Preliminary guidelines for the surveillance of microcephaly in newborns in settings with risk of Zika virus circulation

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These preliminary recommendations were prepared by the PAHO/WHO team, with expert advice and based on currently available data and evidence. This document may be revised and updated in the light of new evidence that may become available.

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RATIONALE

In view of the increased number of notifications of newborns with microcephaly in areas where Zika virus circulates, and the potential link with this virus, the Pan American Health Organization/World Health Organization (PAHO/WHO) issued an epidemiologic alert on December 1, 2015[1]. This alert recommends the Member States to establish and maintain their capacity to detect and confirm cases of Zika virus infection, prepare health care services for a possible increase in demand at all levels of care, including specialized services for

[1] http://bit.ly/1IyPv09

neurological syndromes, and strengthen activities related to antenatal visits and controls.

Together with experts in the surveillance of congenital defects, and based on the available evidence and analysis of the current strategies in the areas where there is an increased prevalence of congenital microcephaly and other manifestations, PAHO/WHO presents this proposal to implement surveillance of newborns with microcephaly and other associated conditions in areas where Zika virus circulates. The criteria and guidelines presented are based on the available information from the experience in Brazil and on the specific literature and expert consensus on the epidemiology and surveillance of congenital defects.

This document provides guidelines for the design and implementation of actions for the surveillance of microcephaly and other associated conditions. These guidelines are for health care workers responsible for the implementation of public health surveillance at the ministries of health in the countries, promoting harmonized criteria for operations and strategies.

Although this document focuses specifically on microcephaly, it is part of a broader initiative for the surveillance of congenital defects in the Region, given the burden of morbidity and mortality they represent (congenital malformations are the second leading cause of child mortality in the Region of the Americas). This process is geared to strengthening the identification of congenital defects in the planning and implementation of public health actions, including surveillance.

In the Region of the Americas, consolidated registries and programs for the surveillance of congenital defects have helped to assess the epidemiological significance of congenital defects and to identify associated conditions and the outcomes of specific interventions.

EPIDEMIOLOGICAL BACKGROUND

Autochthonous transmission of Zika virus

From February 2014 to January 2016, 21 countries and territories have confirmed autochthonous circulation of Zika virus (ZIKV): Barbados, Bolivia, Brazil, Colombia, Chile

(Easter Island), Ecuador, El Salvador, Guadalupe, Guatemala, Guiana, French Guiana, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Puerto Rico, Saint Martin, Suriname, and Venezuela. In only three months, from November 2015 to January 2016, local transmission of the virus was detected in 16 new countries and territories.

Increase in the number of cases of microcephaly and other congenital anomalies

In October 2015, Brazil reported the detection of an unusual increase of newborns with microcephaly in the state of Pernambuco, in the Northeast region of the country. As of the first epidemiological week of 2016, 3,530 suspected cases of microcephaly were recorded, including 46 deaths in 20 states and the Federal District.

In January 2016, eye (macular) lesions were detected in three newborns with microcephaly and brain calcifications, presumably due to intrauterine infection by Zika virus.

Evidence of vertical transmission of Zika virus

In January 2016, the Brazilian Ministry of Health reported the detection of the Zika virus genome by the RT-PCR technique in four cases of congenital malformation in the state of Rio Grande do Norte. The cases correspond to two miscarriages and two full-term newborns (37 and 42 weeks of gestation, respectively) that died within the first 24 hours of life. Immunohistochemistry tests of the tissue specimens from both newborns were also positive for Zika virus.

This evidence complements the finding reported in the epidemiologic alert issued on December 1, 2015, concerning the detection of the Zika virus genome. Using the RT-PCR technique, the genome was detected in the amniotic fluid of two pregnant women in Paraiba, whose fetuses presented microcephaly, as indicated by ultrasonography.

In January, the ICC/Fiocruz laboratory in Parana confirmed the presence of the virus in the placenta of a pregnant woman of the Northeastern region of Brazil, who had a missed abortion in the first trimester of pregnancy.

