Guidelines for surveillance of **Zika** virus disease and its complications

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Pan American Health Organization

World Health Organization
REGIONAL OFFICE FOR THE Americas

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Development of the Guidelines

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Guideline development methods

In response to the declaration of a Public Health Emergency of International Concern (PHEIC) and following the recommendations of the International Health Regulations Emergency Committee, the Pan American Health Organization (PAHO) convened an expert consultation to appropriately make use of the experience gained during the current outbreak in the Americas, the evidence published at the international level, and the World Health Organization (WHO) guidelines. The preparation and review process conducted in March 2016 included an online document review and on-site meeting on 28-30 March 2016 in Washington, D.C.

Declaration of interests

No potential conflicts of interest have been identified among the individuals involved in drafting these guidelines. No specific funds were used for the preparation or review of this document.

These guidelines are based on the best current available evidence and are subject to modifications and updates in light of new information that may emerge.

Contents

Abbreviations and acronyms

CHIKV	Chikungunya virus
CLAP	Latin American Center for Perinatology
CNS	Central nervous system
CSF	Cerebrospinal fluid
DENV	Dengue virus
GBS	Guillain-Barré syndrome
HC	Head circumference
MFS	Miller Fisher syndrome
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

Introduction

Zika virus (ZIKV) is an arbovirus of the genus Flavivirus (family *Flaviviridae*), phylogenetically very close to other viruses, such as the dengue, yellow fever, Japanese encephalitis, and West Nile viruses. It is a mosquito-borne RNA virus, transmitted mainly by the genus *Aedes*, and was first isolated in 1947, from a Rhesus macaque, during a study on the transmission of jungle yellow fever[1] in the Zika Forest of Uganda. In 1968, it was first isolated in humans in Uganda and in the United Republic of Tanzania.[2-5] Subsequently, outbreaks have been recorded in Africa, Asia, the Western Pacific region and, more recently, in the Americas.[6-11]

Sexual and vertical (mother-to-child) transmission of ZIKV have been documented in a limited number of cases,[12-16] as has transmission through blood transfusion.[17] Transmission through breast milk has not been documented, however it may be possible as viral RNA has been found in the breast milk of women who were infected during the peripartum period;[16] more recently, a report of infective ZIKV particles in breast milk has been published.[18]

The symptoms of the disease usually appear after an incubation period of 3 to 12 days, and are similar to those of other arboviral infections; they include rash, fever, conjunctivitis, myalgia, arthralgia, malaise, and headache, and tend to last 4 to 7 days.[9,19]

During an outbreak that occurred in French Polynesia in 2013 and 2014, an increase in cases of Guillain-Barré syndrome (GBS) and other neurological manifestations[19-20] was observed in association with ZIKV infection and recently, in the Americas, it has also been associated with other neurological manifestations.[21-23]

In October 2015, the health authorities of Brazil confirmed an increase in the prevalence of microcephaly at birth in the Northeast region of the country, which coincided in time with an outbreak of the ZIKV. Subsequently, other birth defects, placental insufficiency, intrauterine growth restriction, and fetal death were described in association with ZIKV infection during pregnancy.[24-32] The latter event led the World Health Organization (WHO) to declare on 1 February 2016 a public health emergency of international concern (PHEIC) and to recommend enhancement of surveillance and research on the relationship between new clusters of microcephaly and other neurological disorders, including Guillain-Barre syndrome and ZIKV infection.[33,34]

Purpose and scope

These Guidelines aim to provide guidance to the implementation of ZIKV surveillance, based on the experience acquired during the ongoing epidemic in the Region of the Americas. This document provides overall guidance —albeit not exhaustive— on surveillance actions, which should be adapted by countries according to their capabilities, epidemiological context, and health system characteristics. Furthermore, it includes a brief clinical description of the disease, its neurological manifestations, and congenital syndrome associated with ZIKV infection (based on currently available information) to guide the necessary assessment for case reporting. Finally, case definitions and laboratory procedures for case detection and diagnosis are proposed.

Although this document focuses primarily on ZIKV disease, it also proposes elements for the integration of Zika surveillance into the surveillance of other arboviral diseases and rash/febrile diseases, and addresses aspects of differential diagnosis in the laboratory setting. This topic will undoubtedly be expanded in the near future as more evidence becomes available.

This is a proposal intended to be implemented within the national scope of each country that according to its organizational model must be adjusted to fit the different levels of the health system (local, regional, and national).

These Guidelines are provisional and will be reviewed and adapted as advances are made in the understanding of the disease and the evolution of the epidemic in the Region.

Context of Zika virus infection surveillance

ZIKV is transmitted by the bite of mosquitos of the genus *Aedes*. Vertical transmission, sexual transmission, and transmission by blood transfusion have also been documented.[12, 17]

Following the mosquito bite, symptoms may appear after an incubation period of 3 to 12 days. The infection may be asymptomatic, or may present moderate clinical symptoms and neurological manifestations.

At the time of the drafting of these Guidelines, the relative incidence of arboviral diseases is changing in the Americas. The traditional predominance of the four serotypes of dengue has shifted in the past two years and arboviral disease burden is shared across dengue, chikungunya, and Zika, along with smaller outbreaks of other arboviruses, such as Mayaro fever, West Nile virus, and yellow fever.

Due to this shift, surveillance systems must adapt accordingly.

The goal for the future should be an integrated surveillance of arboviral diseases, which – without discarding the clinical importance to detect suspected cases – recognizes an ever growing role of the laboratory and entrenches activities to maintain the systematic monitoring of vectors.

Zika surveillance should form part of each country's national surveillance system and take into consideration any existing surveillance systems for other arboviral diseases, such as dengue and chikungunya, and diseases that may be part of the differential diagnosis, including, flaccid paralysis, measles, and rubella.

Surveillance objectives

According to the epidemiological context of the country, surveillance should:

- Enable early detection of imported cases in areas/territories where the mosquito vector is absent;
- Permit early detection of the introduction or presence of clusters of ZIKV infection in an area/territory where the mosquito vector is present, but vector-borne transmission has not been previously documented;
- Characterize the epidemiological situation and follow up the outbreak on the basis of the detection of local transmission and monitor the circulation of the virus, taking into account other endemic arboviral diseases;
- Detect unusual events, for example, atypical clinical descriptions of ZIKV infection or a new mode of transmission;
- Detect the occurrence and temporal evolution of neurological manifestations;
- Determine the prevalence of congenital abnormalities at birth, especially those affecting the central nervous system (CNS), such as microcephaly; investigate the birth defects affecting CNS and the potential relation with prior ZIKV infection of the mother;
- Contribute to the knowledge of the disease, its complications, and its sequelae, so as to support the implementation of primary, secondary, and tertiary prevention measures, since it is an emerging disease and its natural history and disease burden are still only partially understood.

Surveillance of Zika virus disease

The following provides a brief clinical description of ZIKV disease is aimed to guide suspected case-finding necessary for the reporting of cases. Case-finding and laboratory diagnosis procedures are also described. Other sections of this document address the surveillance of neurological manifestations and the congenital infection syndrome associated with ZIKV.

