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ORIGINAL ARTICLE

Pregnancy surveillance and Zika disease: a surveillance methodology proposal for a Zika vaccine efficacy trial

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ABSTRACT

Introduction: Surveillance for suspected or confirmed cases of specific diseases allows for the capturing and classification of such cases for the assessment of efficacy in vaccine clinical trials. In the case of Zika Virus Disease surveillance there are major limitations, mainly due to the poorly characterized disease epidemiology and burden of the disease. In this paper we propose a surveillance method for the detection and follow-up of ZIKV infection in pregnant women and their infants up to 1 year of age to be used in the context of a phase III vaccine efficacy study. **Methods:** A systematic review of the current validated national guidelines for Zika surveillance in pregnant women and newborns in three countries of Latin America (Brazil, Mexico and Colombia) and the USA was performed, including comparison. The guidelines of these four specific countries were taken into account because these were targeted for the efficacy trial. The analysis included a comparison between the documents and with those from other international and regional organizations

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Conflict of interests: Diana Coronel MSc, Ana Paula Perroud MSc, Enrique Rivas MD, Joyce Ojeda MD, Margarita Cortés MSc, Betzana Zambrano MD, German Anez MD, Luis Gabriel Bernal MD and Fernando Noriega MD work for Sanofi Pasteur.
Stephen Kennedy MD, Álvaro Izquierdo-Bello MD, Marco Aurelio Sáfadi MD, Ricardo Figueroa MD, Pedro Pires MD and Miguel Antonio Parra-Saavedra MD have no conflict of interests.
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Vigilancia del embarazo y enfermedad Zika: una propuesta metodológica de vigilancia para una prueba de eficacia de la vacuna Zika

RESUMEN

Introducción: *La vigilancia de casos sospechosos o confirmados de enfermedades específicas, permite la captura y clasificación de tales casos para la evaluación de la eficacia en ensayos clínicos de vacunas. En el caso de la vigilancia de la enfermedad por el virus del Zika, existen limitaciones importantes, principalmente debido a la epidemiología de la enfermedad poco caracterizada y la carga de la enfermedad. En este documento, proponemos un método de vigilancia para la detección y el seguimiento de la infección por ZIKV en mujeres embarazadas y sus bebés de hasta un año de edad para usar en el contexto de un estudio de eficacia de la vacuna de fase III.* ***Métodos:*** *Se realizó una revisión sistemática de las guías nacionales validadas actuales para la vigilancia del Zika en mujeres embarazadas y recién nacidos en tres países de América Latina (Brasil, México y Colombia) y los Estados Unidos, incluida la comparación. Las guías de estos cuatro países específicos se tuvieron en cuenta porque fueron el objetivo del ensayo de prueba. El análisis incluyó una comparación entre los documentos y los de otras organizaciones internacionales y regionales (es decir, OMS-Organización Mundial de la Salud, CDC-Centros para el Control y la Prevención de Enfermedades). Se redactó un documento de metodología de vigilancia de consenso y se compartió con expertos clínicos sobre el tema en los países seleccionados. Los antecedentes de estos expertos incluyen neuropediatría, enfermedades infecciosas pediátricas, obstetricia/ginecología y perinatología.* ***Resultados:*** *El grupo elaboró una propuesta de un método de vigilancia regional para la enfermedad del virus del Zika para mujeres embara-*

(i.e. WHO-World Health Organization, CDC-Centers for Disease Control and Prevention). A consensus Surveillance Methodology document was drafted and shared with clinical experts on the topic in the selected countries; the background of these experts included neuropediatrics, pediatric infectious diseases, obstetrics/gynecology and perinatology. **Results:** The group produced a proposal for a regional surveillance method for Zika virus disease for pregnant women and newborns that could be integrated into the assessment of cases for a vaccine efficacy phase III trial in Latin America, while being compliant with national and regional public health authorities' guidelines. This document proposes parameters for the identification of probable Zika infection in pregnant women, ascertaining a probable Zika infection in the fetus and defines early findings of Congenital Zika Syndrome (CZS); for the follow-up of infants during the first year of life. **Conclusions:** Vaccine efficacy trials should have strong disease/infection surveillance methodologies in place that enables the demonstration of the efficacy or futility of the intervention. In the case of a Zika vaccine candidate efficacy phase III trial, it is important to have a clear suspected clinical case definition for the identification of the cases under surveillance, laboratory tests that allows for their confirmation, as well as specific surveillance methods for subgroups of interest such as pregnant women and their children. All these actions will increase the likelihood for assessing the efficacy of a Zika vaccine candidate to prevent infection and disease.

