DISCLAIMER

This paper was submitted to the *Bulletin of the World Health Organization* and was posted to the Zika open site, according to the protocol for public health emergencies for international concern as described in Christopher Dye et al. (http://dx.doi.org/10.2471/BLT.16.170860).

The information herein is available for unrestricted use, distribution and reproduction in any medium, provided that the original work is properly cited as indicated by the Creative Commons Attribution 3.0 Intergovernmental Organizations licence (CC BY IGO 3.0).

RECOMMENDED CITATION

Chibueze EC, Tirado V, da Silva Lopes K, Balogun OO, Takemoto Y, Swa T, et al. Zika virus infection in pregnancy: a systematic review of disease course and complications [Submitted]. Bull World Health Organ. E-pub: 9 June 2016. doi: http://dx.doi.org/10.2471/BLT.16.178426

Zika virus infection in pregnancy: a systematic review of disease course and complications

Ezinne C Chibueze,* Veronika Tirado,† Katharina da Silva Lopes,* Olukunmi O Balogun,* Yo Takemoto,* Toshiyuki Swa,‡ Amarjargal Dagvadorj,§ Chie Nagata,∥ Naho Morisaki,¶ Clara Menendez,∥ Erika Ota,∥ Rintaro Mori,∥ Olufemi T Oladapo

*a Department of Health Policy, National Center for Child Health and Development, 2-10-1 Okura, Setagaya ku, Tokyo, 157-8535 Japan

†Department of Public Health Sciences, Global Health (IHCAR), Karolinska Institutet, Stockholm, Sweden

‡Graduate School of Human Sciences, Osaka University, Osaka, Japan

§Department of Health Informatics, Kyoto University, Yoshida Konoe-cho, Syako-ku, Kyoto, Japan

∥Department of Education for Clinical Research, National Center for Child Health and Development, Tokyo, Japan

¶Department of Social Medicine, National Center for Child Health and Development, Tokyo, Japan

§Barcelona Institute for Global Health (ISGlobal)-Hospital Clinic-Universitat de Barcelona, Barcelona, Spain

∥St. Luke’s International University, Graduate School of Nursing, Global Health Nursing, Tokyo, Japan

‡UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research World Health Organization, Geneva, Switzerland.

Correspondence to Ezinne C Chibueze (email: ezinne.chibueze@gmail.com).

*(Submitted: 8 June 2016 – Published online: 9 June 2016)*
Abstract

Objectives
To characterize maternal Zika virus (ZIKV) infection, including its natural history, risk of adverse pregnancy and birth outcomes, and describe the range of associated clinical manifestations and abnormalities with the aim of complementing evidence base for WHO interim guidance on pregnancy management in the context of ZIKV infection.

Methods
We searched MEDLINE, EMBASE, CINAHL, World Health Organization Global Health Library, Cochrane Central Trials Register, and Cochrane Database of Systematic Reviews from inception until March 2016. Two review authors independently screened and assessed full texts of eligible reports and extracted data from relevant studies. The quality of studies was assessed using the Newcastle-Ottawa Scale (NOS) and the National Institute of Health (NIH) tool for observational studies and case series/reports, respectively.

Results
Among 142 eligible full-text articles, 18 met the inclusion criteria (13 case series/reports and five cohort studies). No study suggested a higher risk of ZIKV infection in pregnant women after Aedes mosquito exposure compared to the non-pregnant population. Common symptoms among pregnant women with suspected/confirmed ZIKV infection were fever, rash and arthralgia. Apart from one case of Guillain-Barré syndrome among ZIKV-infected mothers, no other case of severe maternal morbidity or mortality reported. Complications reported in association with maternal ZIKV infection included a wide range of fetal and newborn neurological and ocular abnormalities; fetal growth restriction, stillbirth and perinatal death. Microcephaly was the main neurological complication reported in eight studies, with an incidence of about 1% in one study. Seven studies reported no symptoms in some ZIKV-infected pregnant women. Normal birth outcomes were also reported. No study reported on clinical features or complications following ZIKV co-infection with other flaviviruses in pregnant women.

Conclusion
Given the wide and variable fetal and newborn presentations/complications associated with prenatal ZIKV infection, identifying effective strategies to reduce the impact of ZIKV infection on families and health systems in resource-constrained settings remains a challenge. This review highlights key evidence gaps that should be urgently addressed in the global response to the current ZIKV outbreaks.

