Guidelines for Surveillance of Zika Virus Disease and Its Complications

2018 edition

Pan American Health Organization

World Health Organization
REGIONAL OFFICE FOR THE Americas

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Abbreviations and Acronyms

ADEM	acute disseminated encephalomyelitis
CHIKV	chikungunya virus
CLAP	Latin American Center for Perinatology
CNS	central nervous system
CSF	cerebrospinal fluid
DENV	dengue virus
ELISA	enzyme linked immunosorbent assay
GBS	Guillain-Barré syndrome
HC	head circumference
HIV	human immunodeficiency virus
IHR	International Health Regulations
MRI	magnetic resonance imaging
PAHO	Pan American Health Organization
PHEIC	public health emergency of international concern
PRNT	plaque reduction neutralization test
RNA	ribonucleic acid
RT-PCR	reverse transcription - polymerase chain reaction
WHO	World Health Organization
ZIKV	Zika virus

Background and Methodology

This document is an update to the *Guidelines for surveillance of Zika virus disease and its complications*, published by PAHO/WHO in May 2016. This updated version incorporates new knowledge about the disease and its complications acquired through research and surveillance activities carried out during the Public Health Emergency of International Concern (PHEIC), which the Director-General of the World Health Organization (WHO) declared over as recommended by the International Health Regulations (IHR) Emergency Committee. The information in the updated guidelines was compiled through a review of scientific literature on Zika virus (ZIKV) and its complications published during the emergency period. The review is complemented with official reports from countries and territories affected by outbreaks.

A literature review and the drafting of the guidelines was performed from March 2017 to April 2018, and included document review by experts, both in person and electronically. A preliminary revised version was submitted to Member States and a group of external advisors for their review in March 2018; their contributions have been incorporated in this final version of the guidelines.

Declaration of interests

All external collaborators and reviewers completed the WHO's declaration of interests form and were reviewed by Pan American Health Organization staff on a case-by-case basis. No conflict of interest was detected in any declaration. No special funds were used for the preparation or review of this document.

Introduction

ZIKV belongs to the genus *Flavivirus* (family *Flaviviridae*), phylogenetically very close to other arboviruses, such as the dengue, yellow fever, Japanese encephalitis, and West Nile viruses. It is primarily a mosquito-borne ribonucleic acid (RNA) virus transmitted by mosquitos of the genus *Aedes* (*A. Stegomyia* species) and was first isolated in 1947 from a Rhesus macaque during a study on the transmission of jungle yellow fever in the Zika Forest of Uganda (*1*). In 1968, it was first isolated in humans in Uganda and the United Republic of Tanzania (*2*). Subsequent outbreaks have been recorded in Africa, Asia, the Western Pacific region (*1-15*), and, more recently, in the Americas (*16-20*).

Sexual and vertical (transplacental) transmission of the virus has been documented (*21-30*), as well as transmission by blood transfusion and organ transplantation (*31-33*). Although ZIKV has been documented in breast milk, there is no evidence of transmission through breast milk. Viral RNA has been detected in the breast milk of women infected during the peripartum period (*25*), and ZIKV infectious particles were found in breast milk (*34*).

Clinical manifestations include acute illness and complications. Symptoms of the disease usually appear after an incubation period of 3 to 14 days, and are similar to those of other arboviral infections and eruptive febrile diseases; they include: rash, fever, conjunctivitis, myalgia, arthralgia, malaise, and headache, and tend to last 4 to 7 days (*11-35*). The most striking complications of the infection involve the nervous system as well as congenital syndrome associated with ZIKV infection.

An epidemiological study in Yap, Micronesia, 2007, estimated that 18% of people infected by ZIKV exhibit signs of infection (*11*). Efforts made during the recent epidemic in the Region of the Americas, to obtain additional evidence to further refine this estimate in the Americas, were unsuccessful, due to reporting rate issues, and the proportion of asymptomatic cases, among others.

The declaration of a PHEIC by the WHO Director-General on 1 February 2016 regarding clusters of microcephaly cases and other neurological disorders in some areas affected by ZIKV facilitated a worldwide response that, in turn, allowed the understanding that ZIKV infection and its related consequences constitute a significant long-term public health problem. In November 2016, the WHO deemed that the event no longer constituted a PHEIC as defined by the IHR, although the virus and its consequences continue to pose a significant and lasting public health problem that require ongoing response.

Many aspects of the disease and its sequelae are still not well understood. Therefore, research must continue as part of a long-term program. Among other challenges, the WHO will need to update its travel advisories periodically as information evolves on the nature and duration of risks related to Zika virus infection (*36*). To this end, a ZIKV surveillance system is needed to detect transmission and the incidence of ZIKV in affected areas.

The WHO Emergency Committee emphasized the need for better scientific understanding of the epidemiology, clinical manifestations, and prevention of ZIKV disease; recommended new areas of research; and reiterated the need to continue research previously initiated, in order to:

- better understand the different viral lineages, including cross-reactivity and cross-immunity between them, as well as their clinical implications;
- assess possible co-factors or risk factors that might increase disease severity;
- better understand the natural history of the disease in children with congenital infection, pregnant women, and other children and adults;
- determine length and location of viral persistence in humans, and their impact on transmissibility;
- better understand the risk of infection and modes of transmission;
- assess the effectiveness of vector control tools and their operational feasibility; and
- continue the search for safe and effective prevention measures (e.g., vaccines).

Purpose and Scope

This document aims to provide guidance for the implementation of longer-term and sustainable ZIKV disease surveillance following the conclusion of the PHEIC. It provides overall guidance—albeit not exhaustive—on surveillance activities, primarily intended for countries expected to have ongoing vector borne transmission of ZIKV in the post-PHEIC phase and should be adapted by countries to their capabilities, epidemiological context, and health system's characteristics. Based on available information, and to guide case reporting, a brief clinical description of the disease is included, encompassing its neurological manifestations and information on congenital ZIKV syndrome. Surveillance strategies are proposed, along with case definitions, and laboratory procedures for detection and diagnosis.

While this document focuses primarily on ZIKV disease, it also proposes elements to integrate ZIKV surveillance with that of other arboviral and rash/febrile diseases, and addresses differential diagnosis in the laboratory.

This proposal is to be implemented at the national level in each country, and, depending on the health system's organization, should be adapted to the different spheres of the health system (local, regional, and national). As with other technical documents, these guidelines should be reviewed and updated as the understanding of the disease and its complications progress.

Context for ZIKV Surveillance

ZIKV infection is transmitted by the bite of mosquitos of the genus *Aedes* (*A. Stegomyia* species). Vertical transmission, sexual transmission, and transmission by blood transfusion (*21-33*) have also been documented.

Along with the reemergence of yellow fever in the Americas, the detection of ZIKV has changed the epidemiological landscape of arboviral diseases. The burden of disease is now shared by the four serotypes of dengue virus (DENV), chikungunya virus (CHIKV), and ZIKV, in addition to outbreaks caused by other arboviruses, such as Mayaro, West Nile, and yellow fever viruses.

Accordingly, surveillance systems must adapt to become sustainable and to allow optimal use of resources. In line with Resolution CD55/16[1] adopted by PAHO Member States, further implementation of integrated surveillance by including ZIKV into that of other arboviruses is proposed, as well as with existing fever and rash diseases surveillance systems. In addition, maintaining and strengthening surveillance of ZIKV infection complications, including congenital ZIKV syndrome and neurological manifestations, is recommended.

Surveillance Objectives

Depending on the national epidemiological situation, surveillance will facilitate increasing knowledge of the disease, its complications and sequelae, support prevention measures, and contribute to the improvement of health and social support systems' capacity to provide integral care to affected individuals.

To this end, surveillance objectives should:

- facilitate early detection of the virus's introduction, or the presence of case clusters;
- determine trends and distribution of ZIKV cases according to time, place, and person;
- detect unusual events, for example, a different clinical presentation;
- detect the onset and temporal distribution of neurological manifestations, including Guillain-Barré syndrome (GBS) and other neurological complications, such as acute myelitis and acute encephalitis, whose relationship to ZIKV has been less studied;
- detect infection in vulnerable populations, such as pregnant women;
- detect the emergence and monitor the incidence of congenital syndrome associated with ZIKV infection;
- detect imported cases in areas/territories where the mosquito vector is absent;
- identify new clinical manifestations of congenital syndrome associated with ZIKV infection;
- contribute data to update WHO travel advisories.

[1] Available at: http://www.paho.org/hq/index.php?option=com_content&view=article&id=12276%3A2016-55th-directing-council-documents&catid=8811%3Adc-documents&Itemid=42078&lang=en

Surveillance of ZIKV disease

ZIKV poses many challenges to surveillance systems, including high rates of asymptomatic infection (*11-37*); therefore, surveillance activities should focus on detection of symptomatic cases. In the latter, however, signs and symptoms, such as fever and rash, are difficult to differentiate from the clinical symptoms of other diseases under surveillance, including those caused by other viruses.

In the post-emergency phase, countries in the Americas should consider incorporating ZIKV surveillance into existing surveillance systems. ZIKV surveillance will require information from various sources, as described below.

Following are proposed events to be monitored as part of ZIKV surveillance. Annex 1 summarizes the proposed data required for surveillance.

Proposed events for monitoring/surveillance

- Incidence of ZIKV disease
- ZIKV-associated neurological complications including GBS, acute myelitis, and encephalitis
- Congenital syndrome associated with ZIKV infection

The use of existing surveillance systems will contribute to the sustainability of ZIKV surveillance in the Americas, while continuing the collection of information on complications. Two existing systems should be considered for integration with ZIKV surveillance, namely measles and rubella and arbovirus surveillance systems.

Integrating ZIKV surveillance with measles and rubella surveillance

In 2012, the Pan American Sanitary Conference adopted the Plan of Action for Maintaining Measles, Rubella, and Congenital Rubella Syndrome (CRS) Elimination in the Region of the Americas (Resolution CSP28/16),[2] urging Member States to maintain a high-quality surveillance system. Within this system, and to guarantee its sensitivity, countries would undertake several activities, including active case finding, and routine external performance evaluations using standardized tools.

The rationale for integrating ZIKV surveillance into measles and rubella surveillance is the similarity of the clinical manifestations of those diseases. In the past, ZIKV outbreaks led some countries and territories to report an increase in fever and rash syndrome detected by their rubella and measles surveillance systems, before ZIKV circulation was confirmed. Furthermore, the sensitivity and coverage of measles and rubella surveillance—through its laboratory analysis of all reported cases and periodic external evaluations of the overall system—contribute to updating WHO travel advisories.

[2] Available at: http://www.paho.org/hq/index.php?option=com_content&view=article&id=7022&Itemid=39541&lang=en

Given the above, adding ZIKV disease to the laboratory algorithm is proposed—once measles and rubella viruses have been ruled out—as well as including a Zika variable in PAHO's and Member States' surveillance software tool.

In many countries, measles and rubella surveillance is already coordinated with dengue surveillance to test negative samples for the first two infections, which is also relevant to ZIKV surveillance.

Integrated ZIKV surveillance with surveillance of other arboviral diseases, such as dengue and chikungunya

During the ZIKV emergency in 2016, PAHO's Directing Council adopted Resolution CD55.R6[3] approving the Strategy for Arboviral Disease Prevention and Control, which urges Member States to strengthen surveillance systems, and promote integrated control of arboviral diseases. There currently is a PAHO/WHO case definition for each disease (chikungunya, dengue, and Zika), with overlapping elements among them, such as the presence of rash or joint pain.

ZIKV surveillance could also be part of an integrated arboviral disease surveillance system with laboratory support, to allow joint monitoring of various arboviruses.

ZIKV etiological surveillance

For Member States that would prefer to continue monitoring ZIKV on a case-by-case basis, these Guidelines propose a case definition and reporting requirements for said approach (Annex 2). This type of surveillance will be more important during interepidemic periods.

ZIKV Disease

Clinical description

As with other infectious disease, determinants of ZIKV disease (ICD10: A92.8) are epidemiological, viral (strains or genotypes), or host-related (e.g., age, sex, and other risk factors for exposure to the vector, or sexual transmission). There is no evidence of differences in clinical manifestations severity based on mode of transmission (e.g., vector-borne or sexual), other than *in utero* transmission that leads to congenital infection. Furthermore, given the lack of a precise, practical, rapid, and economical laboratory test for definitive ZIKV infection diagnosis when there is circulation of other flaviviruses, a description of clinical signs and symptoms is provided below. The clinical description is essential for providing proper care, and for the subsequent recording of cases by epidemiological surveillance teams.

Incubation and onset of clinical manifestations

ZIKV infection is estimated to have an average incubation period of 3 to 14 days (*35*). The disease typically presents with maculopapular cephalocaudal rash, with or without low grade fever (<38.5°C). The rash spreads from the head to the trunk, and upper and lower limbs. The rash is characteristically pruritic,

[3] Available at: http://www.paho.org/hq/index.php?option=com_content&view=article&id=12276&Itemid=42078&lang=en.

and often interferes with daily activities, even hindering sleep. The rash frequently affects the palms of the hands and soles of the feet, where it causes palmar or plantar hyperemia. In the convalescent stage, there may be laminar desquamation of hands and feet, though this can be seen with other infectious (e.g., chikungunya) and non-infectious diseases (e.g., Kawasaki disease) as well. In cases of dengue, pruritic rash usually appears after the fifth or sixth day of onset and marks its end. In ZIKV patients, non-purulent conjunctival hyperemia is often present along with the rash (*11-30*). Lymphadenopathy is less common, but it could affect retroauricular lymph nodes (*38, 39*).

