

Concern over Zika virus grips the world

In the past week, the world has mobilised to tackle the latest threat to global health security—Zika virus, now spreading rapidly in the Americas. Udani Samarasekera and Marcia Triunfol report.



Worldwide concern over Zika virus (panel) and its temporal and geographical association with clusters of birth and neurological conditions escalated this week, with WHO declaring a Public Health Emergency of International Concern.

No doubt not wanting to repeat mistakes made in the west African Ebola outbreak, WHO was quick to raise the alarm. Briefing the WHO Executive Board on Jan 28, WHO Director-General Margaret Chan said Zika virus, now “spreading explosively” in the Americas, was deeply concerning for the organisation. Although a causal relation between infection with the virus and birth malformations and neurological syndromes has not been established, it is strongly suspected, Chan noted. “The possible links...have rapidly changed the risk profile of Zika, from a mild threat to one of alarming proportions. The increased incidence of microcephaly is particularly alarming, as it places a heart-breaking burden on families and communities.”

She told the Executive Board that the concerns about Zika warranted convening an Emergency Committee under the International Health Regulations to advise on the appropriate level of international concern, recommend measures that should be undertaken in affected countries and elsewhere, and prioritise areas where research is most urgently needed. “The level of concern is high, as is the level of uncertainty. Questions abound. We need to get some answers quickly”, she said.

The Emergency Committee met on Feb 1 and concluded that the recent cluster of microcephaly cases and other neurological disorders reported in Brazil, following a similar cluster in French Polynesia in 2014, was an “extraordinary event” and

constituted a Public Health Emergency of International Concern.

On Feb 1, Chan said that WHO had accepted the committees’ recommendation. She explained that declaring an emergency would allow for a coordinated global effort to get underway, enabling surveillance for microcephaly to be standardised and research to be intensified. Chan said that there was no reason to introduce restrictions to travel or trade, but

“...any country in the dengue belt that has *Aedes aegypti* should be looking at whether there is Zika and put in place measures to detect neurological conditions’.”

pregnant women could consider delaying travel to affected areas or seek advice from their physician if they needed to travel and take precautionary measures against infection.

At-risk population

As of Feb 1, 2016, active transmission of Zika virus was being reported in 28 countries and territories (figure), mostly in the Americas, including Brazil, Colombia, Venezuela, Mexico, Haiti, and Barbados. Sylvain Aldighieri, head of International Health Regulations Epidemic Alert and Response at the Pan American Health Organization (PAHO), explained to reporters in a WHO briefing on Jan 28 that the fast dissemination of the virus in the Americas was down to two reasons: the population being immunologically naive to Zika virus and the ubiquitous presence of the vector—*Aedes* mosquitoes. The vector can be found in the region from southern USA to northern Argentina (excluding continental

Chile), an area encompassing around 500 million people.

WHO estimates that there will be 3–4 million cases of Zika infection (including asymptomatic cases) in the Americas in the next 12 months. The figure comes from mathematical modelling based on dengue dynamics in the region and Zika infections in Brazil. An estimated 2 million cases of dengue occurred in the Americas in 2015. But unlike the dengue virus, which has been circulating in the region since the 1980s, Zika is new to the Americas and it is circulating at a very high intensity. The Brazil Ministry of Health estimates that 440 000–1 300 000 suspected cases of Zika virus infection occurred in the country in 2015.

In the Jan 28 briefing, Bruce Aylward, Assistant Director-General, WHO, advised that “any country in the dengue belt that has *Aedes aegypti* should



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For *The Lancet's* Zika virus Resource Centre see www.thelancet.com/campaigns/zika

Panel: Zika virus

Zika virus is an arbovirus of the Flaviviridae family, which includes dengue, West Nile, yellow fever, and Japanese encephalitis viruses. Like other members of the genus, Zika virus contains a positive, single-stranded genomic RNA encoding a polyprotein.

Zika virus was first isolated in 1947 from a rhesus monkey in the Zika forest of Uganda. Transmitted by the *Aedes* genus of mosquito, for decades, the disease mainly affected monkeys in a narrow equatorial belt stretching across Africa and into equatorial Asia. It occasionally affected human beings causing a mild disease.