Keywords: Zika virus, ZIKV, flavivirus, microcephaly, congenital infections, congenital malformation
Introduction
Since the late 1940s, there have been reports of Zika virus (ZIKV) isolated from animals and humans in Uganda and Nigeria (1, 2). At present, ZIKV has a broad distribution across sub-Saharan Africa, South-East Asia, and the Americas (1). ZIKV belongs to the Flaviviridae family of viruses and is transmitted by Aedes mosquitoes. In humans, ZIKV infection is often mild or asymptomatic. However, an exponential increase in the number of symptomatic or suspected cases across continents has intensified international concern (3). Prior to 2007, few cases of ZIKV infection were reported (4). Thereafter, an infectious outbreak affecting 74.6% of the Micronesian Yap population (5) and 32,000 people in the French Polynesian region in 2013–2014 were reported (6, 7). In the latest outbreak in 2015, up to 1.3 million suspected cases were identified in Brazil over a 9-month period (8, 9). In addition to transmission by Aedes mosquitoes, sexual transmission has also been reported (10, 11).

In spite of the international efforts to curb its spread, ZIKV infection has expanded to 62 countries and territories, and is projected to increase due to potential climate change affecting the spread of the ZIKV Aedes vector (12-15). Notably in 2015, a 20-fold increase in the incidence of microcephaly relative to previous years was reported with the onset of ZIKV transmission in northeastern Brazil. This led to the World Health Organization (WHO) declaring a Public Health Emergency of International Concern (PHEIC) on February 1, 2016 (12, 16, 17).

Pregnant women are at exceptional risk of being affected with potential adverse effects of ZIKV infection. Delayed or arrested neurological development and complications common in fetuses and neonates born to ZIKV-infected women may drain family resources due to the need for special care. The health systems in most ZIKV-affected areas have limited resources to manage the current outbreak and its consequences.

Many gaps in the knowledge regarding ZIKV infection exist, including the clinical spectrum of disease presentation in infected pregnant women, the risk of complications in mother, fetus and newborn, as well as the impact of ZIKV co-infection with other flaviviruses on pregnancy. As part of the process to complement the evidence base for WHO interim guidance on pregnancy care in the context of ZIKV infection, we conducted a systematic review to characterize ZIKV infection, including its natural history, risk of adverse outcomes in pregnant women, and describe the range of associated clinical manifestations and associated abnormalities.

Methods
Search strategy
We searched the following electronic databases: MEDLINE, EMBASE, CINAHL, World Health Organization Global Health Library (WHOGL), and Cochrane Central register of Controlled trials (CENTRAL) on March 3, 2016. Search terms were configured for each database according to the level of term indexation by an information specialist. Search terms included flavivirus, chikungunya virus, fever, arbovirus, Zika, congenital malformations, cephalometry, and nervous system abnormalities (Appendix 1). There were no dates, language or study design restrictions. We registered this review in PROSPERO, the international prospective register of systematic reviews of the University of York and the National Institute for Health Research, under the number CRD4201603969.

Selection of studies

We considered all study designs including randomised controlled trials, prospective or retrospective cohorts, cross-sectional, case-control studies and case series/reports. Original reports, briefs, letters, editorials, correspondence and news reports were also considered for inclusion. A minimum of two review authors assessed the title and abstract of references for relevance to review objectives. We evaluated the full text of potentially eligible records for inclusion relative to our review objectives. This included primary data on disease characteristics in ZIKV-infected pregnant women and their babies and the risk of adverse pregnancy outcomes. References of included reports were also searched for potentially eligible studies. Disagreements on eligibility of reports, where present, were resolved in consensus with a third review author.

Types of studies

We considered all studies reporting on ZIKV infection and complications in pregnant women residing in or with a history of travel to areas of ongoing ZIKV transmission or recent ZIKV outbreaks. Studies comparing pregnant and non-pregnant women with ZIKV infection were considered for inclusion where available. We excluded any study or report lacking primary data.

Types of participants

Pregnant women suspected of being at risk of, or diagnosed with ZIKV infection regardless of their location, or who have had sexual contact with a partner who (i) recently returned from an area of active ZIKV transmission, or (ii) was diagnosed with ZIKV infection.
Data extraction and synthesis

Two review authors independently extracted and presented data based on the review objectives in an agreed data collection form. We summarised the data in a descriptive form (Table 1).

We extracted information on study design, sample size, natural history of maternal and fetal ZIKV infection, symptoms, presence and type of clinical features, pregnancy-specific complications during pregnancy, childbirth or postpartum period. The absolute risk of microcephaly and other birth defects was also recorded where available.