PROPOSED OBJECTIVES FOR THE SURVEILLANCE OF MICROCEPHALY

1.1 GENERAL OBJECTIVE

Detect and monitor the prevalence of Zika virus-related microcephaly

1.2 SPECIFIC OBJECTIVES

- Detect an unusual increase in microcephaly and other Zika virus-related congenital anomalies
- Monitor the trend in microcephaly over time
- Disseminate the results in a timely manner
- Provide the basis for undertaking analytical epidemiological studies (case-control and cohorts) that may help to identify and quantify the associated risk factors
- Provide timely information to specialized health care services
- Produce information that may help to characterize the cases

GENERAL RECOMMENDATIONS ON SURVEILLANCE

In terms of the development of information subsystems, depending on the context, the country should:

1. Define the general objective and specific objectives for the surveillance of microcephaly in settings with risk of Zika virus circulation (the objectives set forth in these guidelines may be used as a model).

2. Design an *ad hoc* subsystem specifically for surveillance to identify newborns with microcephaly in settings with risk of Zika virus circulation. Such surveillance necessarily requires the inclusion of variables related to this infection.
    a. Define in advance the data collection tools, notification procedures and channels, routines for database consolidation, data analysis plan[2], and subsequent dissemination (platform, structure, contents, periodicity); and establish information delivery formats for risk communication that are clear and consistent over time.
    b. Plan data quality control mechanisms (incomplete, missing, incorrect, or duplicated data). Generate automated or manual data review protocols, with daily monitoring.

[2] Clearly differentiate the clinical-epidemiological variables from the administrative variables to avoid inappropriate use (e.g., using the "notification date" variable to analyze cases over time, when "date of birth" should be used instead).

c. Define the factors that make it possible to identify cases, while assuring confidentiality.

d. Adapt definitions to the country's situation in terms of availability of systems for the surveillance of congenital defects, other surveillance systems, etc.

3. Integrate the subsystem into the country's existing surveillance platforms.

4. Ensure that the information produced through the microcephaly surveillance system is shared with other related subsystems (congenital malformations, vector-borne diseases, or others).

Case definition of microcephaly

Microcephaly, included in the group of **congenital malformations and defects, and chromosome aberrations** in the 10th Revision of the International Classification of Diseases (ICD-10, code Q02), is a condition in which the occipitofrontal (head) circumference is excessively small for age and sex.

In the definition included in the publication "Surveillance of congenital anomalies: Manual for Program Managers"[3], microcephaly is defined as a condition in which the head circumference is at least two standard deviations below the mean for sex and age. In some cases, it is associated with changes in brain structure and impairment of neurologic development. The presence of a head circumference at least two standard deviations below the mean for sex and age with no signs of structural abnormalities of the brain is not considered a major abnormality. The reference values for head circumference vary essentially depending on gestational age at birth and sex.

In the epidemiologic alert issued on December 1, 2015, PAHO/WHO recommended using two standard deviations as an interim definition of the cut-off criterion for inclusion. Accordingly, for the definition of congenital microcephaly, it is recommended to adopt the criterion of a value below the third percentile on the specific reference curves, depending on gestational age and sex. It is also recommended to record the absolute value of the infant's head circumference in centimeters to one decimal point, together with the value of the corresponding percentile. For easy reference, the chart below shows the absolute values corresponding to the -2 SD and third percentile cut-off points, by sex.

[3] http://www.who.int/nutrition/publications/birthdefects_manual/en/

Table 1: Absolute values for the definition of microcephaly

Cut-off	Girls	Boys
-2 SD	31.5 cm	31.9 cm
3rd percentile	31.6 cm	32.0 cm

As observed in the above table, in full-term newborns the difference between -2 standard deviations and the third percentile is minimal; however, percentiles tend to be more easily understood and are more commonly used by health care teams in the Region.

Hence, the definition proposed for microcephaly is "head circumference, measured in centimeters, below the third percentile on the reference curves, as measured at birth and confirmed 24 hours after birth."

When measuring head circumference, avoid rounding to centimeters; **always record to one decimal point.**

Note that the definitions given in this document are for the purposes of public health surveillance and do not imply any changes in medical practice.

