

Surveillance for Zika virus infection, microcephaly and Guillain-Barré syndrome

Interim guidance

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1. Introduction

1.1 Background

This document provides interim WHO recommendations for the surveillance of Zika virus and potentially related complications. It has been developed in consideration of the declaration on 1 February 2016 by the WHO Director-General of a Public Health Emergency of International Concern with regard to clusters of microcephaly and neurological disorders potentially associated with Zika virus.

Zika virus transmission is primarily vector-borne, mainly via *Aedes* mosquitoes. The virus can also be found in various body fluids and transmission by sexual contact has also been reported. *Aedes aegypti*, the principal vector, is found in tropical and subtropical climates and adapts well to urban areas, living in and around human habitations. The areas affected by Zika virus lie within areas affected by dengue and chikungunya, which are also transmitted by *Aedes* mosquitos. Zika virus disease is usually mild with non-specific signs and symptoms: fever, rash, conjunctivitis, muscle and joint pain.

However, recent outbreaks of Zika virus in Brazil and French Polynesia have been associated with reports of an unusual increase in microcephaly among newborns, as well as with an increased number of cases of Guillain-Barré syndrome and other neurological disorders. Based on a growing body of preliminary research, there is now scientific consensus that Zika virus is a cause of microcephaly and Guillain-Barré syndrome.

Recent case reports suggest there may be a link between Zika and other neurological abnormalities such as myelitis (inflammation of the spinal cord) and brain abnormalities on scan in the absence of microcephaly. Assessment of the evidence for these conditions as well as microcephaly and Guillain-Barré syndrome is ongoing.

This document provides interim recommendations for the surveillance of Zika virus infection, microcephaly and Guillain-Barré syndrome, in four different contexts and describes reporting requirements to WHO. Transmission refers to vector-borne transmission, unless specified differently. Autochthonous infection is considered to be an infection acquired in-country, i.e. among patients with no

history of travel during the incubation period or who have travelled exclusively to non-affected areas during the incubation period. This document does not provide guidance on laboratory investigation [1] or vector surveillance [2]. Guidance on these and other topics related to Zika virus are provided in separate documents and can be accessed at <http://www.who.int/csr/resources/publications/zika>.

There are four contexts classified according to the risk of occurrence of severe complications or sequelae associated with Zika virus infection, as follows:

1. Countries experiencing a Zika virus outbreak, with no evidence of circulation in the past, and with ongoing vector-borne transmission. Referred to as **“Countries with epidemic transmission of Zika virus”**.
2. Countries where there is evidence of Zika virus transmission in the past, with or without ongoing transmission. This group includes countries where transmission appears to occur, or has occurred, at low levels, and countries that experienced an epidemic in the past. Referred to as **“Countries with possible endemic Zika virus transmission”**.
3. Countries with competent mosquito vectors, but where vector-borne transmission of Zika virus has never been documented. These countries are at risk of introduction of the virus and further circulation through vector-borne transmission. Referred to as **“Countries at risk of Zika virus transmission”**.
4. Countries without competent vectors, based on current knowledge and known vector distribution. These countries are at risk of importation of cases with potential for further transmission by modes other than mosquito vectors, and at no risk or low risk of vector-borne transmission. Referred to as **“Countries with no/low risk of mosquito-borne Zika virus transmission”**.

1.2 Target audience

This document is intended to be used by public health authorities and policy makers responsible for communicable disease surveillance and control in order to guide national surveillance strategies and reporting in the context of Zika virus.

2. Surveillance for Zika virus infection

2.1 Countries with epidemic transmission of Zika virus

In countries experiencing epidemics, the surveillance system should be reinforced in order to:

- monitor the geographical distribution and spread and temporal trend of infection;
- characterize disease presentation;
- identify severe complications in all age groups;
- identify and investigate possible non-vector borne routes of transmission; and
- target containment measures and vector control.

Retrospective analysis of stored blood, urine and other samples may be considered in order to determine when the virus was introduced. Serosurveys may be used to estimate the proportion of infected individuals in the population.