Joint and other manifestations

In some cases, joint manifestations appear, usually in the form of polyarthralgia with periarticular, bilateral, and symmetrical edema. Unlike in chikungunya virus (CHIKV) infection, pain in ZIKV tends to be milder and non-incapacitating. Upon physical examination, there may be mild articular edema, without hyperemia or local heat. About a week after the onset of symptoms, those affecting the joints will regress; however, in a few cases, articular involvement can last up to 30 days with periods of relapse. Hands and wrists are most frequently affected, followed by knees and ankles. Chronic symptoms have not been observed in ZIKV cases, as can occur in a notable proportion of CHIKV cases (*18,52*). There may also be other manifestations, such as headache, myalgia, nausea, and vomiting. Unlike in severe dengue, hemodynamic instability is rare in ZIKV infections.

Nervous system impairment

Neurological manifestations may appear during or after the acute phase of infection, with GBS being the most frequent.[4] In a small number of cases, the latter can present as Miller Fisher syndrome, and other less common forms of cranial mononeuritis. Other neurological manifestations associated with ZIKV infection include encephalitis, meningoencephalitis, cerebellitis, acute disseminated encephalomyelitis (ADEM), myelitis, and cranial nerve disorders and impairments, such as optic neuritis (*40-48*). These manifestations are less common, but are important to recognize to provide proper care, and to improve knowledge of the full spectrum of neurological manifestations associated with ZIKV infection.

Differential diagnosis

Table 1 summarizes differential diagnoses of arbovirus infections and other illnesses with similar signs and symptoms.

[4] ZIKV-associated GBS has been described in both its classical demyelinating form (acute demyelinating polyradiculoneuritis) and in some of its electrophysiological variants (e.g., pure motor axonal variant).

Table 1. Differential Diagnosis with other Similar Clinical Manifestations*

Clinical Manifestation	Differential Diagnosis
Diseases with skin rash	Rubella, measles, chikungunya, scarlet fever, meningococcal infection, parvovirosis, human immunodeficiency virus (HIV) primary infection, toxicoderma, rickettsiosis, ehrlichiosis, Lyme disease
Diarrheal diseases	Rotavirus, enterovirus, other enteric infections
Diseases with neurological manifestations	Meningoencephalitis of other etiologies, diphtheria, enterovirus,# neuromyelitis optica (Devic's syndrome)
Hemorrhagic fevers	Leptospirosis, Brazilian hemorrhagic fever, Argentine hemorrhagic fever, Bolivian hemorrhagic fever, yellow fever, severe dengue, etc.
Blood dyscrasias	Proliferative hematological disorders, alterations in coagulation, paraproteinemia

* Adapted from: Pan American Health Organization, 2016. Tool for the diagnosis and care of patients with suspected arboviral diseases. Washington, DC. Available from: http://iris.paho.org/xmlui/handle/123456789/33895.

\# Enterovirus D-68 and D-71, associated with cases of acute flaccid paralysis, have recently been detected circulating in the Region of the Americas in the United States and Argentina.

Based on the local epidemiology, differential diagnosis might include other infections, such as malaria, leptospirosis, typhoid fever, typhus, viral hepatitis, sepsis, septic shock, hantavirus infection, visceral leishmaniasis, yellow fever, and other arboviral diseases (primarily dengue and chikungunya).

Case Definitions
(for integrated surveillance with measles and rubella)

Suspected case of ZIKV (for integrated surveillance with measles and rubella)

Patient who presents with fever or rash

or

a patient whom a healthcare worker suspects has measles or rubella.

Probable case of ZIKV disease

Patient who meets the criteria of a suspected case, **and** has anti-ZIKV IgM antibodies, with negative laboratory results for other flaviviruses.

Confirmed case of ZIKV disease

Patient who meets the criteria for a suspected case **and** has laboratory confirmation of recent ZIKV infection, with presence of:

- ZIKV RNA or ZIKV antigen in serum samples or other specimens (e.g., urine, saliva, tissue, whole blood, or cerebrospinal fluid [CSF]);[5] **or**
- positive anti-ZIKV IgM antibodies **and** plaque reduction neutralization test (PRNT) for ZIKV titers ≥ 10 in the absence of titers for other flaviviruses[6].
- in cases of death,[7] molecular detection of the viral genome in autopsy tissue (fresh or in paraffin) with in situ hybridization tests.

[5] Excluding products of conception, which are discussed in the next section.
[6] The test is done on paired samples of probable cases with positive anti-ZIKV IgM antibodies.
[7] Excluding abortion or stillbirth, discussed in the next section.

Laboratory Diagnosis of ZIKV Disease

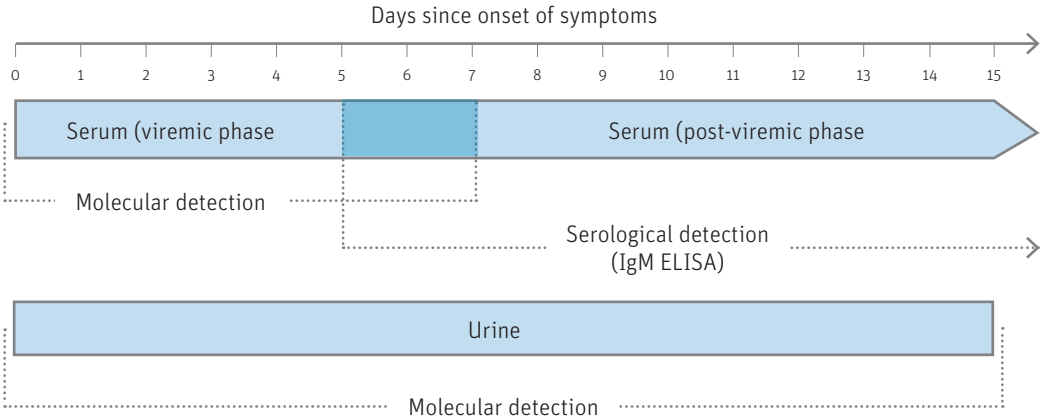
Virologic diagnosis (Algorithms A and B)

Type of sample: serum or urine (5 to 7 cc collected in non-additive test tube)

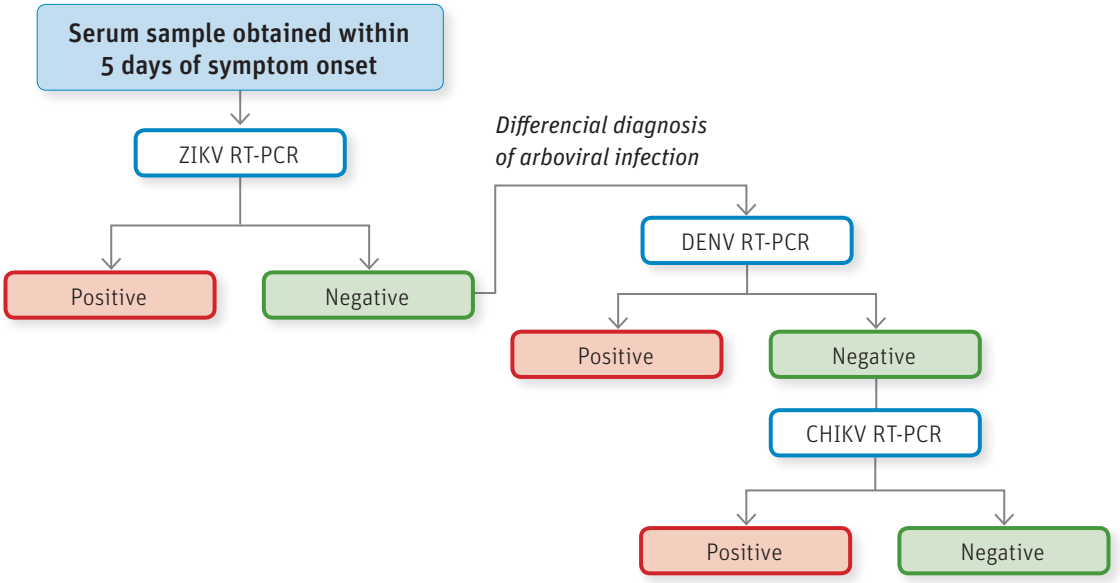
Although the period of viremia has yet to be fully established, the virus has been detected in serum most often within 5 days of symptoms onset, and, in some cases, longer. In urine, however, high viral loads have been detected for a long time after the onset of symptoms (*49-52*). Thus, to improve diagnostic sensitivity, it is recommended that serum and urine samples be obtained at the same time (no later than 15 days after the onset of symptoms) for processing by RT-PCR (*53*) (Figure 1). For differential diagnosis (DENV, CHIKV, etc.), testing should be done on serum samples from the acute phase.

In many cases, initial symptoms may go undetected; also, patients may be late in seeking health care, limiting opportunities for molecular testing.

Figure 1. Recommended diagnosis based on number of days since onset of symptoms and sample type

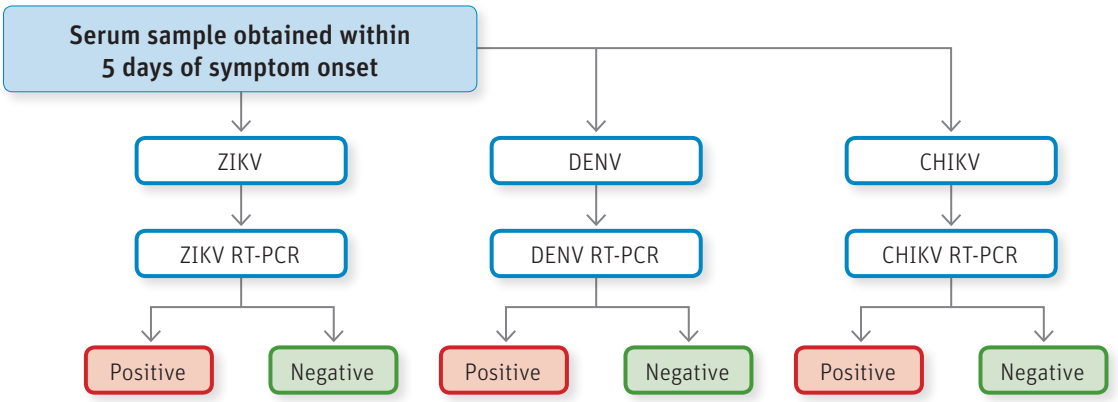


A. Algorithm for virologic testing using serial monoplex RT-PCR of suspected cases of ZIKV infection in areas where other arboviruses* are in circulation



*Based on clinical presentation and the local epidemiology of the area where the case was detected, yellow fever virus should be part of the differential diagnosis.

B. Algorithm for virological testing using a multiplex RT-PCR of suspected cases of ZIKV infection in areas where other arboviruses are in circulation.



Serological detection (algorithm C)

Type of sample: serum (5 to 7 cc collected in non-additive test tube)

ELISA is the recommended serology method to detect specific anti-ZIKV IgM antibodies as of day 6 of the symptoms onset. However, testing of samples collected before day 6 of symptoms could be considered if RT-PCR testing was negative.

Early diagnosis determining or excluding ZIKV infection based on a single serum sample taken during the acute phase is presumptive. Therefore, it is recommended that a second sample be taken one to two weeks after the first, to document seroconversion (negative to positive), a ≥4-fold increase in antibody titer (quantitative test), or negative result to rule out infection.

Although PRNT can detect virus-specific neutralizing antibodies, cross-reactivity has been documented with related flaviviruses, especially dengue or yellow fever (*53-55*). Additionally, PRNT testing is relatively complex and time-consuming. To date, there are no approved validated commercially available tests to detect ZIKV antibodies by PRNT, and obtaining the necessary reagents is difficult.

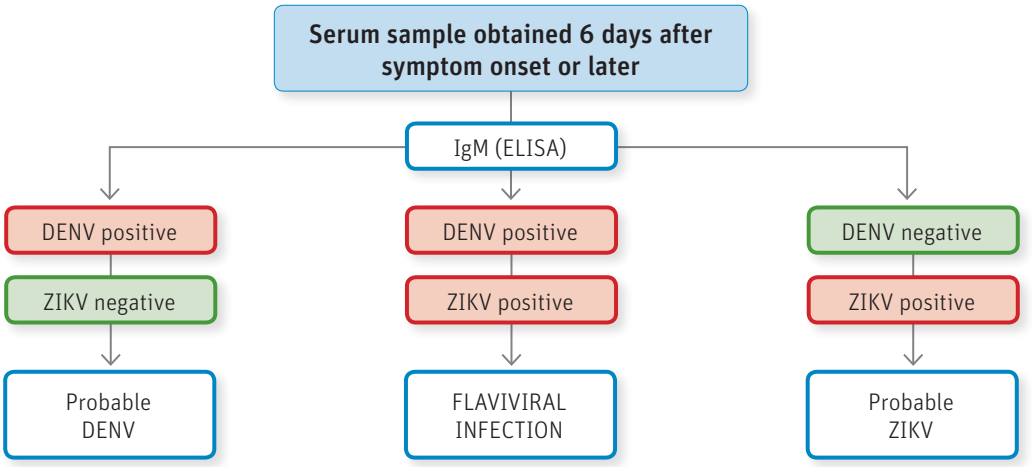
Interpretation of serology results

In primary infections (first flavivirus infection), antibodies are less likely to cross-react with other genetically related viruses in acute phase samples. However, serum from individuals with history of other flavivirus infections (especially dengue and yellow fever, including yellow fever vaccine) can cross-react in these tests. This applies to the detection of IgM by ELISA, and neutralizing antibodies by PRNT (*54-58*).

