

Given the increase of congenital anomalies, Guillain-Barré syndrome, and other neurological and autoimmune syndromes in areas where Zika virus is circulating, the Pan American Health Organization / World Health Organization (PAHO/WHO) recommends its Member States establish and maintain the capacity to detect and confirm Zika virus cases, prepare healthcare facilities to respond to a possible increased demand of specialized care for neurological syndromes, as well to strengthen antenatal care. In addition, Member States are urged to continue with their efforts to reduce the presence of mosquito vectors through an effective vector control strategy and communication to the public.

Situation summary

Autochthonous transmission of Zika virus

From February 2014¹ to 17 January 2016, there are 18 countries and territories in the Americas that have confirmed autochthonous circulation of Zika virus (ZIKV) in 2015 and 2016: Brazil, Barbados, Colombia, Ecuador, El Salvador, French Guiana, Guatemala, Guyana, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Puerto Rico, Saint Martin, Suriname, and Venezuela. Between November 2015 and January 2016, local transmission of the virus was detected in 14 new countries and territories.

Increase in neurological syndromes

Guillain-Barré Syndrome

During the Zika virus outbreak in French Polynesia (2013-2014),² 74 patients had presented neurological syndromes or auto-immune syndromes after the manifestation of symptoms consistent with Zika virus infection. Of these, 42 were classified as Guillain-Barré syndrome (GBS). Of the 42 registered GBS, 24 (57%) were male, and 37 (88%) had signs and symptoms consistent with Zika virus infection (1, 2, 3).

¹ Autochthonous circulation of Zika virus (ZIKV) in the Americas was first confirmed in February of 2014 on Easter Island, Chile, and cases were reported there up to June of 2014.

² With 8,750 suspected cases registered and an estimated 32,000 persons infected.

In July 2015, Brazil reported the detection of patients with neurological syndromes who had recent history of Zika virus infection in the state of Bahia. There were 76 patients with neurological syndromes identified, of which 42 (55%) were confirmed as GBS. Among the confirmed GBS, 26 (62%) had a history of symptoms consistent with Zika virus infection.

In addition, on 25 November 2015, the Aggeu Magalhães Research Center of the Oswaldo Cruz Foundation reported that ZIKV infection was found in 10 of the 224 suspected dengue patients whose samples were analyzed for Zika virus infection. Seven of the 10 samples analyzed corresponded to patients with neurological syndrome.

In January 2016, El Salvador reported the detection of an unusual increase of GBS since early December 2015. On average, El Salvador records 14 cases of GBS per month (169 cases per year), however, between 1 December 2015 and 6 January 2016 there were 46 GBS recorded, two of which died. Twenty-five (54%) were male and 35 (76%) were over 30 years old. All were hospitalized and treated with plasmapheresis or immunoglobulin. Of the deceased patients, one had a history of multiple underlying chronic diseases. In 22 patients whose information was available, 12 (54%) had febrile rash illness between 7 and 15 days prior to the onset of GBS.

Currently, similar situations are being investigated in other countries of the Americas. These findings are consistent with a temporal and spatial link between Zika virus circulation and the increase of GBS. Although the etiopathogenesis and associated risk factors have not yet been well established, Member States should implement surveillance systems to detect unusual increases in cases and prepare health services for care of patients with neurological conditions.

Other neurological syndromes

Zika virus can cause other neurological syndromes (meningitis, meningoencephalitis and myelitis), as described in French Polynesia outbreak (2013-2014). While in the Region of the Americas such syndromes have not been reported so far, health services and practitioners should be alert about their possible occurrence to properly prepare health facilities for rapid detection and appropriate treatment of cases.