Keywords: After a review of different national surveillance policies and experts consultations, we propose parameters for the surveillance and identification of probable Zika infection in pregnant women, ascertaining a probable Zika infection in the fetus and for the follow-up of infants during the first year of life.

Keywords: Zika surveillance, case definition, suspected case, confirmed case, pregnancy infection.

zadas y recién nacidos que podría integrarse en la evaluación de casos para un ensayo de fase III de eficacia de la vacuna en América Latina, a la vez que cumple con las autoridades de salud pública nacionales y regionales. Este documento propone parámetros para la identificación de la infección probable por Zika en mujeres embarazadas, y la infección probable por Zika en el feto, define los hallazgos tempranos del síndrome de Zika congénito (CZS), para el seguimiento de lactantes durante el primer año de vida. ***Conclusiones:*** *Los ensayos de eficacia de la vacuna deben contar con metodologías sólidas de vigilancia de enfermedades/infecciones que permitan la demostración de la eficacia o la inutilidad de la intervención. En el caso de una fase III de eficacia candidata a la vacuna contra el Zika, es importante tener una definición clara de caso clínico para la identificación de los casos bajo vigilancia, pruebas de laboratorio que permitan su confirmación, así como métodos de vigilancia específicos para subgrupos de interés tales como las mujeres embarazadas y sus hijos. Todas estas acciones aumentarán la probabilidad de evaluar la eficacia de una vacuna candidata contra el Zika para prevenir infecciones y enfermedades.*

Puntos clave: *Tras una revisión de las diferentes políticas nacionales de vigilancia y consultas con expertos, proponemos parámetros para la vigilancia e identificación de la probable infección por Zika en mujeres embarazadas, la determinación de una probable infección por Zika en el feto y el seguimiento de los lactantes durante el primer año de vida.*

Palabras clave: *Vigilancia de Zika, definición del caso, caso sospechoso, caso confirmado, infección del embarazo.*

INTRODUCTION

Surveillance of suspected or confirmed cases of specific diseases can be defined as the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health.[1] Such activities are crucial in the design of any vaccine efficacy trial for detecting the cases needed to demonstrate the efficacy of a vaccine.[1] Surveillance in this context includes clinical, laboratory and follow-up methods.[2]

Therefore, in order to evaluate the protective efficacy of a candidate vaccine (or its futility) realistically, the clinical investigators must have a surveillance strategy based on a battery of diagnostic techniques and procedures that are readily available as part of the local standard of care or provided during the study. The decisions made at this stage will impact the overall content of the pre-licensure clinical program.[3] For the purposes of this paper, the considered candidate is a Zika virus (ZIKV) inactivated vaccine. The published WHO/UNICEF (World Health Organization/United Nations International Children's Emergency Fund) Zika Virus Vaccine Target Product Profile (TPP) published for the first time on July 2016, and updated in November 2016,[4] prioritizes prophylactic vaccination as a strategy to prevent prenatal ZIKV infection (ZVI) resulting in microcephaly, other nervous system malformations and pregnancy-related complications, in alignment with the WHO Zika Strategic Response Plan. In accordance with this plan, the main gaps in the research included characterizing ZIKV infection (investigating public health and clinical implications); developing reliable diagnostic tests with good sensitivity and specificity performance; developing a vaccine, with a focus on protecting pregnant women and their fetus; and holding cohort studies of pregnant women to understand better the outcomes

of ZIKV infection on pregnancy as well as long-term developmental outcomes.[5]

Therefore, the design of an efficacy ZIKV vaccine candidate trial which includes women of reproductive age should include a surveillance method for the detection of the ZIKV infection in the subjects as well as a specific surveillance method for pregnant women to evaluate the vaccine's efficacy for protecting the mother and the child against ZVI, Zika Virus Disease (ZVD) and the related birth defects. It is known that due to the temporal nature of biologic analytes in the infected person, multiple assay and sample types are often needed to establish a definitive laboratory diagnosis of ZIKV.[6,7] The high level of antibody cross-reactivity among flaviviruses and their co-circulation has complicated serological approaches to differentially detect ZIKV. To resolve this situation, serologic assays with a high degree of specificity are needed.

