Another piece on the Zika puzzle: assessing the associated factors to microcephaly in a systematic review and meta-analysis.

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Abstract

Background: Although it is known that Zika virus (ZIKV) infection during pregnancy may lead to microcephaly in the foetus, the risk factors associated to this tragic disorder remain unclear. We conducted a systematic review and meta-analysis toto assess risk factors associated with the incidence of microcephaly in congenital ZIKV infection.

Methods: We conducted a comprehensive search in Ovid MEDLINE, Ovid MEDLINE (R) Epub ahead of print, Embase, Embase Classic, Web of Science, CINAHL, Cochrane CENTRAL, LILACS and various thesis databases to identify human studies reporting microcephaly associated with congenital ZIKV infection. We requested primary data from authors of the studies included in this review to calculate summary estimates and conduct meta-analysis of the most prevalent factors.

Results: We screened 4,106 titles and abstracts, and identified 12 studies for inclusion in the systematic review. The assessment of ZIKV infection and the definition of microcephaly varied among studies. A total of 6,154 children/foetuses were enrolled; of those, 1,120 (18.20%) had a diagnostic of ZIKV infection, of which 509 (45.45%) were diagnosed with microcephaly. Nine studies addressed the link between congenital ZIKV infection and neurological findings in foetuses/ children. Half of the studies provided primary data. Two out of eleven factors of interest were associated with microcephaly: infant's sex – males presented a higher risk of microcephaly compared to females (RR 1.30, 95% CI 1.14, 1.49); and the stage of pregnancy when infection occurred - infection in the first trimester of pregnancy had a higher risk of microcephaly (RR 1.41, 95% CI 1.09 to 1.82), compared to infection at other stages of pregnancy.

Conclusion: Our findings support the female-biased resistance hypothesis and reinforce the risk associated with the stage of pregnancy when Zika virus infection occurs. Continued surveillance of ZIKV during pregnancy is needed to identify additional factors that could contribute to developing microcephaly in affected foetuses.

Background

In 2016, the World Health Organisation (WHO), for the fith time in its history, declared a Public Health Emergency of International Concern due to the recognition of the Zika Virus Congenital Infection [1]. After a "pandemic that surprised the world" [2] several studies reported an association between Zika virus (ZIKV) infection during pregnancy and congenital abnormalities [3–6]. Microcephaly is considered as the "tip of the iceberg" in Congenital Zika syndrome (CZS), which define a more complex spectrum of anomalies related to ZIKV congenital infection [7,8]. When present, microcephaly indicates a neurogenesis´ failure that varies in severity [9,10].

Brazil was the first country to investigate this relationship, while it saw the largest outbreak of ZIKV infection to occur - between November of 2015 and November of 2018, with almost 17,000 suspected cases of CZS reported to the Brazilian Ministry of Health. From those, 2,819 were confirmed cases—either tested by laboratory methods or clinical-epidemiology evidence [11]. Data from Brazil revealed a frequency of microcephaly up to 24 times higher following Zika virus infection during pregnancy (PZIK) [12]. In 2016, another study that reviewed data from 2013–2015 French Polynesia ZIKV outbreak estimated a microcephaly risk ratio of 53.4, caused by ZIKV infection in the first trimester of pregnancy [13]. In Hawaii, the island closest to French Polynesia and Yap, there was an increase of three times on the microcephaly rate comparing 2005 (4.8 cases per 10,000 total births in 2005) [14] to 2007—2013 (14.7 per 10,000 total births). This period coincides with ZIKV outbreaks in the Pacific starting in 2007[13,15,16]. Worldwide, a systematic review estimated a prevalence of microcephaly of 2.3% among all Zika virus infection during pregnancy [17].

Although the association between PZIK and microcephaly is considered a "scientific consensus" [6,18], variations on the risks within geographical areas and population groups have been observed [17,19]. It is discussed that some factors may act as effect modifiers, increasing the risk of neurological damage [20], but there is still a lack of evidence on cofactors or component causes that act as associated risks or preventive factors to the incidence of birth defects [21–23]. To address this gap in knowledge, this systematic review and meta-analysis aims to identify maternal and fetal risk factors associated to microcephaly in foetuses and newborns from mothers infected with ZIKV during gestation.

Methods

Protocol and Registration

The systematic review protocol was registered on February 21, 2018, in the PROSPERO (International Prospective Register of Systematic Reviews) database under the number CRD42018088075 [24]. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [25] checklist was filled and can be found in the Additional Table 1.

Information Sources and Search Strategies

The search strategy aimed to find theses and dissertations in addition to published studies. The following databases were searched by a librarian in January 08, 2019: MEDLINE via OvidSP (1946 onward), Embase via OvidSP (1947 onward), Cochrane Central Register of Controlled Trials or "Cochrane CENTRAL" via OvidSP (1991 onward), the Cumulative Index of Nursing and Allied Health Literature or "CINAHL" via EBSCOhost (1981 onward), Web of Science Core Collection (1900 onward), ProQuest Dissertations and Theses Global (1861 onward), and Latin American & Caribbean Health Sciences Literature or "LILACS" (1982 onward). The full electronic search strategies for all databases can be accessed via QSpace, Queen's University's research repository service [http://hdl.handle.net/1974/24246]. No language or date restrictions were applied. The reference list of systematic reviews and reports were searched for additional studies.

We searched ProQuest Dissertations and Theses and thesis databases from Brazil, Colombia, Canada, USA and Europe in January 08, 2019, using the terms "zika" or "zikv" or "zyca" or "zyka". The authors of these, letters, editorials, correspondence and conference abstracts that met the inclusion criteria were searched online for original papers.

Additionally, we identified studies that we believed may have PZIK, the risk factors of interest and microcephaly data, but had not published full results (i.e. conference abstracts). The first and last authors curriculum were screened online and the first author of each of these studies were contacted online. In total, we contacted 17 study investigators at least two times. Responses to seven of the requests were received, all of which informed us of an inability to provide results.