Once autochthonous transmission has been established in a given area, decisions on the need for laboratory confirmation of all suspected Zika virus cases should be based on available resources. Laboratory confirmation may be reserved for detecting circulation of the virus in new areas, investigating severe cases, those with complications, and those with severe outcomes (e.g. pregnant women). Depending on available capacity, only a fraction of samples may be tested for public health surveillance purposes.

Other vector control activities, such as conducting entomological surveillance of *Aedes* mosquitoes, prioritizing breeding sites and monitoring insecticide resistance, should be implemented according to WHO guidance. [2,3]

A brief description of the surveillance and testing strategy (type of surveillance system, who is being tested, whether all or a fraction of samples are being tested, etc.) should be provided to enhance interpretation of the surveillance data.

Reporting requirements

- Number of suspected and confirmed cases of Zika virus infection per week and geographical area (by applicable administrative level) (weekly reporting).
- Any cases of Zika virus infection with atypical clinical presentations as per WHO case definition [4], cases infected via non-vector-borne transmission or other cases that are able to provide new information to guide the national or global risk assessment (weekly reporting).

2.2 Countries with possible endemic Zika virus transmission

Countries where there is evidence of Zika virus transmission in the past, with or without evidence of current transmission, should aim to:

- monitor the geographical distribution and temporal trend of endemic transmission;
- detect changing patterns of Zika virus transmission (for example, increase in incidence, or wider geographical distribution) or disease epidemiology (change in affected age groups or disease severity);
- identify severe complications in all age groups;
- identify and investigate possible non-vector borne routes of transmission; and
- whenever feasible and where appropriate, investigate the extent of prior circulation.

Other vector control activities, such as conducting entomological surveillance of *Aedes* mosquitoes, prioritizing breeding sites and monitoring insecticide resistance should be implemented according to WHO guidance. [2,3]

Reporting requirements

- In case of rediscovery of Zika virus anywhere in the country (after a previous outbreak has been terminated), the first autochthonous confirmed case(s) should be reported within 24 hours of confirmation.
- Any cases of Zika virus infection with atypical clinical presentations as per WHO case definition [4], cases infected via non-vector-borne transmission, or other cases that are able to provide new information to guide the national or global risk assessment (weekly reporting).
- Results of any retrospective analysis conducted on stored samples, as soon as results become available.
- Results of any seroprevalence surveys, as soon as these become available.
- All imported cases in areas without ongoing endemic transmission originating from a country/territory where autochthonous transmission has NOT been previously documented, within 24 hours of confirmation.

2.3 Countries at risk of Zika virus transmission

In countries where competent vectors are present, but where Zika virus has never been documented, the surveillance should aim to:

- detect imported Zika virus disease cases;
- detect the beginning of autochthonous transmission;
- detect instances of Zika virus transmission modes other than vector-borne; and
- whenever feasible and appropriate, investigate whether Zika virus was present in the past and the level of intensity of circulation during earlier introductions.

Other vector control activities, such as conducting entomological surveillance of *Aedes* mosquitoes, prioritizing breeding sites and monitoring insecticide resistance, should be implemented according to WHO guidance. [2,3]

Reporting requirements

- The first autochthonous confirmed case, within 24 hours of confirmation.
- All imported confirmed cases originating from a country/territory where autochthonous transmission has NOT been previously documented, within 24 hours of confirmation.
- Any cases of Zika virus infection with atypical clinical presentations as per WHO case definition [4], cases infected via non-vector-borne transmission or other cases that are able to provide new information to guide the national or global risk assessment (weekly reporting).
- Results of any retrospective analysis conducted on stored samples, as soon as results become available.

Once autochthonous transmission has occurred in a country with no evidence of prior transmission, the country should follow the surveillance recommendations provided in section 2.1 for countries with epidemic transmission of Zika virus.

If evidence of past circulation is identified through studies of stored samples, then the country should follow the recommendations provided in section 2.2 for countries with possible endemic Zika virus transmission.

2.4 Countries with no/low risk of Zika virus transmission

In countries where conditions for Zika virus transmission, in particular the presence of competent vectors, are thought to be absent, surveillance should aim to:

- detect imported Zika virus cases; and
- detect instances of transmission modes other than vector-borne.