For this reason, and as part of the differential diagnosis, in tandem determination of IgM ELISA for both dengue and Zika (and other viruses depending on local epidemiology) is recommended. Results should be interpreted as indicated in algorithm C, below. In addition, and where available, PRNT with different flaviviruses (dengue, yellow fever and others, depending on the epidemiological context) will be useful to complement the diagnosis of ZIKV infection if it demonstrates a neutralizing antibody titer substantially higher for ZIKV than for other viruses (*52, 58-60*). In such cases, clinical and epidemiological criteria are essential for the interpretation of serological results. For example, a case of GBS with positive result for flavivirus infection (DENV and ZIKV) suggests ZIKV infection, given that GBS after DENV infection is unusual.

In cases where ZIKV constitutes the patient's first flavivirus infection (for example, in newborns or in areas where dengue virus or other flavivirus circulation has not been reported), detection of IgM (by ELISA) or neutralizing antibodies tends to be specific for and suggestive of recent ZIKV infection.

C. Algorithm for serological detection in suspected cases of ZIKV infection in areas with circulation of other arboviruses*



* Depending on clinical presentation and local epidemiology in the area where the case has been detected, the inclusion of yellow fever in the differential diagnosis is advised.

Sample Selection and Storage

- Samples to be tested (or sent to a reference laboratory) within 48 hours should be kept refrigerated at 4 °C to 8 °C.
- Samples to be tested after the first 48 hours, but no later than seven days, should be kept frozen at – 10 °C to – 20 °C.
- Samples to be tested after a week should be kept frozen at – 20 °C to – 70 °C. At this temperature samples can be safely stored for extended periods.

Air Shipment of Samples to Reference Laboratories

Shipment of samples to reference laboratories, should do the following:

- guarantee cold chain integrity with dry ice, or, if unavailable, with frozen gel packs (always use triple packaging);
- ship within 48 hours of sample collection;
- pack original samples, label appropriately (if dry ice is used), and document them as category B; and
- always include complete clinical and epidemiological records.

Surveillance of Guillain-Barré syndrome (GBS) and Other Neurological Complications

Neurological manifestations can occur during the acute or convalescence phase of ZIKV infection. To date, GBS has been described as the neurological complication most frequently associated with ZIKV infection. However, after the outbreak in the Region of the Americas, in addition to GBS, other severe neurological complications (e.g., encephalitis, myelitis) have been identified in persons infected with ZIKV. However, the incidence and impact of those other neurological manifestations are currently not well-known. GBS has numerous clinical and electrophysiological variants, described below, including Miller Fisher syndrome (*40, 42, 43, 62-67*).

Guillain-Barré syndrome

Clinical description of GBS and its variants

In its typical form, GBS occurs as an ascending, progressive, subacute, distal symmetrical paralysis, and is accompanied by areflexia. In many cases it is preceded by a history of infection (*62-64*).

The annual incidence of GBS is estimated to range between 1.1 and 1.8 cases per 100,000 population per year. In Europe and North America, GBS is more common among adult males, and its incidence increases linearly with age. The expected case fatality rate is 5% even with optimal care (*68*).

GBS is typically characterized by acute flaccid paralysis that can affect all four limbs, with or without cranial nerve impairment. It consists of a heterogeneous group of diseases of the peripheral nervous system mediated by immunological mechanisms, particularly triggered by infections. The classic form of GBS is an acute demyelinating polyradiculoneuritis. Other clinical variants include Miller Fisher syndrome (ophthalmoplegia, ataxia, and absence of myotatic reflexes), forms of dysautonomic predominance, and other asymmetrical or focal variants, such as the paraparetic, pharyngeal-cervical-brachial, and bulbar forms (*62-66*). Due to the complexity of these variants, when GBS is clinically suspected, a systematic, detailed, and in-depth neurological examination is advised to detect atypical forms of the syndrome that could be underdiagnosed and, consequently, underreported.

Weakness with GBS begins distally in the lower limbs, and can be associated with sensory manifestations. Patients have difficulty walking, climbing stairs, or rising from a seated position. Subsequently, motor weakness can spread to the arms. Sensory changes may develop, such as paresthesia, dysesthesias, or hypoesthesia. Pain (neuropathic, radicular, or musculoskeletal) is common. GBS can sometimes progress to affect the facial nerves, and may produce bulbar involvement and affect respiratory muscles. Approximately, a third of patients will require admission to intensive care units due to respiratory complications and dysautonomia (cardiac arrhythmia or blood pressure changes) (*66*).

GBS diagnosis is based on clinical presentation and neurologic testing (e.g., electromyography). Cerebrospinal fluid (CSF) analysis may reveal albuminocytologic dissociation (an increase in proteins

in the absence of pleocytosis),[8] a finding that contributes to diagnostic certainty. Albuminocytologic dissociation might not be detected during the first few days of symptom onset, but it increases with time, and can be present in up to 75% of patients in three weeks.

Electrophysiological studies can help prognosis determination and GBS subtype (acute inflammatory demyelinating polyradiculoneuritis or AIDP; acute motor axonal neuropathy or AMAN; and acute motor and sensory axonal neuropathy or AMSAN) (*62-67*) (Annex 3).

It is recommended that a complete clinical history and detailed neurological examination be conducted by a neurologist or other appropriately trained physician. The neurological exam should include the level of alertness and consciousness; meningeal signs; cranial nerves; motor functions, including muscle tone and myotatic reflexes; sensation modalities (surface and deep tactile, proprioception, and thermoalgesia); balance; coordination; and gait. Evaluating the pattern and distribution of motor and sensory impairment is important to distinguish GBS from other neurological problems. The clinical history should include information on recent acute illnesses and vaccinations, as well as the progression of neurological symptoms.

GBS and ZIKV

A case-control study conducted on the French Polynesia outbreak documented the relationship between GBS and ZIKV infection. Information was also obtained on the cases' clinical and neurophysiological manifestations. Based on the results of that study, the risk of GBS was estimated at 0.24 per 1,000 ZIKV infections (or 1 case per 4,000 infected individuals) (*40*).

ZIKV-associated GBS cases in French Polynesia were described as the motor axonal variant (40). Those in the Americas, however, consisted primarily of the demyelinating variant (acute demyelinating polyradiculitis), followed by the axonal variant (*47, 69*).

GBS management in the context of ZIKV infection should include immunotherapeutic treatment (plasmapheresis or immunoglobulins), early rehabilitation, pain treatment, and deep vein thrombosis prevention. Care should also address nutritional aspects, early detection of dysautonomia and breathing problems, and management of patient co-morbidities.

Both plasmapheresis and immunoglobulin have proved effective for GBS treatment. Clinical indications for their use include GBS patients who develop inability to walk without support within the first three weeks of onset of symptoms, and ideally within the first 14 days. More detailed recommendations are available online at: http://apps.who.int/iris/bitstream/10665/204474/1/WHO_ZIKV_MOC_16.4_eng.pdf?ua=1.

Clinical care for these patients requires a social healthcare system that provides comprehensive services for seriously ill patients during the acute phase, and manages disabilities in patients with neurological

[8] In the context of albuminocytologic dissociation, pleocytosis refers to any white blood cell count > 50/µL in CSF. Please refer to PAHO's Practical Recommendations for the Implementation of Guidelines for the Detection and Care of Guillain-Barré Syndrome Related to Zika in the Region of the Americas (currently only available in Spanish). Available at: https://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=40289&lang=en.

complications, including congenital syndrome associated with ZIKV infection, through adequate rehabilitation programs.

ZIKV and other neurological syndromes

Other serious neurological manifestations have been described in association with acute ZIKV infection, including encephalitis, meningoencephalitis, cerebellitis, acute disseminated encephalomyelitis, encephalopathies with epileptic crises, inflammatory myelopathy, and alterations of the cranial nerves (*42, 43, 45, 48*). However, there is limited clinical description or epidemiological data on the real incidence of these presentations.

Diagnosis of these neurological manifestations requires a careful clinical assessment. If complex or unusual clinical presentations are suspected, consulting with reference specialists is advised, keeping in mind ZIKV disease as well as other possible etiologies.

Given the limited description of ZIKV-associated cases of myelitis, systematically obtaining a spinal cord MRI is recommended: (i) to determine whether there is any isolated involvement of spinal cord gray or white matter, and to evaluate the surrounding edema; (ii) to evaluate the location and extent of the myelitis (single lesion versus multifocal lesions, number of segments affected); and (iii) to rule out other causes of myelopathy (space-occupying lesions, arteriovenous malformations, medullary tumors, epidural or spinal abscess).

Viral encephalitis is an inflammatory process secondary to direct infection of brain tissues by different viruses. Encephalitis has been described in relation to acute ZIKV infections. Symptoms include fever, headache, photosensitivity, stiff neck, nausea, and vomiting, and, in the most severe cases, confusion, convulsions, paralysis, and coma.

Occasionally, there have been reports of an immunity-mediated demyelinating post-infectious syndrome associated to ZIKV, which presents with gradual quadriplegia, urinary retention, and diminished level of consciousness, and in which hyperdense cerebral and spinal lesions are detected in the MRI (*70, 71*).

Annex 4 provides a description of two clinical cases and the main findings related to the first cases of ZIKV associated myelitis and encephalitis described in the literature (*42, 43*).

Surveillance

Consistent with the general purpose of ZIKV surveillance, i.e., to contribute to the knowledge of ZIKV-associated complications, the core objectives of ZIKV-associated neurological complications surveillance are to:

- determine the incidence, trends, and impact of complications attributable to ZIKV infection;
- determine the proportion of all GBS potentially attributable to ZIKV infection; and
- investigate any increase in the incidence of GBS or neurological syndromes that cannot be explained by other causes.

Surveillance results are expected to support prevention measures – primary, secondary, and tertiary—as well as to contribute to improving the capacity of health systems to plan and provide comprehensive care to affected persons.

The following events should be reported to the corresponding surveillance level:

- any increase in GBS incidence, and
- all GBS cases in which ZIKV infection has been confirmed. Reporting can be updated after the initial report.

Regarding frequency, weekly reporting is advised, including the total number of hospitalized GBS cases during the preceding week, and, of those, the number of suspected or confirmed cases of ZIKV infection.

Case definitions: neurological complications

Case definition – GBS

WHO recommends using Brighton's criteria (62, 63) to define GBS cases for epidemiological surveillance.[9] Diagnostic certainty is classified at three levels (Table 2), based on clinical findings at disease onset, and the availability of CSF testing and neurophysiological studies.

Suspected case of ZIKV-associated GBS

Patient who

- resides in, or recently traveled to,[10] an area with known or suspected ZIKV circulation; or
- has had unprotected sex with a partner who resides in, or recently traveled to an area with known or suspected ZIKV circulation

and

presents the following signs and symptoms (level 3 Brighton criteria [see Table 2]):

- bilateral and flaccid weakness of the limbs; **and**
- decreased or absent deep tendon reflexes in the weakened limbs; **and**
- monophasic illness pattern; interval between weakness onset and nadir ranging from 12 hours to 28 days; and subsequent clinical plateau; **and**
- no alternative cause of weakness identified.

Confirmed case of ZIKV-associated GBS

Suspected case of ZIKV-associated GBS **with** laboratory confirmation of recent ZIKV infection.

[9] The level of diagnostic certainty from the Brighton classification should not be considered a criterion for determining treatment.

[10] History of recent travel for a longer period than in cases of ZIKV disease. In Polynesia, onset of GBS symptoms was, on average, 6 days later (4-10 days) than onset of symptoms for ZIKV infection.

Table 2. Brighton criteria* for GBS case definition

Level 1 of diagnostic certainty	Level 2 of diagnostic certainty	Level 3 of diagnostic certainty
Bilateral and flaccid weakness of the limbs; **and**	Bilateral and flaccid weakness of the limbs; **and**	Bilateral and flaccid weakness of the limbs; **and**
decreased or absent myotatic reflexes in limbs with weakness; **and**	decreased or absent myotatic reflexes in limbs with weakness; **and**	decreased or absent myotatic reflexes in limbs with weakness; **and**
monophasic illness pattern; and interval between onset and nadir of weakness between 12 hours and 28 days; **and** subsequent clinical plateau; **and**	monophasic illness pattern; and interval between onset and nadir of weakness between 12 hours and 28 days **and** subsequent clinical plateau; **and**	monophasic illness pattern; and interval between onset and nadir of weakness between 12 hours and 28 days; **and** subsequent clinical plateau; **and**
absence of identified alternative diagnosis for weakness; **and**	absence of identified alternative diagnosis for weakness; **and**	absence of identified alternative diagnosis for weakness.
cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value) and CSF total white cell count <50 cells/µL; **and**	CSF total white cell count <50 cells/µL (with or without CSF protein elevation above laboratory normal value); **or**	
electrophysiological findings consistent with GBS.	electrophysiological studies consistent with GBS if CSF not collected or CSF test results are not available.	

CSF: cerebrospinal fluid; GBS: Guillain-Barré syndrome.

* Fokke C, van den Berg B, Drenthen J, Walgaard C, van Doorn PA, Jacobs BC. Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria. Brain. 2014 Jan;137(Pt 1):33-43.

Case definition – myelitis

For surveillance purposes, cases of both acute flaccid myelitis and infectious and post-infectious acute transverse myelitis are included, as well as any acute inflammatory myelopathy.