As stated above, **values need to be standardized for gestational age.** For full-term newborns, it is suggested to use the WHO growth curves, by sex. Specific references should be used for pre-term newborns (Fenton, intergrowth study, etc.) by gestational age and sex.

Live newborn (or stillbirth) with microcephaly: Newborn whose head circumference at birth (confirmed 24 hours after birth) is below the third percentile for gestational age and sex

Live newborn with microcephaly associated with Zika virus infection during pregnancy. Definitions of suspected, confirmed, and discarded cases for surveillance purposes.[4] [5]

[4] These definitions refer exclusively to epidemiologic surveillance of Zika virus-associated microcephaly. The clinical approach to newborns with microcephaly is not within the scope of this document.

[5] Adapted from the Brazilian protocol for the surveillance of microcephaly

- **“Suspected case” for surveillance purposes**
  - Live newborn with a gestational age of less than 37 weeks, presenting with a head circumference below the third percentile on Fenton curves, by gestational age and sex.
  - Live newborn with a gestational age of 37 weeks or more, presenting with a head circumference below the third percentile, based on WHO tables by sex.

- **“Confirmed case” for surveillance purposes**
  - Live newborn of any gestational age, classified as a suspected case of Zika virus-associated microcephaly, with identification of Zika virus in either the live newborn’s or mother’s specimens (during pregnancy)

    or:
  - Live newborn of any gestational age, classified as a suspected case of microcephaly potentially associated with Zika virus infection, with intracranial morphological changes diagnosed by any imaging method, having ruled out other known potential causes.

“Discarded case” for surveillance purposes

- Recorded case of live newborn of any gestational age, classified as a suspected case of microcephaly possibly associated with Zika virus infection, with confirmation of specific cause, infectious or not, not including infection by Zika virus in the newborn and mother.

SURVEILLANCE PROCESS

Table 1 summarizes the two options proposed for the notification of microcephaly events, based on the characteristics and/or level of development of the surveillance system in each country.

Option **A** is based on notification by the maternity department or health care facility where the birth occurs to the appropriate surveillance department regarding any event that meets the ***confirmed case*** definition of microcephaly for surveillance purposes.

Option **B** is based on notification by the maternity department or health care facility where the birth occurs to the appropriate surveillance department regarding any event that meets the ***suspected case*** definition of microcephaly for surveillance purposes.

In option **A**, the surveillance system checks whether the reported case data meet the criteria (completeness, consistency, etc.) to be included in the database, and then enter it into the system.

In option **B,** the surveillance system enters the event provisionally, as a suspected case, and triggers a follow-up search for diagnostic tests in order to either include or exclude it as a case related to Zika virus. This process must be done by specialized units, involving clinical assessment (neurological development, genetics, etc.) and complementary diagnostic methods.

Table 1

Option	Description	Procedure	Advantages	Disadvantages
A	Notification of CONFIRMED CASES for surveillance purposes	The surveillance system evaluates whether the reported case data meet the criteria required to be included in the database and then enters it into the system.	- More specific - Increases the responsibility of health care services - Allows more efficient data analysis	- Less sensitive - Less timely - Limited control of the surveillance system
B	Notification of SUSPECTED CASES for surveillance purposes	The surveillance system enters the event provisionally, as a suspected case, and triggers a follow-up search for diagnostic tests in order to either include or exclude it as a case of microcephaly related to Zika virus.	- More sensitive - Allows greater control of the surveillance system	- Less specific - Requires greater effort from the surveillance system

These proposals for the surveillance of Zika virus-associated microcephaly must be adapted to the situation and settings in each country and/or geographical area. It is recommended that after the implementation of the surveillance system, its performance be evaluated periodically to allow for any corrections and improvements required.

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ANNEXES

Annex 1- Technique for measuring head circumference

Measurement should be made of the occipitofrontal circumference at birth. If it meets case definition, the measurement should be confirmed 24 hours after birth to avoid modelling effects.

