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Protocol

Health Outcomes of Children Born/Suspected with Zikv: Protocol for the Zikaction Paediatric Registry in Latin America and the Caribbean

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ABSTRACT

Background: Although the number of Zika Virus (ZIKV) cases has substantially declined in Latin America and the Caribbean since the 2015-2016 outbreaks, the cohort of children born at that time and affected by Congenital Zika Syndrome (CZS) are now around 4-5 years old and experiencing an ongoing impact on their health and development. Gaps in our understanding remain regarding the outcomes of ZIKV exposure in utero and congenital infection and the consequences of congenital Zika Syndrome (CZS) for health throughout childhood.

Methods: The ZIKAction Paediatric Registry is an international multi-centre registry of infants and children with documented ZIKV exposure in utero (i.e. born to mother with confirmed infection in pregnancy) and/or with confirmed or suspected congenital ZIKV infection. Clinical teams at participating sites in Argentina, Brazil and Jamaica conduct retrospective case note reviews of children eligible for inclusion in the Registry and enter pseudonymised data into a central Registry database, with additional data collected prospectively on routine follow-up at some sites. Data collected will include sociodemographic, maternal and pregnancy information, delivery information and newborn assessment, paediatric clinical assessments (physical, neurological, developmental, ophthalmological, audiological), and laboratory results conducted as part of local standard of care. The ZIKAction Paediatric Registry network will conduct pooled analyses to address questions relating to characteristics, health and neurodevelopmental outcomes of this population. The Registry is embedded within a larger programme of research studies conducted by ZIKAction.

Discussion: As the health outcomes of children affected by ZIKV continue to unfold, this paediatric registry will provide comprehensive data on their clinical and neurodevelopmental outcomes, growth and management, as well as on later sequelae. This will inform their support and care and provide potential insights on pathogenesis of the disease, of importance to currently affected families and for the response to possible future outbreaks. It will highlight the service needs of the affected populations in Latin America and the Caribbean and allow the identification of potential participants for future studies.

Keywords: Zika virus; Congenital zika syndrome; Children; Disabilities; Comorbidities

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INTRODUCTION

The Zika Virus (ZIKV) is a vector-borne infection transmitted to humans by Aedes mosquitoes, included in the same Flavivirus family as the Dengue virus. Although initially identified nearly 70 years ago in Uganda, ZIKV re-emerged and gained global attention from 2015 with large-scale epidemics starting in Latin America and the Caribbean (LAC) [1,2], with the Zika epidemic declared a Public Health Emergency of International Concern in 2016 [3]. This new scenario was due to the newly discovered route of transmission from mother-to-child leading to a congenital infection, following an unexpected increase in cases of congenital microcephaly and fetal brain malformations emerging in Brazil in September 2015 [4,5]. There had been no prior indication of adverse outcomes associated with ZIKV infection in pregnancy, although a subsequent retrospective study identified microcephaly cases associated with the earlier ZIKV outbreak in French Polynesia [6]. By April 2016, experts from the US Centers for Disease Control and Prevention concluded that there was sufficient evidence [7], assessed using Shepherd's Criteria for human teratogenicity and the Bradford-Hill Criteria for evidence of causation, that the association between ZIKV infection in pregnancy and microcephaly and other brain abnormalities was causal [8]. Such defects are well known with other congenital infections, such as cytomegalovirus, Toxoplasma gondii and rubella.

Cohort studies, where at risk pregnancies are identified prospectively, are the most methodologically sound approach to investigating the rates, timing and risk factors for vertical transmission of an infection. Then, to obtain a true picture of the full spectrum of congenital infection, all infants with congenital infection should be followed prospectively and not only those neonates presenting with symptomatic infection, given that congenital infections may be subclinical or asymptomatic in the newborn and that there may be delayed manifestation of infection related damage. Vertical transmission of ZIKV is difficult to study for reasons including the high proportion of asymptomatic maternal infections, challenges in diagnosis of ZIKV in populations with past or concurrent exposure to Dengue virus [9] and declining incidence [10,11]. Reported vertical transmission rates range from 9% to 35% in studies with PCR-confirmed ZIKV infection [12-17], whilst a recent evidence synthesis estimated the mean risk of vertical transmission to be 47% in the first trimester, decreasing to 25% in the third [18]. Major cohort studies estimate the risk of congenital abnormalities in ZIKV infection of 4–10% [12,13, 19-22].