Eligibility

We included published data from original research that studied microcephaly as a congenital effect of ZIKV in humans. We included randomized controlled trials, prospective, retrospective or descriptive cohorts, case series (only the case series whose primary data allowed the formation of groups that were prospectively compared regarding the outcome), cross-sectional and case-control studies that could answer the review question.

Studies were excluded if they: (1) were not in humans; (2) were not answering our primary objectives; (3) were in vitro/ cell studies; (4) were not original research, such as literature review, guidelines and manuals, protocol summaries, editorials, opinions pieces, and book chapters; (5) were probable duplicities as multiple publications from the same sources (data from the same sources, but published in different papers); or (6) were case reports, epidemiological analysis/bulletins, or case series that included only one group of outcome.

To avoid double counting in cases that the same individuals or data have been reported in more than one publication, we evaluated publications from the same author or study place (hospital-based, city-based or state-based population). If there was possible duplicity, we used the publication with the most complete information available to extract the data.

Study Selection, Data Extraction and Assessment of Studies

Initial triage of articles was based on independently screening of title and abstract by two evaluators to assess the relevance to the objective of the review. Then, full text read of selected studies was conducted to evaluate inclusion according to eligibility criteria and study question. Data extraction and quality assessment were conducted by two independent authors using a standardized instrument. Disagreements at any stage were solved by consensus or discussion with a third author.

Data extracted included the name of first author, year of publication, period of study, country, language, study design, size, population, any potential patient-related risk factor including demography (maternal age, ethnicity, deprivation, education level, marital status, social support); lifestyle factors (smoking habits, drug use); patient history (including comorbidity, family history); symptom type; health care usage (including screening); presenting behaviour; symptom knowledge and characterization of outcomes.

The methodological quality and risk of biases of the studies was assessed using the Newcastle - Ottawa Quality Assessment Scale (NOS)[26], by two independent reviewers. The studies that got 7–8 stars were considered to be of high quality, those which got 6–5 stars were considered to be of satisfactory quality and those with 4 or less stars were considered to be of low quality [27].

Synthesis of Results and Summary Measures

To ensure comparable and accurated results to perform the meta-analysis, we contacted the corresponding authors of all included studies in the Systematic Review up to three times to ask whether they would be willing to provide results. A standardized table (Additional Table 2) was sent to all the authors for them to complete using their primary data, considering as population of interest only cases of PZIK, the outcome of interest being the presence or absence of microcephaly.

We asked about maternal and infant data, considering the following variables: population size (number of newborn/foetus); maternal age; maternal ethnicity; maternal scholarity; maternal symptoms compatible with ZIKV infection during gestation; maternal smoking habits and/or use of alcohol and/or other drugs; presence of comorbidities in the mother; trimester of pregnancy when infection occurred; prior yellow fever vaccine exposure; prior other vaccines exposure; foetus sex; and newborn gestational age at birth. The results provided by the authors were also used to complement the description of the studies in the qualitative synthesis.

Since the characterization of microcephaly can vary among countries, for the meta-analysis we used the definition recommended by WHO: the measure of the head circumference (HC) of less than two Standard Deviations (SD) below the average for sex and gestational age [28]. Also, as a reliable laboratory diagnostic test of ZIKV was not available during the first part of the outbreak, we used the ZIKV case definition as reported by the study. All the authors were advised to follow these criteria when providing the data.

Meta-analyses were performed if sufficient results were available. Summary measures were calculated for each different variable included. The random effects model was used when the I^2 test for demonstrated a large degree of heterogeneity between studies (I^2 higher than 0.5). When the heterogeneity between studies was equals or lower than 0,5, fixed effect model was used for the analysis. We used the RevMan software to execute the calculation of summary measures and heterogeneity of the studies, and to generate the figures of the meta-analysis (Forest plots).

Results

Characteristics of Included Studies

Our systematic review identified 4,106 records, from which 298 duplicates were removed and 3,808 titles and abstracts were screened. After this process, the reviewers identified 150 unique studies that seemed to be relevant to answer our question and those articles were assessed in full-text for eligibility. From those, 138 studies were excluded based on the exclusion criterias. After full-text review, a total of 12 observational studies were included in the synthesis of the litterature[29–40] (Figure 1). Of the 12 eligible studies, six authors provided the primary data [29,34,37–40], and thus were included in the meta-analysis. This process is summarized in Figure 1.

The twelve included studies were published from 2015 to 2018, ten of them had Research Ethics Board approval and 2 declared to be exempt [30,39]. Five were cohort studies[30,33–36], three were case-controls studies [31,32,38], three were case-series [29,37,39] and one was a cross-sectional study [40]. The studies defined as case-series [29,37,39] were conducted based on surveillance data - local surveillance system and hospital based surveillance –, and reported only ZIKV infected cases with different outcomes. For that reason, since it was possible to compare the microcephaly group and the non-microcephaly group, for the meta-analysis we considered them as “prospective observational studies” in the same group as the cohort studies of PZIK.

All the 12 studies were conducted on the American Continent, three of them in the United States [30,36,38], one in the Caraibbean and eight in South America (Brazil, French Guiana and Colombia). The total population enrolled in the 12 included studies is 6,154 children/foetuses. From those, 1,120 (18.20%) had a diagnosis of ZIKV infection, of whom 509 (45.45%) were diagnosed with microcephaly. Most of the studies [30–34,36,38–40] addressed the link between PZIK and neurological findings or other outcomes in foetuses/children, however the laboratory confirmed ZIKV infection was not consistent in all the studies.

The assessment of PZIK varied among studies. From the 12 included studies included in this review, one [39] also included women that did not perform any laboratory test to determine ZIKV infection. In this study, the definition of ZIKV infection was due to epidemiological link and clinical characteristics, as accepted by the Ministry of Health. Regarding laboratory evidence, six tested the mothers/ pregnant women [33,35–39], and six tested both [29–32,34,40] (Table 1). RT-PCR was used in seven studies [29,30,33–37] in at least one phase of the diagnosis, but only two of them used this test as the confirmation tool for all the cases [29,33]. Plaque reduction neutralisation test (PRNT) was used in five studies [30–32,34,36] and 10 used serological test to detect either IgG or IgM antibodies [29–32,34–38,40].