Risk of bias Assessment

Two independent review authors assessed the quality of included studies. For individual case series/reports, a quality assessment of the National Institute of Health Tool (NIH) (18) was applied. This tool includes questions based on nine criteria to which either of the binary answers (Yes/No) was allotted. Based on the number of ‘Yes’ answers, a rating of good (7 - 9), fair (4 - 6) or poor (≤3) was allocated to the individual study and differences in quality rating amended by consensus. Studies for which the criteria were irrelevant were labelled ‘not applicable’ and ‘cannot determine’ if such information was lacking in the study.

For observational studies, we applied the Newcastle-Ottawa Scale (19) which consisted of lead questions aimed at assessing three domains – selection, comparability and outcome to which a maximum of three points could be allotted as previously described (20).

Results

Search Results

Search strategies identified 2316 records as shown in the PRISMA flow chart in Figure 1. Of 142 eligible full texts, 18 studies met our inclusion criteria (reasons for exclusion are outlined in Appendix 2).

Characteristics of included studies

All but one study were published in 2016 (21). The studies were conducted largely in South America: Brazil (11), Colombia (1), Puerto Rico (1), and Venezuela (1). Other studies were conducted in France (1), Slovenia (1) and the USA (2). In all studies, pregnant women were either living in areas of ongoing transmission (21-36), had resided in (37), or travelled (38) to ZIKV-affected areas during pregnancy.
Regarding study design, there were 13 case series/reports (21, 23-26, 28, 29, 31, 33, 35-38) and five observational studies (22, 27, 30, 32, 34). The observational studies were either prospective (34), retrospective (22, 39) or mixed (30, 32) in design. All presented information on clinical manifestations, pregnancy-specific complications and diagnoses in women and their fetuses/newborns.

Diagnostic tests to confirm the presence of ZIKV infection in pregnant women included reverse transcription polymerase chain reaction (RT-PCR) for ZIKV nucleic material (21, 26, 30, 31, 34, 36, 40) and tests on serum (21, 25), breastmilk (21), amniotic fluid (38) and urine (25) samples. IgG and IgM antibody tests for viral ZIKV exposure were also conducted (25, 29, 34, 36) (41). Eleven of the 18 included studies conducted serological tests to exclude other infections such as dengue (21, 28, 33, 34), chikungunya (33), toxoplasmosis (22, 23, 25, 28, 29, 33, 35), rubella (22, 23, 25, 28, 29, 33, 34), cytomegalovirus (22, 23, 25, 28, 29, 33, 34), herpes simplex virus (22, 23, 25, 28, 29, 33), HIV (22, 23, 25, 28, 29, 33, 36), Human T-cell lymphotrophic virus (36), Hepatitis C Virus (36) and Hepatitis B Virus (25).

For fetal imaging, ultrasound (25, 31, 33, 36-38), computed tomography scanning for brain calcifications (27) and magnetic resonance imaging (38) were employed.

In some studies, ocular examinations were also conducted for the mother (23, 35) and newborn (22, 23, 35).

**Characteristics of maternal ZIKV infection**

**Symptoms /signs/complications**

No study suggested a greater likelihood of acquiring ZIKV infection in pregnant women after exposure to *Aedes* mosquitoes compared to the non-pregnant population. Most studies only presented fetal and newborn features without further information on how these varied with the gestational age at the time of maternal ZIKV infection.

Rash was the most common sign of ZIKV infection in pregnant women in 15 of 18 included reports (21-30, 33-35). Two of the remaining three studies (one observational study, one case series) did not report clinical manifestations during pregnancy as they focused on the newborns of ZIKV-infected mothers (31, 32). Rash was absent in the third study as the mothers were asymptomatic (36). In seven reports the rash was further qualified as ‘a pruritic cutaneous rash with itching in the back and hands’, ‘generalised, descending macular’ or ‘generalised maculopapular’ (21, 29, 34, 37), ‘petechial’ or ‘generalised’ (21, 29, 33, 34, 38, 42). Only one case-series reported on symptom
occurrence after delivery in two ZIKV-infected pregnant women (43). A four-day duration of persistent rash in one pregnant woman and a pruritic rash on the third day after delivery in the second case was observed. In the former, the rash started two days before and ended two days after delivery of a healthy infant. In the latter case, a mild fever and myalgia were also reported.

Other reported signs and symptoms included fever (22, 24, 25, 28-30, 33, 34, 37), chills (24, 25), malaise (25, 30, 35), arthralgia (22, 25, 29, 30, 34, 35), myalgia (24, 25, 30, 33, 34, 37, 43), myotonia (24), asthenia (25), jaundice (25), paraesthesia (34), hemiparesis (25), headache (22, 29), conjunctivitis or conjunctival injections (24, 34, 44), lymphadenopathy (34), pain (eye, abdominal, lumbar, pelvis, body and joint) (25, 30, 37, 44), anaemia (25), edema in lower limbs (25), nausea (26, 34), vomiting (34), dermal bleeding (34) and ‘respiratory findings’ (34).