Reporting requirements

- Imported cases originating from a country/territory where autochthonous transmission has NOT been previously documented, within 24 hours of confirmation.
- Any cases of Zika virus infection with atypical clinical presentations as per WHO case definition [4], cases infected via non-vector-borne transmission or other cases that are able to provide new information to guide the national or global risk assessment (weekly reporting).

3. Surveillance for microcephaly and other congenital brain abnormalities

3.1 Countries with epidemic transmission of Zika virus

The main objectives of surveillance for microcephaly and other congenital brain abnormalities are to:

- establish a historic baseline (prior to the outbreak) and monitor the incidence, time trends and geographical distribution of microcephaly and associated infant deaths;
- detect and investigate all new cases of microcephaly [5] to determine the likely etiology and whether or not there is a history of Zika virus infection;
- if possible, establish a historic baseline (prior to the outbreak) of stillbirths and miscarriages and congenital brain abnormalities, and monitor trends;
- investigate any observed increase compared to baseline in the incidence of microcephaly cases, other congenital brain abnormalities and stillbirths; and
- identify and register pregnant women with clinical signs and symptoms of Zika virus infection, in order to investigate and conduct follow-up as per WHO guidance. [6,7]

The following surveillance activities should be conducted.

- Review existing sources of information (registers, hospital data, scientific publications, etc.) to establish the baseline/historical incidence of microcephaly. If feasible, the baseline should be based on several years of historical data.
- Whenever appropriate and feasible, conduct analytical observational studies (cohort or case-control studies, etc.).

Reporting requirements

- First case of microcephaly associated with Zika virus, within 24 hours of diagnosis.
- An increase in the incidence of microcephaly, and the best possible estimated baseline, as soon as available.
- An increase in the incidence of stillbirth and congenital brain abnormalities, and the best possible estimated baseline, as soon as available.
- All cases of microcephaly for which there is indication of Zika virus infection either during the pregnancy or in the neonate or infant, along with the results of the investigation and the differential diagnosis performed (monthly reporting).
- Number of confirmed Zika virus-infected pregnant women under follow-up (monthly reporting).

3.2 Countries with possible endemic Zika virus transmission

Countries where Zika virus has been documented in the past, with or without continuing transmission should:

- establish a historic baseline and monitor the incidence, time trends and geographical distribution of microcephaly and associated deaths and miscarriages;
- detect and investigate all new cases of microcephaly [5];
- if possible, establish a historic baseline of stillbirths and congenital brain abnormalities, and monitor trends;
- investigate any observed increase in the incidence of microcephaly cases, other congenital brain abnormalities and stillbirths; and
- identify and register pregnant women with clinical indication of Zika virus infection, in order to investigate and conduct follow-up as per WHO guidance. [6,7]

The following surveillance activities should be conducted.

- Review existing sources of information (registers, hospital data, scientific publications, etc.) to establish the baseline/historical incidence of microcephaly. If feasible, the baseline should be based on several years of data.

Reporting requirements

- First case of microcephaly associated with Zika virus within 24 hours of diagnosis.
- An increase in the incidence of microcephaly, and the best possible estimated baseline, as soon as available.
- An increase in the incidence of stillbirths and congenital brain abnormalities, and the best possible estimated baseline, as soon as available.
- All cases of microcephaly for which there is indication of Zika virus infection either during the pregnancy or in the neonate or infant, along with the results of the investigation and the differential diagnosis performed (monthly reporting).
- Number of confirmed Zika virus-infected pregnant women under follow-up (monthly reporting).

3.3 Countries at risk of Zika virus transmission

In these countries, the main objective of the surveillance should be to:

- identify and register pregnant women potentially exposed to Zika virus in order to investigate and conduct follow-up as per WHO guidance [6,7];
- identify and investigate cases of microcephaly [5] and other congenital brain abnormalities in the fetuses of pregnant women or infants, during pregnancy or after birth; and
- if possible, establish a baseline for and monitor the incidence and trends of microcephaly and associated deaths, stillbirth and congenital brain abnormalities.

The following surveillance activities should be conducted.