The microcephaly definition varied across studies, along the time and between the studies. Regarding the moment of the detection, the microcephaly was diagnosed after delivery in all the 12 studies, but three of them also performed fetal ultrasounds [29,33,35] to detect microcephaly.

Based on the NOS, four studies [30,33,38,40] were deemed to be of good quality and seven [29,31,32,34–36,39] were of satisfactory quality. We summarized the characteristics of all the 12 selected studies in Table 1 and the characteristics of the population enrolled in Table 2.

Regarding the quantitative synthesis, six authors provided the primary data that was used in the meta-analysis. Three of them [34,37,39] were cohorts (total N = 1593), two [29,38] were case-controls (total N = 18) and one study with 32 cases was cross-sectional [40]. The total number of participants that had microcephaly were 638 (40.05%) in the prospective studies and 12 (85.71%) in the retrospective studies. Ventura et al [40] also provided the primary data, but since it is the only cross-sectional study, we did not include their results in the meta-analysis. It was not possible to explore publication bias, since there was less than four studies included using the same methodology, most of them with small sample sizes.

Microcephaly

The 12 selected studies reported a higher risk of microcephaly in the presence of ZIKV infection during gestation, with an Odds Ratio (OR) as high as 21.9 (95% Confidence Interval - CI of 7. 0, 109.3) [32] and a Relative Risk (RR) of 6.63 (95% CI, 0.78, 57.83) [34] when compared to no ZIKV infection during gestation. Whenan alysing only cases with ZIKV infection during gestation, microcephaly was prevalent in up to 54.82% of the children enrolled in one study [37]. Considering the 705 foetuses/newborns diagnosed as ZIKV positive, whose mother's had symptoms of ZIKV infection during pregnancy described in the published papers [24–32, 34, 35], we found a prevalence of microcephaly of 52.63% (CI95% = 48.3, 56.95) in the symptomatic group versus a prevalence of microcephaly of 45.64% (CI95% = 41.02, 50.26) in the asymptomatic group.

Schaub et al. [29], reported 14 cases of ZIKV infection during gestation. They found microcephaly in nine (64.28%) of them. But, only one of the pregnancies resulted in a livebirth (newborn at 40 weeks with microcephaly) and one case of intra-uterine death at 25 weeks. The 12 other participants had termination of pregnancy varying on 18 weeks and 3 days to 34 weeks of gestation. For that reason, the data on "gestational age at birth" of this study was not included in the analysis.

Assesed Risk Factors

The symptoms of ZIKV infection during pregnancy were assessed in all studies except in Kumar et al [33], which performed laboratory analyses of stored plasma samples from mothers who gave birth to babies with microcephaly and healthy babies collected prior to ZIKV became linked with microcephaly. Overall, symptoms of ZIKV infection during gestation were present in 705 of the 1116 pregnant women infected (63.17%). (n =.. From the studies with available informationta [31–35,37,39,40], 270 of the 513 women who reported symptoms during pregnancy (52.63%), delivered an infant with microcephaly.

The trimester of pregnancy when the infection occured was assessed in eight studies [30,31,33–35,37,39,40]. From the cases of ZIKV infection during the first trimester (N = 324), 42.59% exhibited microcephaly. Among those with ZIKV infection during other stages of pregnancy [second trimester (N = 332) and third trimester (N = 141)], 21.99% exhibited microcephaly.

Sanz Cortes et al. [35] and Schaub et al. [29] informed maternal nutritional status [mean maternal Body Mass Index (BMI) of 24.38 kg/m2 (SD 5.56) and 26.54 kg/m2 (SD 5.76), respectively]. The mean maternal BMI in the microcephaly group was 25.88 kg/m2 (SD 3.83) in the study of Sanz Cortes et al. [35], and 27.84 kg/m2 (SD 6.77) in the study of Schaub et al. [29]; while the mean maternal BMI for the non-microcephaly group was 19.89 kg/m2 (SD 8.43) [35] and 24.20 kg/m2 (SD 2.39) [29].

Although Vargas et al. [39] measured all the variables of interest, they mentioned that five (8.3% of the total population) cases were due to other congenital infection and did not explore the data separately. For that reason, it was not possible to use their data separately. For that reason, it was not possible to use their data for analysis of PZIK.

Concerning comorbidities, other infections were excluded in most of the studies (7/12). Infections known to have teratogenic effects such as syphilis, toxoplasmosis, rubella, cytomegalovirus and herpes simplex (STORCH) were excluded in six studies [29,33–35,37,40]; dengue virus infection in four [29,30,32,33]; HIV in four [29,33,35,40]; chikungunya in two [24, 28]; parvovirus in one [33]; and other sexually transmitted infections in one [35].

Three studies [33,35,40] provided information regarding the consumption of licit or illicit drugs during pregnancy. Sanz Cortes et al. [35] used these exposures as exclusion criteria, Brasil et al. [33] informed that all included women reported no medication use and Ventura et al. [40] reported four cases (12.5%), all of them in the microcephaly group (13.79% of the microcephaly outcomes), but didn't mention which particular drug was assessed.

Three studies reported the presence of singleton versus multiple gestation [30,33,34] and the delivery method among the PZIK cases was reported in two studies. Brasil et al. (2017), reported a C-section rate of 82.4% (N = 89/108), and Sanz Cortes et al. (2018), of 66.67% (N = 6/9).