Clinical description

ZIKV disease (CIE 10: U06) is characterized by the sudden onset of rash, which is usually maculopapular. Often, though not always, this is accompanied by a low-grade fever (< 38.5 °C). The rash spreads in a cephalocaudal (cerebro-caudal) manner (head, trunk, and upper and lower extremities, frequently affecting the palmar and plantar surfaces; in the convalescent stage, there may be laminar desquamation). A marked feature of the rash is that it is pruritic, and often inteferes with the patient's daily activities, even hindering sleep.[35]

Non-purulent conjunctival hyperemia usually occurs. Adenopathy or lymphadenopathy is rare, and when it occurs, the retroauricular ganglia lymph nodes are affected.[32,36,37]

In some cases, articular impairment is observed, usually in the form of polyarthralgia with bilateral, symmetrical periarticular edema. In contrast to Chikungunya infection, pain associated with ZIKV disease tends to be milder and is not debilitating. On physical examination, there may be mild articular edema, without hyperemia or local heat. The joints of the hands and wrists are most frequently affected, followed by the knees and ankles.[37,38]

Other possible manifestations include headache, myalgia, nausea, diarrhea, and vomiting. In ZIKV infections no instances of hemodynamic impairment have been observed as is seen in severe dengue cases.[32,36,37]

Nervous system impairment

Neurological manifestations may appear during or after the acute phase of infection. Guillain-Barré syndrome (GBS) is the most frequent neurological complication, usually in its typical clinical form or in one of its variants (such as Miller Fisher syndrome). Although less frequent, other manifestations include encephalitis, meningoencephalitis, cerebellitis, acute disseminated encephalomyelitis, inflammatory myelopathy, and cranial nerve disorders or impairments.[19-23]

Case definitions

These are interim case definitions based on preliminary data obtained during the course of the epidemic in the Region of the Americas and may be subject to further modification according to advances in knowledge of the disease and the etiologic agent.

Suspected case of Zika virus disease

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

- fever, usually <38.5 °C
- conjunctivitis (non-purulent/hyperemic)
- arthralgia
- myalgia
- peri-articular edema

* usually maculopapular and pruritic

Suspected case of Zika virus disease in geographic areas without autochthonous transmission and without the presence of vectors

Patient who meets the criteria for a suspected case **AND** who:

- in the 2 weeks prior to onset, traveled to, or resided in, a geographic area with local transmission of the ZIKV or presence of vectors; **OR**
- has a history of unprotected sex in the 2 weeks prior to onset, with a person who in the previous 8 weeks resided in or traveled to a geographic area with local transmission of the ZIKV or presence of vectors.

Probable case of Zika virus disease

Patient who meets the criteria of a suspected case **AND** also has anti-ZIKV IgM antibodies, without laboratory results indicating infection by other flaviviruses.

Confirmed case of Zika virus disease

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

- RNA or ZIKV antigen in any serum sample or other type (for example, urine, saliva, tissue or whole blood); **OR**
- Positive anti-ZIKV IgM antibodies **AND** Plaque reduction neutralization plate (PRNT90) for ZIKV titers ≥ 20 and four or more times higher than for other flaviviruses; and exclusion of other flavivirus;* **OR**
- In deceased individuals,† molecular detection of the viral genome in autopsy tissue (fresh or in paraffin), or specific viral antigen detection by immuno-histochemistry testing.

* Test performed only in probable cases positive for anti-ZIKV IgM antibodies.
† Other than abortion or fetal death, which are discussed in a subsequent chapter.

Laboratory diagnosis of Zika virus disease

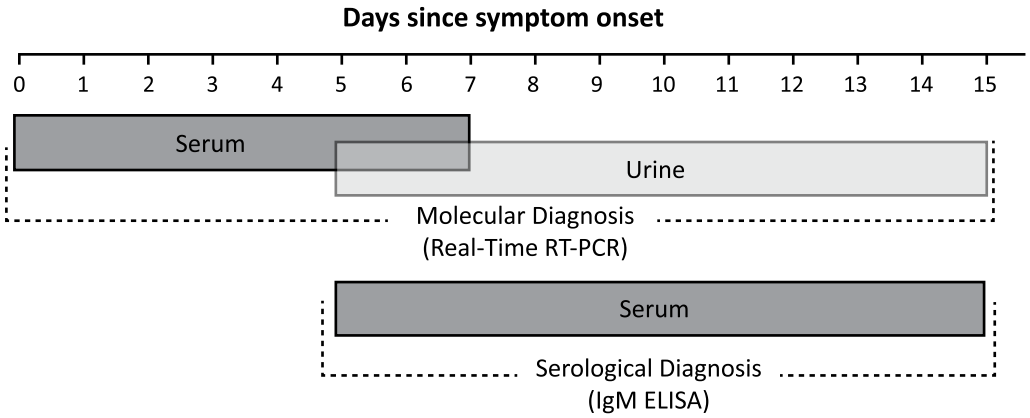
Virologic diagnosis (Algorithms A and B)

Type of sample: serum or urine (5 to 7 cc collected in a dry tube).

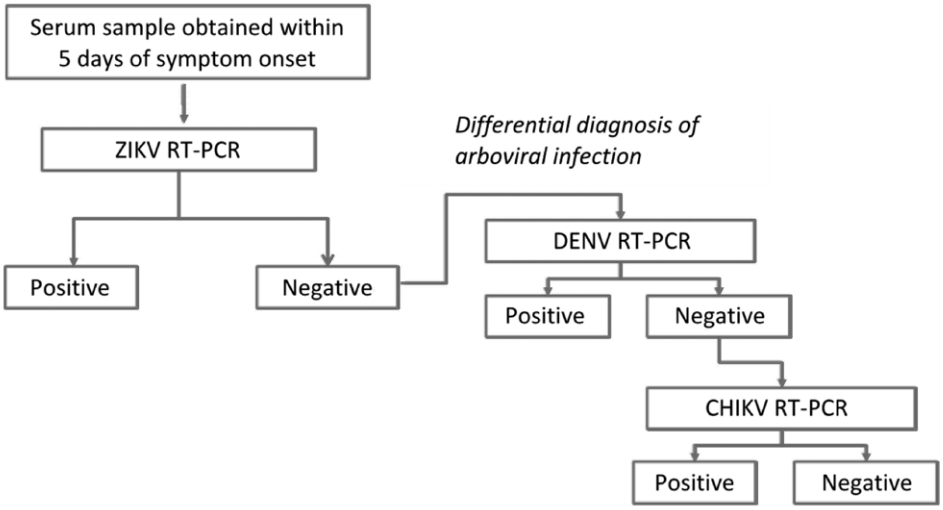
Although the period of viremia has yet to be fully established, the virus has been detected in serum most often within 5 days of symptom onset, and, in some cases, until the seventh day. On the other hand, in some cases high viral loads have been detected in urine for a prolonged time during the acute phase.[38] Thus, to improve the sensitivity of diagnosis, it is recommended that a serum sample be obtained at the same time of urine sampling (no later than the 15th day after symptom onset) for processing by RT-PCR (Figure 1).[39]

In many cases, the initial symptoms may go undetected or patients may present late to a health facility, thus limiting opportunities for biological testing.

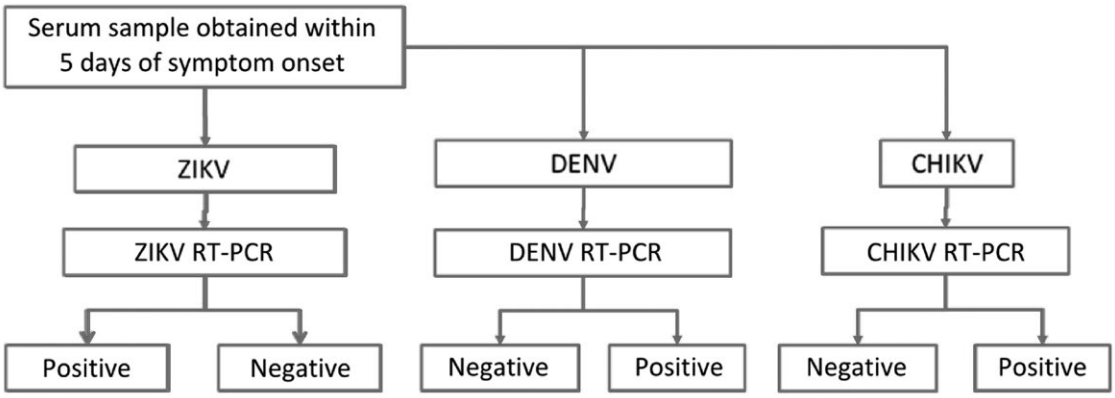
Figure 1. Diagnostic indications, according to day of symptom onset and sample type.



A. Algorithm for virological confirmation of suspected cases of ZIKV infection in areas where other arboviruses are in circulation



B. Algorithm for virological confirmation of suspected cases of ZIKV infection in areas where other arboviruses are in circulation (multiplex PCR).