In 2007, the first documented outbreak of Zika occurred in the Federated States of Micronesia where 185 suspected cases were reported, of which 49 were confirmed and 59 were considered probable. Between 2013 and 2014, four additional Pacific Island nations documented large Zika outbreaks. In French Polynesia, the Zika outbreak was associated with neurological complications, but at a time when the virus was co-circulating with dengue.

In May, 2015, WHO confirmed the presence of Zika virus in the Americas. As of Feb 1, 2016, active transmission has been reported in 28 countries and territories, mainly in the Americas, but also in Africa (Cape Verde) and Oceania (American Samoa, Samoa).

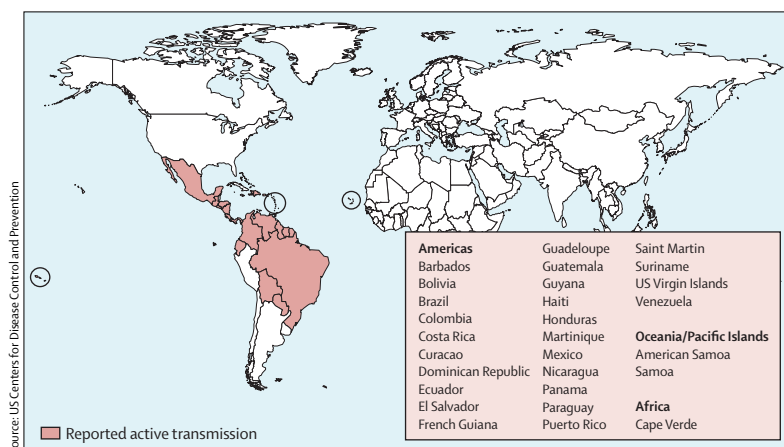


Figure: Countries and territories reporting active Zika virus transmission as of Feb 1, 2016

be looking at whether there is Zika and put in place measures to detect neurological conditions”.

He said that WHO would not be giving advice to women, as some countries in the Americas have, about delaying pregnancy, but it would give advice about how they can lower their risk of infection. On WHO’s website that advice (as for any mosquito-borne disease) is: use insect repellent; cover as much of the body as possible with long, light-coloured clothing; empty, clean, or cover containers that can hold water to remove places mosquitoes can breed; and sleep under mosquito nets.

Health concerns

Most people infected with Zika virus will not show any clear symptoms. However, in about one in five people, Zika causes a mild disease, with symptoms lasting from several days to a week. The most common symptoms are fever, rash, joint pain, and conjunctivitis. Severe disease requiring admission to hospital is uncommon.

The major concern in the present outbreak is related to the microcephaly clusters in Brazil, which have captured the attention of not only WHO but also the world’s media. During October and November, 2015, the Ministry of Health in Brazil began reporting an unusual increase in cases of microcephaly, first, in the state of

Pernambuco, located in the northeast of Brazil, then in three other states. On Nov 11, Brazil declared the situation a national public health emergency and began undertaking clinical, laboratory, and ultrasound analysis of affected newborn babies and their mothers. On Nov 17, WHO and PAHO issued an epidemiological alert, calling upon Member States to remain alert to the occurrence of similar events in their territories and to notify their occurrence through the channels established under the International Health Regulations.

Health authorities in Brazil have also reported an unusual increase in Guillain-Barré syndrome. The US Centers for Disease Control and Prevention (CDC) is currently working with public health officials in the country to investigate whether there is any link between Zika infection and the rare neurological disorder.

The other country to have seen similar neurological events in a Zika outbreak is French Polynesia. At the end of October, 2013, around 10 000 infections were registered in the Pacific Island nation, around 70 of which were severe cases, including neurological (Guillain-Barré syndrome, meningoencephalitis) or autoimmune (thrombocytopenic purpura, leucopenia) complications. Retrospectively, there were a small number of microcephaly cases in

the country after the Zika outbreak, Aylward noted. However, both Brazil and French Polynesia have also experienced outbreaks of dengue and chikungunya, raising the possibility of co-infections.