- Review of existing sources of information (registers, hospital data, scientific publications, etc.) to establish the baseline/historical incidence of microcephaly. If feasible, the baseline should be based on several years of data.

Reporting requirements

- The number of pregnant women potentially exposed to Zika virus under follow-up (monthly update).
- All cases of microcephaly and other congenital brain abnormalities with indications of association with Zika virus, within 24 hours of diagnosis.

3.4 Countries with no/low risk of Zika virus transmission

In these countries, the main objective of the surveillance should be to:

- identify and register pregnant women potentially exposed to Zika virus, in order to investigate and conduct follow-up as per WHO guidance [6,7]; and
- identify and investigate cases of microcephaly [5] and other congenital brain abnormalities in the fetuses of pregnant women or infants, during pregnancy or after birth.

Reporting requirements

- Number of potentially exposed pregnant women under follow-up (monthly update).
- All cases of microcephaly and other congenital brain abnormalities with indications of association with Zika virus, within 24 hours of diagnosis.

4. Surveillance for Guillain-Barré syndrome (GBS)

4.1 Countries with epidemic transmission of Zika virus

In countries with documented Zika virus circulation, the main objectives of the surveillance are to:

- if possible, establish a historic baseline of GBS;
- monitor GBS incidence and trends;
- if possible, detect and investigate all new cases or clusters of GBS [8];
- investigate any increase in the incidence of GBS cases; and
- if possible, detect and investigate other neurological diseases possibly associated with Zika virus infection, such as meningoencephalitis or myelitis.

The following surveillance activities should be conducted.

- Review existing sources of information (registers, hospital data, scientific publications etc.) to establish the baseline incidence of GBS.
- Review data from acute flaccid paralysis (AFP) surveillance from which to estimate GBS trends, acknowledging the age-group difference between AFP (<15y) surveillance and occurrence of GBS (more frequent in adults).
- Whenever appropriate, and if resources allow, conduct analytical observational studies (cohort or case-control studies, etc.).

Reporting requirements

- An increase in the incidence of GBS, and the best possible estimated baseline, as soon as such information is available.
- The first case of GBS with an indication of an association with Zika virus, within 24 hours of diagnosis.
- Thereafter, all GBS cases and deaths which have indications of an association with Zika virus, along with detailed results of the investigation into each case (monthly basis).
- Any neurological conditions other than GBS, such as meningoencephalitis or myelitis, that may be associated with Zika virus infection and are able to provide new information to guide the regional or global risk assessment, within 24 hours of diagnosis.

4.2 Countries with possible endemic Zika virus transmission

In countries with possible endemic Zika virus transmission, the main objectives of the surveillance are to:

- if possible, establish a historic baseline for GBS;
- monitor the incidence and trends of GBS;
- if possible, detect and investigate all new cases or clusters of GBS [8];
- investigate any increase in the incidence in cases of GBS; and
- if possible, detect and investigate other neurological diseases possibly associated with Zika virus infection, such as meningoencephalitis or myelitis.

The following surveillance activities should be conducted.

- Review existing source of information (registers, hospital data, scientific publications etc.) to establish the baseline incidence of GBS.
- Review data from AFP surveillance from which to estimate GBS trends, acknowledging the age-group difference between AFP (<15y) surveillance and occurrence of GBS (more frequent in adults).
- Whenever appropriate and if resources allow, conduct analytical observational studies (cohort or case-control studies, etc.).

Reporting requirements

- An increase in the incidence of GBS, and the best possible estimated baseline, as soon as such information is available.
- The first case of GBS with an indication of an association with Zika virus, within 24 hours of diagnosis.
- Thereafter, all GBS cases and deaths which have indications of an association with Zika virus, along with detailed results of the investigation into each case (monthly basis).
- Any neurological conditions other than GBS, such as meningoencephalitis or myelitis, that may be associated with Zika virus infection and are able to provide new information to guide the regional or global risk assessment, within 24 hours of diagnosis.

4.3 Countries at risk of Zika virus transmission

Surveillance

In these countries, the main objective of the surveillance should be to:

- identify and investigate cases of GBS [8] in travellers returning from an area with Zika virus transmission;
- if possible, establish a historic baseline for GBS; and
- monitor the incidence and trends of GBS and investigate any increase in the incidence in reported cases of GBS.