Increase in microcephaly and other congenital anomalies

In October 2015, the Brazil International Health Regulations (IHR) National Focal Point (NFP) notified the detection of an unusual increase in microcephaly³ cases in public and private healthcare facilities in Pernambuco state, Northeast Brazil.⁴ As of epidemiological week 1 of 2016, there were 3,530 microcephaly cases recorded, including 46 deaths, in 20 states and the Federal District. Between 2010 and 2014, an average of 163 (standard deviation 16.9) microcephaly cases was recorded nationwide per year.⁵ Figure 1 shows the comparative

³ Microcephaly is a neurological disorder in which the occipitofrontal circumference is smaller than that of other children of the same age, race, and sex.

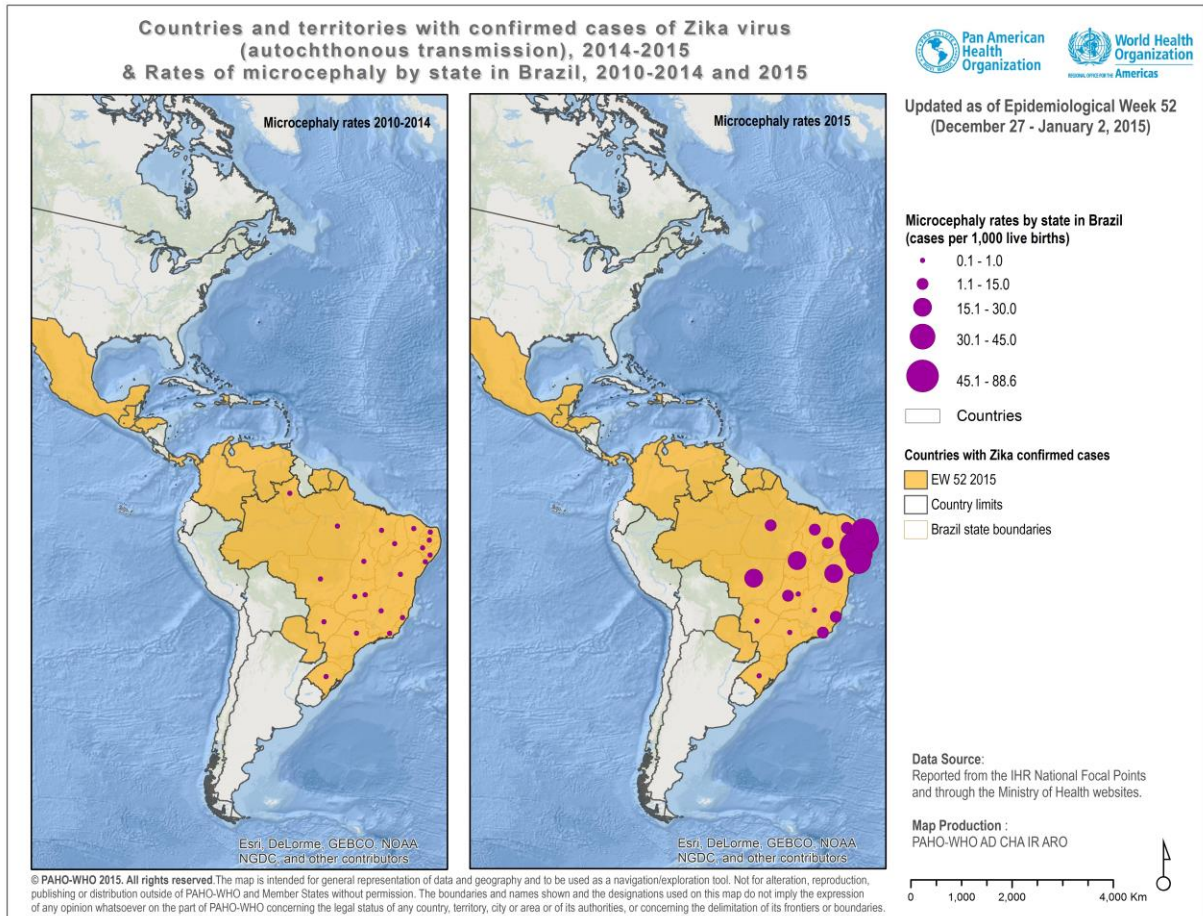
⁴ PAHO/WHO 17 November 2015, Epidemiological Alert available at: http://www.paho.org/ha/index.php?option=com_docman&task=doc_view&Itemid=270&gid=32285&lang=en

⁵ The Sinac is a universal system, that captures information on birth throughout the Brazil national territory. Available at: <http://www2.aids.gov.br/cgi/tabcgi.exe?caumul/anoma.def>

distribution of microcephaly case (annual average between 2010 and 2014 compared with cases registered in 2015) (4).

