was attentive to the international epidemiological scenario and encouraged the production of a Guest Column on the topic. To that, it invited experts in the area. The article named “Febre pelo vírus Zika” was published on the last Ress volume in 2015 (LUZ; SANTOS; VIEIRA, 2015). That was the first article on the Zika virus epidemic published in a Brazilian scientific journal.

The Boletim Epidemiológico of the SVS, also edited by the CGDEP/SVS/MS, was one of the first publications approaching the theme and has served as important means to the timely dissemination of information on the Zika virus epidemic in Brazil.

The efforts of the CGDEP/SVS/MS team, however, were not limited to the contribution by its editorial team. They also comprise several activities in the field of support to research, training of human resources in health, and participation in managerial spaces to cope with the public health emergency. These efforts are described below.

CONTRIBUTION BY THE EPIDEMIOLOGIA E SERVIÇOS DE SAÚDE (RESS) JOURNAL

The Ress is a journal of scientific nature and open access, published quarterly in hardcopy and electronic format. Its main mission is to disseminate the epidemiological knowledge applicable to actions of surveillance, prevention and control of diseases and conditions of public health concern to improve the services offered by the Unified Health System (SUS).

This journal edited by the CGDEP/SVS/MS was created in 1992 as the Informe Epidemiológica do SUS, in the institutional scope of the National Epidemiology Center of the National Health Foundation (Cenepi/Funasa). In 2003 it was named Epidemiologia e Serviços de Saúde: revista do Sistema Único de Saúde do Brasil. It became part of the Scientific Electronic Library Online (SciELO) Brazil collection in 2014; SciELO Saúde Pública in 2015, and in October 2016 it was indexed in the MEDLINE bibliographic database. The indexation on these collections, resulting from the compliance with strict criteria for admission and maintenance of journals, evidences the editorial quality of the Ress which is now among the main Brazilian scientific journals in the field of collective health.

All regular editions of the Ress from the last one in 2015 to the first edition in 2017 bring articles related to the Zika virus epidemic. These include three editorials, three guest columns, one review paper and four original articles (Chart 1). Moreover, there are other
articles on the theme in different stages of the editorial process and that are likely to be published in further editions of the journal.

### Chart 1
ARTICLES RELATED TO THE ZIKA VIRUS EPIDEMIC PUBLISHED IN THE EPIDEMIOLOGIA E SERVIÇOS DE SAÚDE (RESS) JOURNAL FROM OCTOBER 2015 TO MARCH 2017*

<table>
<thead>
<tr>
<th>Journal Edition</th>
<th>Type</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESSE v.24 n.4, Oct-Dec 2015</td>
<td>Guest Column</td>
<td>Febre pelo vírus Zika (LUZ; SANTOS; VIEIRA, 2015)</td>
</tr>
<tr>
<td>RESSE v.25 n.1, Jan-Mar 2016</td>
<td>Editorial</td>
<td>Desafios para o enfrentamento da epidemia de microcefalia (HENRIQUES; DUARTE; GARCIA, 2016)</td>
</tr>
<tr>
<td>RESSE v.25 n.2, Apr-Jun 2016</td>
<td>Editorial</td>
<td>Pesquisa e desenvolvimento para o enfrentamento da epidemia pelo vírus Zika e suas complicações (DUARTE; GARCIA, 2016)</td>
</tr>
<tr>
<td></td>
<td>Review paper</td>
<td>Estratégias de controle do Aedes aegypti: uma revisão (ZARA et al., 2016)</td>
</tr>
<tr>
<td></td>
<td>Review paper</td>
<td>Zika, dengue e chikungunya: desafios e questões (VALLE; PIMENTA, 2016)</td>
</tr>
<tr>
<td>RESSE v.25 n.3, Jul-Sept 2016</td>
<td>Guest Column</td>
<td>Sem bala mágica: cidadania e participação social no controle de Aedes aegypti (VALLE; 2016)</td>
</tr>
<tr>
<td>RESSE v.25 n.4, Oct-Dec 2016</td>
<td>Editorial</td>
<td>Evidências da vigilância epidemiológica para o avanço do conhecimento sobre a epidemia do vírus Zika (GARCIA; DUARTE, 2016)</td>
</tr>
<tr>
<td></td>
<td>Original Article**</td>
<td>Descrição dos primeiros casos de febre pelo vírus Zika investigados em municípios da região Nordeste do Brasil, 2015 (FANTINATO et al., 2016)</td>
</tr>
<tr>
<td></td>
<td>Original Article**</td>
<td>Características dos primeiros casos de microcefalia possivelmente relacionados ao vírus Zika notificados na Região Metropolitana de Recife, Pernambuco (VARGAS et al., 2016)</td>
</tr>
<tr>
<td></td>
<td>Original Article**</td>
<td>Microcefalia no Brasil: prevalência e caracterização dos casos a partir do Sistema de Informações sobre Nascidos Vivos (Sinasc), 2000-2015 (MARINHO et al., 2016)</td>
</tr>
<tr>
<td>RESSE v.26 n.1, Jan-Mar 2017</td>
<td>Original Article***</td>
<td>Síndrome de Guillain-Barré e outras manifestações neurológicas possivelmente relacionadas à infecção pelo vírus Zika em municípios da Bahia, 2015 (MALTA et al., 2016)</td>
</tr>
</tbody>
</table>