Congenital Zika Syndrome (CZS) has been outlined as a pattern of structural anomalies and functional disabilities secondary to central and peripheral nervous system damage [23]. However, the lack of a standard definition has led to inconsistencies in the use of this term. While some authors define severe microcephaly as the most prominent feature of this syndrome, other studies have demonstrated that its absence at birth does not exclude congenital ZIKV infection or the presence of Zika related brain and other abnormalities, which can sometimes manifest as postnatal microcephaly [24-28]. Besides, evidence to define the CZS phenotype is still accumulating, and the full spectrum of clinical manifestations of congenital ZIKV infection is not yet delineated, with the oldest children affected by the recent outbreaks now five years old.

The current literature has reported a range of clinical and neurodevelopmental manifestations in children with congenital ZIKV infection including abnormalities in muscle tone and severe motor impairment, neurological abnormalities, profound developmental delays, ocular manifestations, epilepsy, arthrogryposis, hearing abnormalities, feeding challenges, and sleeping difficulties [11,22,29-34]. In addition, there is some evidence of the presence of comorbidities such as pneumonia and urinary tract infections [35]. Although the severe phenotype of CZS is now well established, the health outcomes of infants born with congenital ZIKV infection continues to unfold, with the spectrum of disease expanding as the children grow up and later presenting manifestations identified [11].

This paper reports the establishment and protocol of the ZIKAction Paediatric Registry. ZIKAction is a project funded by the European Commission's Horizon 2020 Framework Programme, with an international consortium consisting of partners in LAC, the United States and Europe. ZIKAction conducts an interdisciplinary programme of research studies within its network to address key knowledge gaps relating to ZIKV epidemiology, natural history and pathogenesis, with a particular emphasis on maternal and child health. This Paediatric Registry complements the ZIKAction birth cohort studies of prospectively followed infants born to ZIKV infected mothers, setting out to capture information on children with confirmed or suspected CZS and/or born to mothers with diagnosed ZIKV infection in pregnancy being cared for in the ZIKAction network.

The Registry is being implemented in Brazil, Jamaica and Argentina. As already discussed, Brazil was where the first CZS cases were described, and is home to the largest number of children with this condition worldwide. In Brazil, the transmission of Zika virus was confirmed in May 2015 [36]. In late 2015, an unexpected outbreak of newborns with microcephaly due to congenital ZIKV infection occurred in major cities in northeastern Brazil and a state of public health emergency was declared. By the end of 2020, 19,492 cases of suspected CZS were reported in the country, with 3.563 of then confirmed. Most of the newborns with CZS were born in 2015-2017, with sporadic cases notified since then [37].

In Jamaica, by September 2016, there had been over 7000 reported ZIKV cases, including over 600 in pregnant women, the epidemic continued through 2017, with cases of dengue and chikungunya also circulating [38]. At the height of the ZIKA epidemic, children with the neuro developmental sequelae of acute myelitis, acute disseminated encephalomyelitis and Guillain Barre Syndrome were reported, as well as infants with microcephaly and the characteristic features of CZS [39,40]. In Argentina, local ZIKV transmission was first reported in February 2016, with subsequent outbreaks focussed in the tropical northern provinces. The first infant with CZS was delivered in November 2016, but there have been relatively few CZS cases reflecting the relatively restricted circulation of the virus nationally [41,42].

METHODS

Overview

The aim of the ZIKAction Paediatric Registry is to establish an international multi-centre registry of infants and children with documented ZIKV exposure in utero (i.e. born to mother with confirmed infection in pregnancy) and/or with confirmed or suspected congenital ZIKV infection to accomplish the following specific objectives: a) to characterize the clinical, radiological, neurodevelopmental and laboratory features of included children; b) to collect observational follow-up data to describe subsequent outcomes, longer-term sequelae and management in specific groups of children; and c) to provide a platform for future studies, such as clinical trials and assessment of the role of host genetic factors in the susceptibility to ZIKV infection.

The classification of the ZIKAction Paediatric Registry is therefore a non-population-based, disease/exposure-specific registry that is physician-driven [43]. The Registry is a component of the work package 2 (ZIKA-PED) of the ZIKAction project, with agreed participation from sites in Argentina, Brazil and Jamaica.

Eligibility criteria

Children meeting at least one of the following criteria will be eligible for Registry entry.

- Were exposed to ZIKV in utero (i.e. mother received laboratory confirmation of ZIKV infection during pregnancy through positive RT-PCR, IgM or IgG seroconversion) based on definitions and test availability over time.
- Have laboratory-confirmed congenital ZIKV infection (i.e. positive RT-PCR or IgM for ZIKV in any of the biological samples collected after birth), with or without CZS.
- Meet the ZIKAction Paediatric Registry definition of suspected CZS without laboratory evidence of in-utero exposure or congenital infection AND who do not have a laboratory-confirmed congenital infection other than ZIKV or a genetic or other confirmed cause of microcephaly or other abnormalities listed in the case definition.

