Annals of Epidemiology xxx (2017) 1–8

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Review article

Maternal Zika virus infection and newborn microcephaly—an analysis of the epidemiological evidence

Leonelo E. Bautista MD, DrPH *

Department of Population Health Sciences, School of Medicine and Public Health, University of Wisconsin at Madison

ARTICLE INFO

Article history:
Received 5 April 2017
Accepted 20 November 2017
Available online xxx

Keywords:
Zika virus
Microcephaly
Disease outbreaks
Time series analysis
Brazil

ABSTRACT

Purpose: To evaluate whether existing data and evidence support a causal link between maternal Zika virus (ZIKV) infection and newborn microcephaly.
Methods: I quantified and compared the prevalence of all and severe microcephaly in Brazil, during and before 2015–2016, to assess whether an outbreak has occurred, used time series analysis to evaluate if the presumed outbreak was linked to a previous outbreak of ZIKV infections, and quantitatively synthesized published data from observational studies testing this association.
Results: The prevalences of microcephaly in 2015–2016 were similar or lower than background levels (prevalence ratio [PR] for all microcephaly: 0.19; 95% confidence intervals [CI]: 0.17, 0.20). Changes in the number of cases of ZIKV infections at times matching 11–18 weeks of pregnancy were not followed by changes in the number of microcephaly cases (PR for infection at 12 weeks: 1.02; 95% CI: 0.99, 1.05). In observational studies, the prevalence of microcephaly was not significantly increased in newborns of Zika-infected mothers (average PR: 1.30; 95% CI: 0.84, 2.02).
Conclusions: Existing evidence is insufficient to claim maternal ZIKV infection causes microcephaly. Although a public health response seems sensible, it should be consistent with existing knowledge and consider risks, potential benefits and harm, and competing priorities.

Introduction

An outbreak of Zika virus (ZIKV) infection in Northeast Brazil, in 2015, followed by an outbreak of newborn microcephaly, led to the hypothesis that gestational infection was a risk factor for microcephaly at birth [1–3]. Concerned about an increase in the number of cases, in November 19, 2015, the Brazilian Ministry of Health (MoH) implemented an ad hoc public health surveillance system (AHSS) to characterize and identify the causes of the outbreak of microcephaly [3]. The MoH concluded the two outbreaks were temporally related and a causal link was likely, called for further research to confirm this link, and advised pregnant women to avoid mosquito bites [3].

On April 3, 2016, based on a review of the evidence, the Centers for Disease Control concluded ZIKV caused microcephaly and other severe fetal brain defects [2,4]. Two weeks later, the World Health Organization declared there was scientific consensus that ZIKV caused microcephaly [5]. At that time, only one analytical study of the ZIKV-microcephaly association had been published [6], and its evidence had been qualified as weak, inconsistent, and only partially meeting causal criteria [4,7]. Also, concerns had been raised that the observed increase in cases of microcephaly was due to active search and overdiagnosis [8–10]. To date, the hypothesis of a causal relationship rests mostly on the timing of both outbreaks, on reports of cases of microcephaly whose mother had gestational ZIKV infection, on the detection of ZIKV in the amniotic fluid of women with microcephalic fetuses [11,12] and in the blood and brain of a newborn with severe microcephaly [13], and on findings from two observational studies [6,15,14].

In this study, I evaluate whether an outbreak of microcephaly actually occurred in Northeast Brazil and was associated with a previous outbreak of ZIKV infection. I also assess the evidence of a causal link from published case reports and observational studies. In view of the scarcity of counterfactual evidence, findings from this study could further our understanding of a link between ZIKV and microcephaly and inform current ZIKV public health policies, patient care, and research.

The authors have no conflicts of interest to disclose.

* Corresponding author. Department of Population Health Sciences, School of Medicine and Public Health, University of Wisconsin at Madison, 610 Walnut Street, WARF 703, Madison, WI 53726-2397. Tel.: +1-608-265-6176; fax: +1-608-263-2820.
E-mail address: lebautista@wisc.edu.

https://doi.org/10.1016/j.annepidem.2017.11.010
1047-2797/

Methods

Relevant articles and data sources were identified through a systematic search of databases of biomedical sciences journal citations, using the keywords ZIKV and/or microcephaly, plus Brazil, plus outbreak and/or epidemic and by reviewing the references in each article.

Assessment of the outbreak of microcephaly

Data sources

Data on prevalence of microcephaly during the outbreak period (2015–2016) were obtained from two published AHSS reports [3,16] and a report from Araújo de Soares et al. [16] who retrieved recorded head circumference (HC) values from a random sample of 16,208 newborns from 21 maternity centers in the Paraíba Pediatric Cardiology Network (PPCN) [17]. The PPCN is a collaboration established by the Government of Paraíba, Northeast Brazil, to screen newborns for heart defects. It covers over 60% of all births in public hospitals and has records on more than 100,000 children born since January 1, 2012.