In addition, a vaccine efficacy trial will need to distinguish immune response elicited by vaccination from those obtained after natural infection (with or without clinical symptoms) in an endemic setting. This latter distinction would have to be customized according to the characteristics of the vaccine being used. In this case, the envisioned study would use a Purified Inactivated Zika Vaccine that during the process of purification loses the soluble ZIKV non-structural protein 1 (NS1). Therefore, assays detecting a specific response to ZIKV NS1 could be used as indicators of natural infection. Specific human monoclonal antibody assays to detect ZIKV NS1 are being developed by different groups. The sensitivity and specificity of at least one of these tests in the context of a serological surveillance trial has been confirmed with RT-PCR.[8]

In this study we present a surveillance method for the detection and follow-up of ZIKV infection in pregnant women and their babies, in the context of a phase III vaccine efficacy study. The aims of this surveillance methodology are to establish parameters for the identification of ZIKV infection in pregnant women; the parameters to ascertain probable Congenital Zika Syndrome (CZS) in the fetus; the parameters to ascertain ZIKV infection and CZS in newborns arising from infected pregnancies; and the parameters to ascertain the evolution of CZS in infants during the first year of life.

METHODS

A systematic review of the current validated national guidelines for ZIKV surveillance in four countries of Latin America (Colombia, Brazil, Mexico and Puerto Rico) and the CDC guidelines was performed. The countries selected to be included in a Phase III, vaccine efficacy trial were chosen based on the disease burden in the region at the time of study design. These guidelines and regulatory documents were obtained from the official web sites of the respective four Ministries of Health and the US CDC.[9-17] These documents were then compared with other international and regional guidelines in order to build a unique, consensus document with robust and realistic algorithms for the accurate detection of ZVI. The Surveillance Methodology document was drafted and shared with clinical experts on the topic in the selected countries from the following specialties: pediatric neurology, pediatric infectious diseases, gynecology/obstetrics and perinatology. The parameters taken in account for the selection of the final algorithms were: serological and virological confirmatory assays, radiological tests and other biological and developmental tests, and biological samples availability, as well as possible clinical sites infrastructure and medical services net including quality certifications in selected countries such as Colombia, Mexico and Brazil.

RESULTS

The main outcome of this exercise was a ZIKV Disease and Infection in Pregnant Women and Infants Surveillance Protocol for phase III vaccine efficacy trial with a target population including women of reproductive age, living in high risk areas for ZIKV infection. The protocol is focused on women that could conceive during the trial with follow-up of the resulting children up to 1 year of age.

Case definitions

Clinical case definitions were developed for ZIKV disease and ZIKV infection for the general population including pregnant women *(Table I)*.

ZIKV disease in pregnant women

All women of reproductive age who might conceive during the trial and acquire ZIKV infection and disease are potential study participants. When the staff at the study sites are notified of a pregnancy, they will ask the women for a blood sample to detect anti-ZIKV-NS1 serology.

Table I: Case definition of ZVD for general population and pregnant women.

General population	Pregnant women
• Appearance of any of the following clinical signs/symptoms: Rash (pruritic or not) • Axillary temperature ≥ 37.5 °C, • Conjunctivitis (nonpurulent/hyperemic) • Arthralgia/arthritis/myalgia/peri-articular edema, or sign(s)/symptom(s) of: • A neurologic/neuroinflammatory disorder such as: – Acute disseminated encephalomyelitis, [including site specific variants], – Cranial nerve disorders [including paralyses/paresis], – GBS-including MFS and other variants, – Immune-mediated peripheral neuropathies or plexopathies, – Optic neuritis, – Multiple sclerosis, – Narcolepsy, – Transverse myelitis, – Meningitis, or meningoencephalitis not explained by other medical conditions And • Rt-PCR positive to Zika on blood or urine Or • NS1 Ab (blocking ELISA) seroconversion at predetermined time-points	General population case definition, Or NS1 Ab (blocking ELISA) seroconversion at any time during pregnancy