A suspected CZS case was defined if any of the following was present: congenital or postnatal microcephaly, fetal brain disruption sequence, intracranial calcifications, malformations of cortical development (including simplified gyral pattern, polymicrogyria and pachygyria), arthrogryposis or joint contractures. Microcephaly could be defined according to the Intergrowth 21st reference charts standards [44] and/or the WHO Child Growth Standards [45], with head circumference more than two standard deviations below the mean for age and sex classified as microcephaly. Fetal brain disruption sequence is defined as a variable combination of microcephaly, partial cranial bone collapse, cranio-facial disproportion, pronounced occipital prominence, very small fontanels and redundant scalp skin.

DATA COLLECTION

Identification of cases for inclusion in the Registry

Each site has a research group composed by health professionals (paediatricians, other physicians and research nurses) that will identify children fulfilling the inclusion criteria for recruitment into the Registry. Processes will vary from site to site. In Jamaica, where a national ZIKV surveillance database will be used to identify eligible cases, the research group has applied for a waiver for informed consent for inclusion of pseudonymised retrospective data. In some, the paediatrician will screen patients in their care to determine eligibility and then proceed with informed consent and registration if eligible. In other sites, eligible cases may be identified from pre-existing national databases of children with CZS.

Participant information sheets and informed consent forms for parents have been produced and translated for local use. Due to the COVID-19 pandemic, informed consent procedures have been adapted to policies and measures of each country to avoid the spread of infection and take account of the reduced face-to-face interactions with patients and families. In this manner, for example, Brazilian and Argentinian researchers will obtain a signed consent form from the parents of eligible children using a combination of phone calls and courier delivery of documentation.

Data extraction and entry

The Registry collects relevant socio-demographic, clinical and laboratory data using standardised Case Report Forms (CRFs) via. retrospective clinical case note review for mother and child at the time of registration. The information collected can be broadly grouped into the following: socio-demographics; maternal/obstetric history; pregnancy data (including details of ZIKV-compatible symptoms and laboratory results); delivery information and newborn assessment; and history of children's health that include clinical and radiological evaluations (physical, neurological, developmental, ophthalmological, audiological), and laboratory results that were conducted as part of their local standard of care. Wherever appropriate, harmonisation of data items with the ongoing ZIKAction prospective cohorts of pregnant women and their children has occurred, which in turn have been harmonised with other international ZIKV research consortia, to facilitate future meta-analyses [46].

Research groups at participating clinical sites will enter the information in a paper version of the standardised Case Report Forms (CRF) written in a native language, and thereafter these data will be entered and managed using REDCap (Research Electronic Data Capture: https://projectredcap.org/) [47,48] hosted at Penta Foundation Onlus. Follow-up data from routine visits will be collected via. chart review for children in the Registry.

Governance, ethical and legal issues

ZIKAction is funded by the European Commission's Horizon 2020 Framework Programme, and oversight of the ZIKAction Paediatric Registry is provided via the ZIKAction governance structures, with a Steering Committee which receives guidance from an International Advisory Board. The study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guidelines, and applicable legislation on non-intervention studies.

Thereby, the study protocol was revised and approved by the corresponding health authorities and ethics boards in every research site. Local, national, and international rules on data protection will be followed and the General Data Protection Regulation EU 2016/679 will be adhered to, as well as the relevant national laws and regulations.

Data security and management

Adequate measures to ensure data protection and confidentiality will be duly taken into account by all investigators. The Registry collects pseudonymised data only; patient identifiable information can only be linked to data included in the Registry by the study staff at each site with no identifying information transferred between sites or to the Registry database.

The Registry REDCap database is held on a secure, dedicated server maintained by the ZIKAction project coordinator (Penta Foundation). Access to the web-based database for data input and retrieval is restricted to research teams with appropriate authentication (personal log-in and password), following training and completion of a user responsibility agreement.

In addition to validation checks built into the Registry REDCap database, the quality of the data will be evaluated and improved by source data verification that will be responsibility of each research group. Data quality checks will be performed centrally prior to any statistical analyses being undertaken, with liaison with participating sites to resolve any data queries.

Use of Registry data and statistical analyses

It is envisaged that a number of analyses will be conducted on data within the Registry. After the initial enrolment phase, the Registry data manager will produce a "snapshot" report of the data held in the Registry (e.g. numbers enrolled in different clinical categories) for circulation to all participating centres in order to provide context and high-level data to help determine what analyses can be conducted. Investigators are required to submit a concept sheet for any proposed analyses. Children eligible for inclusion in specific analyses will be identified by the Registry data management team. This team may also identify children meeting inclusion criteria for recruitment into external clinical studies, and return their Registry-specific study numbers to clinical teams who retain identifiers of the children, and would follow local protocols regarding their invitation to take part in other studies. Participation of sites in specific analyses is optional; writing groups for each analysis/project will have representatives from all centres that have contributed data.