Research pipeline

Aylward said that four types of studies were underway to try to answer some of the many questions about the Zika virus: case investigations and ecological, case-control, and cohort studies. He noted that Marie-Paule Kieny, WHO Assistant Director-General for Health Systems and Innovation, was leading a scoping exercise to assess the research—including diagnostics and vaccine research—being done worldwide. “Within a couple of weeks, WHO will have a good idea of where we are, what the research pipeline is”, said Aylward. This knowledge will help the agency assess the merit of an accelerated agenda for product development. However, Aylward cautioned that a vaccine might not be available any time soon, noting that the timeframe for a dengue vaccine was many years.

In a briefing organised by the CDC on Jan 28, Anthony Fauci, Director of the National Institutes for Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH), outlined the NIH’s plans. “Within NIH, we have long supported research on viruses...With the emergence of the Zika virus, we are focusing efforts on several fronts”, he said, including the development of animal models.

“We are also supporting, along with the CDC, the development of diagnostic platforms that can rapidly determine if a patient is infected with Zika or has been infected either recently or in the past, and distinguish it from other viruses, particularly dengue infection. Such diagnostic tools will be critical to reassure the unaffected pregnant women in areas where Zika is occurring and pregnant women returning from such areas.”

He noted that researchers at NIAID are working on vaccine candidates to prevent Zika virus infection. Approaches being pursued include a DNA-based vaccine strategy, similar to the one used to develop a vaccine candidate against West Nile virus. NIAID was also evaluating a live-vaccine approach, similar to the strategy used to develop a vaccine against dengue virus. However, echoing Aylward's sentiments, Fauci cautioned that "while these approaches are promising, it is important to understand we will not have a widely available safe and effective Zika vaccine this year and probably not in the next few years; although, we may be able to begin an early phase 1 clinical trial actually within this calendar year".

NIH has also issued a call to the research community to highlight its interest in funding a number of areas of research on Zika. In addition to accelerated research towards diagnostics, treatments, and vaccines, it is calling for basic research to understand Zika virus infection. NIH is already studying the evolution and emergence of the virus, and is planning studies of the pathogen's distribution and natural history in collaboration with the CDC. "NIH is actively pursuing answers to the numerous scientific questions related to Zika infection, and we are sharing this information in real time, refining our avenues for accelerating research", Fauci said.

Brazil's Ministry of Health has said that plans to develop a vaccine are also underway in the country. According to Pedro Vasconcelos, a doctor and researcher at Instituto Evandro Chagas, one of the three institutes in the country involved in the project, the vaccine will take 3–5 years to develop. The work is planned to start in February and will be done in collaboration with the University of Texas Medical Branch in Galveston, USA.

Speaking to *The Lancet*, Trudie Lang, head of the Global Health Network—a forum to help clinical researchers with trials—said that a digital platform for

Zika research (www.zikainfection.tghn.org) has been launched by the International Severe Acute Respiratory and Emerging Infection Consortium and its international partners. "This is a resource that has been set up to enable research to get underway as quickly as possible. Here research tools and documents are being openly shared in order that studies can start as soon as possible and everyone collects data in the same way, so that it can then be pooled and shared."

Such an approach is important because there are many research questions that need to be answered quickly, she said.

Reporting problems

According to the latest epidemiological report by health authorities in Brazil, 4180 cases of microcephaly have been reported between November, 2015, and the third week of January, 2016. The northeast region has the highest number of notified cases, accounting for almost 80%, with Pernambuco reporting more than any other state.

However, some scientists in Brazil believe that the increase is not as high as it seems and might be even smaller when considering only those cases associated with Zika infection. Mauro de Freitas Rebelo, a professor and researcher at the Environmental and Molecular Biology Lab at the Federal University of Rio de Janeiro, for example, thinks that the fact that notification became mandatory in 2015 adds a bias that overestimates the increased rate of microcephaly in Brazil in the past year.

Additional problems lie in the fact that there are two different notification systems to report microcephaly cases in Brazil. The official notification system for all babies born in the country—SINESC—proved too complex to report cases of microcephaly during the outbreak. To expedite notification, the Ministry of Health developed a new form—Registry of Events in Public Health (RESP)—and advised



that suspected cases of Zika-related microcephaly be reported using this form. However, in another document issued in November, 2015, the Ministry of Health said that all cases of microcephaly should be reported in the RESP form.