Source: Ministry of Health of Brazil.

* All articles are available online at the SciELO Portal: www.scielo.br/ress
** Articles published ahead of print.
The huge interest on the Zika virus epidemic has impacts on the Ress bibliometric indicators. From its online publication to October 2016, the guest column *Febre pelo vírus Zika* (LUZ; SANTOS; VIEIRA, 2015) had almost 22 thousand hits at the SciELO portal, followed by the editorial *Desafios para o enfrentamento da epidemia de microcefalia* (HENRIQUES; DUARTE; GARCIA, 2016) with almost 7 thousand hits in the same period. These were the Ress articles with more hits since the journal’s indexation to the SciELO Brazil Collection.

It is worth mentioning that, aiming at the quick and timely dissemination of the results of studies related to the Zika virus epidemic, from v. 25, n. 4 (Oct-Dec 2016) on the Ress started publishing articles in the ahead of print modality. This modality allows disclosing the articles approved by the Editorial Committee on the electronic version of the journal before the finalization of the other articles to be published in the same edition. The Ress adopted the ahead of print modality because of the situation of Public Health Emergency of National and International Concern that the Zika virus epidemic represented, in an attempt to contribute with the scientific development and the consolidation of evidence to subsidize the decision-making in clinics and public health (GARCIA; DUARTE, 2016).

Another relevant initiative of the Ress editorial team was to compile a list of sources of relevant information about dengue, chikungunya, Zika and *Aedes aegypti*, and make it available on the journal website (http://ress.iec.gov.br) still by the end of 2015. The list includes links to web pages of national and international institutions and publications that are reliable sources of updated and open access information relevant to understand the Zika virus epidemic.

---

SUPPORT TO RESEARCH

In recent years prior to the Zika virus epidemic in Brazil, the Health Surveillance Department (SVS) had approved, with resources from its own budget, more than R$12,815,000.00 to support strategic research works related to actions of surveillance, prevention and control of dengue (Chart 2). The CGDEP/SVS/MS monitors these research works and promotes the integration between scientific research and health surveillance management, promoting the debate of partial or final results during the Studies Cycle sessions or at the Scientific Meeting of Research Applied to Health Surveillance.

After the epidemic event detection, the Health Surveillance Department (SVS) of the Ministry of Health has mobilized financial resources for research works on the Zika virus and microcephaly, under the modality of direct contract, pursuant to the National Plan to Combat the *Aedes aegypti* and Microcephaly.