Suspected case of ZIKV-associated myelitis

Patient who

- resides in, or traveled to, an area with known or suspected ZIKV circulation during the two weeks prior to onset of symptoms; **or**
- has had unprotected sex with a partner who resides or traveled to an area with known or suspected ZIKV circulation during the two weeks prior to onset of symptoms;

and

presents the following signs and symptoms:[11]

- acute focal motor weakness in one or more limbs with or without associated sensory signs or symptoms;[12] **and**
- CSF with pleocytosis (white blood cell count >5 cells/mm^3, adjusting for presence of red blood cells by subtracting 1 white blood cell for every 500 red blood cells); **and**
- spinal cord MRI compatible with myelitis; **and**
- no other cause of weakness identified.[13]

Confirmed case of ZIKV-associated myelitis

Suspected case of ZIKV associated myelitis **with** laboratory confirmation of recent ZIKV infection.

[11] Adapted from the case definition of the Centers for Disease Control and Prevention of the United States (US-CDC). Available at: https://www.cdc.gov/acute-flaccid-myelitis/hcp/case-definition.html.

[12] Sensory signs are those associated with the presence of paresthesia affecting one or more extremities; signs to look for: presence of hypesthesia or anesthesia at a spinal cord level.

[13] A study of CSF is critical for ruling out other etiologies, particularly infectious, inflammatory, or demyelinating ones.

Case definition – encephalitis

For surveillance of ZIKV-associated encephalitis, both encephalitis and meningoencephalitis are notifiable under this case definition.

Suspected case of ZIKV-associated encephalitis

Patient who

- resides in, or traveled to, an area with known or suspected ZIKV circulation during the two weeks prior to onset of symptoms; or
- has had unprotected sex with a partner who resides or traveled to an area with known or suspected ZIKV circulation during the two weeks prior to onset of symptoms;

and

- presents the following signs and symptoms:[14]
  - a combination of various symptoms, including fever, headache, photosensitivity, stiff neck, nausea, and vomiting, **and**
  - acute episode of lost consciousness or behavioral changes; **or**
  - new epileptic crisis; **or**
  - new focal neurological signs;

and

- CSF with pleocytosis (>5 leukocytes/mm^3, adjusting for presence of red blood cells by subtracting 1 white blood cell for every 500 red blood cells) with elevated proteins and reduced glucose;

and

- no other explanation for the clinical manifestations,[15] documented by magnetic resonance imaging (scanner or MRI).

Confirmed case of ZIKV-associated encephalitis

Suspected case of ZIKV associated encephalitis **with** laboratory confirmation of recent ZIKV infection.

[14] Adapted from the criteria of the Association of British Neurologists. Management of suspected viral encephalitis in adults – Association of British Neurologists and British Infection Association National Guidelines. J Infection 2012;64:347-73.

[15] Studying CSF is critical in order to rule out other etiologies, including herpes simplex, varicella zoster, enterovirus, and others agents depending on local epidemiology. Neuroimaging tests should be used to rule out space occupying lesions, vascular causes, etc.

Both myelitis and encephalitis may also be defined by Brighton's criteria (Annex 5). Diagnostic certainty is classified in three levels, based on clinical findings at the onset of symptoms, and on the possibility of testing CSF and conducting neurophysiologic studies. These criteria were originally developed to detect encephalitis or myelitis complications in children exposed to new vaccines; therefore, when applied to complications of viral myelitis or encephalitis in adults, their sensitivity may not be the same.

Laboratory Diagnosis

Laboratory diagnosis of ZIKV associated with GBS and other neurological manifestations

Diagnosis of ZIKV infection in a GBS patient can be made by applying previously described criteria for ZIKV disease. If GBS is suspected to be caused by flavivirus infection (positive anti-DENV and anti-ZIKV IgM, algorithm C), this is highly suggestive of ZIKA infection, as GBS after dengue infection is unusual based on existing literature. However, because of the potential persistence of IgM antibodies for several months following infection, other causes of GBS should be considered and ruled out before determining that GBS is likely associated with a recent ZIKV infection.

Usually, the occurrence of a neurological syndrome is suspected after the viremia period. Nevertheless, it is recommended that RT-PCR viral RNA detection be attempted in serum or urine, as well as the detection of IgM antibodies by ELISA in a serum sample. Of both methods, detection in urine has higher sensitivity. Although a positive RT-PCR result is confirmatory of ZIKV infection, a negative result does not rule out said infection.

Molecular analysis (RT-PCR) and the detection of anti-ZIKV IgM antibodies by ELISA can also be performed in a CSF sample obtained by medical indication for the diagnosis of the neurological syndrome, but not exclusively for diagnosing ZIKV infection (Annex 6, Samples).

Other Neurological Manifestations

Whenever a patient who resides in or has traveled to areas with ZIKV circulation develops clinical symptoms affecting the nervous system, ZIKV infection should be considered in the differential diagnosis. This also applies to those who have had unprotected sex with persons who reside or have traveled to such areas.

For neurological complications other than GBS, it is important to collect CSF for diagnostic confirmation of the association with ZIKV, through the same panel of diagnostic, serological, and molecular tests (see algorithm A, B, and C, above). While antibodies and viral genetic material can be detected in CSF, there is no evidence regarding how long after the onset of symptoms these markers remain detectable. For this reason, a negative result does rule not out recent Zika infection.

For patients with other confirmed neurological complications associated with ZIKV infection, the same surveillance and reporting approach as for GBS applies.

At the beginning of the ZIKV generated public health emergency of international concern in February 2016, WHO's Director-General emphasized the need to enhance surveillance of microcephaly associated with said infection, and to develop a case definition.

Surveillance of ZIKV-Associated Congenital Syndrome

Research prompted by the emergency led to rapid generation of evidence, and an expansion of the initial approach, to include a set of signs and symptoms of congenital anomalies in newborns of mothers exposed to ZIKV infection, which were found to constitute a syndrome (*72-80*).

Characterizing such syndrome is challenging, given the nonspecific nature of the clinical symptoms, the knowledge gaps regarding the clinical spectrum and course of the disease, and the definition of microcephaly, among others. In many countries, this challenge is compounded by a limited availability of tools and techniques for measuring head circumference (HC), and to precisely determine gestational age at birth. Variations of those measurements (including HC) by sex and gestational age require the use of demographic references for standardization.

Successful surveillance of ZIKV-associated congenital syndrome depends on the use of standardized operational procedures and the active involvement of healthcare workers.

Clinical Description of Congenital Syndrome Associated with ZIKV Infection[16]

This syndrome, as currently described, includes the presence of microcephaly with other signs, such as cranial-facial and other anthropometric disproportions, for example, redundant scalp with roughness, collapse of the calvaria, hypertonia or spasticity, irritability, and epileptic seizures (*25-80*). The syndrome also includes a variety of central nervous system and joint disorders (*38, 73-80, 82, 83*).

In some cases, there have been reports of cerebral hypoplasia, and hypoplasia or agenesis of the corpus callosum. Cerebral calcifications, mainly cortical and subcortical, are often present, as are alterations in the cerebral ventricles, anomalies of the posterior fossa, and lissencephaly, as well as auditory and visual abnormalities, such as central hearing loss, focal retinal pigment epithelium changes, and chorioretinal atrophy, predominantly in the posterior pole and especially in the macula, and optic nerve hypoplasia (*81, 83, 84, 86*).

Joint impairments in newborns can be severe and are likely secondary to central nervous system involvement. The manifestations of arthropathy can range from clubfoot to severe malformations (arthrogryposis) of the hands and feet (*80, 81, 83*).

An increase in the number of spontaneous abortions and stillbirths has also been reported; the latter exhibited other alterations associated with ZIKV infection that are still not well understood, including pulmonary hypoplasia (*87-89*).

[16] This description is preliminary and subject to change as more evidence becomes available.

Microcephaly

Microcephaly is defined as head circumference (HC) < –2 standard deviations from the reference population mean, standardized by age and sex. The International Fetal and Newborn Growth Consortium for the 21st Century (Intergrowth-21st)[17] provides greater precision for the evaluation of microcephaly in pre-term and full-term newborns, and it is therefore recommended that countries adopt this new standard. Its correct use requires reliable data on gestational age (from first-trimester ultrasound, or date of last menstrual period).

In full-term newborns for whom reliable information on gestational age at birth is not available, the use of WHO's Multicentre Growth Reference Study standards is recommended.[18] To measure HC, using the measuring tape developed by the Latin American Center for Perinatology is advised. It is also recommended that health services emphasize the need to measure and record HC in all newborns.

Objectives of ZIKV-Associated Congenital Syndrome Surveillance

The key objectives of congenital syndrome associated with ZIKV infection surveillance are as follows:

- establish a baseline and monitor the prevalence and trends of congenital syndrome, using microcephaly or other associated disorders as tracer events;
- investigate any increase in the prevalence of microcephaly at birth and other associated conditions;
- identify and investigate all new cases of congenital malformations (including microcephaly) not explained by other known causes; and
- identify the presence of infection in newborns of pregnant women who are in follow up care due to ZIKV detection.

[17] https://intergrowth21.tghn.org/site_media/media/articles/newbornsize.pdf.
[18] http://www.who.int/childgrowth/standards/en/.

RECOMMENDATIONS

Based on the experience obtained in the countries of the Region, the following are recommended activities for the design and implementation of a subsystem for surveillance of congenital syndrome associated with ZIKV infection:

- use an existing, or design an ad hoc, subsystem specifically for the identification of abortions, stillbirths, and live newborns with congenital syndrome in areas at risk of ZIKV circulation. This subsystem should be supported by existing sources of information (registries, data from referral hospitals, etc.);
- integrate said subsystem with the national surveillance system, and develop a database—within the latter—where generated data can be collected and accessed;
- establish or strengthen event surveillance in countries where routine surveillance does not allow for monitoring microcephaly incidence trends. To this end, it is important to raise awareness and provide information to sonographers, obstetricians, and maternal and child hospitals, on case reporting that meet the criteria of suspected cases of ZIKV-associated congenital syndrome;
- predefine data collection tools, reporting procedures and channels, database consolidation procedures, and analysis plans. Information dissemination needs to be defined (support, structure, content, frequency), the same as output reports, which must be clear and consistent over time for purposes of risk communication;
- plan for data quality control (incomplete, missing, incorrect, or duplicate data). Establish protocols for daily data review and quality control (automated or manual); and
- define elements that allow case identification while ensuring confidentiality.

Congenital syndrome associated with ZIKV infection

Case Definitions

Suspected case of congenital syndrome associated with ZIKV infection

Live newborn who presents with

- microcephaly: head circumference < –2 standard deviations measured after 24 hours of birth, according to standardized[19] references for gestational age and sex; **or**
- any congenital malformation of the central nervous system; **and**

whose mother, during pregnancy

- resided in or traveled to, an area with known or suspected ZIKV circulation; **or**
- had unprotected sex with a partner who resided in, or traveled to, an area with known or suspected ZIKV circulation.

Probable case of congenital syndrome associated with ZIKV infection

Live newborn who meets the criteria of suspected case of congenital syndrome associated with ZIKV, **and**

- who has intracranial morphological alterations diagnosed by any imaging method, and excluding other known possible causes; **or**
- whose mother had a rash during pregnancy.

Confirmed case of congenital syndrome associated with ZIKV infection

Live newborn of any gestational age who meets the criteria for suspected case of congenital syndrome associated with ZIKV infection, and has laboratory confirmation of ZIKV infection, independent of the detection of another microorganism.

In countries with presence of vectors for ZIKV or other arboviruses, surveillance could be expanded to other previously described congenital anomalies (especially CNS, auditory, and visual anomalies) that could be associated with ZIKV infection, and study these for the presence of potential causative agents.

[19] https://intergrowth21.tghn.org/site_media/media/articles/newbornsize.pdf.

Note

Head circumference (HC) should be measured or confirmed after 24 hours of birth. In newborns that are discharged earlier than 24 hours after birth, measurements should be taken before discharge from the healthcare facility. A new measurement of HC should then be obtained, preferably, during the first week of life, as part of follow-up monitoring of the child's growth and development. This information should be forwarded to the local surveillance authority. If measurements are taken after the first week of life, the appropriate reference growth tables for age and sex should be used.

When measuring head circumference, avoid rounding to the nearest centimeter, always record one decimal place.

Laboratory Diagnosis

Laboratory diagnosis of ZIKV-associated with congenital syndrome

ZIKV infection in pregnant women can be diagnosed based on previously described criteria. Furthermore, as vertical transmission of the infection is known to occur, strict monitoring of the mother and newborn is essential (25, 39, 73, 75-77, 80, 81, 83-85).

In intrauterine ZIKV infections, viral genetic material can be detected for extended periods by molecular techniques (50), so testing serum (neonatal and maternal) or blood from the umbilical cord or placenta is recommended to (see Annex 6, Table 6.2). When testing umbilical cord serum, extreme caution should be used not to contaminate the sample with maternal blood. However, the chance of molecular detection in these cases is low, which makes serological testing extremely important. In addition, because the possibility of the newborn having had a previous flavivirus infection is low, detection of IgM antibodies against ZIKV in neonatal serum constitutes an important finding indicative of intrauterine infection.

Molecular analysis (RT-PCR) and the detection of anti-ZIKV IgM antibodies by ELISA can also be performed in a CSF sample obtained by medical indication for the diagnosis of the congenital syndrome, but not exclusively for diagnosing ZIKV infection (Annex 6, Samples).

When congenital infection is suspected, laboratory tests to determine the presence of congenital infection by cytomegalovirus, herpes simplex virus, rubella, HIV, toxoplasmosis, and syphilis are recommended. Screening tests for intrauterine ZIKV infection are still in development.

ZIKV-Associated Abortion or Stillbirth

Suspected ZIKV-associated abortion or stillbirth

Abortion or stillbirth[20] in a woman who, during her pregnancy

- presented rash **and**
- resided in, or traveled to, an area with known or suspected ZIKV circulation **or**
- had unprotected sex during pregnancy with a partner who resided in, or traveled to, an area with known or suspected ZIKV circulation.