In January 2016, ophthalmological findings were reported in three children with microcephaly and cerebral calcifications detected by CT scans and presumable intrauterine ZIKV infection. The three infants had unilateral ocular findings involving the macular region and loss of foveal reflex. In one child a well defined macular neuroretinal atrophy was detected (5).

Figure 1. Countries and territories with confirmed cases of Zika virus (autochthonous transmission), 2015-2016 and rates of microcephaly by state in Brazil, 2010-2014 and 2015.



Evidence of vertical transmission of Zika virus

On 13 January 2016, the Brazil Ministry of Health reported the detection of Zika virus genome, through the RT-PCR technique in four cases of congenital malformation in the state of Rio Grande do Norte. The cases correspond to two miscarriages and two full-term newborns (37 and 42 weeks respectively) who died in the first 24 hours of life. Tissue samples from both newborns were also positive for Zika virus by immunohistochemistry (4).

This adds to the evidence reported in the [Epidemiological Alert of 1 December 2015](#) with respect to the detection of Zika virus genome through RT-PCR technique in the amniotic fluid

of two pregnant women in Paraiba, whose fetuses presented with microcephaly according to the ultrasound (6).

Recommendations for public health authorities

While there is currently only ecological evidence of an association between increased microcephaly, neurological and autoimmune syndromes, and prior infection with Zika virus; the possible causative nature of the association cannot be ruled out with the evidence available.

Given this situation and considering the continued expansion of Zika virus in the Region of the Americas, the Pan American Health Organization / World Health Organization (PAHO/WHO) **reinforces** the recommendations relating to the Zika virus surveillance, including monitoring neurological syndromes and congenital anomalies, which were published in the [1 December 2015 Epidemiological Alert](#). In addition to those recommendations, further guidelines on monitoring neurological syndromes and the clinical management of Guillain-Barré syndrome are provided herein.

Recommendations will be reviewed and updated as new evidence becomes available.

Surveillance

Surveillance of neurological and autoimmune complications

Member States are advised, particularly in situations of possible ZIKV circulation, to implement or intensify surveillance of neurological syndromes in all age groups.

This surveillance can be established as hospital-based, syndromic surveillance or surveillance of cases. If case surveillance is implemented, a case definition should be defined; including Guillain-Barre syndrome, Fisher syndrome, encephalitis, meningitis, and meningoencephalitis is suggested.

Guillain-Barré syndrome in its typical form is an acute polyradiculoneuropathy that produces a lower, bilateral, and symmetrical sensorimotor development deficit, associated with generalized areflexia. In many cases there is a history of infection that causes the immune response in the nerves. Between 3.5 and 12% of patients die from complications during the acute phase. The annual incidence of GBS is estimated to be between 0.4 and 4.0 cases per 100,000 inhabitants per year.⁶ In North America and Europe GBS is more common in adults and increases steadily with age. Several studies indicate that men tend to be more affected than women (7, 8).

Fisher syndrome (or Miller Fisher syndrome) is characterized by impairment of eye movements, abnormal coordination and loss of tendon reflexes. While the clinical triad (ataxia, ophthalmoplegia and areflexia) is easily recognizable, sometimes it overlaps with the GBS so some authors consider it as a variant of GBS and it is associated with the autoimmune inflammation of nerves after an infection.

⁶ The value depends on the methodology used to calculate. Prospective studies in developed countries suggest an incidence of 1-2 cases per 100,000 inhabitants per year.