Serologic detection (Algorithm C)

Type of sample: serum (5 to 7 cc collected in dry tube)

The recommended serologic diagnostic method is ELISA to detect specific anti-ZIKV IgM antibodies from day 6 after onset of symptoms. Diagnosis based on a single sample of serum taken during the acute phase is speculative; therefore, it is recommended that a second sample be obtained one to two weeks after the first sample to document seroconversion (negative to positive) or a ≥ 4-fold increase in antibody titer (quantitative test).

Although the plaque reduction neutralization technique (PRNT) has greater specificity for the detection of neutralizing antibodies (IgG), cross-reactivity has been documented with other flaviviruses, especially dengue, yellow fever, and West Nile virus.[40] Furthermore, PRNT testing is relatively complex and time-consuming. To date, there are no formally validated, commercially available tests for the determination of ZIKV by PRNT, and it is difficult to obtain the necessary reagents.

Interpretation of serology results

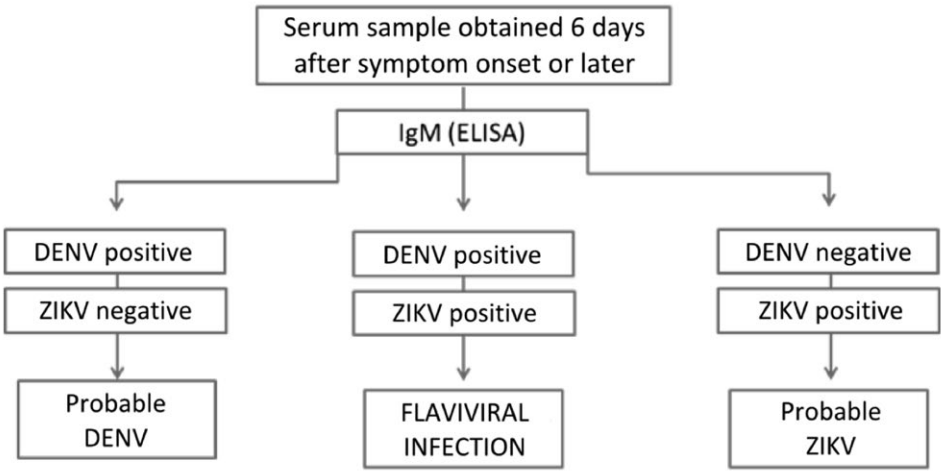
In the case of primary infections (first *Flavivirus* infection), antibodies do not cross-react with other genetically related viruses. However, serum from individuals with a history of another flaviviral infection (especially dengue, yellow fever—including yellow fever vaccine—or West Nile virus) can cross-react with these tests. This applies both for the detection of IgM by ELISA and for the PRNT neutralizing antibody technique.[39,40]

For this reason, and as part of the differential diagnosis, it is recommended to conduct in tandem the determination of IgM ELISA for both dengue and Zika. In addition and where available, PRNT using different *flaviviruses* (dengue, yellow fever, others according to the epidemiological context of the country) will be useful to complement the diagnosis of Zika if it demonstrates a neutralizing antibody titer up to fourfold greater than for the other viruses.[39,41,42]

In such cases, clinical and epidemiological criteria are essential for the interpretation of serology results. For example, in a case of GBS with a positive result for flaviviral infection (DENV and positive ZIKV), the clinician should take into account that GBS after dengue infection is unusual; therefore, the result suggests ZIKV infection.

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

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



Sample selection and storage

- Samples that will be processed (or sent to a reference laboratory) within 48 hours should be kept refrigerated at 4 °C to 8 °C.
- Samples that will be tested after the first 48 hours but no later than 7 days should be kept frozen at -10 °C to -20 °C.
- Samples that will be processed after a week should be kept frozen at -20 °C to -70 °C. Such samples will keep for prolonged periods.

Shipment by air to reference laboratories

Upon shipment of samples to reference laboratories, one should ensure the following:

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

Surveillance of Guillain-Barré syndrome (GBS) and other neurological complications

Neurological manifestations can occur during the acute or convalescent phase of ZIKV infection. To date, GBS has been described as the most frequent neurological complication, whether in its typical, clinical form or in one of its variants (such as Miller Fisher syndrome).[19-23]

Clinical description of GBS and its variants

In its typical form, GBS occurs as an ascending, progressive, symmetrical, subacute muscular paralysis that reaches peak severity by 4 weeks and is accompanied by areflexia (absence of reflexes). In many cases, it is preceded by a history of infection.[43-45]

The annual incidence of GBS is estimated to range between 0.4 and 4.0 cases per 100,000 population per year. In North America and Europe, GBS is more common among adult males, and its incidence increases directly with age. Between 3.5% to 12% of patients die of complications during the acute phase.[44]

A study conducted during the outbreak in French Polynesia documented the relationship between GBS and prior ZIKV infection, including information on the clinical and neurophysiological manifestations of the cases, which occurred primarily in the form of acute motor axonal neurophathy. Based on those findings, the risk of GBS has been estimated at 0.24 per 1,000 ZIKV infections, as determined from an attack rate of 66% in the general population.[20]

Classical GBS is clinically characterized by an acute flaccid paralysis that can affect all four limbs, with or without cranial nerve impairment. GBS is actually considered a heterogeneous group of autoimmune diseases, which includes the Miller Fisher syndrome and the motor, sensory, sensorimotor, and pure dysautonomic variants. The Miller Fisher syndrome is characterized by ophthalmoplegia, ataxia, and areflexia. Other asymmetrical or focal variants have been reported, such as the paraparetic, pharyngeal-cervical-brachial, and bulbar forms.[43-48]

In the typical forms, weakness begins distally in the lower limbs, with 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 the respiratory muscles. A significant percentage of patients will require

intensive care unit admission due to respiratory complications and dysautonomia (cardiac arrhythmia or blood pressure changes).[47]

GBS is a clinical diagnosis. Analysis of cerebrospinal fluid allows for the detection of albuminocytologic dissociation (an increase in proteins in the absence of pleocytosis: < 50 leukocytes per microliter), a finding that contributes to diagnostic certainty. Electrophysiological studies can help define the prognosis and characterize the subtypes of GBS (acute demyelinating polyradiculoneuritis, motor axonal form, among others) (see also Annex 1).[43-48]

It is recommended that a complete clinical history and detailed neurological examination be conducted for all patients with suspected GBS. The clinical history should include information on previous diseases, triggering factors, and progression of neurological symptoms.

GBS is uncommon in children, in whom a more detailed neurological approach is recommended.

Surveillance

The core objectives of GBS surveillance are:

- To establish the baseline of neurological complications.
- To determine the incidence and trend of neurological complications.
- To detect and investigate all new cases of GBS and its variants.
- To investigate any increase in the incidence of GBS or of neurological syndromes that cannot be explained by other causes.
- To contribute to appropriate clinical case management in order to reduce the morbidity and mortality associated with GBS.

Surveillance should include the following activities:

- Review of existing sources of information (clinical records, data from tertiary referral hospitals, and others) in order to establish a baseline incidence of GBS.
- Monitoring of immunoglobulin dispensing and administration as a proxy indicator of an increase in incidence of GBS.
- Review of surveillance data on acute flaccid paralysis, which can also be used as a proxy indicator of GBS.

Case definitions

WHO recommends the use of the Brighton criteria[44-45] to establish case definitions of GBS for epidemiological surveillance.[‡] Diagnostic certainty is classified at three levels (Table 1), based on clinical findings at disease onset and on the availability of CSF testing and electrophysiological neurophysiological studies.

Suspected case of Zika-virus-associated GBS[§]

Patient who:

- resides in, or recently traveled to, an area with presence of vectors for the ZIKV; **OR**
- has had unprotected sex with someone who resides in, or recently traveled to an area with circulation of vectors for the ZIKV;

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; 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.

Confirmed case of Zika-virus-associated GBS

Patient meeting the criteria for suspected of Zika-virus-associated GBS with laboratory confirmation of recent infection with the ZIKV.