Confirmed ZIKV-associated abortion or stillbirth

A suspected case where ZIKV infection is confirmed from blood or urine samples from either the mother or products of conception.

Laboratory Diagnosis

Laboratory diagnosis of ZIKV infection associated with abortion or stillbirth indicative of congenital infection

In cases of abortion and stillbirth, a serum sample should be obtained, if possible, for the detection of IgM antibodies (by ELISA) and, in any case, a tissue sample must be collected (brain, kidney, liver, or different slices of undifferentiated tissue). Maternal serum samples should be analyzed in tandem to determine the presence of IgM antibodies. If a sample of amniotic fluid is available (obtained by medical indication for the diagnosis of other syndromes), it can be used for molecular detection using RT-PCR (see Annex 6).

[20] Based on national definition.

Vertical Transmission of ZIKV without Congenital Syndrome

Case Definitions

To contribute to the description of various complications resulting from ZIKV infection in utero, surveillance of vertical transmission events is recommended, even in cases of apparently healthy newborns.

Suspected vertical transmission of ZIKV without congenital syndrome

Live newborn of any gestational age, who has not met the criteria for a suspected case of ZIKV-associated congenital syndrome **and** whose mother has been classified as a suspected, probable, or confirmed case of ZIKV during pregnancy.

Probable case of ZIKV vertical transmission without congenital syndrome

Live newborn who meets the criteria for a suspected case of ZIKV infection by vertical transmission, **and** whose sample of umbilical cord blood contains anti-ZIKV IgM detected by ELISA, or viral RNA detected by RT-PCR.

Confirmed case of vertical transmission of ZIKV without congenital syndrome

Live newborn who meets the criteria for a suspected case of ZIKV infection by vertical transmission, **and** in whose serum sample anti-ZIKV IgM antibodies are detected by ELISA. A positive viral RNA result by RT-PCR could indicate perinatal transmission rather than vertical transmission; therefore, a follow up serology test is recommended.

Annexes

Annex 1.
ZIKV Surveillance: Core Data for Case Reporting

The following section lists the recommended core data for ZIKV surveillance and reporting, which countries can supplement and adapt to meet their specific requirements.

These data can be collected as part of universal case-by-case surveillance, but can also be adapted by countries that have integrated or syndrome-based surveillance systems. The timing of reporting should be defined by each country, depending on its epidemiological scenario. It is important that each country take into account IHR reporting requirements.

Section 1: General information

Patient identification

- Unique identifier
- Full name*
- Age
- Sex
- Address*
- Telephone number*
- E-mail address*

*Information should be obtained and retained by local health authorities; these data should not be transmitted to national authorities. Information sent to national health authorities should be linked by a unique identifier.

Diagnosis

- Zika virus (ZIKV) disease (suspected/probable/confirmed)
- GBS associated with ZIKV infection (suspected/confirmed)
- Other neurological complications associated with ZIKV infection, such as myelitis and encephalitis associated with Zika virus infection (suspected / confirmed)
- Other neurological complications associated with ZIKV infection (suspected/probable/confirmed)
- Congenital syndrome associated with ZIKV (suspected/probable/confirmed)
- Abortion or stillbirth associated with ZIKV infection (suspected/confirmed)
- Vertical transmission of ZIKV without congenital syndrome (suspected/probable/confirmed)

Identification of reporting individual: name, contact information (telephone, e-mail); reporting facility.

Section 2: Relevant information for each reported diagnosis (see corresponding section)

ZIKV Disease

- Date of illness onset
- Risk factor
  - Resident of area with known or suspected ZIKV circulation/traveler/sexual partner
- Initial case classification (suspected/probable/confirmed)
- Relevant patient characteristics:
  - Pregnant: ❑ Yes ❑ No (gestational weeks): _____
  - Hospitalized: ❑ Yes ❑ No (facility): _____
  - Dead: ❑ Yes ❑ No
- Laboratory diagnosis
  - RT-PCR: type of sample (serum, blood, urine); result (positive, negative, pending, or not performed); date of sample collection (day/month/year).
  - Anti-Zika IgM serology: type of sample (serum); result (positive, negative, pending, or test not performed); date of sample collection. Neutralization test conducted ❑ Yes ❑ No; result (positive, negative, pending).
  - Fatal cases: molecular detection of viral genome in autopsy tissue specimen ❑ Yes ❑ No ❑ pending ❑ not performed. Specific detection of viral antigen in autopsy specimen by immunohistochemistry.

ZIKV infection-associated Guillen-Barré syndrome

- Risk factor
  - Resident of area where the vector is present / traveler / sexual partner
- Date of onset of neurological symptoms
- Classification according to Brighton criteria (1/2/3)
- CSF: white blood cell count, proteins (mg/dl), glucose (mg/dl)
- Electrophysiological studies (AIDP, AMAN, AMSAN)
- History of rash: ❑ Yes ❑ No + dates (day/month/year): _____
- Initial classification of case (suspected / confirmed)
- Relevant patient characteristics:
  - Pregnant: ❑ Yes ❑ No (gestational weeks): _____
  - Hospitalized: ❑ Yes ❑ No (facility): _____
  - Dead: ❑ Yes ❑ No

- Comorbidity:
  HIV ❑ Yes ❑ No; diabetes ❑ Yes ❑ No; autoimmune disease ❑ Yes ❑ No; other

  _____

- Laboratory diagnosis:
  - PCR: Type of sample (serum, blood, urine, CSF); result (positive, negative, pending, or not performed); date of sample collection (day/month/year) _____
  - Anti-Zika IgM serology: Type of sample (serum, CSF); result (positive, negative, pending, or not performed); date of sample collection (day/month/year). Neutralization test carried out ❑ Yes ❑ No; result (positive, negative, pending).

Other neurological manifestations associated with Zika virus infection

a) *Myelitis*

- Risk factor
  - Resident of area where the vector is present/traveler/sexual partner
- Date of onset of neurological symptoms
- Meet criteria for myelitis ❑ Yes ❑ No
- MRI ❑ Yes ❑ No; date (day/month/year); site (cervical/thoracic/lumbar); number of medullary segments involved
- History of rash ❑ Yes ❑ No; date (day/month/year) _____
- Initial classification of the case (suspected/confirmed)
- Patient characteristics:
  - Pregnant woman ❑ Yes ❑ No (gestational week): _____
  - Hospitalized: ❑ Yes ❑ No (facility): _____
  - Dead: ❑ Yes ❑ No
  - Comorbidity:
    HIV ❑ Yes ❑ No; diabetes ❑ Yes ❑ No; autoimmune disorder ❑ Yes ❑ No; other

    _____

- Laboratory diagnosis
  - PCR: type of sample (serum, blood, urine, CSF); result (positive, negative, pending, or not tested). Date of sample collection (day/month/year)
  - Anti-Zika IgM serology: type of sample (serum, CSF); result (positive, negative, pending, or not tested). Date of sample collection (day/month/year). Neutralization test conducted ❑ Yes ❑ No; result (positive, negative, pending).

b) ***Encephalitis/acute meningoencephalitis***

- Risk factor
  - Resident of area where the vector is present/traveler/sexual partner
- Date of onset of neurological symptoms
- Meet criteria for encephalitis ❑ Yes ❑ No
- CSF: white blood count, proteins (mg/dl), glucose (mg/dl)
- History of rash ❑ Yes ❑ No; date (day/month/year) _____
- Initial classification of the case (suspected/confirmed)
- Patient characteristics:
  - Pregnant woman ❑ Yes ❑ No (gestational week): _____
  - Hospitalized: ❑ Yes ❑ No (facility): _____
  - Dead: ❑ Yes ❑ No
  - Comorbidity:
    HIV ❑ Yes ❑ No; diabetes ❑ Yes ❑ No; autoimmune disorder ❑ Yes ❑ No; other
- Laboratory diagnosis
  - PCR: type of sample (serum, blood, urine, CSF); result (positive, negative, pending, or not tested). Date of sample collection (day/month/year)
  - Anti-Zika IgM serology: type of sample (serum, CSF); result (positive, negative, pending, or not tested). Date of sample collection (day/month/year). Neutralization test conducted ❑ Yes ❑ No; result (positive, negative, pending).

c) ***Other less common neurological complications:*** *acute disseminated encephalomyelitis, cranial neuropathies, and encephalopathy with or without epileptic episodes*

Report as individual cases to determine the incidence of these neurological manifestations.

Congenital syndrome associated with ZIKV infection

- Pregnancy outcome: live newborn/abortion/stillbirth
- Identification of the newborn, gestational age, sex, birthweight, and length at birth
- Information on the mother
  - Risk factor: resident of area where the vector is present/traveler/sexual partner
  - History of rash ❑ Yes ❑ No; date (day/month/year) _____
  - Full-term pregnancy ❑ Yes ❑ No
  - Date of delivery or termination of pregnancy (date/month/year) _____
- Initial congenital syndrome classification (suspected/probable/confirmed)
  - Microcephaly ❑ Yes ❑ No; head circumference in centimeters (round to nearest decimal) _____
  - Intracranial calcifications ❑ Yes ❑ No ❑ unknown; detected in the prenatal period/ after birth

- Other intracranial morphological alterations ❑ Yes ❑ No ❑ unknown; detected in the prenatal period/at birth/after birth
- Other birth defects ❑ Yes ❑ No ; Which?: _____

- Diagnostic support and laboratory tests
  - PCR: type of sample (serum, cord blood, urine, CSF, amniotic fluid); result (positive, negative, pending, or not tested). Date of sample collection (day/month/year)
  - anti-Zika IgM serology: Type of sample (serum, CSF, amniotic fluid); result (positive, negative, pending, or not performed). Date of sample collection (day/month/year). Neutralization test performed ❑ Yes ❑ No; result (positive, negative, pending)
  - Clinical autopsy ❑ Yes ❑ No
  - Histopathology: type of sample (tissue from _____). Result (positive, negative, pending or not performed). Date of sample collection (day/month/year)

ZIKV infection-associated abortion or stillbirth

- Outcome of the fetus (abortion/stillbirth)
- Information on the fetus: gestational age in weeks, weight (in grams)
- Information on the mother
  - Risk factor. Resident of an area where the vector is present/traveler/sexual partner
  - History of rash in the pregnant woman ❑ Yes ❑ No; date (gestational week)
  - Date of termination of pregnancy (day/month/year)
- Initial classification of the case (suspected/confirmed)

Diagnostic support and laboratory tests

Pregnant woman:

- PCR: type of sample (serum, blood, urine); result (positive, negative, pending, or not tested). Date of sample collection (day/month/year)
- Anti-Zika IgM serology: type of sample (serum, CSF, amniotic fluid); result (positive, negative, pending, or not tested). Date of sample collection (day/month/year). Neutralization test performed ❑ Yes ❑ No; result (positive, negative, pending).

Product of pregnancy:

- PCR: type of sample: (tissue, blood). Result (positive, negative, pending or not tested). Date of sample collection (day/month/year) _____
- Clinical autopsy ❑ Yes ❑ No
- Histopathology: sample type (tissue: indicate_____); result (positive, negative, pending, or not tested); Date of sample collection (day/month/year) _____

Vertical transmission of ZIKV without congenital syndrome

- Outcome (newborn/stillbirth)
- Identification of the newborn: gestational age, sex, birthweight, and length at birth
- Information on the mother
  - Risk factor: resident of an area where the vector is present/traveler/sexual partner
  - Classification of mother's Zika case (suspected/probable/confirmed)
  - Onset of Zika symptoms (gestational week) _____
  - Full-term pregnancy ❑ Yes ❑ No
  - Date of delivery (day/month/year) _____
- Initial classification of the vertical transmission (suspected/probable/confirmed)
  - Birth defects other than congenital syndrome ❑ Yes ❑ No
    Which?: _____
- Diagnostic support and laboratory tests
  - PCR: type of sample (cord blood, serum, CSF, amniotic fluid). Result (positive, negative, pending, or not tested). Date of sample collection (day/month/year)
  - Anti-Zika IgM serology: type of sample (cord blood, serum, CSF, amniotic fluid). Result (positive, negative, pending, or not performed). Date of sample collection (day/month/year). Neutralization test conducted ❑ Yes ❑ No. Result (positive, negative, or pending).
  - Clinical autopsy ❑ Yes ❑ No
  - Histopathology: type of sample (tissue:_____). Result (positive, negative, pending, or not tested). Date of sample collection (day/month/year).

Annex 2.
Case definitions

For integrated surveillance with measles and rubella

Probable case of ZIKV disease

Patient who presents with fever or rash

or

in whom a healthcare worker suspects measles or rubella.

Probable case of ZIKV disease

Patient who meets the criteria of suspected case **and** has anti-ZIKV IgM antibodies, with negative laboratory results for other flaviviruses.

Confirmed case of ZIKV disease

Patient who meets the criteria for a suspected case **and** has laboratory confirmation of recent ZIKV infection, with presence of:

- ZIKV RNA or ZIKV antigen in serum samples or other specimens (e.g., urine, saliva, tissue, whole blood, or CSF); **or**
- positive anti-ZIKV IgM antibodies and plaque reduction neutralization test (PRNT) for ZIKV titers ≥ 10 in the absence of titers for others flaviviruses;[21] **or**
- In cases of death,[22] molecular detection of the viral genome in autopsy tissue (fresh or in paraffin) with in situ hybridization tests.