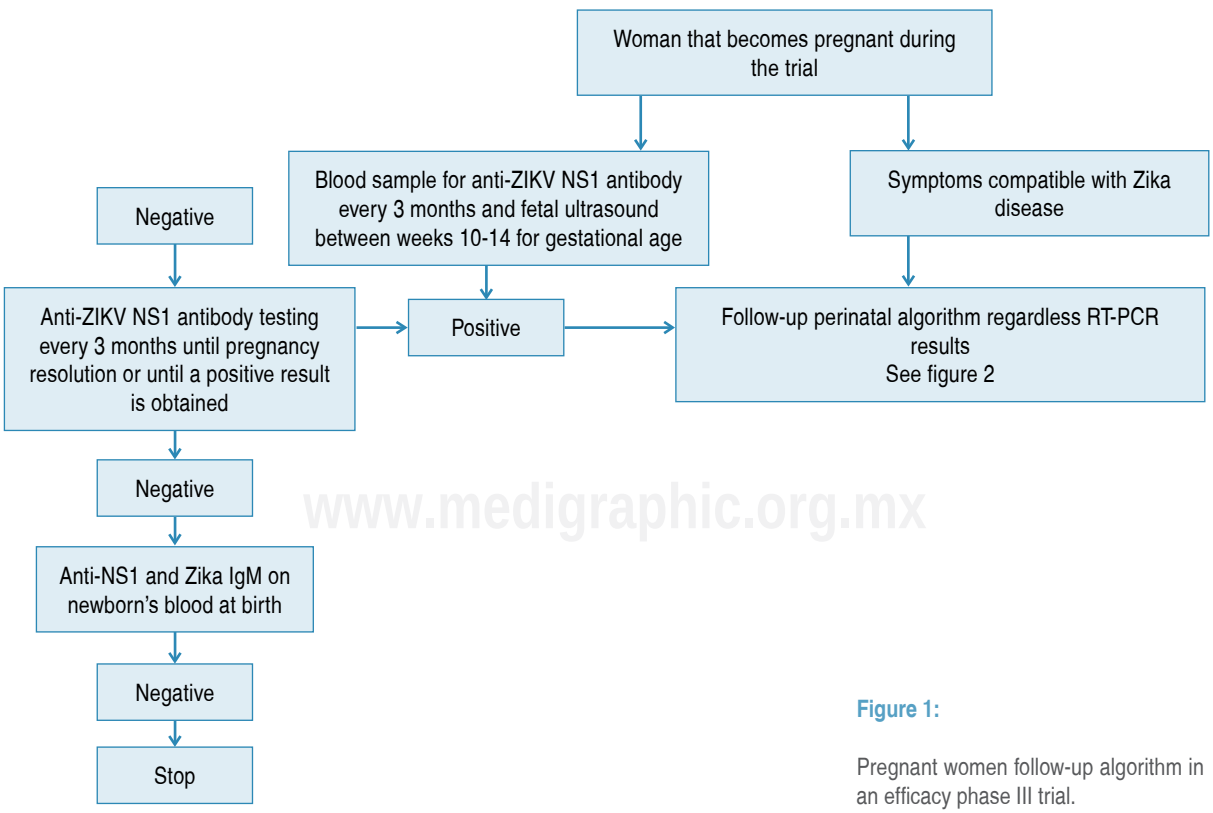


Figure 1:

Pregnant women follow-up algorithm in an efficacy phase III trial.