[‡] The level of diagnostic certainty, as defined by the Brighton classification, should not be used as a criterion to decide on treatment.
[§] Level 3 diagnostic certainty is proposed.

Table 1 lists the Brighton criteria for diagnostic certainty in GBS.[47]

Table 1. Brighton criteria for case definition of the GBS.

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 limbs; **AND**
• Decreased of absent deep tendon reflexes in weak limbs; **AND**	• Decreased or absent deep tendon reflexes in weak limbs; **AND**	• Decreased or absent deep-tendon reflexes in weak limbs; **AND**
• Monophasic illness pattern; and interval between onset and nadir of weakness between 12h and 28 days; and subsequent clinical plateau; **AND**	• Monophasic illness pattern; and interval between onset and nadir of weakness between 12h and 28 days; and subsequent clinical plateau; **AND**	• Monophasic illness pattern; and interval between onset and nadir of weakness between 12h 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**	
• Electrophysiologic findings consistent with GBS.	• Electrophysiologic studies consistent with GBS if CSF not collected or results not available.	

*Cerebrospinal fluid (CSF)

Laboratory diagnosis of Zika-virus-associated with GBS

The diagnosis of ZIKV infection in a patient with GBS can be carried out according to the criteria described for viral infection. In a case of GBS with a positive *Flavivirus* screening test result (positive DENV and ZIKV IgM, as per algorithm C), one should take into account that GBS after dengue infection is unusual, and the result is thus highly suggestive of ZIKV infection.

Usually, the suspicion of neurological syndrome occurs outside the viremia period; nevertheless, it is recommended that viral detection in serum or urine through RT-PCR be attempted, as well as the detection of IgM antibodies in a serum sample by ELISA.

Virologic (RT-PCR) analysis and the detection of anti-ZIKV IgM antibodies by ELISA can also be performed using a cerebrospinal fluid (CSF) sample obtained by a physician's determination for the diagnosis of the neurological syndrome (see Annex 2, recommended samples).

All of the following events should be reported to the corresponding surveillance level:

- All increases in the incidence of GBS.
- All GBS cases in which ZIKV infection has been confirmed. Case information can be updated after the initial report.

In addition, the total number of GBS cases hospitalized in the preceding week and the number of such cases with suspected or confirmed ZIKV infection should be reported on a weekly basis.

Other neurological manifestations

Even though other neurological manifestations (encephalitis, meningoencephalitis, cerebellitis, acute disseminated encephalomyelitis, inflammatory myelopathy, and cranial nerve impairment/disorders) have been described in isolated clinical cases,[22,23] sufficient epidemiological information concerning the real incidence of these conditions is not currently available. Diagnosis of these neurological manifestations requires a careful clinical assessment; furthermore, it is recommended to consult specialists at referral centers, taking into account both the possibility of ZIKV infection and other potential etiologies.

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

In patients in whom other neurological complications associated with Zika infection are confirmed (encephalitis, myelitis, multiple cranial nerve impairment, etc.), it is recommended to follow the same surveillance and reporting as for GBS.

Surveillance of congenital syndrome associated with Zika virus infection

During the declaration of the Public Health Emergency of International Concern (PHEIC) on 1 February 2016, the Director General of the WHO emphasized the need to enhance and standardize surveillance of microcephaly associated with ZIKV infection.

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 birth defects in neonates born to mothers exposed to ZIKV infection, which were found to constitute a syndrome.[16-24-32] Unpublished information on the clinical details of this syndrome were provided during a clinical expert consultation held in Washington, D.C., United States, from 23 to 25 January 2016 as part of the development of the document, "Instrument for the clinical detection of patients with suspected arbovirosis."[35]

The rapid generation of data from research stimulated by the emergency led to an expansion of the initial approach to include a set of signs and symptoms of congenital abnormalities in newborns of mothers exposed to Zika infection, which constitute a syndrome. Unpublished information about the clinical details of the syndrome was provided during a consultation of clinical experts held 23 to 25 January 2016 in Washington, D.C., to develop the document "Instrument for the clinical detection of patients suspected of arbovirus infection.

Characterization of the congenital syndrome associated with ZIKV infection is challenging, given the nonspecific nature of the clinical symptoms of the infection, the knowledge gaps regarding its clinical spectrum and the clinical course of the disease, and the definition of microcephaly, among others.

This challenge is compounded by limitations in the availability of instruments and techniques for the measurement of the head circumference and the precise determination of gestational age at birth; furthermore, there is a lack of practice of many health professionals in using the appropriate population-level references. Variation by sex and gestational age of anthropometric measures, including head circumference requires the use of demographic references for standardization of the measure.

Successful surveillance of the congenital syndrome associated with ZIKV depends on the use of standardized operational procedures and the active involvement of health professionals.

Clinical description of the congenital syndrome associated with Zika virus infection**

The syndrome as currently described includes the presence of microcephaly with other signs, such as facial or other disproportionality cranial-facial disproportion and other

** This characterization is preliminary and is subject to change as more evidence becomes available.

anthropometric disproportions, such as redundant scalp with roughness, hypertonia or spasticity, irritability, and epileptic seizures.[16,51]

Furthermore, patients may present with a broad spectrum of central nervous system and joint disorders.[26-32,49-56]

In some cases, there have been reports of cerebral hypoplasia, hypoplasia or agenesis of the corpus callosum. The presence of cerebral calcifications (mainly cortical and subcortical) is characteristic, as are alterations in the cerebral ventricles, anomalies abnormalities 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.[51-55]

Joint impairment in newborns can be secondary to severe central nervous system compromise or to a direct action of ZIKV on joint and bone tissues. The manifestations of arthropathy can range from a clubfoot to severe malformations (arthrogryposis) of the hands and feet.[50-52]

An increase in the number of spontaneous abortions and fetal deaths has also been reported that exhibit other alterations associated with ZIKV infection that are still not well understood, including pulmonary hypoplasia.[56]

Microcephaly

Microcephaly is defined as an head circumference (HC) < -2 standard deviations from the reference population average as standardized for age and sex.

The recently published International Fetal and Newborn Growth Consortium for the 21st Century (Intergrowth-21st)†† includes standards that provide a greater precision for the evaluation of microcephaly in premature and full-term newborns. Therefore, it is recommended that countries adopt this new standard, which is currently being reviewed by the WHO. Its correct use requires having 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 unavailable, it is recommended to use the standards from the WHO Multicentre Growth Reference Study.‡‡ To measure the HC it is recommended to use the tape developed by the Latin American Center for Perinatology (CLAP).

†† https://intergrowth21.tghn.org/site_media/media/articles/newbornsize.pdf
‡‡ http://www.who.int/childgrowth/standards/es/

Objectives for surveillance of the congenital syndrome associated with Zika virus infection

The principal objectives for the surveillance of the congenital syndrome possibly associated with ZIKV infection are to:

- Establish the baseline and monitor the prevalence of births and trends of the congenital syndrome associated with ZIKV infection, with microcephaly as a tracer event.
- Investigate any increase in the prevalence of microcephaly at birth or other associated conditions.
- Detect and investigate all new cases of congenital malformations (including microcephaly) not explained by other known causes.
- Detect the presence of infection in newborns of pregnant women who are receiving follow-up due to detection of ZIKV.

Recommendations

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

- Design an *ad hoc* subsystem specifically for the detection of newborns with congenital syndrome, and miscarriage, and fetal deaths in areas with risk of ZIKV circulation. This subsystem should be supported by existing sources of information (registries, data from referral hospitals, etc.);
- Integrate this subsystem with the national surveillance system and set up a database—within the existing information system—where the data generated can be collected and accessed;
- In countries where current surveillance does not permit the monitoring of microcephaly incidence trends, event surveillance should be established or strengthened. To this end, it is important to raise awareness and provide information to sonographers, obstetricians, and maternal and child hospitals about case reporting that meets criteria for microcephaly;
- Define *a priori* the data collection tools, reporting procedures and circulation channels, database consolidation procedures, and analysis plans, as well as the dissemination format (support, structure, content, frequency), and establish information outputs formats that are clear and consistent over time for the purposes of risk communication;
- Plan data quality control measures (incomplete, missing, incorrect, or duplicate data). Establish protocols for daily data review and quality control (automated or manual); and
- Define elements that permit case identification while guaranteeing the confidentiality of information.