Grade of fever was provided in three reports, a low grade fever of 37.5 to 38.0 °C in two reports (21, 34) and a “high fever” (37) in the third. Fever was absent in ZIKV-infected pregnant women in two case reports (36, 44).

An observational study reported a significantly higher frequency of lymphadenopathy and conjunctival injections in ZIKV-infected compared with uninfected pregnant women (34).

Twelve studies provided information on trimester-specific occurrence of symptoms (21, 23-25, 27-30, 33, 35, 37, 44). Symptoms were observed more commonly in the first trimester (23, 25, 27-29, 33, 35, 37, 38, 44). Among the ZIKV-infected pregnant women in individual reports, seven studies reported no signs or symptoms (22, 23, 25, 27, 29, 35, 36).

Neurological complications were reported in ZIKV-infected pregnant women in one case report (24) and in one observational study (34). Guillain-Barré syndrome (GBS) at 28 weeks gestation in addition to other typical ZIKV signs and symptoms were reported in one case report only (24). The patient had respiratory distress that prompted intensive care unit (ICU) admission. She fully recovered within three weeks and gave birth to a normal infant at 39 weeks of gestation.

Preterm birth necessitating emergency caesarean delivery was reported in two observational studies (28, 34) and in one case series (21). In the two observational studies, intrauterine growth restriction (IUGR) was an underlying complication. In one of the studies (34), the two preterm births reported were due to IUGR accompanied by
oligohydramnios, macular hypoplasia and placental insufficiency in one fetus and anhydramnios in the other.

Miscarriages were reported in five ZIKV-infected pregnant women in two case series (28, 38) and one observational study (34). Stillbirths were also recorded in three pregnant women in one observational study and one case report (34, 36).

**Characteristics of fetuses/newborns of ZIKV infected pregnant women**

**Fetuses**

**Complications**

A wide spectrum of complications was reported in association with maternal ZIKV infection (Table 2). Microcephaly visible on fetal ultrasound was the main neurologic complication in two observational studies and six case series/reports (25, 28, 30, 31, 33, 34, 36, 37). Among them, ocular abnormalities (22, 23, 29, 31, 33, 35), cerebral calcifications and cerebellar abnormalities were commonly reported (23, 25, 31, 33-38). In one observational study of 35 infants with microcephaly (27), 11 fetuses had intrauterine brain injury accompanied by stunting of cerebral growth prior to birth. Cerebral abnormalities included brain atrophy, absent corpus callosum and ventriculomegaly. Ocular abnormalities included intraocular calcifications and microphthalmia (31, 33). In fetuses of ZIKV-infected pregnant women, placental and umbilical (33, 34, 38) and amniotic fluid (34) abnormalities were reported.

IUGR was reported in five studies (two observational, three case-series/reports) (21, 34, 39, 41, 45) and stillbirths in three studies (34, 36). Despite normal fetal biometrics at 14 weeks in one case of an asymptomatic ZIKV-infected pregnant woman, IUGR was detected at 18 weeks and accompanied by other neurological abnormalities including microcephaly, hydranencephaly, hydrops fetalis and eventual stillbirth (36).

Fetal deaths were reported in two studies (one case series and one observational study). Deaths occurred in four fetuses at > 30 weeks gestation (28, 34) and elective termination of pregnancies reported in seven pregnant women (32, 38).

**Newborns**

**Symptoms/signs**

Rash described as ‘transient isolated diffuse’ was reported in an infant on the fourth day post-delivery (43). Other symptoms reported included conjunctivitis or conjunctival injections (25, 29).
Complications

Similar to fetuses, microcephaly was observed at birth in 11 studies (four observational and seven case series/reports) (22, 23, 27-31, 33-35, 38) with accompanying ocular and brain abnormalities. In four studies, microcephaly that was observed at birth was preceded by fetal diagnosis of IUGR (27, 34, 36, 37). Ocular abnormalities included focal pigment mottling, chorioretinal macular atrophy, optic nerve abnormalities, cataracts, intra-ocular calcifications, microphthalmia, conjunctival injections, optic disc cupping, lens subluxation in addition to bilateral iris coloboma, foveal reflex loss, macular hypoplasia and scarring (22, 29, 35, 46).

Musculoskeletal abnormalities reported included clubfoot (34) and severe arthrogryposis (31, 33) in two case series. In one case report, ‘arthrogryposis’ was also reported at post-mortem examination (36).