This conflicting information has resulted in health authorities in each state developing their own interpretation of which system to use and how. For instance, the state of São Paulo, one of the largest in the country, only reports in the RESP registry microcephaly cases in which some evidence of a connection with infection by Zika is established.

Meanwhile, Alexandre Chieppe, superintendent of Environmental and Epidemiological Surveillance, State Secretary of Health, Rio de Janeiro, said that in the state of Rio de Janeiro, all cases of microcephaly, regardless of any connection with Zika, are notified in the RESP system. He explained that "a potential connection between microcephaly and infection by Zika during pregnancy depends on a comprehensive investigation that is done by a team of doctors and that requires a number of exams and analyses done later on".

Pernambuco

In Brazil, microcephaly was initially defined as head circumference below 33 cm and later corrected to 32 cm. In the state of Pernambuco, although 1373 cases have been notified, only 248 have been investigated and 138 confirmed as microcephaly associated with some infectious aetiology, which may or may not



Christophe Simon

A health worker fumigates an area in Salvador, Bahia, Brazil on Jan 29, 2016

include Zika. Patricia Ismael Carvalho, director general of Information and Strategic Actions for Epidemiological Surveillance at the State of Pernambuco Health Department, noted that the high number of microcephaly notifications in the state may result from the fact that Pernambuco was the first to report on cases of microcephaly and therefore included a number of babies whose heads were 33 cm and not 32 cm as later recommended by the Ministry of Health in Brazil.

Additionally, the state has not adopted either the RESP or the SINESC forms to report microcephaly and instead has created a third system for notification. The numbers of notified cases of microcephaly in different regions in Brazil, including the high number reported in Pernambuco, might therefore illustrate some of the disparities in the way microcephaly has been notified since 2015.

Underestimated?

While some experts believe the number of potential Zika-related microcephaly cases is overestimated, others think it is underestimated because many pregnant women do not have any symptoms when infected by Zika. Thus, many cases of microcephaly are not reported in the RESP registry

because no connection with Zika virus has been established.

Additionally, Zika infection can only be confirmed by PCR and the current capacity for doing PCR tests for Zika diagnosis in Brazil is very limited. Only five laboratories are equipped to do the test and together they run no more

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than 100 tests per week. Even when PCR is available, the window of opportunity to do the test is very small as viral RNA is best identified in the blood of infected patients in the first few days after symptoms appear.

Reproductive issues

Even though the alarming number of microcephaly notifications is still limited to Brazil, in some countries in the Americas—Colombia, Jamaica, El Salvador, and Panama—governments have advised women to postpone pregnancy. In Brazil, health authorities have not issued any official statement in this regard, although Cláudio Maierovitch, the director of the communicable disease surveillance

department at the Ministry of Health, has stated that now is not a good time to get pregnant in high-risk areas.

There are initial reports that panic is spreading among pregnant women, with some wanting an abortion if they get infected by Zika during the first months of gestation. Abortion in Brazil is legal only in cases where pregnancy represents a risk for the life of the mother or is the result of rape. The law also allows for abortion when it is confirmed that the newborn will have a severe disease or congenital malformation. Because the link between Zika infection and microcephaly has not been confirmed, and the diagnosis of microcephaly can only be determined in the last weeks of pregnancy, at birth, or even later, some pregnant women infected with Zika have sought abortion illegally.

Losing battle

The Brazilian Government has launched several campaigns to mobilise the population against the mosquito and has deployed military forces to visit all households in the country to educate people on vector control. However, this strategy does not seem to be working and the Health Minister Marcelo Castro and the Brazilian President Dilma Rousseff have both announced that the country is losing the battle against the mosquito. Many experts believe that the population is not doing its part in stopping mosquitoes breeding in stagnant water, others say that there is little the population can actually do and that the government needs to invest in research projects to eradicate the mosquito. Strategies such as the releasing of *Wolbachia*-infected *A aegypti* mosquitoes have been done in Brazil since 2014 in a few small areas but no results have been announced.

As the world mobilises to answer the questions surrounding the Zika virus and congenital neurological conditions, Brazil is one country hoping that the answers will come soon.

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