Case definitions

Congenital syndrome associated with Zika virus infection

Suspected case of congenital syndrome associated with Zika virus infection

Live newborn who presents with:

- microcephaly: head circumference below -2 standard deviations measured at 24 hours after birth according to the standardized guidelines for gestational age and sex; **OR**
- other congenital malformation of the central nervous system;

AND whose mother during pregnancy:

- resided in or traveled to an area with the presence of ZIKV vectors; **OR**
- had unprotected sex with a partner who resided in, or traveled to, an area with the presence of ZIKV vectors.

Probable case of congenital syndrome associated with Zika virus 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 other known possible causes; **OR**
- whose mother had rash during pregnancy.

Confirmed case of congenital syndrome associated with Zika virus infection

Live newborn of any gestational age who meets the criteria for a suspected case of congenital syndrome associated with ZIKV, **AND** with laboratory confirmation of ZIKV infection, independent of the detection of other agents.

In countries with vector circulation that have the necessary capacity, surveillance could be expanded to other previously described congenital malformations (especially of the central nervous system, auditory, and visual) that could be associated with ZIKV infection, and study these for the presence of the potential causative agent.

Note

Head circumference (HC) should be measured or confirmed within 24 hours of birth. If the child is discharged less than 24 hours after birth, measurement should be carried out before they leaving the health facility. A new measurement of HC should then be obtained, preferably during the first week of life, as part of the control of the child's growth and development. This information should be forwarded to the local surveillance authority. If the measurement is carried out after the first week of life, the growth reference tables corresponding to age and sex.

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

Laboratory diagnosis of Zika virus infection associated with the congenital syndrome

ZIKV infection in pregnant women can be diagnosed according to the criteria previously described. Furthermore, as vertical transmission of the infection is known to occur, strict monitoring of the mother and newborn is essential.[16,27-29,31-32,50-56]

It has been shown that, during intrauterine ZIKV infection, viral genetic material can be detected for a prolonged period through molecular techniques.[51] For this reason, it is recommended to test serum (neonatal and maternal) or umbilical cord blood (Annex 2). In addition, as the possibility of previous flaviviral infection is low, the detection of IgM antibodies against ZIKV in neonatal serum (in the absence of IgM against other flaviviruses) constitutes an important finding indicative of intrauterine infection.

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 mandatory. Screening tests for intrauterine ZIKV infection are still in development, however it is expected to have serological tests that can demonstrate exposure to the virus.

Zika-virus-associated abortion or stillbirth

Suspected Zika-virus-associated abortion or stillbirth

Abortion or stillbirth in a woman, who during her pregnancy

- presented rash **AND**
- resided in or travelled to an area where ZIKV vectors were present; **OR**
- had unprotected sex during pregnancy with a partner who resided in or travelled to an area where ZIKV vectors were present.

Confirmed Zika-virus-associated abortion or stillbirth

All suspected cases where ZIKV infection is confirmed from blood or urine samples from either the mother or puerperal or abortion or fetal death tissue.

Laboratory diagnosis of Zika virus infection associated with miscarriage or fetal death indicative of congenital infection

In cases of miscarriage and fetal death, a serum sample should be obtained if possible for the detection of IgM antibodies (by ELISA) and, in any case, a tissue sample should be ensured (brain, kidney, liver, or different slices of undifferentiated tissue). Furthermore, it is recommended that to analyze maternal serum samples in tandem for the presence of IgM antibodies (see Annex 2).

Furthermore, if an amniotic fluid sample is available (obtained by medical indication for the diagnosis of other syndromes), it can be used for molecular detection by RT-PCR (see Annex 2).[49]

Vertical transmission of Zika virus without congenital syndrome

Suspected vertical transmission of Zika virus without congenital syndrome

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

Probable case of vertical transmission without congenital syndrome

Live newborn who meets the criteria for a suspected case of ZIKV infection by vertical transmission **AND** in whose umbilical cord blood sample Anti-ZIKV IgM antibodies are detected by ELISA or virus RNA is detected by RT-PCR.

Confirmed case of vertical transmission 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-Zika IgM antibodies are detected by ELISA.*

** When only RT-PCR is available and it is positive, follow-up serology is advised because the viral detection could be from perinatal rather than vertical transmission.*

Surveillance according to epidemiological scenarios

These Guidelines for the Region of the Americas consider four potential epidemiological scenarios, adapted from the WHO proposal:[§§]

- Areas with **epidemic transmission** of ZIKV;
- Areas with **endemic transmission** of ZIKV;
- Areas **without** autochthonous cases and **presence** of ZIKV vectors;
- Areas **without** autochthonous cases and **absence** of ZIKV vectors.

At this time, the countries of the Americas are in a phase of epidemiological transition in relation to the ZIKV due to its recent introduction in the continent.

In some countries, two or three of the aforementioned scenarios may occur in different geographic areas, which means that the surveillance strategy implemented should take into account this diversity of contexts. For the purposes of this guide, a geographic area can be a country, territory, state, department, province, or any other geographical subdivision.

Areas with epidemic transmission of Zika virus

The surveillance system should focus on surveillance of geographical and temporal trends of ZIKV and other arboviruses that circulate in the area (for example, dengue, chikungunya, West Nile viruses). Efforts should be made to monitor jointly the trend of all arboviral diseases. To this end, the following activities are required:

- Characterize the cases of ZIKV disease and its clinical spectrum, including the detection of complications;
- Monitor neurological complications and the congenital abnormalities anomalies as described in previous sections of this Guideline;
- Study the circulating viral strains, when the capacity to do so is available;
- Include vector surveillance; and

[§§] http://www.who.int/csr/resources/publications/zika/surveillance/en/

- Detect non-vector-borne transmission of ZIKV (for example, sexual transmission and blood transfusions).

In geographic areas where local circulation of the virus is already established, it is recommended that a fraction of all suspected cases detected during each week (ideally, 10%) be confirmed by laboratory tests.

In addition, laboratory testing is recommended in all of the following:

- All pregnant women with a suspected ZIKV disease;
- All patients who present with a neurological manifestation;
- All older adults or people with comorbidities who present with a suspected clinical picture;
- All newborns with microcephaly or other congenital abnormality of the central nervous system, regardless of the maternal history of infection;
- All miscarriages, stillbirths, and newborns whose mothers have a history of suspected or confirmed ZIKV infection; and
- All deaths linked to suspected ZIKV infection.

All suspected, probable, or confirmed case should be reported in an individualized manner to the corresponding surveillance level, with the frequency defined by the national system. Annex 3 provides a list of the basic patient data that must be included in reporting instruments.

In those countries or territories with only syndromic surveillance in place, surveillance of acute undifferentiated febrile illness and febrile rash syndrome should be strengthened.*** In addition, the possibility of implementing surveillance of all rash illnesses should be evaluated.

Areas with endemic transmission of Zika virus

In the Americas, endemic transmission has not yet been established. Some areas have already presented a first wave of Zika transmission, but there are many uncertainties about what will happen in the coming months.

Should ZIKV become endemic, the Member States could consider sentinel surveillance for weekly reporting of suspected cases of arboviral disease in

*** Note that some cases of Zika virus infection do not present with fever.

aggregate form and individualized reporting of cases managed at designated sentinel sites. A fraction of suspected cases detected at sentinel sites should undergo laboratory testing to confirm the causative agent.