The following surveillance activities should be conducted.

- Review existing sources of information (registers, hospital data, scientific publications etc.) to establish the baseline incidence of GBS.
- Review data from acute flaccid paralysis (AFP) surveillance from which to estimate GBS trends, acknowledging that AFP surveillance is done in the group aged <15y whereas GBS is more frequent in adults.

Reporting requirement

- All cases of GBS with an indication of an association with Zika virus, within 24 hours of diagnosis.

4.4 Countries with no/low risk of Zika virus transmission

Surveillance

In these countries, the main objective of the surveillance should be to:

- identify and investigate cases of GBS [8] in travellers returning from an area with Zika virus transmission.

Reporting requirement

- All cases of GBS with an indication of an association with Zika virus, within 24 hours of diagnosis.

5. Surveillance activities

Table 1 summarizes the surveillance activities countries may consider implementing to reach their objectives. [9]

Table 1. Surveillance activities in the context of Zika virus

	Countries with epidemic transmission of Zika virus	Countries with possible endemic Zika virus transmission	Countries at risk of Zika virus transmission	Countries with no risk of mosquito-borne Zika virus transmission
Indicator-based surveillance*	X	X	X	X
Event-based surveillance†	X	X	X	X
Retrospective analysis of stored samples	(X)	X	X	
Seroprevalence surveys	(X)	X		

(X) indicates activities that may be conducted if resources are available

*Indicator-based surveillance is that in which numbers of suspect or confirmed cases, together with incidence and risk, are gathered through nationwide or sentinel surveillance, and includes laboratory-based surveillance, syndromic surveillance, arbovirus disease surveillance.

†Event-based surveillance is that in which unstructured ad hoc information regarding health events is collected, monitored, assessed and interpreted so that acute risks to human health are detected.

6. Guidance development

6.1 Acknowledgements

This document has been developed by a guideline development group composed of WHO staff from the Departments of Global Capacities, Alert and Response (Stephane Hugonnet, Philippe Barboza), Pandemic and Epidemic Diseases (Erika Garcia, William Perea), Maternal, Newborn, Child and Adolescent Health (Anthony Costello, Nigel Rollins), Reproductive Health and Research (A. Metin Gülmezoglu, Clara Menendez), Mental Health and Substance Abuse (Tarun Dua), Strategy, Policy and Information (Christopher Dye), and WHO regional offices: AMRO (Maria Almiron), EMRO (Abdinasir Abubakar), EURO (Colleen Acosta, Joao Pires), SEARO (Bardan Rana) and WPRO (Takuya Yamagishi).

An external group of experts was consulted to review this guidance and provided substantial inputs. This group was composed of Global Outbreak Alert and Response Network (GOARN) response partners and the following individuals provided significant inputs: Christopher Gregory (US Centers for Disease Control and Prevention); Angie Rose (The University of the West Indies, Caribbean Regional Zika Task Force); Delia Enria (Instituto Nacional de Enfermedades Virales Humanas, Argentina); Laura Rodrigues (London School of Hygiene and Tropical Medicine, UK); Martha Lucia Ospina (Instituto Nacional de Salud, Colombia); John Topping (Public Health Agency Canada).

6.2 Guidance development methods

A draft of this interim guidance was developed by a guideline development group of WHO staff, and circulated for feedback to an external group of experts, composed of GOARN partners and individual experts with experience in the field of infectious diseases, surveillance and outbreak detection and response. The recommendations in this document were developed with the inputs and feedback from this group, and through discussion of expert opinion.

6.3 Declaration of interests

All external contributors completed a standard WHO Declaration of Interests (DOI) form. These forms were reviewed by WHO staff and managed in accordance with WHO guidelines on a case-by-case basis. No competing interests precluding participation in the guideline development process were identified from any of the external contributors.

6.4 Review date

These recommendations have been produced under emergency procedures and will remain valid until October 2016, unless revised earlier. The Department of Global Capacities, Alert and Response at WHO Geneva will be responsible for reviewing this guideline at that time, and updating it as appropriate.

7. References

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