Four studies reported the birth of healthy infants (24, 34, 40, 43) and one study reported early neonatal deaths in three infants with microcephaly within 20 hours of delivery (28).

Absolute risk of fetal microcephaly (and other birth defects) in women with ZIKV infection

No report provided detailed information from which factors related to ZIKV infection could be described. One observational study provided a trimester-specific modelling estimate risk for microcephaly in first [95 cases (95% confidence interval (CI) 34-191)], second [84 cases (95% CI 12-196)] and third [0 case (95% CI 0-251)] trimesters, per 10,000 ZIKV-infected pregnant women (32). The baseline prevalence for the risk of microcephaly were 2 (0 – 8), corresponding to a risk ratio of 53.4 (95% CI 6.5 – 1061.2) in the first trimester; 4 (95% CI 0 – 12), corresponding to a risk ratio of 23.2 (95% CI 1.4 – 407.8) in the second trimester; and 10 (95% CI 3 – 18), corresponding to a risk ratio of 0 (95% CI 0 – 49.3) in the third trimester.

Fetal abnormalities, including microcephaly, were detected in women who underwent ultrasound at time-points ranging between 26 and 30 weeks (31, 36, 42).

Impact of ZIKV co-infection in pregnancy

There was a lack of information on co-infection with other flaviviruses and common congenital infections. Serological tests were conducted in studies to exclude possible co-infections and/or antibody tests for previous exposure to other related flaviviruses.
Eleven reports excluded co-infections that included toxoplasmosis (22, 25, 28, 29, 33, 35, 36, 46), dengue (21, 28, 33), chikungunya (28, 33), HIV (22, 25, 28, 29, 33, 34, 36, 46), hepatitis B virus (HBV) (25), hepatitis C virus (HCV) (36), cytomegalovirus (CMV) (22, 25, 28, 29, 33, 34, 36, 46), herpes simplex virus (HSV) (22, 25, 28, 29, 33, 46), Epstein-Barr virus (EBV) (25), rubella (22, 25, 28, 29, 33, 34, 36, 46), human T lymphotrophic virus (HTLV) (36), parvovirus B19 (33), syphilis (25, 29, 33) and rheumatoid fever (25).

Four reports assessed previous exposure to other infections based on the presence of IgG (25, 29, 34, 36) and IgM (29, 36) antibody positivity to cytomegalovirus, rubella and toxoplasmosis (25, 34, 36) infections. IgG positivity to infections indicating exposure to dengue virus in 88% of 88 pregnant women was reported in one observational study (34), and toxoplasmosis and rubella in three of 28 women (25) in two case series/report.

**Risk of Bias Assessment**

We judged the overall risk of bias as fair or good for all the included case series/reports except one, which we rated as poor (44) due to selective reporting (Table 2).

Four of five observational studies included in the review were assigned an average quality rating of four to five stars based on the NOS. One observational study (22) was assigned a very low quality rating of one star as it provided sparse information (Table 3).

**Discussion**

No study clearly described the natural history of maternal ZIKV infection and its effects on newborns of affected mothers. Most studies focused on presenting symptomatology and associated complications in pregnant women and their fetuses/newborns. Relative to non-pregnant women or the general population (11, 47), symptoms and complications of ZIKV infection were comparable.

Maternal ZIKV infection tended to have more adverse effects on the fetus and the infant than on the mother, as most maternal symptoms were self-limiting. A wide spectrum of presentation was observed in fetuses and newborns of ZIKV-infected mothers, ranging from normal to abnormal ultrasound findings during pregnancy to healthy newborns or newborns with abnormality. A similar pattern was observed in ZIKV-infected pregnant women, ranging from symptomatic and asymptomatic clinical presentation to uncomplicated deliveries in a majority of studies. Severe pregnancy-specific complications were uncommon and no maternal deaths were recorded. This highlights a
challenge for both health providers and mothers at risk because of the increased likelihood of missed opportunities due to frequent asymptomatic presentation.

The diagnostic accuracy of tests employed in the ZIKV context is still unclear (48) because existing studies are based on epidemiological models. In some women, ZIKV positivity was confirmed later in pregnancy, although the standard RT-PCR tests done in early trimesters were negative. Fetal ultrasound tests that were negative in the first and second trimesters were positive in late pregnancy stage (36). The absolute risk of developing fetal abnormalities is also unclear, but microcephaly is unlikely being a rare condition.