Gestational age at birth in newborns with microcephaly due to PZIK was not provided in four studies [30,32,37,39]. One study [29] had only one newborn (7%), 40 weeks at birth, all other analysed cases (13 cases, 93%) had a termination of pregnancy at different times of the gestational outcome. Aragão et al.[31] and Sanz Cortes et al.[35] presented the mean and SD of all the population included, finding respectively 36.29 (SD 8.71) weeks of gestation and 37.8 (SD 1.15) weeks of gestation. The study of Brasil et al. [33], provided the gestational age at birth of the 58 (43.3%) participants who had any abnormal finding at birth. From those, four (6.9%) were in the microcephaly group and two of them were born preterm. From the non-microcephaly group, 11.63% (n = 5) newborns were born preterm. Shiu et al.[36] (2018), reported data of 86 women with laboratory evidence of PZIK. They did not provide the data regarding the presence or absence of microcephaly, but 34 (39.5%) of the participants were still pregnant by the time of the report, 8 (9.3%) had preterm delivery and 44 (51.1%) had term delivery. From the remaining population (N = 314) [34,38,40], the studies provided mean and SD. The weighted mean and SD from the microcephaly group (n = 60) was 37.91 (SD 2.72) gestational weeks at birth and from the infants in the non-microcephaly group was 38.06 (SD 2.42).

Meta-analysis

Ventura et al.[40] provided data on 148 cases of PZIK, 140 (94.6%) of these infants with the microcephaly status (presence or absence) reported. From those, 124 (88.6%) infants presented microcephaly. In the microcephaly group, 56.45% (n = 70) were female, while in the non-microcephaly group, the majority were males (n = 9/16, 56,25%). The information on maternal symptomatology of PZIK was available for 132 infants (116 with microcephaly). From them, 108 women reported symptoms (such as rash, pruritus and conjunctivitis) being 97 (83.6%) of which belonged to the microcephaly group. The use of licit or ilicit drugs was available for 132 maternal (118 in the microcephaly group) and 13 mother's reported the use of these substances. From the microcephaly group, 12 (10.2%) mothers reported this behavior and from the non-microcephaly group, one mother (7.1%) reported it. As for the gestational trimester of infection, most of the participants in the microcephaly group were infected in the first trimester (n = 48, from 100 with this information available) and the majority (n = 7, from 13 with this information available) of the non-microcephaly group had ZIKV infection in the second trimester. There was no sufficient data on maternal scholarity and previous

vaccines (Yellow Fever vaccine or other vaccines) to conduct an analysis. Regarding the methodological quality, this study was assessed as good quality.

We thus, conducted meta-analysis to assess the rate of microcephaly detection according to seven identified characteristics: (i) sex (proportion of boys); (ii) maternal age; (iii) maternal ethnicity (proportion of non-white); (iv) gestational age at birth; (v) presence of symptoms during gestation; (vi) presence of comorbidities; (vii) gestational trimester of infection; and (viii) smoking habits and/or alcohol or other drugs consuption.

Regarding the meta-analysis of prospective studies, only three variables showed to be significant (presented in Figure 2). In relation to foetus/infant's sex, females presented a lower risk of microcephaly compared to males (RR 0.79; 95% CI 0.70, 0.88; I2 = 0%) (Figure 2a). Infection in the first trimester of pregnancy (Figure 2b) was a risk factor (RR 1.42; 95% CI 1.09, 1.84, I2 = 0%) for microcephaly, compared to infection in the second and third trimesters of pregnancy. A decrease in the microcephaly detection rate risk was observed in women who did not presented symptoms of PZIK (RR 0.68; 95% CI 0.60, 0.77; I2 = 38%), such as conjunctivitis, prutitus and rash (Figure 2c).

Although not significant, the Maternal ethnicity—white (RR 0.91; 95% CI 0.77, 1.08; I2 = 0%) and no smoking habits and/nor alcohol nor other drugs consuption (RR 0.84, 95% CI 0.55, 1.29, I2 = 0%) had indicated, in a point estimate, to be protective. Maternal age and gestational age at birth—analysed using mean and SD, were similar between groups. The meta-analysis data of the factors that did not significantly increase the risk are illustrated in the Additional Figure 1.

As to methodological quality of the prospective studies included in the meta-analysis, França et al. [37] was the only included study assessed as low quality. Pomar et al.[34] and Vargas et al. [39] were considered as satisfactory quality.

In relation to the retrospective studies[29,38], Kumar et al.[38] tested archived blood samples collected at delivery at the Kapiolani Medical Center for Women and Children in Hawaii; and Schaub et al.[29] investigated 12 cases diagnosed during pregnancy, but 11 cases resuted in pregnancy termination and only one live birth. Only infant's sex could be tested as an exposure factor. There was a decrease of the Odds Ratio (OR) of microcephaly in females, even though it was not significant (OR 0.54; 95% CI 0.08, 3.66, I2 0%) (Additional Figure 2a). It was not possible to analyse the data on trimester of infection, presence of symptoms, smoking habits and vaccines exposure since only one study had this data vailable. Also, maternal age, maternal ethnicity and presence of comorbidities were not estimated, since the study of Kumar et al.[38] had only one case without microcephaly and Schaub et al.[29] included only non-white individuals without comorbidities (Additional Figure 2b). With reference to quality assessment, Kumar et al.[38] was assessed as good methodological quality and Schaub et al.[29] as satisfactory methodological quality.

Discussion

To our knowledge, this is the first systematic review to evaluate maternal and fetal risk factors that could contribute to the presence of microcephaly in newborns and foetuses wherein the mother was infected with ZIKV during pregnancy. Our meta-analysis showed that the infection in the first trimester of pregnancy may increase the risk of microcephaly by 41% when compared to other trimesters, and female foetuses have a lower risk of developing microcephaly. Our study did not show difference between groups regarding the presence maternal symptoms compatible with ZIKV infection during gestation, consumption of alcohol or other drugs during gestation and maternal comorbidities.

In relation to trimester of infection, other STORCH infections also confer differential risk of congenital defects according to the stage of pregnacy where they occur [41–44]. These events are related to both the development of the Central Nervous System (CNS) and also the foetus immune response [45]. Even though the ZIKV infection in the second and third trimester of pregnancy seemed to be a lower risk compared to ZIKV infection in the first trimester, it is important to highlight that this infection carries a risk for the development of microcephaly and other adverse pregnancy outcomes throughout the full duration of pregnancy [4,46,47]. There is still a lack of knowledge on the magnitude of the risk of newborns infected by ZIKV developing microcephaly later in childhood [48,49].