For etiological surveillance of ZIKV disease

Suspected case of ZIKV disease

Patient with rash* and two or more of the following signs or symptoms:

- fever, usually ≥38.5 °C
- conjunctivitis (non-purulent/hyperemic)
- arthralgia
- myalgia
- periarticular edema

** usually maculopapular and pruritic.*

[21] The test is done on paired samples of probable cases with positive anti-ZIKV IgM antibodies.

[22] Excluding abortion or stillbirth, discussed in the next section.

Probable case of ZIKV disease

Patient who meets the criteria of a suspected case, **and** has anti-ZIKV IgM antibodies, with negative laboratory results for other flaviviruses.

Confirmed case of ZIKV disease

Patient who meets the criteria for a suspected case **and** has laboratory confirmation of recent ZIKV infection, with presence of:

- ZIKV RNA or ZIKV antigen in serum samples or other specimens (e.g., urine, saliva, tissue, whole blood, or cerebrospinal fluid [CSF)];[23] **or**
- positive anti-ZIKV IgM antibodies and plaque reduction neutralization test (PRNT) for ZIKV titers ≥ 10 in the absence of titers for other flaviviruses[24].
- In cases of death,[25] molecular detection of the viral genome in autopsy tissue (fresh or in paraffin) with *in situ* hybridization tests.

Guillain-Barré Syndrome (GBS)

Suspected case of ZIKV-associated GBS[h]

Patient who:

- resides in, or recently traveled[26] to, an area with known or suspected ZIKV circulation; **or**
- has had unprotected sex with a partner who resides in, or recently traveled to, an area with known or suspected ZIKV circulation,

and

presents the following signs and symptoms (level 3 Brighton criteria):

- bilateral and flaccid weakness of the limbs; **and**
- decreased or absent deep tendon reflexes in the weak limbs; **and**
- monophasic illness pattern; interval between weakness onset and nadir ranging from 12 hours to 28 days; and subsequent clinical plateau; **and**
- no alternative cause of weakness identified.

Confirmed case of ZIKV-associated GBS

Suspected case of ZIKV-associated GBS **with** laboratory confirmation of recent ZIKV infection.

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[23] Excluding abortion or stillbirth.

[24] The test is done on paired samples of probable cases with positive anti-ZIKV IgM antibodies.

[25] Excluding abortion or stillbirth.

[26] One must consider a history of recent travel for a longer period than in cases of ZIKV disease. In Polynesia, onset of GBS symptoms was, on average, 6 days later (4-10 days) than onset of symptoms for ZIKV infection.

Other ZIKV-associated neurological syndromes

a) ZIKV-associated myelitis

For surveillance purposes, both acute flaccid motor myelitis and acute transverse infectious and post-infectious myelitis are included.

Suspected case of ZIKV-associated myelitis

Patient who:

- resides in, or traveled to, an area with known or suspected ZIKV circulation during the two weeks prior to onset of symptoms; **or**
- has had unprotected sex with a partner who resides in, or traveled to, an area with known or suspected ZIKV circulation during the two weeks prior to onset of symptoms;

and

presents the following signs and symptoms:[27]

- acute focal motor weakness in one or more limbs with or without associated sensory signs or symptoms;[28] **and**
- CSF with pleocytosis (white blood cell count > 5 cells/mm^3, adjusting for presence of red blood cells by subtracting 1 white blood cell for every 500 red blood cells); **and**
- spinal cord MRI compatible with myelitis; **and**
- no other cause of weakness identified.[29]

Confirmed case of ZIKV-associated myelitis

Suspected case of ZIKV-associated myelitis **with** laboratory confirmation of recent ZIKV infection.

b) ZIKV-associated encephalitis

For epidemiological surveillance purposes, both ZIKV-associated encephalitis and meningoencephalitis are deemed notifiable under this case definition.

Suspected case of ZIKV-associated encephalitis

Patient who:

- resides in, or traveled to, an area with known or suspected ZIKV virus circulation during the two weeks prior to onset of symptoms; **or**
- has had unprotected sex with a partner who resides in, or traveled to, an area with known or suspected ZIKV circulation during the two weeks prior to onset of symptoms;

and

[27] Adapted from the case definition of the Centers for Disease Control and Prevention of the United States (US-CDC). Available at: https://www.cdc.gov/acute-flaccid-myelitis/hcp/case-definition.html

[28] Sensory signs are considered those associated with the presence of parethesias affecting one or more extremities; signs to look for: presence of a hypo or anesthesia at a spinal cord level.

[29] A CSF study is critical for ruling out other etiologies, particularly infectious, inflammatory, or demyelinating ones.

- presents the following signs and symptoms:[30]
  - a combination of various symptoms including fever, headache, photosensitivity, stiff neck, nausea and vomiting; **and**
  - acute episode of lost consciousness or behavioral changes; **or**
  - new epileptic crisis; **or**
  - new focal neurological signs;

and

- CSF with pleocytosis (> 5 leukocytes/mm^3, adjusting for presence of red blood cells by subtracting 1 white blood cell for every 500 red blood cells) with elevated proteins and reduced glucose;

and

- no other explanation for the clinical manifestations,[31] documented with magnetic resonance imaging (MRI).

Confirmed case of ZIKV-associated encephalitis

Suspected case of ZIKV associated encephalitis **with** laboratory confirmation of recent ZIKV infection.

Congenital syndrome associated with ZIKV infection

Suspected case of congenital syndrome associated with ZIKV infection

Live newborn who presents with

- microcephaly: head circumference < –2 standard deviations measured 24 hours after birth according to standardized[32] references for gestational age and sex; **or**
- any congenital malformation of the central nervous system (CNS); **and**

  whose mother, during pregnancy:

  - resided in, or traveled to, an area with known or suspected ZIKV circulation; **or**
  - had unprotected sex with a partner who resided in, or traveled to, an area with known or suspected ZIKV circulation.

Probable case of congenital syndrome associated with ZIKV infection

Live newborn who meets the criteria for a suspected case of congenital syndrome associated with ZIKV, **and**

- who has intracranial morphological alterations diagnosed by any imaging method, and excluding

[30] Adapted from the criteria of the Association of British Neurologists. Management of suspected viral encephalitis in adults – Association of British Neurologists and British Infection Association National Guidelines. J Infection, 2012;64:347-73.

[31] Studying CSF is critical in order to rule out other etiologies, including herpes simplex, varicella zoster, enterovirus, and others agents depending on local epidemiology. Neuroimaging tests should be used to rule out space occupying lesions, vascular causes, etc.

[32] https://intergrowth21.tghn.org/site_media/media/articles/newbornsize.pdf.

other known possible causes; **or**

- whose mother had rash during pregnancy.

Confirmed case of congenital syndrome associated with ZIKV infection

Live newborn of any gestational age who meets the criteria for a suspected case of congenital syndrome associated with ZIKV, **and** has laboratory confirmation of ZIKV infection, independent of the detection of another microorganism.

ZIKV-associated abortion or stillbirth

Suspected ZIKV-associated abortion or stillbirth

Abortion or stillbirth[33] in a woman who, during her pregnancy presented rash and

- resided in, or traveled to, an area with known or suspected ZIKV circulation **or**
- had unprotected sex during pregnancy with a partner who resided in, or traveled to, an area with known or suspected ZIKV circulation.

Confirmed ZIKV-associated abortion or stillbirth

A suspected case where ZIKV infection is confirmed from blood or urine samples from either the mother or products of conception.

Vertical transmission of ZIKV without congenital syndrome

Suspected vertical transmission of ZIKV without congenital syndrome

Live newborn of any gestational age, who has not met the criteria for a suspected case of ZIKV-associated congenital syndrome, **and** whose mother has been classified as a suspected, probable, or confirmed case of ZIKV during pregnancy.

Probable case of vertical transmission of ZIKV without congenital syndrome

Live newborn who meets the criteria for a suspected case of ZIKV infection by vertical transmission, **and** whose umbilical cord blood sample contains anti-ZIKV IgM detected by ELISA, or viral RNA detected by RT-PCR.

Confirmed case of vertical transmission of ZIKV without congenital syndrome

Live newborn who meets the criteria for a suspected case of ZIKV infection by vertical transmission, **and** in whose serum sample anti-ZIKV IgM antibodies are detected by ELISA. A positive viral RNA result by RT-PCR could indicate perinatal transmission rather tan vertical transmission; therefore, a follow up serology test is recommended.

[33] Based on national definition.

Annex 3.
Guillain-Barré Syndrome (GBS) Diagnosis

Required clinical findings

- Progressive limb weakness
- Hyporeflexia or areflexia*

* Approximately 10% of GBS patients can present with normal or heightened myotatic reflexes; their assessment depends on the examiner.

Suggestive clinical findings

- Rapid progression of symptoms, with deficits plateauing in <4 weeks (90%)
- Relative symmetrical weakness
- Sensory and motor symptoms*
- Cranial nerve involvement (usually facial and bilateral)
- Autonomic dysfunction (cardiac arrhythmia, especially tachycardia, abnormalities in blood pressure, such as orthostatic hypotension and hypertension, vasomotor symptoms) which may fluctuate
- Most start recovery 2 - 4 weeks after plateau period

*Some sensory symptoms and distal paresthesia may be present in GBS and can precede the occurrence of motor deficit.

Laboratory (cerebrospinal fluid)

Albuminocytologic dissociation (increased concentration of protein in the absence of pleocytosis in CSF).*

*Pleocytosis >50 cells/mm^3 suggests infectious inflammatory process, such as myelitis, encephalomyelitis, encephalitis, meningoencephalitis, or meningitis, which are part of the differential diagnosis.

Other recommended tests

- HIV serological testing is advised.
- Other laboratory tests to identify possible etiologies, depending on local epidemiological context and clinical presentation (schistosomiasis, *Campylobacter jejuni*, diphtheria, enterovirus, cytomegalovirus, arbovirus, etc.).

Electrophysiological study

Acute inflammatory demyelinating polyneuropathy (AIDP):

- Slowed motor nerve conduction velocities
- Prolonged motor distal latency

- Increased F-wave latency
- Conduction block
- Temporal dispersion

Motor axonal form:

- Absence of electrophysiological findings suggestive of demyelination

Findings that call into question a GBS diagnosis

- Marked, persistent asymmetry of motor weakness
- Initial or persistent alteration of sphincter control
- Pleocytosis (>50 white blood cells/mm^3 in CSF) or presence of polymorphonuclear lymphocytes
- Presence of sensory level (suggestive of myelitis and other medullary pathologies)

Findings that rule out a diagnosis of GBS

- History of exposure to neurotoxins (organophosphorus compounds, heavy metals, solvents, etc.)
- Abnormal porphyrin metabolism
- History of recent diphtheria infection
- Definitive poliomyelitis diagnosis
- Botulism diagnosis

Differential diagnosis of a clinical syndrome of rapid, progressive weakness

- Myelopathies

Acute flaccid paralysis syndrome constitutes a differential diagnosis from GBS and can have numerous causes. A neurological examination, CSF analysis, and (if possible) neuroimaging studies (particularly magnetic resonance imaging of the spinal cord) are recommended for diagnosing myelopathy.

In recent years, enterovirus-associated outbreaks of acute flaccid paralysis have been reported, especially in young adults and children. For this reason, when enterovirus infection is suspected, it is recommended that a nasopharyngeal swab be taken to detect rhinovirus/enterovirus, particularly in children and young people.

- Other central nervous system inflammatory processes

Encephalitis, acute disseminated encephalomyelitis, meningitis, or brain stem compression/inflammatory/ischemic syndrome can present with motor involvement.

Any patient with an altered level of consciousness, symptomatic epileptic crises, and signs of brain stem involvement should be evaluated with additional neuroimaging studies (computed tomography or magnetic resonance imaging). After the neuroimaging test, once a space-occupying lesion has been ruled out, and if a CNS inflammatory process is suspected, it is recommended that lumbar puncture be done for CSF analysis.

Nerve roots and peripheral nerves

Diphtheria, porphyria, hypokalemic paralysis, critical illness polyneuropathy

Myoneural junction

Myasthenia gravis, botulism

Muscle

Polymyositis and other inflammatory myopathies, acute rhabdomyolysis, critical illness myopathy

Annex 4.
Main findings in first clinical cases of ZIKV-associated myelitis and encephalitis

Clinical case 1 – ZIKV-associated myelitis: summary (42)

Female, 15 years of age. Guadeloupe.

Clinical presentation: onset with frontal headaches, and conjunctival hyperemia, and pain of the left arm. A week later, the patient developed left-sided weakness and proximal pain of the left arm and leg.

Magnetic resonance imaging: the MRI showed spinal cord edema, and lesions of the cervical and thoracic spinal cord.

ZIKV diagnosis: positive RT-PCR in serum, urine, and cerebrospinal fluid as of day nine of onset of symptoms.

Evolution and treatment: the patient was administered high doses of corticoids, resulting in favorable clinical response and evidence of improvement in the MRI.

Clinical case 2- Meningoencephalitis – summary (43)

Male, 81 years of age. France.

Clinical presentation: 10 days after returning from a trip to the Pacific, the patient presented fever, reduced level of consciousness, and paresis of the right upper limb.

Magnetic resonance imaging: the MRI showed hyperintensities in subcortical white matter

Cerebrospinal fluid: moderate neutrophilic pleocytosis, with slightly elevated protein level and normal glucose level.

ZIKV diagnosis: positive RT-PCR and viral CSF culture on the first day of hospital admission.

Evolution and treatment: Support treatment. Clinical improvement and cognitive recovery was complete 38 days after admission. Residual weakness (4/5) of the left arm persisted.