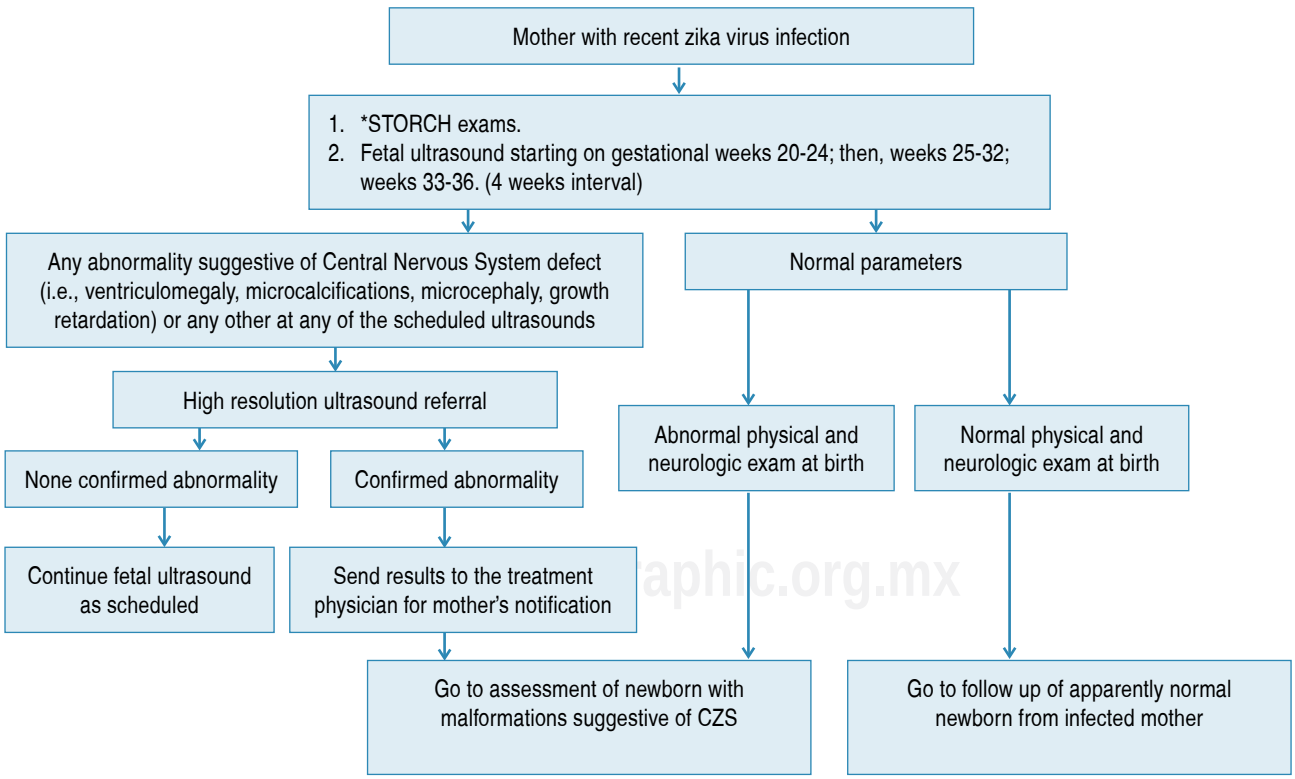
If the Anti-ZIKV NS1 test is negative, then it should be repeated every 3 months until the end of the pregnancy or a positive result is obtained. In addition symptomatic case ascertainment will continue during the pregnancy as for the general study population. If Anti ZIKV-NS1 remains negative until the end of pregnancy and there is a lack of suggestive signs in the newborn anti-NS1 and Zika IgM should be performed on the newborn's blood at birth and follow-up should stop if it is negative.

If anti ZIKV-NS1 is positive at any time during pregnancy, RT-PCR in whole blood and urine should be performed and the fetal follow up must be initiated (regardless of RT-PCR results).

As a point of reference, all pregnant women will have a fetal ultrasound scan at 10-14 weeks to determine gestational age accurately *(Figure 1)*.