In relation to the infant's sex, the relationship between fetal sex and advese pregnancy outcome is controversial [50,51]. The male sex, especially in low-risk pregnancies, seems to have an effect on adverse pregnancy outcomes[52], such as preterm birth [53,54]

and stillbirths [55]. Regarding Zika infection, in the Yap Island outbreak it was also found a higher prevalence of IgM antibody against ZIKV in men, compared to women[15]. Our It should be pointed out that the meta-analysis - point estimates - of either prospective and retrospective studies showed that females had a lower risk than males, but the OR was not significant (0,54, IC95% 0.08, 3.66), probably due to the small number of individuals included in the retrospective studies of our meta-analysis. Additionally, the studies of Pomar et al.[34] and Vargas et al. [39], both of satisfactory quality, did not observe a statistically significant relation. Nonetheless, our findings reinforce previous studies that support a male-biased incidence in infectious diseases [51,56] pointing out a probable relation of microcephaly and fetal sex, being males at higher risk than females.

Concerning maternal symptoms, its is important to highlight that that the symptoms of ZIKV infection - both in men and women - are often mild and infrequent [4,15,57,58]. There is still uncertainty if the symptoms can be addressed as a reliable indicator of vertical transmission or disease severity [59–61]. Other infections that lead to congenital malformation, such as cytomegalovirus, also have a high number of asymptomatic cases, but, when present, symptoms might indicate an adverse outcome [62].

Our meta-analysis results suggest an association of microcephaly with symptoms, probably restricted by the heterogeneity of the studies. Even so, this association may be influenced by recruitment and selection, gven that tree studies [29, 37, 40] performed the recruitment based on the children, increasing their microcephaly rate compared to the microcephaly rate observed in studies that included all pregnant women infected with ZIKV. Furthermore, two studies [37,39] used also cases of presumed ZIKV infection—diagnose based on clinical-epidemiological evidence and not laboratory tests. In this sense, although the low-viremia induced by ZIKV infection increases the false negative results[63], the most reliable diagnose test is RT-PCR in the newborn's sample.

Regarding socioeconomic, demographic and environmental factors linked to adverse pregnancy outcomes, such as maternal ethnicity, low family income, maternal scholarity and maternal age, this review was unable to determine if those variables can act as an additional risk factor to microcephaly development, since only a few studies assessed these exposures. The risk ratio - point estimates - of maternal ethnicity (non-white, RR 0.91, CI 95% 0.77, 1.08) and no consumption of alcohol, tobacco and other drugs during pregnancy (RR 0.84, CI 95% 0.55, 1.29) suggest that these are protective factors for microcephaly, yet the differences were not statistically significant. Since those factors are being reported in the literature as being capable of interaction with other risk factors increasing the risk of worst outcomes [64–67], we believe that the low statistical power of the studies included in the meta-analysis might have restricted our results.

The heterogenecity of the studies also influenced the analysis concerning health factors, such as microcephaly history in the family, maternal comorbidities and nutritional status. Nevertheless, our review was able to indicate that the presence of comorbidities might raise the risk of microcephaly, though, we were not able to find statistically significant differences. The presence of antibodies for other flaviviruses, that may act as modulators of worst outcomes such as Dengue and Yellow Fever, as well as the prior exposure to Yellow fever vaccine were not explored in most of the studies, thus hampering the analysis of possible effect modifiers. This is likely related to the urgency of assess the relationship between PZIK and intergenerational effects[68–70] at the time that most of the studies were conducted.

Regarding the methodological quality of the studies included in the meta-analysis, França et al.[37] was the only low-quality study. This study used secondary data and was able to collect information on 1258 ZIKV infected pregnant women—the highest number of included individuals. In the same perspective, Pomar et al.[34] was deemed to be as of satisfactory quality and included 278 ZIKV infected participants. On the other hand, Kumar et al. [38] included four cases and was assessed as good quality.

The complexity of the risk factors associated with microcephaly due to Zika infection during pregnancy and broader socioeconomic context in which it is inserted, including a greater social and economic impact worsened by the Congenital Zika Syndrome must be considered when designing preventive programs or providing health care. Although this review and meta-analysis only approached individual levels factors the most appropriate interventions might be in ecological level, especially in low-income countries addressing pathways of infection, such as mosquito-byte control and protective measures to sexual transmission.

Limitations of this Systematic Review

Common sources of bias in any meta-analysis are publication bias and heterogeneity between studies. We assessed the publication bias by reviewing the grey literature and contacting the authors. Despite this effort, the meta-analysis only included published studies. Because of the small number of included studies, we were not able to perform tests to detect publication bias. Since non-significant results have a decreased likelihood of publication, we believe that the included studies might be reporting a higher association between PZIK and birth defects. However, in terms of associated risk factors for the development of microcephaly, our exposures of interest, it is unlikely that publication bias would affect our results. Regarding to summary measures, we understand that our data reflect, also, the number of participants included in each study (and not the methodological quality of them), as is observed in all unweighted summary measures.

Concerning the design of the studies, the case-series studies did actually include all the available population, using surveillance strategies. A small number of individuals was included at the end, that makes it a case-series design with a tendency to be interpreted as a descriptive cohort study. Also, the small number of individuals included in the retrospective studies restricted the power of the meta-analysis.

Specific limitations of our review were the elegibility criteria of not including in vitro studies, since some authors have reported that the ZIKV strain can be related to different outcomes [71,72]; and the inherent differences between studies, especially in regard to the ZIKV infection definition and data collection. There is still a lack of consensus on diagnostic strategies for ZIKV [63], and the studies identified in this review used different tools for this purpose. Also, as cited, most of the studies did not assess possible effect modifiers that this review was seeking to analyse.

It is necessary to point out that the systematic review might have some duplication of cases, since the study of França et al.[37] included all the notified cases in Brazil from October 2015 to February 27th, 2016. Other studies using this time-frame have probably used individuals that were notified in the national system. However, the data used on meta-analysis does not overlap in time or place, so this was not considered a hurdle for those results.