Birth defects surveillance

Surveillance should be aimed at the detection of an unusual increase of birth defects, and of monitoring the trend when an outbreak is detected. Surveillance provides a basis for epidemiologic research (including risk factors) and prevention programs.

Detecting an unusual increase

For countries with an established system of birth defects surveillance, it is recommended to analyze (the) database(s) in which birth defects/anomalies or neurological disorders are recorded in order to detect any unusual increase.

For countries without an established system of birth defects surveillance, the implementation of a system of detection of cases in healthcare facilities or hospitals is recommended. When establishing a new congenital anomalies surveillance program, the initial anomalies that are included can be limited to microcephaly and then gradually expanded to include other congenital anomalies, depending on the capacity and resources of the health system in the country.

It is essential that a clear and operational case definition be included in establishing the surveillance protocol, as well as the frequency and flow of data (for example, including from local to regional, then national, weekly or monthly). In addition, aspects related to confidentiality, referrals and counter-referrals of cases should be ensured.

Event-based surveillance is a useful tool in detecting unusual conditions or events. For this reason, healthcare professionals involved in antenatal care, as well as child care, should be encouraged to notify any unusual events.

Microcephaly is defined as a head circumference of 2 standard deviations (SD) below the mean for age and sex or about less than the third percentile (9). There are no absolute values to define microcephaly given that it varies by sex and gestational age. For this reason, the WHO child growth standards tables on head circumference-for-age, with percentiles, and expanded tables for constructing national health tables are provided. These tables provided resources to assess the head circumference in full-term newborns and are available at: http://www.who.int/childgrowth/standards/hc_for_age/en/. To assess the head circumferences of preterm newborns, other references such as Fenton are recommended.

Any increase of microcephaly or other neurological congenital disorders must be assessed, investigated, and reported to the appropriate public health authorities.

Guidelines for international reporting

Given the recent introduction of Zika virus in the Americas and to contribute to integrated arbovirus surveillance, national public health authorities are encouraged to inform PAHO/WHO through the established IHR channels, of any laboratory-confirmed cases of Zika virus infection that are registered in the countries and territories of the Region of the Americas.

Additionally, in order to contribute to the knowledge of the possible complications and sequel of this virus, PAHO/WHO urges Member States to notify any increase of neurological and autoimmune syndromes (in adults and children), or congenital malformations in newborns that cannot be explained by other known causes.

Case management

Guillain-Barré Syndrome

GBS treatment is symptomatic and supportive. Recovery can take several weeks or months and can often cause prolonged disability requiring rehabilitation by a multidisciplinary team (doctors, nurses, physiotherapists, etc.).

Given the autoimmune nature of the disease, the treatment strategy used in the acute phase is immunotherapy, such as plasma exchange and intravenous immunoglobulin. Corticosteroids given alone do not significantly hasten recovery from GBS or affect the long-term outcome.

The aim of plasma exchange is to remove from the bloodstream antibodies and replace them with artificial plasma, usually albumin. Plasma exchange is most beneficial when initiated within 7 – 14 days from onset of the disease.

Intravenous immunoglobulin hastens recovery, as does plasma exchange, and it is much easier to manage. It should begin within two weeks from the onset of symptoms.

Even under the best quality available medical care, approximately 5% of patients with Guillain-Barre syndrome die from complications such as sepsis, pulmonary embolism or unexplained cardiac arrest. Thus, these complications must be identified early by healthcare workers, with frequent monitoring of vital functions and prevention of pulmonary embolism. When possible, patients should be treated in an intensive care unit in order to maintain continuous monitoring and to respond immediately to any urgency.

Microcephaly and other birth defects

Infants who meet the criteria of microcephaly should be evaluated by qualified medical teams to determine the extent of neurological impairment and other possible abnormalities. Additional studies (laboratory and radiological) should be conducted according to local protocols, including diagnosis of other causes of microcephaly, especially those requiring treatment (e.g., congenital syphilis, cytomegalovirus, or toxoplasmosis). After clinical evaluation of the newborn, a plan of care and clinical monitoring of these newborns with microcephaly should be developed and implemented.