Statistical analyses are expected to include assessment of child health outcomes associated with congenital ZIKV infection or exposure. Standard statistical methods will be used, as appropriate, in the analysis of different types of exposure and outcome data, including adjustment for confounding e.g. through multivariable modelling. Varying durations of follow-up and missing data items are to be expected; the analysis approach will depend on the research question and the amount and likely mechanisms of missing data.

DISCUSSION

In 2017, the number of Zika cases started to decline in LAC [49], although vectorial transmission is ongoing across the arbovirus belt and larger outbreaks outside this area in the future are a possibility due to the emerging climate crisis, globalisation and tourism [50-52]. Despite this, the consequences of congenital ZIKV infection represent a significant health challenge. This is not only because many questions remain regarding the longer-term developmental outcomes of infected children (those born with normal head size, as well as those with congenital or postnatal microcephaly and/or meeting current definition of CZS) but also because of the substantial population of affected children who are growing up with this condition, largely living in the LAC region.

Disease registries are well recognised as important information systems and tools for clinical research and for improving patient care, particularly for rare diseases [43,53,54]. Although long-term follow-up of birth cohorts of children exposed to ZIKV infection in utero will be needed to identify the full clinical spectrum of congenital infection, the ZIKAction Paediatric Registry will address gaps in our understanding of the consequences on development and function of congenital infection by bringing together harmonised data from different settings.

The ambition for the Paediatric Registry is to generate data to help to inform guidance to health care providers, pregnant women, affected families and policy makers about natural history, prognosis and follow-up, as well as providing potential insights on pathogenesis of the disease. For example, Registry data may be able to identify predictors of presence or severity of specific neurodevelopmental outcomes, or patterns of neurological abnormalities in different groups (e.g. those with congenital microcephaly, postnatal microcephaly or normal head circumference). The conditions associated with CZS, particularly microcephaly, are lifelong and require multidisciplinary clinical management alongside educational and social support. It is envisaged that the Registry will contribute to ongoing work to establish the burden of ZIKV-related disability and highlight the service needs of the affected populations in LAC, potentially also identifying where early intervention may be feasible.

It is important to acknowledge that there are likely to be some limitations to this paediatric registry regarding the data available for inclusion. Firstly, the reduction of "face to face" clinics during the COVID-19 pandemic from March 2020 onwards. Secondly, some gaps in availability of clinical and laboratory information are expected, due to disparities in local practices to document patients' records, non-attendance for scheduled visits, lack of resources to perform some clinical evaluations or laboratory tests, etc. Given the diagnostic challenges already mentioned, it is expected that laboratory evidence of maternal and/or infant infection may be lacking for some children, particularly those born during the first waves of ZIKV outbreaks in LAC when laboratory capacity to implement RT-PCR was limited in some places. However, difficulties in obtaining laboratory evidence of congenital ZIKV infection can exist even where maternal infection is documented and the infant has characteristic symptoms [55,56]. Thirdly, the health information of some children-mostly those with complex needs who require referral to specialized institutions, can be spread across several hospitals demanding more effort to gather it. Conversely, the primary strength is the presence of highly experienced paediatricians in

the research sites who will be able to collect data rigorously using standardized CRF. Another major strength is the collection of harmonised data in a multi-country, multi-site registry will allow us to address research questions that require larger sample sizes and which thus may not be feasible within single sites or countries.

To conclude, the goal of the ZIKAction Paediatric Registry is to represent a valuable resource providing comprehensive and accurate clinical, laboratory, neurodevelopmental, growth and management data on CZS cases and, where possible, children exposed to ZIKV infection in utero, reported in three LAC countries, as well as providing a platform for future studies, for example, by identifying potential participants.

DECLARATIONS

Ethics approvals and consent to participate

Argentina: Hospital de Pediatria Garrahan, Buenos Aires, Comité Revisor de Investigacion, Ref: 962.

Brazil: Santa Casa de Misericórdia de São Paulo, Comitê de Ética em Pesquisas, protocol 3.510.512/2019.

Jamaica: The Ethics and Medico Legal Panel of the Jamaican Ministry of Health and Wellness, Kingston, Ref: 2019/37. University Hospital of the West Indies, Research Ethics Committee, Kingston (ECP 9 19/20).

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Authors' contributions

The study design was initially conceptualised by CT, CG, HB and AS-A, with the remaining authors contributing to the protocol development (ERB, ICS, RMC, CDCC, GB, PP, AO, BLA, MLCL). All authors contributed to revisions of the manuscript and the final manuscript has been approved by all (ERB, ICS, RMC, RMB, CDCC, GB, AS-A,, HB, PP, AO, BLA, MLCL, CV, CT).

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