Finnaly, the methodological quality of included studies was considered, predominantly, satisfactory and only four studies were assessed as good quality[30,32,38,40]. Moreover, our findings are supported only by observational studies. For these reasons, our results should be interpreted cautiously so as not to influence the prenatal care, nor the health surveillance strategies used to detect and prevent new cases.

Conclusions

This systematic review and meta-analysis found that male sex, the occurrence of ZIKV infection in first trimester and symptomatic infection increase the risk of microcephaly. These findings should be interpreted cautiously, since ZIKV is an emergent disease and its effects are still under study. Conversely, the effect of other factors remain unclear. This study only reviewed risk factors for microcephaly related to ZIKV, but the Congenital Zika Syndrome effects is inconstant and these and other factors might be associated to different outcomes of Zika infection during pregnancy. Although there was a high demand and production of studies to understand the pathogenicity of ZIKV in the last three years, the studies conducted had high heterogeneity on methods performed and data collection. This highlights the need for dialogue between researchers seeking to investigate an emergent problem in public health. Future research needs to homogenize definitions of relevant outcomes, test hypotheses of potential disease modulators, include other aspects of the Congenital Zika Syndrome other than microcephaly and include other variables that can impact birth defects.

List Of Abbreviations

CZS—Congenital Zika Syndrome

PZIK—Zika virus infection during pregnancy

WHO—World Health Organization

ZIKV - Zika virus

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study as well as data not included in the analysis, are available from the corresponding author, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LGG, BAM, JLMC, WNA and MVdesigned the review. LGG and MV coordinated the review. LGG registred the study protocol. SM conducted the literature searches, imported records, and removed duplicates. LGG screened the records, extracted the data and appraised the quality of evidence of all records, contacted the authors to request primary data and led the writing of the paper. BAM, JLMC, JEC, ACESP and EM conducted the screening of titles and abstracts. JEC and ACESP extracted data and ACESP appraised the quality of evidence of the included studies. LGG and ACESP analysed the data of the systematic review and meta-analysis. GAS, WNA, BAM, JLMC and MV contributed with the analysis and interpretation of data and assisted with the writing. MV solve the disagreenments and coordinated the review. BS, CVV, GVAF, LP, LOV, VRN contributed equally, conducted the primary studies and provided the data included in the meta-analysis. All authors were responsible for revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Protocol registration

This systematic review was registred with the International Prospective Register of Systematic Reviews (PROSPERO), registration no. CRD 42018088075.

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Tables

Table 1 - Characterization of the selected studies

Authors (year)	Type of study	Country	Period of Study	Aim of the study	Definition of Zika virus positive	Quality assessment
Aragao, MFVV *et al.* (2017) [31]	Case-control	Brazil	Dec 2015 – Nov 2016	*"to review neuroimaging of infants to detect cases without microcephaly and compare them with those with microcephaly"*	Laboratory evidence: ZIKV IgM in cerebral spinal fluid and/or serum samples	Satisfactory
Schaub, B *et al.* (2017) [29]	Case-control	Martinique	Jan 2016 - Nov 2016	*"to describe the early ultrasound markers and progression of the fetal cerebral insults during the pregnancy"*	Laboratory evidence: ZIKV RNA (RT-PCR) or ZIKV IgM or IgG in serum, amniotic fluid, placenta, amnion, cerebrospinal fluid, or brain samples	Satisfactory
Krow-Lucal, ER *et al.* (2018) [32]	Case-control	Brazil	Aug 2015 - Feb 2016	*"to assess the association of microcephaly and Zika vírus"*	Laboratory evidence: ZIKV IgM in blood samples. Presumed infection also acceptable.	Satisfactory
Honein, M A *et al.* (2017) [30]	Cohort	USA	Dec 2015 – Sep 2016	*"to estimate the preliminary proportion of foetuses or infants with birth defects after maternal Zika virus infection by trimester of infection and maternal symptoms"*	Laboratory evidence: ZIKV RNA (rRT-PCR), ZIKV IgM (PNRT ≥ 10) and either a DenV- IgM or a DenV PRNT<10 (or both) in serum, placenta or other tissue samples	Good
Kumar, M *et al.* (2016) [38]	Case-control	USA	2009 - 2012	*"to find a link between ZIKV infection and babies born with microcephaly" in Hawaii*	Laboratory evidence: ZIKV IgM and IgG in serum samples	Good
Brasil, P *et al.* (2016) [33]	Cohort	Brazil	Sep 2015 - May 2016	*"to describe clinical manifestations in mothers and repercussions of acute ZIKV infection in infants"*	Laboratory evidence: ZIKV RNA (RT-PCR) in serum and/or urine samples	Good
Pomar, L *et al.* (2017) [34]	Cohort	French Guyana	Jan 2015 - Jul 2016	*"to establish the incidence of fetal central nervous system (CNS) anomalies (including microcephaly), signs of congenital infection and fetal loss in pregnant women infected with Zika virus (ZIKV) and non-infected pregnant women in western French Guiana"*	Laboratory evidence: ZIKV RNA (RT-PCR) or ZIKV IgM or PRNT in serum, placenta, urine, amniotic fluid and fetal samples	Satisfactory
Sanz Cortes, M *et al.* (2018) [35]	Cohort	Colombia	Dec 2015 to Jul 2016	*"(1) to assess the prevalence of microcephaly and the frequency of the anomalies that include a detailed description based on ultrasound and magnetic resonance imaging in foetuses and ultrasound, magnetic resonance imaging, and computed tomography imaging postnatally, (2)*	Laboratory evidence: ZIKV IgM or IgG in serum samples, if positive ZIKV	Satisfactory