The patient's head must be free from any objects, and preferably should not be in contact with the crib (the newborn may be held upright by an observer, not the person making the measurement). Ideally, a 1.0-cm-wide Teflon tape should be placed on the largest perimeter of the infant's head, using the point of the occiput (back of the head) and the glabella (between the eyebrows). The tape must be horizontal, so that it is at the same height on both sides of the head. The zero on the tape must meet the front of the head (between the two eyebrows) and the reading must be made there. When measuring, the tape must be pressed slightly so as to flatten the hair and skin a little. The measurement should be rounded to the nearest 0.1 cm and compared with the reference tables mentioned above.

Annex 2 - Proposed microcephaly surveillance form

Below is a list of the key data that should be included in the surveillance system:

<u>Identification of the newborn</u>

Given name: First family name: Second family name:

ID number (document, medical record #, etc.)

Sex: (male, female, undetermined, no data)

Date of birth: (day/month/year)

Type of pregnancy: (single, multiple, no data)

Gestational age at birth: (in full weeks)

Weight at birth: (in grams)

Length at birth: (in centimeters)

Head circumference at birth (in centimeters, to one decimal point)

Head circumference at birth < third percentile (YES/NO)

Head circumference 24 hours after birth: (in centimeters, to one decimal point)

Head circumference 24 hours after birth < third percentile (YES/NO)

Reference used: (WHO, Fenton, INTERGROWTH, other (specify))

Date of diagnosis of Zika-related microcephaly: day/month/year

Result of neuroimaging study (brain echography; MRI; CT): (with/without findings)

Observations:

Does the newborn present any other congenital abnormality (YES/NO)?
If so, use a free-text field to describe all the congenital anomalies observed in the newborn.

Describe all features, signs, or symptoms that may help to better characterize cases.

State whether any tissue specimens or blood samples were taken to identify the presence of Zika:

Blood: YES/NO. If so, state the result.

Tissue: YES/NO. If so, state the result.

In the case of a stillbirth or live newborn that dies within the first hours after birth:

Was an autopsy performed? YES/NO

If so, describe the report:

<u>Identification of the infant's mother</u>

Given name: First family name: Second family name:

Clinical record #:

Type of document:

Document number:

Mother's date of birth: day/month/year

Home state/province/district:

Home city/municipality:

Neighborhood:

Zip code:

Address (Street, Avenue, Road):

Number:

Contact information

Mother's telephone # (land line or mobile):

(Two other close contacts)

1.-

2.-

Mother's clinical history

Pregnancy and delivery

The mother presented with rash during pregnancy: YES/NO. Indicate first period of occurrence:

Perform laboratory testing for, at least one of the following in pregnancy or postpartum: syphilis, toxoplasmosis, rubella, cytomegalovirus, herpes virus. Note: If performed, include results in General Comments.

During pregnancy, the mother was diagnosed with:

Dengue:	Clinical	Laboratory
Chikungunya:	Clinical	Laboratory
Zika:	Clinical	Laboratory

Site of the event

Health facility information:

Name of health facility:

State/Province/Department:

City/District:

Address of health facility (street, avenue and number):

Health facility contact telephone (landline or mobile):

General Comments

Comments

INSTRUCTIONS: Report the results of the laboratory tests performed for syphilis, toxoplasmosis, other infectious diseases, rubella, cytomegalovirus, or herpes virus. State whether any tests were performed for dengue, chikungunya or Zika virus; whether the physician has a clinical suspicion of Zika virus or other infections during pregnancy; whether any medicines were taken during pregnancy (if so, which ones?); whether the mother is a drug user (if so, which drugs? how frequently?); conclusions/summary of the imaging studies (echo, ultrasound, MRI, tomography) and report whether any calcifications were observed in the images, or any other relevant data.

Total characters remaining:

Notifier

Record your data so the surveillance team may contact you:

First name and family name of notifier:

Notifier's e-mail:

Notifier's contact telephone (landline or mobile):

Newborn referral

Department the newborn is referred to for follow-up:

Contact information:

Annex 3 - Growth curves for newborns (full term and preterm)

3.1.- Fenton curves

- Boys
- Girls

3.2.- WHO curves

- Boys
- Girls