ZIKV shares the same vector with other arboviruses including chikungunya and dengue. TORCH (Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus (CMV), and Herpes) infections have been associated with congenital malformations including central nervous system anomalies. In the included reports, the absence of co-infection with or previous exposure to other viruses was established in most of the pregnant women. In some studies, IgG-positivity to dengue and toxoplasma were observed. Immunity to rubella and CMV were also reported in some women with poor outcomes. Potential synergy due to the presence of immunity and/or seropositivity to other viruses could not be ascertained as clinical presentation varied from the absence of symptoms to the presence of typical symptoms seen in ZIKV-infected pregnant women. In one study, about half of the pregnant women presented with rash had lymphadenopathy (34), which is commonly observed in dengue infection due to lymphatic infiltration (49). Although inconclusive, the history of lymphadenopathy in some pregnant women in this study in addition to the presentation of rash may show a possible role for dengue in extending the spectrum of maternal or fetal presentation.

Indirect evidence from the natural history of viral infections that share similar characteristics and complications with ZIKV, such as CMV, may be important in understanding ZIKV infection.

In some studies, sample selection was based on the clinical features presented. Limitation of the study population to only pregnant women presenting with rash and fetuses with microcephaly as seen in some reports could be misleading as clinical features were limited to these presentations. The rigorous search strategy, inclusion of foreign language studies and exclusion of overlapping studies add to the strength of this review.

The broad spectrum of presentation and complications in fetuses and newborns of ZIKV-infected pregnant women provides an insight into the potential liability for affected women, their families and health systems in resource-constrained settings.
There is a need to respond to the remaining critical gaps in the knowledge that would help to guide control policies for ZIKV in pregnancy. This review highlights key evidence gaps that need to be urgently prioritized by the international community.

**Acknowledgements**

We are grateful to Chiemi Kataoka and Miwako Segawa for help with full text retrieval. We would also like to thank Dr. Julian Tang of the Department of Education for Clinical Research, National Center for Child Health and Development, for proofreading and editing this article. The preparation of this review was financially supported by the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research, World Health Organization; Research on Global Health Issues, Japan Agency for Medical Research and Development (AMED), Clinical Research Program for Child Health and Development from Japan Agency for Medical Research and Development (AMED) and the National Center for Child Health and Development (NCCHD). The manuscript represents the views of the named authors only.

**Abbreviations**

MEDLINE Medical Literature Analysis and Retrieval System Online

EMBASE Excerpta MEdata Database

CINAHL Cumulative Index of Nursing and Allied Health Literature

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-analyses

WHOGL World Health Organization Global Health Library

CENTRAL Cochrane Central Register of Controlled Trials

**Authors’ contributions**

OTO conceived the study. Hand-searching, screening, data extraction, was performed by ECC, VT, KSL, YT, OBO, AD, CN and NM. TS assisted with search strategy and conducted the search. RM and OTO gave guidance on project design, data extraction and methodological assessments. ECC and VT drafted the manuscript. CN, NM, CM, EO, RM, and OTO revised and edited the manuscript. All authors read and approved the final manuscript for publication.

**Declaration of interests of review authors**

The review authors have no conflict of interest to declare.
References

1. Dick G, Haddow A. Uganda S virus: A hitherto unrecorded virus isolated from mosquitoes in Uganda.(I). Isolation and pathogenicity. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1952;46(6):600-18.

2. Haddow A, Williams M, Woodall J, Simpson D, Goma L. Twelve isolations of Zika virus from Aedes (Stegomyia) africanus (Theobald) taken in and above a Uganda forest. Bull World Health Organ. 1964;31(1):57.

3. World Health Organization. Zika situation report: Zika and potential complications. 2016. Available at: http://www.who.int/emergencies/zika-virus/situation-report/12-february-2016/en/ (Accessed March 05 2016).

4. Macnamara F. Zika virus: a report on three cases of human infection during an epidemic of jaundice in Nigeria. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1954;48(2):139-45.

5. Duffy MR, Chen T-H, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, federated states of Micronesia. N Engl J Med. 2009;360(24):2536-43.

6. Gatherer D, Kohl A. Zika virus: A previously slow pandemic spreads rapidly through the Americas. J Gen Virol. 2016;97(2):269-73.

7. Paixao ES, Barreto F, da Gloria Teixeira M, da Conceicao N Costa M, Rodrigues LC. History, Epidemiology, and Clinical Manifestations of Zika: A Systematic Review. Am J Public Health. 2016;106(4):606-12.

8. Cao-Lormeau V-M, Musso D. Emerging arboviruses in the Pacific. The Lancet. 2016;384(9954):1571-2.

9. Resources and latest news about zika virus disease available from ECDC. Eurosurveillance. 2016;21(5).

10. Hills SL, Russell K, Hennessey M, Williams C, Oster AM, Fischer M, et al. Transmission of Zika Virus Through Sexual Contact with Travelers to Areas of Ongoing Transmission - Continental United States, 2016. MMWR Morb Mortal Wkly Rep. 2016;65(8):215-6.