Annex 5.
Brighton Criteria for Myelitis and Encephalitis Case Definition

Table 5.1. Brighton criteria for myelitis case definition (*89*)

Level 1 of diagnostic certainty	Level 2 of diagnostic certainty	Level 3 of diagnostic certainty
Demonstration of acute inflammation of spinal cord (± meninges) by histopathology	Myelopathy (development of sensory, motor, or autonomic dysfunction attributable to the spinal cord, including upper- and/or lower-motor neuron weakness, sensory level, bowel and/or bladder dysfunction, erectile dysfunction), **and** **Two or more** of the following indicators suggestive of spinal cord inflammation: 1. Fever (temperature >38°C); 2. CSF pleocytosis (> 5 WBC/ mm3 in children >2 months of age; >15 WBC/ mm^3 in children <2 months of age); 3. Neuroimaging findings demonstrating acute inflammation (+/– meninges), or demyelination of the spinal cord.	Myelopathy (development of sensory, motor, or autonomic dysfunction attributable to the spinal cord, including upper- and/or lower-motor neuron weakness, sensory level, bowel and/or bladder dysfunction, erectile dysfunction), **and** **One** of the following indicators suggestive of spinal cord inflammation: 1. Fever (temperature >38°C); 2. CSF pleocytosis (>5 WBC/ mm^3 in children >2 months of age; >15 WBC/ mm3 in children <2 months of age); 3. Neuroimaging findings demonstrating acute inflammation (+/– meninges), or demyelination of the spinal cord.

Table 5.2. Brighton criteria for encephalitis case definition (*89*)

Level 1 of diagnostic certainty	Level 2 of diagnostic certainty	Level 3 of diagnostic certainty
Demonstration of acute inflammation of nervous system parenchyma (± meninges) by histopathology.	Encephalopathy (e.g. depressed or altered level of consciousness, lethargy, or personality change lasting >24 hours), **and** ONE OR MORE of the following: 1. Decreased or absent response to environment, as defined by response to loud noise or painful stimuli; 2. Decreased or absent eye contact; 3. Inconsistent or absent response to external stimuli; 4. Decreased arousability; 5. Seizure associated with loss of consciousness. **or** Focal or multifocal findings referable to the central nervous system, including **one or more** of the following: 1. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness); 2. Cranial nerve abnormality/ abnormalities; 3. Visual field defect/defect(s); 4. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/sucking reflex); 5. Motor weakness (either diffuse or focal; more often focal); 6. Sensory abnormalities (either positive or negative; sensory level); 7. Altered deep tendon reflexes (hypo- or hyperreflexia, reflex asymmetry); 8. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus; **and** **TWO OR MORE** of the following indicators of inflammation of the CNS: 1. Fever (temperature >38 °C) 2. CSF pleocytosis (>5 WBC/mm^3 in children >2 months of age 3. EEG findings consistent with encephalitis, or 4. Neuroimaging consistent with encephalitis.	Encephalopathy (e.g. depressed or altered level of consciousness, lethargy, or personality change lasting >24 hours), **and** ONE OR MORE of the following: 1. Decreased or absent response to environment, as defined by response to loud noise or painful stimuli; 2. Decreased or absent eye contact; 3. Inconsistent or absent response to external stimuli; 4. Decreased arousability; 5. Seizure associated with loss of consciousness. **or** Focal or multifocal findings referable to the central nervous system, including **one or more** of the following: 1. Focal cortical signs (including but not limited to: aphasia, alexia, agraphia, cortical blindness); 2. Cranial nerve abnormality/ abnormalities; 3. Visual field defect/defect(s); 4. Presence of primitive reflexes (Babinski's sign, glabellar reflex, snout/ sucking reflex); 5. Motor weakness (either diffuse or focal; more often focal); 6. Sensory abnormalities (either positive or negative; sensory level); 7. Altered deep tendon reflexes (hypo- or hyperreflexia, reflex asymmetry); 8. Cerebellar dysfunction, including ataxia, dysmetria, cerebellar nystagmus; **and** **ONE** of the following indicators of inflammation of the CNS: 1. Fever (temperature >38 °C) 2. CSF pleocytosis (>5 WBC/mm^3 in children >2 months of age; >15 WBC/mm^3 in children >15 WBC/mm^3 in children >2 months of age 3. EEG findings consistent with encephalitis, or 4. Neuroimaging consistent with encephalitis.

EEG: electroencephalogram; CSF: cerebrospinal fluid; CNS: central nervous system.

Annex 6.
Indications for Sample Collection and Conservation Depending on Laboratory Test

Table 6.1. Samples for surveillance and diagnosis of ZIKV associated with GBS and other neurological manifestations

Sample	Days ater symptoms onset	Quantity	Transport medium	Transport conditions	Conservation >1 week	Laboratory test
Serum	1 to 5	3-7 mL	No additives	2 to 8 °C	-20 to -70 °C	PCR
Serum	5 to 7	3-7 mL	No additives	2 to 8 °C	-20 to -70 °C	PCR + ELISA IgM
Serum	7 and up	3-7 mL	No additives	2 to 8 °C	-20 to -70 °C	ELISA IgM
Urine	1 ti 15	3-7 mL	No additives	2 to 8 °C	-20 to -70 °C	PCR
CSF*		0,5 mL	No additives	2 to 8 °C	-20 to -70 °C	PCR + ELISA IgM

* By medical indication for diagnosis of neurological disease.

Table 6.2. Samples for ZIKV-associated congenital syndrome or deaths

Sample	Quantity	Transport medium	Transport conditions	Conservation >1 week	Laboratory test
Serum from the mother	3-7 mL	No additives	4 to 8 °C	-20 to -70 °C	PCR, ELISA IgM, PRNT, other
Cord blood	3-7 mL	No additives	4 to 8 °C	-20 to -70 °C	PCR, ELISA IgM, PRNT, other
Placenta	3 x 3 cm (approx.)	Buffered formaldehyde	4 °C – RT*	4 °C – RT*	Immunohisto-chemistry
Placenta	3 x 3 cm (approx.)	No additives	4 to 8 °C	-20 to -70 °C	PCR
Umbilical cord (tissue)	3 x 3 cm (approx.)	Buffered formaldehyde	4 °C – RT*	4 °C – RT*	Immunohisto-chemistry
Umbilical cord (tissue)	3 x 3 cm (approx.)	No additives	4 to 8 °C	-20 to -70 °C	PCR
Newborn serum	0,5-1 mL	No additives	4 to 8 °C	-20 to -70 °C	PCR, ELISA IgM, PRNT, other
CSF new-born*	0,5 mL	No additives	4 to 8 °C	-20 to -70 °C	PCR, ELISA IgM, PRNT, other
Whole blood of the mother	3-7 mL	EDTA, other	4 to 8 °C	4 °C	Biochemistry, others
Whole blood of the new-born	2-5 mL	EDTA, other	4 to 8 °C	4 °C	Biochemistry, others
Tissue†	3 x 3 cm (approx.)	Buffered formaldehyde	4 °C – RT*	4 °C – RT*	Immunohisto-chemistry
Tissue†	3 x 3 cm (approx.)	No additives	4 to 8 °C	-20 / -70 °C	PCR

RT: room temperature; CSF: cerebrospinal fluid; PCR: polymerase chain reaction.
* By medical indication for diagnosis of neurological disease.
† Fatal cases: brain, liver, kidney.

References

1. Dick GW, Kitchen SF, Haddow AJ. Zika virus. Isolations and serological specificity. Trans R Soc Trop Med Hyg. 1952 Sep;46(5)509–20. doi: http://dx.doi.org/10.1016/0035-9203(52)90042-4
2. Smithburn KC. Neutralizing antibodies against certain recently isolated viruses in the sera of human beings residing in East Africa. J Immunol. 1952 Aug;69(2):223–34.
3. Macnamara FN. Zika virus: a report on three cases of human infection during an epidemic of jaundice in Nigeria. Trans R Soc Trop Med Hyg. 1954 Mar;48(2):139–45.
4. Robin Y, Mouchet J. Serological and entomological study on yellow fever in Sierra Leone. Bull Soc Pathol Exot Filiales. 1975 May-Jun;68(3):249–58.
5. Dick GW. Zika virus pathogenicity and physical properties. Trans R Soc Trop Med Hyg. 1952 Sep; 46(5):521–34.
6. Simpson DI. Zika virus infection in man. Trans R Soc Trop Med Hyg. 1964 Jul;58(4):335–8. http://dx.doi.org/10.1016/0035-9203(64)90201-9 PMID:14175744
7. Moore DL, Causey OR, Carey DE, Reddy S, Cooke AR, Akinkugbe FM, et al. Arthropod-borne viral infection of man in Nigeria, 1964–1970. Ann Trop Med Parasitol. 1975 Mar;69(1):49–64.
8. Fagbami AH. Zika virus infections in Nigeria: virological and seroepidemiological investigations in Oyo State. J Hyg (Lond). 1979 Oct;83(2):213–9.
9. Olson JG, Ksiazek TG, Suhandiman T. Zika virus, a cause of fever in Central Java, Indonesia. Trans R Soc Trop Med Hyg. 1981;75(3):389–93.
10. Tognarelli J, Ulloa S, Villagra E, Lagos J, Aguayo C, Fasce R, et al. A report on the outbreak of Zika virus on Easter Island, South Pacific, 2014. Arch Virol. 2016;161(3):665–8.
11. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med. 2009 Jun;360(24):2536–43.
12. Yee-Sin Leo. Zika virus has arrived in Singapore. Lancet Infect Dis. 2016 Dec;16(12):1317–9.
13. Duong V, Dussart P, Buchy P. Zika virus in Asia. Int J Infect Dis. 2017 Jan;54:121–8. doi: 10.1016/j.ijid.2016.11.420.
14. Salehuddin AR, Haslan H, Mamikutty N, Zaidun NH, Azmi MF, Senin MM, et al. Zika virus infection and its emerging trends in Southeast Asia. Asian Pacific J Trop Med. 2017 Mar;10(3):211–9.
15. The Singapore Zika Study Group. Outbreak of Zika virus infection in Singapore: an epidemiological, entomological, virological, and clinical analysis. Lancet Infect Dis. 2017 May; 17(8):813-21
16. Pan American Health Organization/World Health Organization. Zika Epidemiological Alert, May 7, Washington, DC: PAHO/WHO; 2015.
17. Daudens-Vaysse E, Ledrans M, Gay N, Ardillon V, Cassadou S, Najioullah F, et al. Zika emergence in the French Territories of America and description of first confirmed cases of Zika virus infection on Martinique, November 2015 to February 2016. Euro Surveill. 2016 Jul;21(28):30285.
18. Cardoso CW, Paploski I, Kikuti M, Rodrigues MS, Silva M, Campos GS, et al. Outbreak of Exanthematous Illness Associated with Zika, Chikungunya, and Dengue Viruses, Salvador, Brazil. Emerg Infect Dis. 2015 Dec;21(12):2274-76.
19. Diaz-Quinonez JA, Lopez-Martinez I, Torres-Longoria B, Vasquez-Pichardo M, Cruz-Ramirez W, Ramirez-Gonzalez JE. Evidence of the presence of the Zika virus in Mexico since early 2015. Virus Genes. 2016 Dec;52(6):855–7.

20. Ikejezie J, Shapiro CN, Kim J, Chiu M, Almiron M, Ugarte C et al. Zika virus transmission — Region of the Americas, May 15, 2015–December 15, 2016. MMWR Morb Mortal Wkly Rep 2017 Mar;66(12):329–34. doi: http://dx.doi.org/10.15585/mmwr.mm6612a4.

21. Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. Emerg Infect Dis. 2015 Mar;21(3):552.

22. Foy BD, Kobylinski KC, Chilson Foy JL, Blitvich B, Travassos da Rosa A, Haddow A, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. Emerg Infect Dis. 2011 May;17(5):880–2.

23. Venturi G, Zammarchi L, Fortuna C, Remoli ME, Benedetti E, Fiorentini C, et al. An autochthonous case of Zika due to possible sexual transmission, Florence, Italy, 2014. Euro Surveill. 2016;21(8):30148.

24. Hills SL, Russell K, Hennessey M, Williams C, Oster A, Fischer M, et al. Transmission of Zika virus through sexual contact with travelers to areas of ongoing transmission — continental United States, 2016. MMWR Morb Mortal Wkly Rep. 2016 Mar;65(8):215–6.

25. Besnard M, Lastere S, Teissier A, Cao-Lormeau V, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. Euro Surveill. 2014 Apr;19(13).

26. D'ortenzio E, Matheron S, Lamballerie J, Hubert B, Piorkowski , Maquart M , et al. Evidence of sexual transmission of Zika virus. N Engl J Med. 2016 Jun;374(22):2195–8.

27. Deckard DT, Chung WM, Brooks JT, Smith JC, Woldai S, Hennessey M, et al. Male-to male transmission of Zika virus – Texas, January 2016. MMWR Mob Mortal Wkly Rep. 2016 Apr;65(14):372–4.

28. Turmel JM, Abgueguen P, Hubert B, Vandamme YM, Maquart M, Guillou-Guillemette H, et al. Late sexual transmission of Zika virus related to persistence in the semen. Lancet. 2016 Jun;387(10037):2501.

29. Frank C, Cadar D, Schlaphof A, Neddersen N, Günther S, Schmidt- Chanasit J, Tappe D. Sexual transmission of Zika virus in Germany, April 2016. Euro Surveill. 2016 Jun;21(23):30252.

30. Moreira J, Peixoto TM, Siqueira AM, Lamas CC. Sexually acquired Zika virus: a systematic review. Clin Microbiol Infect. 2017 May;23(5):296–305.

31. Musso D, Nhan T, Robin E, Roche C, Bierlaire D, Zisou K, et al. Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. Euro Surveill. 2014 Apr 10, 19(14). Erratum in: Euro Surveill. 2014;10(19):15.