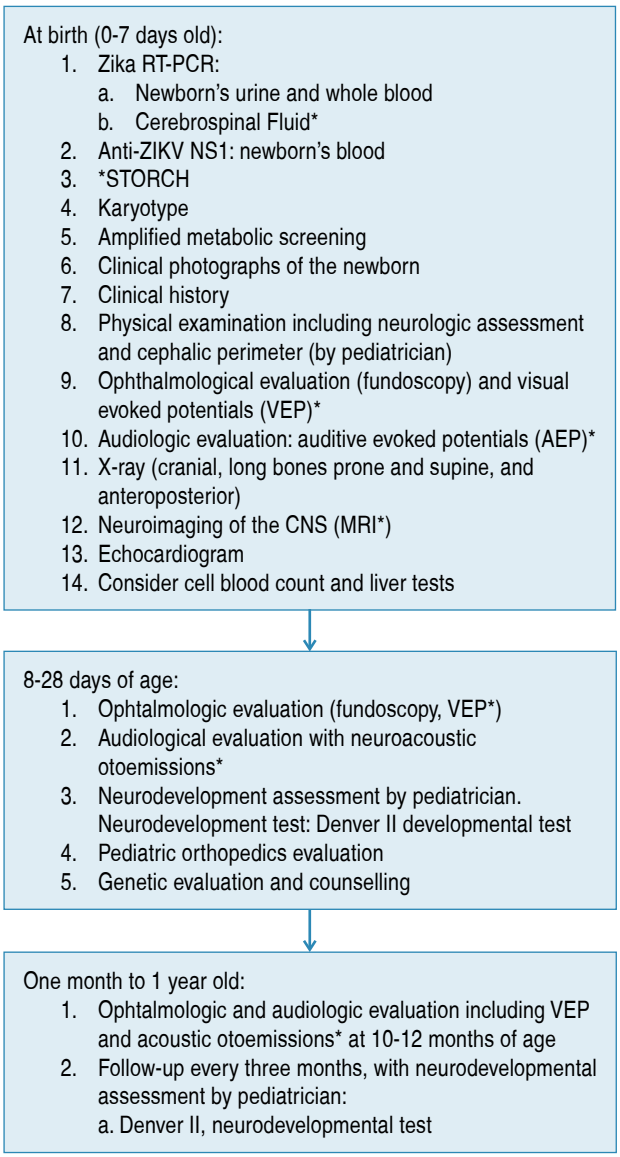
Perinatal follow-up from an infected woman

If ZIKV infection is confirmed during pregnancy, a 2D fetal ultrasound scan should be performed by certified/trained personnel every 4 weeks thereafter, i.e. at 15-19, 20-24, 25-32; and 33-36 weeks' gestation to identify: a) growth restriction using the international INTERGROWHT-21st Fetal Growth Standards[18] and/or b) Central Nervous System (CNS) abnormalities (ventriculomegaly, micro-calcifications, microcephaly). If any of these abnormalities are detected, the pregnant woman should be referred for High Resolution Ultrasound (HRUS) by trained and certified personnel, identified before the trial starts. If the abnormality is confirmed, the results will be given to the obstetrician responsible for the woman's care so as to notify the woman. As HRUS may not necessarily be available at every study site, it will be important to provide the investigators and affected subjects with access to defined centers of reference for the trial. 2D and HRUS scans should be performed in accordance with the trial's standard operative procedure. For quality control purpose, the HRUS results should be reviewed by ultrasound experts on an Independent Data Monitoring Committee *(Figure 2)*.



*STORCH = Syphilis, toxoplasmosis, rubella, cytomegalovirus, herpes simplex.

Figure 2: Perinatal follow-up from a pregnancy with ZIKA infection.



*STORCH = Syphilis, toxoplasmosis, rubella, cytomegalovirus, herpes simplex.

Figure 3: Follow-up recommended tests for the newborn and infant with Congenital Zika Syndrome.

Newborn and infant follow-up

The newborns of infected women will be classified as those with and without CZS.

In the case of a newborn with CZS, we recommend perform a series of tests at the following time points:

- Around the time of birth (day 0-7).
- Between days 8 to 28 days of age.
- Between 1 month and 1 year of age.