Areas with no autochthonous cases and presence of Zika virus vectors

The surveillance system should focus on:

- Detecting and investigating clusters of rash illness, taking differential diagnoses into account;
- Investigate travelers returning from areas where ZIKV is known to circulate and who present with clinical pictures consistent with ZIKV infection;[†††]
- Monitor the neurological complications and birth anomalies defined in the corresponding sections of this Guideline; and
- Detect non-vector-borne transmission of ZIKV (e.g., by sexual transmission and blood transfusion).
- Laboratory testing of ZIKV infection is recommended in the following cases:
  - All cases that meet the definition of a suspected ZIKV disease case, including pregnant women, regardless of travel history;
  - All patients who present with neurological manifestations (GBS, encephalitis, myelitis, etc.);
  - All neonates with microcephaly or other congenital abnormalities or functional or structural changes in the central nervous system, regardless of a history of maternal infection;
  - All miscarriages, stillbirths, and neonates whose mothers have a history of suspected or confirmed ZIKV infection;
  - All deaths linked to suspected ZIKV infection.

Every suspected, probable, or confirmed case should be individually reported at the corresponding surveillance level, with the frequency defined by the national system.

In those countries or territories in which syndromic surveillance alone is in place, surveillance of acute undifferentiated febrile illness and febrile rash syndrome should be enhanced,[‡‡‡] and the possibility of implementing surveillance of all rash illnesses should be assessed.

[†††] To increase detection capabilities, and if the health care system allows, one potential strategy is to encourage the population to self-report symptoms consistent with ZIKV infection.
[‡‡‡] Note that some cases of ZIKV infection do not present with fever.

Areas with no autochthonous cases and absence of Zika virus vectors

The surveillance system should focus on:

- Detecting and monitoring imported cases of ZIKV disease, especially in groups at high risk of complications, such as pregnant women.
- Detecting non-vector-borne transmission of ZIKV (for example, by sexual transmission and blood transfusion).
- Laboratory testing of ZIKV infection is recommended all of the following:
  - All persons with a clinical picture consistent with the case definition and a history of travel to areas with known ZIKV transmission or presence of the ZIKV vector;
  - All persons with a history of unprotected sexual relations with a partner who traveled to an area with known ZIKV transmission or presence of the ZIKV vector;
  - All neonates born to mothers with a history of ZIKV infection or of travel to areas where the virus is circulating.§§§ This includes newborns with congenital anomalies consistent with ZIKV infection;
  - All patients who present with neurological manifestations (GBS, encephalitis, myelitis) and have a history of travel to areas with known ZIKV transmission or presence of the ZIKV vector, or who have had unprotected sexual relations with a partner with the aforementioned travel history.
  - Every miscarriage and fetal death in which the mother met the definition of a suspected, probable, or confirmed case of ZIKV disease.****

Every suspected, probable, or confirmed case should be individually reported at the corresponding surveillance level, with the frequency defined by the national system.

To increase detection capacity and facilitate self-reporting, the public health authorities should provide information on the symptoms of ZIKV infection to all travelers to areas where there is active virus transmission.

§§§ The travel history of the mother's sexual partner during pregnancy should also be taken into account.
**** This guidance may be modified as the epidemic progresses in each country. Laboratory tests should only be performed in countries that have planned to provide a distinct set of care measures to affected children, regardless of the presence of lesions.

Entomological surveillance of *Aedes aegypti*

Entomological surveillance is the systematic, continuous, orderly, and planned process of collecting data on disease vectors and their environment, in order to describe, analyze, evaluate, interpret, and make decisions related to vector control. The combination of entomological surveillance and disease surveillance enables implementation of the appropriate control measures. It follows that implementation of rational control measures requires hard data that can serve as a reference. Entomological surveillance is a component of epidemiological surveillance and an essential vector control activity. It should be carried out in the dry and wet seasons alike, and should encompass both the early and adult stages of the vector.

Consideration of this component focuses exclusively on surveillance of the mosquito species *A. aegypti,* which, according to the currently available evidence, is the main vector of ZIKV and other arboviruses. Due to the complexity of vector surveillance, if information arises to suggest that other species are potential ZIKV vectors, these guidelines would have to be modified and their scope expanded accordingly.

Entomological surveillance objectives

Entomological surveillance has the following main objectives:

- To detect the presence of the vector in a given geographic area;
- To ascertain the density of vector populations;
- To determine the areas of greatest entomologic risk, including surveys of infected mosquitoes;
- To identify the major and most productive breeding sites;
- To ascertain the degree of vector resistance to insecticides; and
- To support monitoring of the quality and effectiveness of ongoing interventions.

Furthermore, entomological surveillance provides inputs to support the mass communication and social mobilization interventions necessary to ensure physical control of mosquito breeding sites by individuals and families in their homes and places of work and study.

Definition of areas with and without *A. Aegypti* infestation

Areas under surveillance can be classified as:

Areas infested with *A. aegypti*
Areas in which all stages of *A. aegypti* are present in dwellings and/or public spaces.

Areas not infested with *A. aegypti*
Areas in which none of the stages of the vector is found and in which a surveillance system (oviposition traps, larvae traps, or active case-finding of the different stages of the mosquito) is in place.

Surveillance of infestation

Several indicators based on sampling of the different life stages of the vector have been described to measure the severity of *A. aegypti* infestation. The following section described these indicators and procedures according to their utility.

The *adult index,* which measures the number of adults captured in traps or found by active searches, provides the best indicator to measure the epidemiological risk of transmission of arboviruses, including dengue, chikungunya, and Zika, as well as information on vector density and its fluctuations. However, sampling of adult mosquitoes poses a variety of operational challenges.

Determining the *proportion of adult mosquitoes infected* with arbovirus not only provides information on which viruses are circulating in a population, but can also serve as an early warning and surveillance system for outbreaks or epidemics.

The use of *oviposition traps, or ovitraps*, is a sensitive and low-cost method for detection of *A. aegypti* when infestation levels are low and larval sampling is usually unproductive. These traps are especially useful for early detection of new infestations in areas where the mosquito had been eliminated or had not yet arrived. Oviposition traps are also useful for surveillance in international seaports and airports, which, in accordance with the International Health Regulations (IHR), should remain free of mosquitoes in any stage (eggs, larvae, pupas, or adults).

Pupal surveys by person or by area are one of the methods used to determine which containers are most productive in terms of adult mosquito output. This method consists

of counting the total number of pupas in different types of containers within a given community. Collection of demographic data enables establishment of a relationship between the number of pupas (which are representative of adult mosquitoes) and the number of people in the community.

The method most widely used in vector surveillance is *larvae sampling*. However, the information generated by this sampling modality may not reflect the population of adult mosquitoes; as a result, its utility is limited. In this method, containers are inspected for the presence of mosquito larvae, pupas, and larval and pupal remains. Depending on the objectives of inspection, the survey can be terminated as soon as Aedes larvae are found or may continue until all containers have been inspected. Indicators routinely calculated to estimate the severity of infestation with *A. aegypti* larvae include the container index, the house index or premises index, and the Breteau index.[57]

Monitoring of resistance to insecticides

Monitoring of resistance to insecticides consists of evaluating the response of local *A. aegypti* populations to the insecticides used regularly for control of this vector. Such surveillance should be systematic and periodic, and is essential to ensure the quality of vector control interventions and mitigate the risk of selection of resistant mosquitoes within vector populations.[58]

Monitoring of the effectiveness of interventions

Most entomological evaluation procedures employ the same techniques used for surveillance.[57]

To evaluate the result of space spraying with the Ultra-Low Volume (ULV) technique, used in emergencies to rapidly reduce adult vector populations, the caged mosquito bioassay and droplet measurement devices can be used to confirm insecticide penetration into exposed and hidden sites within and around dwellings. However, mortality of caged mosquitoes does not necessarily reflect mortality in the natural mosquito population, which means that the aforementioned methods described for infestation surveillance can be used.

When *A. aegypti* resting surfaces are sprayed with residual insecticides, the duration of the residual effect and its effectiveness should be monitored. This is done by exposing mosquitoes to the sprayed surfaces using the cone bioassay method and the WHO-defined procedures for entomological evaluation of residual spraying.[59]

The effectiveness of larvicide application, biological control measures, or elimination of mosquito breeding sites can be evaluated directly, using standardized techniques such as larval surveys and bioassays.[57]

Surveillance should take into account that the quality of spraying depends on optimal, periodic equipment calibration, on quality assurance of insecticides and larvicides, and on rigorous adherence to established standards for the application of insecticides or larvicides.