With the current available information, the possible consequences or presence of other functional defects in microcephaly cases related to Zika virus are unknown. Hence the need to ensure the clinical follow up of newborns, with further clinical evaluation is emphasized. There is no specific treatment for microcephaly.

Personal preventive measures

PAHO recommends that anyone living in or traveling to areas where the Zika virus is circulating take precautions to avoid mosquito bites.

PAHO also has specific recommendations for pregnant women (see below) living in areas where this virus is circulating as well for those living in areas without transmission who are planning to travel to areas where the Zika virus is circulating. For the latter women, consultation with a doctor or health care provider to get advice before traveling is strongly recommended.

PAHO acknowledges that its Member States, which may have specific epidemiological contexts in terms of presence of mosquito vectors capable of Arbovirus transmission, should decide the most appropriate recommendations to make for their national context based on their assessment using available evidence about Zika virus infections and taking into account possible risk factors and consequences as they relate to their own populations.

PAHO's advice for pregnant women living or traveling to areas with Zika virus transmission is available at:

http://www.paho.org/hq/index.php?option=com_content&view=article&id=11552&Itemid=41672&lang=en.

References

1. Institut de Veille Sanitaire (InVS). Bulletin hebdomadaire international du 5 au 11 mars 2014. N°442. France : InVS ; 2014. Available at: <http://www.invs.sante.fr/Publications-et-outils/Bulletin-hebdomadaire-international/Tous-les-numeros/2014/Bulletin-hebdomadaire-international-du-5-au-11-mars-2014.-N-442>
2. European Centre for Disease Prevention and Control. Rapid risk assessment: Microcephaly in Brazil potentially linked to the Zika virus epidemic – 24 November 2015. Stockholm: ECDC; 2015. Available at: <http://ecdc.europa.eu/en/publications/Publications/zika-microcephaly-Brazil-rapid-risk-assessment-Nov-2015.pdf>
3. Millon P. Epidémiologie des syndromes de Guillain-Barré en Nouvelle-Calédonie entre 2011 et 2014 : influence des arboviroses. Faculte de Medecine de Grenoble: Universite Joseph Fourier; 2015. Available at: <http://dumas.ccsd.cnrs.fr/dumas-01153577/document>
4. Brazil Ministry of Health. The public health Emergency Operations Center report on microcephaly. Epidemiological Week 1 of 2016. Brazil; 2016. Available at: <http://portalsaude.saude.gov.br/images/pdf/2016/janeiro/13/COES-Microcefalias---Informe-Epidemiol--gico-08---SE-01-2016---Valida----o-12jan2016---VALIDADO-PELO-CLAUDIO--e-com-os-estados-por-webconfer--n.pdf>
5. Ventura C, Maia M, Bravo-Filho v, Góis Adriana, Belfort Jr R. Zika virus in Brazil and macular atrophy in a child with microcephaly. Correspondence. The Lancet. Enero 2016. Available at: [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(16\)00006-4/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)00006-4/abstract)
6. Brazil Ministry of Health. Microcephaly – Ministry of Health releases epidemiological bulletin [Internet]. Available at: <http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/20805-ministerio-da-saude-divulga-boletim-epidemiologico>.
7. McGrogan A, Madle GC, Seaman HE, de Vries CS. The epidemiology of Guillain–Barre Syndrome worldwide. A systematic literature review. Neuroepidemiology. 2008 Dec 17;32(2):150–63.
8. Yuki N, Hartung P. Guillain-Barré Syndrome. N Eng J Med. 2012 ; 366 : 2294-304.
9. WHO/CDC/ICBDSR. Birth defects surveillance: a manual for programme managers. Geneva: World Health Organization; 2014.