11. Goorhuis A, von Eije KJ, Douma RA, Rijnberg N, van Vugt M, Stijnis C, et al. Zika virus and the risk of imported infection in returned travelers: Implications for clinical care. Travel Med Infect Dis. 2016;14(1):13-5.

12. Fauci AS, Morens DM. Zika virus in the americas-yet another arbovirus threat. N Engl J Med. 2016;374(7):601-4.

13. Gatherer D, Kohl A. Zika virus: a previously slow pandemic spreads rapidly through the Americas. J Gen Virol. 2016;97(2):269-73.

14. Yakob L, Walker T. Zika virus outbreak in the Americas: The need for novel mosquito control methods. The Lancet Global Health. 2016;4(3):e148-e9.

15. Weaver SC, Reisen WK. Present and future arboviral threats. Antiviral Res. 2010;85(2):328-45.

16. Chang C, Ortiz K, Ansari A, Gershwin ME. The Zika outbreak of the 21st century. J Autoimmun. 2016;68:1-13.

17. Victora CG, Schuler-Faccini L, Matijasevich A, Ribeiro E, Pessoa A, Barros FC. Microcephaly in Brazil: How to interpret reported numbers? The Lancet. 2016;387(10019):621-4.

18. National Heart LaBI. Quality Assessment Tool for Case Series Studies. National Institutes of Health; 2014. URL: http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case_series [updated March 2014]; Accessed April 18 2016.

19. Wells G, Shea B, O’connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.

20. Chibueze EC, Parsons AJ, Ota E, Swa T, Oladapo OT, Mori R. Prophylactic antibiotics for manual removal of retained placenta during vaginal birth: a
systematic review of observational studies and meta-analysis. BMC pregnancy and childbirth. 2015;15(1):1.

21. Besnard M, Lastere S, Teissier A, Cao-Lormeau V, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. Euro Surveill. 2014;19(13).

22. McCarthy M. Severe eye damage in infants with microcephaly is presumed to be due to Zika virus. Bmj. 2016;352:i855.

23. Ventura CV, Maia M, Bravo-Filho V, Góis AL, Belfort Jr R, Belfort R, Jr. Zika virus in Brazil and macular atrophy in a child with microcephaly. Philadelphia, Pennsylvania: Lancet; 2016. p. 228-8/9p.

24. Reyna-Villasmil E, Lopez-Sanchez G, Santos-Bolivar J. [Guillain-Barre syndrome due to Zika virus during pregnancy]. Med Clin (Barc). 2016;146(7):331-2. Sindrome de Guillain-Barre debido al virus del Zika durante el embarazo.

25. Villamil-Gómez WE, Mendoza-Guete A, Villalobos E, González-Arismendy E, Uribe-García AM, Castellanos JE, et al. Diagnosis, management and follow-up of pregnant women with Zika virus infection: A preliminary report of the ZIKERNCOL cohort study on Sincelejo, Colombia. Travel Medicine and Infectious Disease. 2016((Villamil-Gómez W.E.) Infectious Diseases and Infection Control Research Group, Hospital Universitario de Sincelejo, Sincelejo, Sucre, Colombia).

26. Thomas DL, Sharp TM, Torres J, Armstrong PA, Munoz-Jordan J, Ryff KR, et al. Local Transmission of Zika Virus - Puerto Rico, November 23, 2015-January 28, 2016. MMWR: Morbidity & Mortality Weekly Report. 2016;65(6):154-8 5p.

27. Schuler-Faccini L, Ribeiro EM, Feitosa IML, Horovitz DDG, Cavalcanti DP, Pessoa A, et al. Possible Association Between Zika Virus Infection and Microcephaly -- Brazil, 2015. MMWR: Morbidity & Mortality Weekly Report. 2016;65(3):59-62 4p.

28. Brasil Martines R, Bhatnagar J, Kelly Keating M, Silva-Flannery L, Muehlenbachs A, Gary J, et al. Evidence of Zika Virus Infection in Brain and Placental Tissues from Two Congenitally Infected Newborns and Two Fetal Losses - Brazil, 2015. MMWR: Morbidity & Mortality Weekly Report. 2016;65(6):159-60 2p.

29. de Paula Freitas B, de Oliveira Dias JR, Prazeres J, Sacramento GO, Ko AI, Maia M, et al. Ocular findings in infants with microcephaly associated with presumed Zika virus congenital infection in Salvador, Brazil. JAMA ophthalmology. 2016.