Annexes

Annex 1. Guillain-Barré syndrome (GBS) diagnosis

Mandatory clinical findings

- Progressive limb weakness
- Hyporeflexia or areflexia

Suggestive clinical findings

- Rapid progression of symptoms, with deficits plateauing in <4 weeks (90%)
- Relative symmetry
- Sensory and motor symptoms
- Cranial nerve involvement (usually facial and bilateral)
- Autonomic dysfunction (arrhythmia, postural hypotension, hypertension, vasomotor symptoms), which can be fluctuating
- Start of the recovery 2-4 weeks after the plateau period

Laboratory (CSF)

Albuminocytologic dissociation

Other recommended tests

- HIV serological testing is advised
- Other laboratory tests to identify possible etiologies depending on local epidemiological context (schistosomiasis, *Campylobacter jejuni*, enterovirus, arbovirus)

Electrophysiological study

Acute inflammatory demyelinating polyneuropathy:

- 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 demyelinization

Findings that call into question a GBS diagnostic

- Markedly and persistently asymmetrical weakness
- Initial or persistent alterations of sphincter control
- Pleocytosis (>50 leukocytes/mm^3) and/or polymorphonuclear leukocytes in CSF
- Presence of a sensory level (suggestive of myelitis).

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 diagnosis of poliomyelitis
- Diagnosis of botulism

Differential diagnosis of a clinical syndrome of rapid, progressive weakness

- **Central nervous system***
  Encephalitis, acute disseminated encephalomyelitis, inflammatory myelopathy, compressive/inflammatory/ischemic brainstem or cervical spinal cord syndrome
- **Motor neuron disease**
  Poliomyelitis, spinal muscular atrophy
- **Nerve roots and peripheral nerves**
  Diphtheria, porphyria, hypokalemic paralysis, critical illness polyneuropathy
- **Neuromuscular junction**
  Myasthenia gravis, botulism
- **Muscle**
  Polymyositis, acute rhabdomyolysis, critical illness myopathy

** Neuroimaging studies are not required to diagnose GBS; however, they should be carried out in patients in whom central nervous system involvement is suspected.*

Annex 2. Recommendations for sample collection and storage according to laboratory test

Samples for surveillance of GBS and other neurological manifestations

Sample	Days from symptom onset	Volume	Transport medium	Transport conditions	Storage >1 week	Lab test
Serum	1 to 5	5-7 mL	No additives	4/8 °C	-20/-70 °C	PCR
Serum	5 to 7	5-7 mL	No additives	4/8 °C	-20/-70 °C	PCR + IgM ELISA
Serum	≥ 7	0.5-1 mL	No additives	4/8 °C*	-20/-70 °C	IgM ELISA
Urine	5 to 15	5-7 mL	No additives	4/8 °C	-20/-70 °C	PCR
CSF**		0.5 mL	No additives	4/8 °C	-20/-70 °C	PCR + IgM ELISA

* It is essential that urine be stored under refrigeration to prevent bacterial overgrowth.

**Only if clinically indicated for diagnosis of a neurological condition.

Samples for congenital syndrome and/or fatal cases

Sample	Volume	Transport medium	Transport conditions	Storage >1 week	Lab test
Maternal serum	5-7 mL	No additives	4/8 °C	-20/-70 °C	PCR, IgM ELISA, PRNT, others
Cord blood	0.5-1 mL	No additives	4/8 °C	-20/-70 °C	PCR, IgM ELISA, PRNT, others
Placenta	3x3 cm (approx.)	Buffered formalin	4 °C – RT*	4 °C – RT*	Immunohistochemistry
Placenta	3x3 cm (approx.)	Saline solution	4/8 °C	-20/-70 °C	PCR
Umbilical cord (tissue)		Buffered formalin	4 °C – RT*	4 °C – RT*	Immunohistochemistry
Umbilical cord (tissue)		Sterile saline solution or dry tube	4/8 °C	-20/-70 °C	PCR
Neonatal serum	0.5-1 mL	No additives	4/8 °C	-20/-70 °C	PCR, IgM ELISA, PRNT, others
Amniotic fluid**	0.5-1 mL	No additives	4/8 °C	-20/-70 °C	PCR
Neonatal CSF**	0.5 mL	No additives	4/8 °C	-20/-70 °C	PCR, IgM ELISA, PRNT, others
Maternal whole blood	5-7 mL	EDTA, other additives	4/8 °C	4 °C	Biochemistry, others
Neonatal whole blood	2-5 mL	EDTA, other additives	4/8 °C	4 °C	Biochemistry, others
Tissue***	3x3 cm (approx.)	Buffered formalin	4 °C – RT*	4 °C – RT*	Immunohistochemistry
Tissue***	3x3 cm (approx.)	Sterile saline solution or dry tube	4/8 °C	-20/-70 °C	PCR

* Room temperature.

**Only if clinically indicated due to suspicion of neurological condition.

***In fatal cases: Brain, liver, kidney, products of conception, etc.

Annex 3. Zika surveillance: Core data for case reporting

The following section lists the recommended minimal core data for Zika surveillance reports. Countries can supplement the suggested data and adapt them to their specific requirements. The information contained in these parameters is the bare minimum needed to carry out surveillance actions. It is suggested that research instruments be supplementary and specific for each case definition.

These data can be collected as part of universal case surveillance, but can also be adapted by countries that are implementing an integrated or syndrome-based surveillance system. The timing of reporting should be defined by each country depending on its epidemiological scenario. Furthermore, each country should take into account the reporting requirements defined in the IHR for the IHR National Focal Point.

Section 1: General Information

Patient identification
- Name
- Age
- Sex
- Address

Diagnosis
- ZIKV disease (suspected/probable/confirmed)
- GBS associated with ZIKV infection (suspected/confirmed)
- Congenital syndrome associated with ZIKV infection (suspected/probable/confirmed).
- Abortion or fetal death associated with ZIKV infection
- Vertical transmission of ZIKV without the congenital syndrome

Reporter identification: Name, contact information (telephone, e-mail), reporting facility.

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

ZIKV disease
- Date of rash onset
- Risk factor
    - Resident of area where the vector is present/traveler/sexual partner

- Initial case classification (suspected/probable/confirmed)
- Relevant patient characteristics:
  - Pregnant/not pregnant (+ gestational age in weeks)
  - Hospitalized/not hospitalized (+ facility)
  - Dead/alive
- Laboratory diagnosis
  - PCR: Type of sample (serum, blood, urine); positive, negative, pending, or not performed. Date of sample collection (day/month/year).
  - Anti-ZIKV IgM serology: Type of sample (serum); positive, negative, pending, or not performed. Date of sample collection. Neutralization test carried out (yes/no) + result (positive, negative, pending).
  - If dead: Molecular detection of viral genome in autopsy tissue specimen (yes/no/not performed/pending). Specific detection of viral antigen in autopsy specimen by immunohistochemistry.

GBS associated with ZIKV infection

- 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)
- History of rash (yes/no) + dates (day/month/year)
- Initial case classification (suspected/confirmed)
- Relevant characteristics of the patient:
  - Pregnant/not pregnant (+ gestational age in weeks)
  - Hospitalized/not hospitalized (+ facility)
  - Dead/alive
  - Comorbidity: HIV (yes/no) Diabetes (yes/no) Autoimmune disease (yes/no), etc.
- Laboratory diagnosis
  - PCR: Type of sample (serum, blood, urine); positive, negative, pending, or not performed. Date of sample collection (day/month/year).
  - Anti-ZIKV IgM serology: Type of sample (serum); positive, negative, pending, or not performed. Date of sample collection. Neutralization test carried out (yes/no) + result (positive, negative, pending).