The SVS/MS has supported priority studies through direct contracting. The following are outstanding: studies series of cases, case-control to explain the associations of microcephaly occurrence with the Zika virus infection and of the infection with other neurological complications and, more recently, studies of cohort to assist pregnant women and children. Moreover, studies to investigate the Zika virus permanence in different body fluids, as well as studies to evaluate strategies to combat the *Aedes aegypti* are being contracted. The CGDEP/SVS/MS supported the hiring and monitoring of these assays that contributed with important inputs to understand the Zika infection. These are expected to provide, in the short-term, new scientific evidence to improve the diagnosis, therapeutics and implementation of responsive actions on surveillance, prevention and control.
### CHART 2
**RESEARCH ON SURVEILLANCE, PREVENTION AND CONTROL OF DENGUE SUPPORTED BY THE SVS/MS PRIOR TO THE DETECTION OF THE EPIDEMIC EVENT, 2009-2015**

<table>
<thead>
<tr>
<th>Research title</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implementation of viral surveillance of dengue using real-time PCR (RT-PCR) and geoprocessing in medium-size city in the state of São Paulo: what lessons about the epidemics we can learn from the population, vectors and space</td>
<td>Universidade Estadual Paulista (Unesp)</td>
</tr>
<tr>
<td>Evaluation of traps to the entomological surveillance of the <em>Aedes aegypti</em> to elaborate new infestation indexes</td>
<td>Fundação Oswaldo Cruz (Fiocruz)</td>
</tr>
<tr>
<td>Evaluation of traps to the entomological surveillance of the <em>Aedes aegypti</em> to elaborate new infestation indexes – Phase II</td>
<td>Fundação Oswaldo Cruz (Fiocruz)</td>
</tr>
<tr>
<td>Death from dengue as sentinel event to evaluate factors associated with the underreporting of dengue</td>
<td>Instituto de Medicina Integral Professor Fernando Figueira (Imip)</td>
</tr>
<tr>
<td>Development of a system of alert about dengue outbreaks using hybrid data from social networks, and entomological, epidemiological and climate monitoring</td>
<td>Fundação Oswaldo Cruz (Fiocruz)</td>
</tr>
<tr>
<td>Validation of the prognostic factors associated with dengue severity</td>
<td>Fundação de Medicina Tropical Dr. Heitor Vieira Dourado (FMT-HVD)</td>
</tr>
<tr>
<td>Risk factors to the severe forms of and deaths from dengue</td>
<td>Universidade Federal de Minas Gerais (UFMG)</td>
</tr>
<tr>
<td>Planning to introduce the vaccine against dengue in Brazil: characterization of the transmission dynamic, morbidity and mortality and immune responses to the different clinical forms of the acute phase of dengue, defining the best strategy to introduce the vaccine against dengue among our population</td>
<td>Associação Paulista para o Desenvolvimento da Medicina (SPDM)</td>
</tr>
<tr>
<td>Public expenses with actions of surveillance, prevention and control of dengue, tuberculosis, malaria and infection with HIV/AIDS</td>
<td>Fundação Oswaldo Cruz (Fiocruz)</td>
</tr>
<tr>
<td>DENGUE WEB: on-line system of real time information about dengue</td>
<td>Universidade Federal da Bahia (UFBA)</td>
</tr>
</tbody>
</table>

Source: Ministry of Health of Brazil.

### EDUCATIONAL INITIATIVES

Among others, the CGDEP/SVS/MS is tasked with the duty of promoting and monitoring the educational initiatives focused on the training and capacity-building of the SVS staff members, and of supporting the qualification of the SUS professionals aiming at the epidemiology development in health services.

The Zika virus epidemic was an unexpected and emergent event in Brazil, with limited knowledge reported in the scientific literature by the time it was declared to be a situation of Public Health Emergency of National Concern, soon followed by the declaration of Public Health Emergency of International Concern. In face of that, training human resources was crucial to cope with the epidemic, mainly in the clinical area.

---

*Free translation of the titles.*
The CGDEP/SVS/MS participated in the design and offer of three distance courses, offered in open access, about (i) clinical management of dengue; (ii) clinical management of the chikungunya fever; and, (iii) Zika: clinical approach in the basic health care. The courses were developed in partnership with the Department of Work and Education in Health Management (SGTES) of the Ministry of Health; the SUS Open University System (UNA-SUS); the Health Care Department (SAS) of the MoH; and, education institutions (Federal University of Mato Grosso do Sul – UFMS and Oswaldo Cruz Foundation – Fiocruz). Almost 40 thousand participants attended the course on Zika. Altogether, this initiative resulted in more than 100 thousand professionals from all states and the Federal District enrolled in these initiatives (Table 1), showing the huge capillarity of this education modality.