32. Motta I, Spencer B, Cordeiro da Silva S, Arruda M, Dobbin J, Gonzaga Y, et al. Evidence for transmission of Zika virus by platelet transfusion. Engl J Med 2016 Sep;375(11):110–3. doi: 10.1056/NEJMc1607262

33. Nogueira ML, Estofolete C, Terzian A, Mascarin do Vale E, da Silva RC, da Silva RF et al. Zika virus infection and solid organ transplantation: a new challenge. Am J Transplant 2017 Mar;17(3):791-5.

34. Dupont-Rouzeyrol M, Biron A, O'Connor O, Huguon E, Descloux E. Infectious Zika viral particles in breastmilk. Lancet. 2016 Mar;387(10023):1051. pii:S0140-6736(16)00624-3.

35. Krow-Lucal ER, Biggerstaff BJ, Staples JE. Estimated incubation period for Zika virus disease. Emerg Infect Dis. 2017 May;23(5):841-5.

36. World Health Organization. Information for travellers visiting Zika affected countries. Available at:http://www.who.int/csr/disease/zika/information-for-travelers/en/.

37. Flamand C, Fritzell C, Matheus S, Dueymes M, Carles G, Favre A, et al. The proportion of asymptomatic infections and spectrum of disease among pregnant women infected by Zika virus: systematic monitoring in French Guiana, 2016. Euro Surveill. 2017 Nov;22(44):17-00102.

38. Weitzel T, Cortes C. Zika virus infection presenting with postauricular lymphadenopathy. Am J Trop Med Hyg. 2016 Aug 3;95(2):255–6.

39. Brasil P, Pereira J, Moreira M, Ribeiro Nogueira R, Damasceno L, Wakimoto M, et al. Zika virus infection in

pregnant women in Rio de Janeiro. N Engl J Med. 2016 Dec; 375(24):2321-34 Preliminary Report.

40. Cao-Lormeau VM, Blake A, Mons S, Lastère S, Roche C, Vanhomwegen et al. Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. Lancet. 2016 Apr;387(10027):1531-39.
41. Rozé B, Najioullah F, Fergé JL, Apetse K, Brouste Y, Cesaire R, et al; GBS Zika Working Group. Zika virus detection in urine from patients with Guillain-Barré syndrome on Martinique, January 2016. Euro Surveill. 2016;21(9) 30154.
42. Mécharles S, Herrmann C, Poullain P, Tran TH, Deschamps N, Mathon G, et al. Acute myelitis due to Zika virus infection. Lancet. 2016 Apr;387(10026):1481.
43. Carteaux G, Maquart M, Bedet A, Contou D, Brugières P, Fourati S et al. A. Zika Virus Associated with Meningoencephalitis. N Engl J Med. 2016 Apr. 374(16):1595-6
44. Pan American Health Organization/World Health Organization. Zika Epidemiological Update, 24 February 2016. Washington, D.C.: PAHO/WHO; 2016.
45. Soares C, Brasil P, Carrera RM, Sequeira P, de Filippis AB, Borges VA et al. Fatal encephalitis associated with Zika virus infection in an adult. Journal of Clinical Virology. 2016 Oct; 83: 63-65.
46. dos Santos T, Rodriguez A, Almiron M, Sanhueza A, Ramon P, de Oliveira WK et al. Zika virus and the Guillain-Barré syndrome – case series from seven countries. N Engl J Med 2016 Oct;375(16):1598–601.
47. Parra B, Lizarazo J, Jimenez-Arango J, Zea-Vera A, González-Manrique G, Vargas J, et al. Guillain-Barré syndrome associated with Zika virus infection in Colombia. N Engl J Med 2016 Oct; 375(16):1513¬-23.
48. Nascimento OJM, Frontera JA, Amitrano DA, Filippis AB, da Silva IRF. Zika virus-infection-associated acute transient polyneuritis. Neurology. 2017 Jun;88(24):2330-¬2.
49. Gourinat A, O'Connor O, Calvez E, Goarant C, Dupont-Rouzeyrol M. Detection of Zika virus in urine. Emerg Infect Dis. 2015 Jan;21(1):84–6.
50. Center for Disease Control and Prevention. Guidance for U.S. laboratories testing for Zika virus infection. Atlanta: CDC; 2017 May. Available at: https://www.cdc.gov/zika/laboratories/lab-guidance.html.
51. Mansuy JM, Mengelle C, Pasquier C, Chapuy-Regaud S, Delobel P, Martin-Blondel G, et al. Zika virus infection and prolonged viremia in whole-blood specimens. Emerg Infect Dis. 2017 May;23(5):863–5.
52. Waggoner JJ, Gresh L, Vargas MJ, Ballesteros G, Tellez Y, Soda KJ, et al. Viremia and clinical presentation in Nicaraguan patients infected with Zika virus, chikungunya virus, and dengue virus. Clin Infect Dis. 2016 Dec;63(12):1584–90.
53. Lanciotti R, Kosoy O, Laven J, Velez J, Lambert A, Johnson A, et al. Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007. Emerg Infect Dis. 2008 Aug;14(8):1232–9.
54. Hayes E. Zika virus outside Africa. Emerg Infect Dis. 2009 Sep;15(9):1347–50.
55. Collins MH, McGowan E, Jadi R, Young E, Lopez CA, Baric RS, et al. Lack of durable cross-neutralizing antibodies against Zika virus from dengue virus infection. Emerg Infect Dis. 2017 May;23(5):773–81.
56. Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika virus. N Engl J Medicine. 2016 Apr;374(16):1552–83.
57. Rabe IB, Staples JE, Villanueva J, Hummel KB, Johnson JA, Rose L, et al. Interim guidance for interpretation of Zika virus antibody test results. MMWR Morb Mortal Wkly Rep. 2016 May;65(21):543-6.
58. van Meer MPA, Mogling R, Klaasse J, Chandler FD, Pas SD, van der Eijk AA, et al. Re-evaluation of routine dengue virus serology in travelers in the era of Zika virus emergence. J Clin Virol. 2017 Jul;92:25–31.
59. Martin DA, Muth DA, Brown T, Johnson AJ, Karabatsos N, Roehrig JT. Standardization of immunoglobulin M capture enzyme-linked immunosorbent assays for routine diagnosis of arboviral infections. J Clin Microbiol 2000 May 1;38(5):1823–6.

60. Hunsperger E, Yoksan S, Buchy P, Nguyen V, Sekaran S, Enria D, et al. Evaluation of commercially available anti-dengue virus immunoglobulin M tests. Emerg Infect Dis. 2014 Oct;8(10):436–40.

61. Martelli CMT, Castanha P, Cortes F, Rodrigues L, Marques ET, Eder M. High levels of exposure of Zika and Dengue infections detected using plaque reduction neutralization assay in Brazil. Int J Infect Dis. 2016 Dec;53:15.

62. Wakerley BR, Uncini A, Yuki N; GBS Classification Group. Guillain-Barré and Miller Fisher syndromes—new diagnostic classification. Nat Rev Neurol. 2014 Sep;10(9):537–44. doi: 10.1038/nrneurol.2014.138. Epub 2014 Jul 29. Review. Erratum in: Nat Rev Neurol. 2014 Nov;10(11):612.

63. Fokke C, van den Berg B, Drenthen J, Walgaard C, van Doorn PA, Jacobs BC. Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria. Brain. 2014 Jan;137(Pt 1):33–43.

64. World Health Organization. Identification and management of Guillain-Barré syndrome in the context of Zika virus. Interim guidance, 25 February 2016. Geneva: WHO; WHO/ZIKV/MOC/16.4.

65. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol. 1990;27 Suppl:S21–4.

66. Van der Meché FG, van Doorn PA, Meulstee J, Jennekens FG; GBS-consensus group of the Dutch Neuromuscular Research Support Centre. Diagnostic and classification criteria for the Guillain-Barré syndrome. Eur Neurol. 2001;45(3):133–9.

67. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. Lancet. 2016 Aug;388(10045):717-27.

68. McGrogan A, Madle GC, Seaman HE, de Vries CS. The epidemiology of Guillain-Barré syndrome worldwide: a systematic literature review. Neuroepidemiol. 2009;32(2):150–63.

69. Ferreira da Silva IR, Frontera J, Filippis AMB, Nascimento OJ, RIO_GBS_ZIKV Research Group. Neurological complications associated with the Zika virus in Brazilian adults. JAMA Neurol. 2017 Oct;74(10):1190–8.

70. Niemeyer B, Niemeyer R, Borges R, Marchiori E. Acute disseminated encephalomyelitis following Zika virus infection. Eur Neurol. 2017;77(1-2):45–56.

71. Brito Ferreira ML, Antunes de Brito CA, Moreira ÁJP, de Morais Machado M, Henriques-Souza A, Codeiro MT, et al. Guillain-Barré syndrome, acute disseminated encephalomyelitis and encephalitis associated with Zika virus infection in Brazil: detection of viral RNA and isolation of virus during late infection. Am J Trop Med Hyg. 2017 Nov;97(5):1405–9.

72. Mlakar J, Korva M, Tul N, Popovic M, Poljšak-Prijatelj M, Mraz J et al. Zika virus associated with microcephaly. New England J Medicine. 2016 Mar;374(10):951–8.

73. Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D et al. Association between Zika virus and microcephaly in French Polynesia, 2013-15: a retrospective study. Lancet. 2016 May, 387(10033):2125-32. DOI: 10.1016/S0140-6736(16)00651-6.

74. Kleber de Oliveira W, Cortez-Escalante J, De Oliveira WT, do Carmo GM, Henriques CM, Coelho GE, et al. Increase in reported prevalence of microcephaly in infants born to women living in areas with confirmed Zika virus transmission during the first trimester of pregnancy - Brazil, 2015. MMWR 2016 Mar;65(9):242–7. doi: 10.15585/mmwr.mm6509e2

75. Meaney-Delman D, Hills SL, Williams C, Galang RR, Iyengar P, Hennenfent AK, et al. Zika virus infection among US pregnant travelers — August 2015– February 2016. MMWR 2016 Mar 4;65(8):211-4.

76. Hawaii Department of Health-DOH News release: Hawaii Department of health receives confirmation of Zika infection in baby born with microcephaly [accessed 2 March 2016]. Available at: http://governor.hawaii.gov/newsroom/doh-news-release-hawaii-department-of-health-receives-confirmation-of-zika-infection-in-baby-born-with-microcephaly/.

77. Butler D. First Zika-linked birth defects detected in Colombia. Nature. 2016 Mar 10;531(7593):153.

78. Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika virus and birth defects – Reviewing the evidence for causality. N Eng J Med. 2016 May;374(20):1981–7. Available at: http://dx.doi.org/10.1056/NEJMsr1604338

79. del Campo M, Feitosa IML, Ribeiro EM, Horovitz DDG, Pessoa ALS, Franca GVA, et al. The phenotypic spectrum of congenital Zika syndrome. Am J Med Genetics. 2017 April;173(4):841–7. Available at: htpp://dx.doi.org/10.1002/ajmg.a.38170

80. Oliveira Melo A, Malinger G, Ximenes R, Szejnfeld P, Alves Sampaio S, Bispo de Filippis A. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? Ultrasound Obstet Gynecol. 2016 Jan;47(1):6–7.

81. Driggers RW, Ho CY, Korhonen EM, Kuivanen S, Jääskeläinen AJ, Smura T, et al. Zika virus infection with prolonged maternal viremia and fetal brain abnormalities. N Engl J Med. 2016 Jun:374(22):2142-51.

82. Sarno M, Sacramento GA, Khouri R, do Rosário MS, Costa F, Archanjo G, et al. Zika virus infection and stillbirths: a case of hydrops fetalis, hydranencephaly and fetal demise. PLoS Negl Trop Dis. 2016 Feb25;10(2):e0004517.

83. Schuler-Faccini L, Ribeiro EM, Feitosa IM, Horovitz DD, Cavalcanti DP, Pessoa A, et al. Possible association between Zika virus infection and microcephaly — Brazil, 2015. MMWR Morb Mortal Wkly Rep. 2016 Jan;65(3):59–62.

84. Ventura CV, Maia M, Bravo-Filho V, Góis AL, Belfort R Jr. Zika virus in Brazil and macular atrophy in a child with microcephaly. Lancet. 2016 Jan;387(10015):228.

85. Ventura CV, Maia M, Ventura BV, Linden VV, Araújo EB, Ramos RC, et al. Ophthalmological findings in infants with microcephaly and presumable intra-uterus Zika virus infection. Arq Bras Oftalmol. 2016 Feb;79(1):1–3.

86. de Paula Freitas B, de Oliveira Dias JR, Prazeres J, Sacramento GA, Ko AI, Maia M, et al. Ocular Findings in infants with microcephaly associated with presumed Zika virus congenital infection in Salvador, Brazil. JAMA Ophthalmol. 2016 Feb;134:529–35.

87. van der Eijk AA, van Genderen PJ, Verdijk RM, Reusken CB, Mogling R, van Kampen JJA, et al. Miscarriage associated with Zika virus infection. N Engl J Med. 2016 Sep;375(10):1002–4.

88. Pomar L, Malinger G, Ville Y, Rousset D, Hcini N, Pomar C, Jolivet A, Lambert V. Association between Zika virus and fetopathy – a prospective cohort study in French Guyana. Ultrasounds in Obst Gynecol. 2017 June;49(6):729–36.

89. Sejvar JJ, Kohl KS, Bilynsky R, Blumberg D, Cvetkovich T, Galama J, et al.. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug 1;25(31):5771-92. Epub 2007 May 11.

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