Congenital syndrome associated with ZIKV infection

- Final condition of the newborn or fetus (abortion or stillbirth)
- Identification of the neonate, gestational age, birthweight, length at birth
- Information on the pregnant woman
  - Risk factor (resident of area where the vector is present/traveler/sexual partner)
  - History of rash (yes/no), dates (gestational week or trimester)
  - Full-term pregnancy (yes/no)
  - Date of delivery or termination of pregnancy (day/month/year)

- Initial classification of the congenital syndrome (suspected/probable/confirmed)
  - Microcephaly (yes/no), head circumference in centimeters (rounded to nearest decimal)
  - Intracranial calcifications (yes/no/unavailable). Detected prenatally or postnatally?
  - Other intracranial morphological alterations (yes/no/unavailable). Detected prenatally or postnatally?
  - Other birth defects (yes/no). Which? (free-text field)
- Diagnostic support and laboratory tests
  - PCR: Type of sample (serum, cord blood, urine, CSF, amniotic fluid); positive, negative, pending, or not performed. Date of sample collection
  - Anti-ZIKV IgM serology: Type of sample (serum, CSF, amniotic fluid); positive, negative, pending, or not performed. Date of sample collection. Neutralization test carried out (yes/no) + result (positive, negative, pending).
  - Clinical autopsy (yes/no)
  - Type of histopathology specimen (tissue from…). Result (positive, negative, pending, not performed). Date of sample collection (day/month/year)

Miscarriage or fetal death associated with ZIKV infection

- Final condition of the fetus (abortion or fetal death)
- Information on the fetus: gestational age (weeks), weight (grams)
- Information on the pregnant woman
  - Risk factor (resident of area where the vector is present/traveler/sexual partner)
  - History of rash (yes/no), dates (gestational week or trimester)
  - Date of termination of pregnancy (day/month/year)
- Initial case classification (suspected/confirmed)
- Diagnostic support and laboratory tests
  - Pregnant woman
    - PCR: Type of sample (serum, blood, urine); positive, negative, pending, or not performed. Date of sample collection (day/month/year).
    - Anti-ZIKV IgM serology: Type of sample (serum, CSF, amniotic fluid); positive, negative, pending, or not performed. Date of sample collection. Neutralization test carried out (yes/no) + result (positive, negative, pending).
  - Newborn or fetus
    - PCR: Type of sample (tissue, blood); positive, negative, pending, or not performed. Date of sample collection (day/month/year).
    - Clinical autopsy (yes/no)
    - Type of histopathology specimen (tissue from…). Result (positive, negative, pending, not performed). Date of sample collection (day/month/year)

Vertical transmission of ZIKV without congenital syndrome

- Final condition of the newborn (live birth/perinatal death)
- Identification of the neonate, gestational age, birthweight, length at birth
- Information on the pregnant woman
  - Risk factor (resident of area where the vector is present/traveler/sexual partner)
  - Classification of ZIKV disease in the mother (suspected/probable/confirmed), dates of clinical symptoms of ZIKV disease (gestational week or trimester)
  - Full-term pregnancy (yes/no)
  - Date of delivery (day/month/year).
- Initial classification of vertical transmission (suspected/probable/confirmed)
  - Birth defects other than the congenital syndrome (yes/no) Which? (free-text field)
- Diagnostic support and laboratory tests
  - PCR: Type of sample (cord blood, serum, CSF, amniotic fluid); positive, negative, pending, or not performed. Date of sample collection.
  - Anti-ZIKV IgM serology: Type of sample (cord blood, serum, CSF, amniotic fluid); positive, negative, pending, or not performed. Date of sample collection. Neutralization test carried out (yes/no) + result (positive, negative, pending).
  - Clinical autopsy (yes/no)
  - Type of histopathology specimen (specify source of tissue). Result (positive, negative, pending, not performed). Date of sample collection (day/month/year)

Annex 4. Case definitions

Suspected case of ZIKV disease

Patient who presents with rash* **AND** at least **two or more** of the following signs or symptoms:

- Fever, usually <38.5 °C
- Non-purulent conjunctivitis/conjunctival hyperemia
- Arthralgia
- Myalgia
- Peri-articular edema

** usually pruritic and maculopapular*

Suspected case of Zika virus disease in geographic areas without autochthonous transmission and where there are no vectors present

Any patient who meets the criteria for a suspected case of ZIKV disease **AND**

- in the 2 weeks prior to onset, traveled to, or resided in, a geographic area where there is known local transmission of the ZIKV or there is vector presence; **OR**
- had un-protected sex, in the 2 weeks prior to onset, with a person who traveled, in the previous 8 weeks, to a geographic area with (a) local transmission of the ZIKV or (b) presence of vector.

Probable case of Zika virus disease

Any patient who meets the criteria for a suspected case and also has anti-ZIKV IgM antibodies, without laboratory results indicating infection by other flaviviruses.

Confirmed case of Zika virus disease

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

- RNA or ZIKV antigen in any serum sample or other type (for example, urine, saliva, tissue, or whole blood); **OR**
- Positive anti-ZIKV IgM antibodies **AND** plaque reduction neutralization test (PRNT90) titers for ZIKV both ≥ 20 **AND** fourfold or greater than for other flaviviruses; **AND** exclusion of other flavivirus;[††††] **OR**
- In deceased individuals,[‡‡‡‡] molecular detection of viral genome in autopsy tissue (fresh or in paraffin) or specific viral antigen detection by immuno-histochemistry testing.

[††††] Test performed only in probable cases positive for anti-ZIKV IgM antibodies.

[‡‡‡‡] Other than abortion or fetal death, which are discussed in a subsequent chapter.

Suspected case of GBS associated with ZIKV infection
Any patient who

- resides in, or recently traveled to, an area where there are vectors for the ZIKV; **OR**
- has had unprotected sex with someone who resides in, or recently traveled to an area of circulation of vectors for the ZIKV; **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 weak limbs; **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.

Confirmed case of Zika-virus-associated GBS
Patient meeting the criteria for suspected of Zika-virus-associated GBS with laboratory confirmation of recent infection with the ZIKV.

Suspected case of congenital syndrome associated with Zika virus infection
Live newborn who presents with:

- microcephaly: head circumference below -2 standard deviations for gestational age and sex, measured at 24 hours after birth according to the standardized reference;[§§§§] **OR**
- other congenital malformation of the central nervous system;

AND whose mother during pregnancy:

- traveled to, or resided in, an area where ZIKV vectors were present; **OR**
- had unprotected sex with a partner who resided in, or traveled to, an area with the presence of ZIKV vectors.

Probable case of congenital syndrome associated with Zika virus infection
Live newborn who meets the criteria for a suspected case of congenital syndrome associated with ZIKV **AND**

- who has intracranial morphological alterations detected by any imaging method, and not explained by other known 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 infection **AND** with laboratory-confirmed ZIKV infection, independent of the detection of other agents.

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§§§§ https://intergrowth21.tghn.org/site_media/media/articles/newbornsize.pdf

Suspected Zika-virus-associated abortion or stillbirth
Abortion or stillbirth in a woman, who during her pregnancy.

- presented rash **AND**
- resided in or travelled to an area where ZIKV vectors were present; **OR**
- had unprotected sex during pregnancy with a partner who resided in or travelled to an area where ZIKV vectors were present.

Confirmed Zika-virus-associated abortion or stillbirth
All suspected cases where ZIKV infection is confirmed from blood or urine samples from either the mother or puerperal or abortion or fetal death tissue.

Suspected case of vertical transmission of ZIKV without congenital syndrome
Live newborn of any gestational age, who does not meet the criteria for a suspected case of congenital syndrome associated with ZIKV, **AND** whose mother has been classified as a suspected, probable, or confirmed case of ZIKV disease during pregnancy.

Probable case of vertical transmission 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 PCR.

Confirmed case of vertical transmission without congenital syndrome
Liveborn infant who meets the criteria for a suspected case of ZIKV infection by vertical transmission **AND** whose serum sample contains anti-ZIKV IgM detected by ELISA.*

** When only RT-PCR is available and it is positive, follow-up serology is advised because the viral detection could be from perinatal rather than vertical transmission.*

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