A highlight was the course on Zika, adapted and translated by PAHO/Brazil to be delivered in Spanish, and which reached 8,300 professionals enrolled with 89% of conclusion.

Under the Program on Institutional Development (PROADI) and in partnership with the Sírio Libanès Hospital, the SVS/MS has offered, under the CGDEP supervision, the Specialization Course in Health Surveillance, firstly to the states in the Northeast Region (800 vacancies) and, in the first quarter of 2017, to all the other Brazilian regions (800 vacancies). The topic of the Zika virus epidemic and its consequences was approached with the specialization students to make the training process more useful.

Another initiative focused on training the SVS professionals was implemented in partnership with the Johns Hopkins Bloomberg School of Public Health, a renowned institution in public health. The partnership was established in 2012 and in 2016 prioritized the training of eight Brazilian professionals in the Epidemiology Certificate Program (PCE). Of the five intervention projects developed, one approached the increased standard of microcephaly occurrence in

### TABLE 1

<table>
<thead>
<tr>
<th>Courses Offered</th>
<th>Offer Starting on</th>
<th># of participants enrolled</th>
<th>Partner Institutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zika: Clinical approach in Basic Health Care</td>
<td>Fev/16</td>
<td>42,767</td>
<td>UNA-SUS and UFMS</td>
</tr>
<tr>
<td>Zika: Clinical approach in Basic Health Care (in Spanish)</td>
<td>Aug/16</td>
<td>8,300</td>
<td>UNA-SUS and UFMS (translation by the PAHO)</td>
</tr>
<tr>
<td>Chikungunya Clinical Management</td>
<td>Dec/15</td>
<td>34,675</td>
<td>UNA-SUS and UFMS and Fiocruz/MS</td>
</tr>
<tr>
<td>Updating of the Dengue Clinical Management</td>
<td>May/12</td>
<td>37,675</td>
<td>UNA-SUS and UFMS</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>–</strong></td>
<td><strong>123,398</strong></td>
<td><strong>–</strong></td>
</tr>
</tbody>
</table>

Source: Ministry of Health of Brazil.

*Data updated as of November 2016.
Brazil, while two approached the increased incidence of dengue in different contexts (Pernambuco and Costa Rica). The professionals enrolled in the PCE had unlimited access to the international scientific literature, and were mentored by the JHU professors to design intervention projects.

Since July 2016 the CGDEP/SVS/MS held eight sessions of the Studies Cycle that were aired in real time all over Brazil and aimed to discuss the emergency-related aspects (Chart 3). The sessions were attended on-site by 273 professionals and had more than 3 thousand virtual accesses, evidencing huge interest in debating the topics approached.

### CHART 3
CONSOLIDATED OF THE SESSIONS OF THE SVS STUDIES CYCLE THAT APPROACHED ASPECTS RELATED TO THE ZIKA VIRUS EPIDEMIC, 2016

<table>
<thead>
<tr>
<th>Date</th>
<th>Topic</th>
<th>Lecturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/27/2016</td>
<td>Overview of <em>Aedes aegypti</em>-borne arboviral diseases in Brazil and in the world</td>
<td>Raimunda do Socorro da Silva Azevedo (Evandro Chagas Institute/SVS/MS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ana Carolina Faria e Silva Santelli (CGPNCD/SVS/MS)</td>
</tr>
<tr>
<td>8/19/2016</td>
<td>Update on the lab and imaging diagnosis of dengue, chikungunya and Zika and the associated complications</td>
<td>Ana Maria Bispo (Fiocruz/RJ)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maria de Fátima Aragão (Colégio Brasileiro de Radiologia)</td>
</tr>
<tr>
<td>9/23/2016</td>
<td>Microcephaly associated with Zika virus infection as Public Health Emergency and the Brazilian response</td>
<td>Wanderson Kleber de Oliveira – (CGVR/SVS/MS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maria de Fátima Marinho de Souza (DANTPS/SVS/MS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enrique Vazquez (PAHO).</td>
</tr>
<tr>
<td>10/14/2016</td>
<td>Strategies to control the <em>Aedes aegypti</em></td>
<td>Carlos Frederico Campelo de Albuquerque e Melo (PAHO)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flúvia Pereira Amorim da Silva (SMS – Goiânia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tatiana Mingote Ferreira de Azara (CGPNCD/SVS/MS)</td>
</tr>
<tr>
<td>11/11/2016</td>
<td>Recent evidence on the implication of the Zika virus on the microcephaly causality</td>
<td>Wanderson Kleber de Oliveira (CGVR/SVS/MS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Celina Maria Turchi Marlli (Merg Group)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patrícia Brasil (Fiocruz/RJ)</td>
</tr>
<tr>
<td>11/18/2016</td>
<td>Consequences of the Zika virus infection and implications to the health services organization</td>
<td>Vanessa Dios (Anis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mariana Bertol Leal (SAS/MS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cristina Valença Azevedo Mota (SES/PE)</td>
</tr>
<tr>
<td>11/25/2016</td>
<td>Zika virus infection and associated neurological complications</td>
<td>Raquel Lima Miranda (CDC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maria Lúcia Brito (Hospital da Restauração/Recife)</td>
</tr>
</tbody>
</table>