				to provide quantitative measures of fetal and infant brain findings by magnetic resonance imaging with the use of volumetric analyses and diffusion-weighted imaging, and (3) to obtain additional information from placental and fetal histopathologic assessments and postnatal clinical evaluations"	RNA (RT-PCR) in serum and amniotic fluid offered	
Shiu, C *et al.* (2018) [36]	Cohort	USA	Jan 2016 – Dec 2016	*"to assess clinical outcomes and challenges associated with Zika virus screening and testing"*	Laboratory evidence: ZIKV RNA (rRT-PCR), ZIKV IgM in serum, placenta or other tissue samples	Satisfactory
Vargas, A *et al.* (2016) [39]	Case series	Brazil	Aug 2015 - Oct 2015.	*"to describe the first cases of microcephaly possibly related to Zika virus in live born babies reported in the Metropolitan Region of Recife, Pernambuco State, Brazil"*	Presumed infection	Satisfactory
França, G V A *et al.* (2016) [37]	Case series	Brazil	Nov 2015 – Feb 2016**	*"to describe these newborn babies in terms of clinical findings, anthropometry, and survival"*	Laboratory evidence: ZIKV RNA (RT-PCR) or ZIKV IgM or IgG in serum samples. Presumed infection also acceptable *	Low
Ventura, L O *et al.* (2017) [40]	Cross-sectional	Brazil	*May 2015 – Dec 2015*	*"to describe the visual impairment associated with ocular and neurological abnormalities in a cohort of children with congenital Zika syndrome (CZS)"*	Laboratory evidence: ZIKV IgM in cerebral spinal fluid samples	Good

*Presumed infection: when clinical-epidemiological diagnosis were used to determine a ZIKV infection. It can be supported by image data or by discarding other diseases.
** All notified cases in different studies and areas from Brazil during this period are included in this study, i.e., data from Aragão et al., 2017 from December 2015 to fev 2016; Krow-Lucal et al., 2018, from November, 2015 to February, 2016; Brazil et al., 2016, from November 2015 to February 2016; Ventura et al., 2017, November and December 2015.

Table 2 - Population characteristics of the studies included in the meta-analysis

Study	# enrolled ZIKV+ pregnant women	# enrolled ZIKV+ foetus/infants	# ZIKV+ foetus/infants with microcephaly	Sex (male/total)		Maternal ethnicity (%)		Maternal age – mean (SD)
				Microcephaly +	Microcephaly -	Microcephaly +	Microcephaly -	
Aragao, MFVV *et al.* (2017) [31]	U*	19	16	-	-	-	-	
Schaub, B *et al.* (2017) [29]	14	14	9	5/9	4/3	9/9	-	26,78 (6.33)
Krow-Lucal, ER *et al.* (2018) [32]	U*	115	43	-	-	-	-	
Honein, M A *et al.* (2017) [30]	442	55	18	-	-	-	-	
Kumar, M *et al.* (2016) [38]	4	4	3	1/3	0/1	3/3	1/1	27 (5.57)
Brasil, P *et al.* (2016) [33]	134	134	4	-	-	-	-	
Pomar, L *et al.* (2017) [34]	301	278	28	15/28	126/250	27/28	244/250	28,08 (7.75)
Sanz Cortes, M *et al.* (2018) [35]	12	9	7	-	-	-	-	
Shiu, C *et al.* (2018) [36]	8	87	5	-	-	-	-	
Vargas, A *et al.* (2016) [39]	U*	40	40	20/43	5/14	12/43	2/14	23.5 (8)
França, G V A *et al.* ** (2016) [37]	1501	602	330	244/567[!]	221/691[!]	495/567[!]	591/691[!]	24.79 (6.668)
Ventura, L O *et al.* (2017) [40]	U*	32	29	54/148	9/148	-	-	27.36 (7.28)

* Unknown (Not reported in the paper)
** All notified cases in different studies and areas of Brazil, during this period, are included in this study, i.e., data from Aragão et al., 2017 from December 2015 to fev 2016; Krow-Lucal et al., 2018, from November, 2015 to February, 2016; Brazil et al., 2016, from November 2015 to February 2016; Ventura et al., 2017, November and December 2015.