Data on background prevalence (before 2015) were obtained from one report from the regular Brazilian Live Birth Information System (Sistema de Informacoes sobre Nascidos Vivos [SINASC]) [3], one report from the PPCN [16], and three reports from the Latin American Collaborative Study of Congenital Malformations (ECLAMC) [10,18,19]. ECLAMC is a maternity hospital network started in 1967 that examines around 200,000 newborns per year in South American countries [20]. ECLAMC data from Brazil came from 52 clinics in 19 cities from seven states [21]. Estimates of prevalence were also obtained from the distribution of HC in 1595 Brazilian newborns (normal, with mean of 34.2 cm and SD of 1.2) who participated in InterGrowth-21st, a population-based study that assessed fetal growth and newborn size in eight urban populations [22].

Definitions of microcephaly

All microcephaly and severe microcephaly are traditionally defined as HC less than or equal to 2 and less than or equal to 3 SD below the mean, respectively [23,24]. Before the start of the AHSS, data on severe microcephaly were collected prospectively through SINASC, and cases were defined as HC less than or equal to 30.3 or less than or equal to 30.7 cm in full-term girls/boys (gestational age greater than or equal to 37 weeks) [3]. In contrast, in the AHSS, cases were identified retrospectively from the start of the year to mid-November 2015 and prospectively thereafter, using three different definitions for all microcephaly [25]. From November 17 to December 12, 2015, the AHSS cut points were HC less than or equal to 33 cm for term newborns and HC less than or equal to third centile of Fenton reference by gestational age and sex in preterm newborns. From December 12, 2015 to March 12, 2016, cut points were changed to less than or equal to 32 cm for term newborns but remained unchanged for preterm newborns. Starting on March 13, 2016 cut points were changed to less than 31.5/31.9 cm for term girls/boys and less than −2 SDs of InterGrowth reference by gestational age and sex [22].

Estimating and comparing prevalences

I used prevalence values from the original reports or calculated them when needed (see Appendix, item 1). I estimated the prevalence of severe and all microcephaly in 2015–2016, defined by SINASC [3] and AHSS [25] cut points, using Brazilian newborn HC data from InterGrowth [22]. A thousand random samples of 1 million observations each were drawn from this distribution. The mean of the prevalence in all samples was taken as the expected prevalence, and the upper and lower 2.5% values of the empirical distribution were taken as 95% confidence limits [26]. I corrected for possible overestimation resulting from using overall HC mean and SD in these simulations, instead of gender-specific and gestational age–specific values (see Appendix, item 2).

I compared the prevalences of all and severe microcephaly in 2015–2016 to background prevalences from published reports [16,18,27] and to that obtained by simulation of HC values [22,25], to assess if an unusual increase in the number of cases had actually occurred in that period.

Assessment of the temporal correlation between the two outbreaks

Data sources

I used data from a published report of outbreaks of acute exanthematous illness (AEI) (attributed to ZIKV infection) and microcephaly in Salvador, Bahia [28]. AEI cases were patients with rash, with or without fever, not meeting diagnostic criteria for dengue, chikungunya, measles, or rubella [28]. They were identified retrospectively from February 2015 to April 2015 and prospectively thereafter, in 10 health centers designed as surveillance units. Data on microcephaly came from the AHSS. Retrospective reviews of hospital records yielded no cases of microcephaly before mid-July 2015 [28].

Data analysis

I used Poisson autoregressive models to account for overdispersion and autocorrelation of the outcome and tested whether a change in the weekly number of cases of AEI was associated with a change in the weekly number of cases of microcephaly weeks later [29,30]. I used a mixture of sine and cosine functions to model periodic fluctuations in the number of cases of microcephaly [31,32] and included the changes in the number of cases of ZIKV infection per week in the previous 20–27 weeks, one at a time, as exposures [33–35]. For pregnant women, this corresponded to the 11th to the 18th week of pregnancy (see Appendix, item 3).

Assessment of the ZIKV-microcephaly association in observational studies

Data sources

I included a cohort study [6,14] and a case-control study that measured the association between ZIKV infection and microcephaly [15].

Data analysis

I used the Laplace/DeMorgan correction [36] and profile-likelihood confidence intervals (CI) [37] to address issues of separation data bias in the original studies [38–40]. The Laplace correction, adding 1 to each cell of the 2×2 table, is more accurate than exact logistic regression and the traditional Haldane correction (i.e., adding 0.5 to each cell). Profile-likelihood produces CIs with better coverage when the distribution of the parameter of interest is non-normal [37]. Whenever possible, the effect of ZIKV infection during the first trimester of pregnancy was calculated. An average of the prevalence ratio (PR) from these studies and from the assessment of the temporal correlation between the two outbreaks was obtained using a random effects model (see Appendix, item 4) [41].

Results

Assessment of the outbreak of microcephaly

Based on AHSS data, and using the SINASC definition, Oliveira et al. [3] estimated a prevalence of severe microcephaly of 5.60/10,000