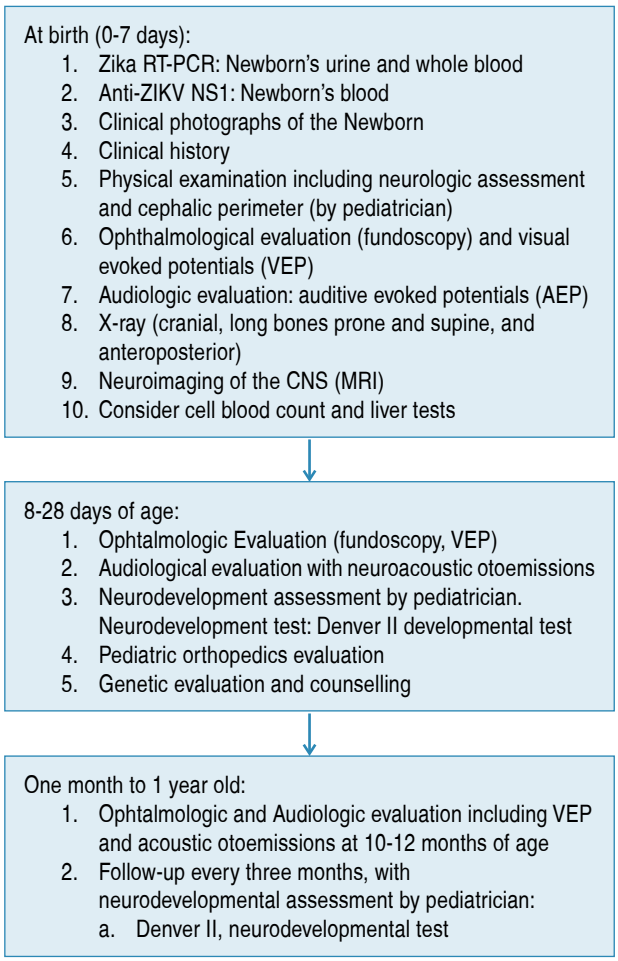


Figure 4: Follow-up tests for an apparently normal newborn and infant from and infected mother.

The tests recommended aim to ascertain the presence and evaluate the extent of ophthalmological lesions, such as hypoplasia of the optic nerve, macular abnormalities, lacunar maculopathy, choriorretinal scarring and congenital glaucoma;[19] neurological defects, such as microcephaly, lissencephaly, hydrocephalus, polymicrogyria, agyria, ventriculomegaly, holoprosencephaly and brain calcifications; hearing loss; and skeletal disorders, such as arthrogriposis and hip dislocation.[20] For the evaluation of the neurodevelopmental milestones, the DENVER II test will be used. The principal value of this test is to provide an organized clinical impression of a child's overall development and to alert the user to potential developmental difficulties; it is also a standardized test available worldwide that is commonly used in Latin America[21] *(Figure 3)*.

In the case of an apparently normal newborn from an infected mother, the same tests already recommended for newborns with CZS are indicated with the following exceptions around the time of birth (0-7 days of age): cerebrospinal fluid RT-PCR, echocardiogram, karyotype and amplified metabolic screening are not recommended *(Figure 4)*.

DISCUSSION AND CONCLUSIONS

The surveillance protocol presented in this paper resulted from a thorough review of the national policies in the selected countries, the international published guidelines and the scientific literature.[22,23] Once this review was performed the information was shared with clinical experts from Brazil, Colombia and Mexico with the objective of creating a surveillance proposal that could be easily adapted under the scope of a Zika vaccine efficacy trial in Latin America. An efficacy trial needs to have strong disease/infection surveillance methodologies in place that enables the demonstration of the efficacy or futility of the intervention. In the case of a Zika vaccine efficacy phase III trial it is important to have a clear suspected clinical case definition and laboratory tests readily available that allow case ascertainment on pregnant women and the resulting babies. This surveillance strategy should help to determine not only the occurrence of asymptomatic or sub-clinical infections, clinical cases and their severity but also the sequelae or delayed findings/manifestations that are known to occur in CZS. Feasibility then must include the continuous assessment of the virus' epidemiology, evaluation of health authorities' support for studying ZIKV in their territories, evaluation of the health infrastructure of potential clinical sites, national standards of care, feasibility for taking specific biological samples, their processing (including export to a central laboratory, if/as needed), and the availability of radiological and any other required procedures. After all of these operational aspects are evaluated, it is desirable to have a standardized protocol that can be adopted with the same rigor at every study site of a multinational clinical trial, as it will facilitate the pooling of results from different countries in the overall analysis of efficacy.

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