Figures

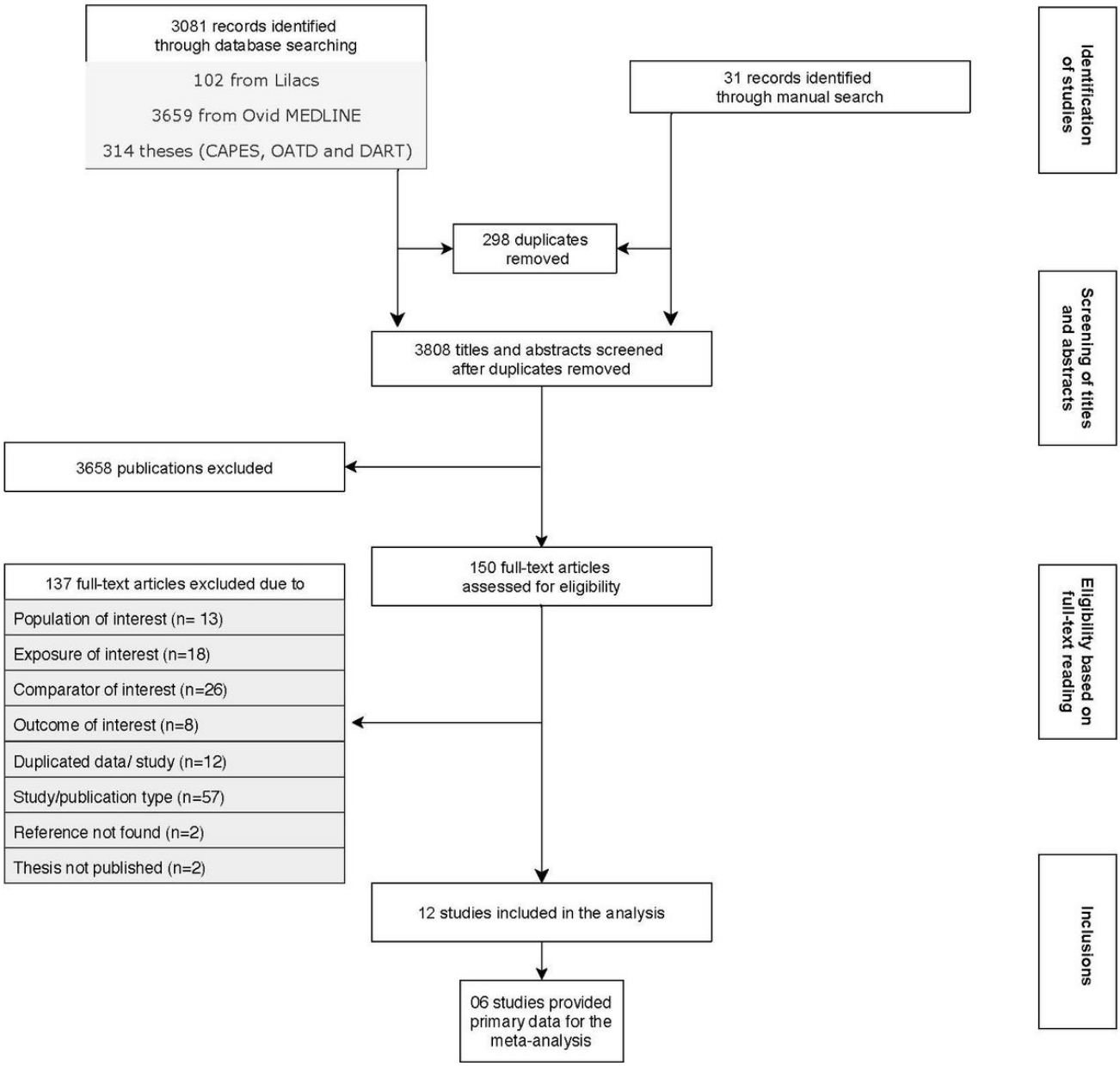

Figure 1

Flow diagram of Selection of studies for the systematic review and meta-analysis

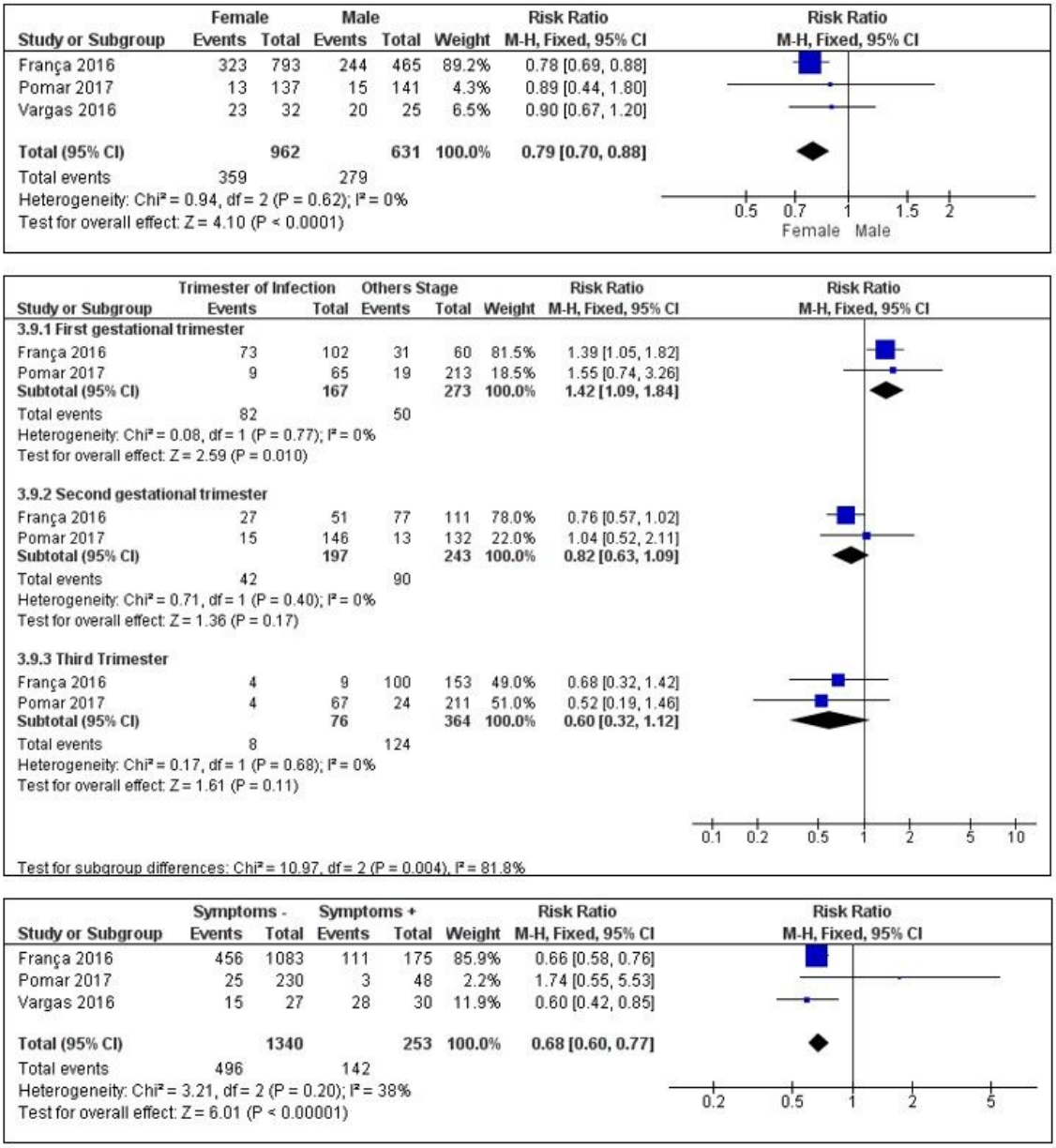

Figure 2

Meta-analysis forest plot for prospective studies studies. 2a. Sex of the foetus/infant. 2b. Trimester of pregnancy when ZIKV infection occurred. 2c. Symptoms of ZIKV infection during pregnancy

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