Source: Ministry of Health of Brazil.
PARTICIPATION IN THE MANAGERIAL SPACES

Since when the epidemic started, the CGDEP/SVS/MS has contributed with several activities to cope with the public health emergency. One example is the participation in the Public Health Emergencies Operations Center (Coes) established in November 2015 by the Ministry of Health. In principle, the center aimed to monitor the investigations and responses to the change on the epidemiological standard of microcephaly cases in Brazil. Over time, this goal was expanded to cope with the emergency.

The CGDEP/SVS/MS has also participated in the workshop about priority research on arboviral diseases. Organized by the Science and Technology Department, in partnership with the CGDEP/SVS/MS, this workshop was held in March and aimed to define priority research on the study of the Aedes aegypti-borne arboviral diseases (dengue, Zika and chikungunya).

Another role performed by the CGDEP/SVS/MS regards the participation in the National Network of experts in Zika and related diseases (Renezika) (Ordinance # 1046). The CGDEP/SVS/MS holds a seat in the Network Executive Secretariat as alternate representative of the SVS/MS, and in the Research, translation and dissemination of knowledge Work Group. This group is intended to subsidize the monitoring of studies related with the Zika virus and related diseases, and to promote the integration of research groups, identify funding sources and contribute to knowledge dissemination.

Also in partnership with the SCTIE/MS, the CGDEP/SVS/MS discussed guidelines to draft the Call 14/2016, carried out with the participation of the Brazilian Scientific and Technological Development Council/Ministry of Science, Technology and Innovation (CNPq/MCTI) and of the Coordination for Higher Education Personnel Improvement/Ministry of Education (Capes/MEC). Around R$65 million were invested to support the approved research projects. From November 30 to December 2, 2016 the CGDEP participated in the Ground Zero Workshop to discuss the required methodological adjustments and alignment of the 60 research projects approved under the Call MCTIC/FNDCT-CNPq/MEC-CAPES/MS-Decit/Nº 14/2016-Prevention and Combat to the Zika virus.

FINAL REMARKS

The unexpected Zika virus epidemic in Brazil challenged managers, Health professionals and national and international researchers to better understand and cope with the emergency of public health concern. The MoH coordinated the response to the epidemic and, since the beginning of the process, the CGDEP/SVS/MS has tried to shorten the gap between epidemiological evidence and the health decision-making process as scientific knowledge unveiled the aspects of that epidemic (which are not yet fully understood).

The regular publications of the Ress and the Boletim Epidemiológico, the offer of educational initiatives to the SVS and the SUS professionals, the induction and monitoring of priority research, and the discussion about their findings were the work fronts. The participation of the CGDEP/SVS/MS in the collegiate rooms established by the MoH and the SVS allowed the alignment between these actions and the emergency response coordinated by the MoH. The current epidemiological scenario and the persisting uncertainties on the epidemic course makes crucial to support and monitor the development of new studies; expand forms of discussion and appropriation of findings; train the SUS professionals; and, timely disseminate data on the monitoring and new scientific evidence to provide suitable response to cope with this situation.
REFERENCES