30. Kleber de Oliveira W, Cortez-Escalante J, De Oliveira WTGH, do Carmo GMI, Henriques CMP, Coelho GE, et al. Increase in Reported Prevalence of Microcephaly in Infants Born to Women Living in Areas with Confirmed Zika Virus Transmission During the First Trimester of Pregnancy - Brazil, 2015. MMWR Morb Mortal Wkly Rep. 2016;65(9):242-7.

31. Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis AM. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? Ultrasound in Obstetrics & Gynecology. 2016;47(1):6-7.

32. Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D, et al. Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. The Lancet. 2016. doi: 10.1016/S0140-6736(16)00651-6 PMID: 26993883.

33. Calvet G, Aguiar RS, Melo AS, Sampaio SA, de Filippis I, Fabri A, et al. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. The Lancet Infectious diseases. 2016.

34. Brasil P, Pereira J, Jose P, Raja Gabaglia C, Damasceno L, Wakimoto M,
Ribeiro Nogueira RM, et al. Zika virus infection in pregnant women in Rio de Janeiro—preliminary report. N Engl J Med. 2016.

35. Ventura CV, Maia M, Ventura BV, Linden VVD, Araujo EB, Ramos RC, et al. Ophthalmological findings in infants with microcephaly and presumable intra-uterus Zika virus infection. Arq Bras Oftalmol. 2016;79(1):1-3.

36. Sarno M, Sacramento GA, Khouri R, do Rosario MS, Costa F, Archanjo G, et al. Zika Virus Infection and Stillbirths: A Case of Hydrops Fetalis, Hydranencephaly and Fetal Demise. PLoS Negl Trop Dis. 2016;10(2):e0004517.

37. Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, et al. Zika Virus Associated with Microcephaly. N Engl J Med. 2016;374(10):951-8 8p.

38. Meaney-Delman D, Hills SL, Williams C, Galang RR, Iyengar P, Hennenfent AK, et al. Zika Virus Infection Among U.S. Pregnant Travelers - August 2015-February 2016. MMWR: Morbidity & Mortality Weekly Report. 2016;65(8):211-4 4p.

39. Schuler-Faccini L, Ribeiro EM, Feitosa IML, Horovitz DDG, Cavalcanti DP, Pessoa A, et al. Possible Association Between Zika Virus Infection and Microcephaly - Brazil, 2015. MMWR Morb Mortal Wkly Rep. 2016;65(3):59-62.

40. Meaney-Delman D, Hills SL, Williams C, Galang RR, Iyengar P, Hennenfent AK, et al. Zika Virus Infection Among U.S. Pregnant Travelers - August 2015-February 2016. MMWR Morb Mortal Wkly Rep. 2016;65(8):211-4.

41. Sarno M, Sacramento GA, Khouri R, do Rosário MS, Costa F, Archanjo G, et al. Zika Virus Infection and Stillbirths: A Case of Hydrops Fetalis, Hydranencephaly and Fetal Demise. PLoS Neglected Tropical Diseases. 2016;10(2).

42. Mlakar J, Korva M, Tul N, Popovic M, Poljsak-Prijatelj M, Mraz J, et al. Zika Virus Associated with Microcephaly. N Engl J Med. 2016;374(10):951-8.

43. Besnard M, Lastère S, Teissier A, Cao-Lormeau VM, Musso D. Evidence of perinatal transmission of zika virus, French Polynesia, December 2013 and February 2014. Eurosurveillance. 2014;19(13).

44. Thomas DL, Sharp TM, Torres J, Armstrong PA, Munoz-Jordan J, Ryff KR, et al. Local Transmission of Zika Virus - Puerto Rico, November 23, 2015-January 28, 2016. MMWR Morb Mortal Wkly Rep. 2016;65(6):154-8.

45. Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, et al. Zika virus associated with microcephaly. N Engl J Med. 2016;374(10):951-8.

46. Ventura CV, Maia M, Bravo-Filho V, Góis AL, Belfort R. Zika virus in Brazil and macular atrophy in a child with microcephaly. The Lancet. 2016;387(10015):228.

47. Zika virus infection: global update on epidemiology and potentially associated clinical manifestations. Wkly Epidemiol Rec. 2016;91(7):73-81.

48. Chibueze EC, Parsons AJQ, da Silva Lopes K, Yo T, Swa T, Nagata C, Horita N, Morisaki N, Balogun OO, Ota E, Mori R, Oladapo OT. Accuracy of ultrasound scanning relative to reference tests for prenatal diagnosis of microcephaly in the context of Zika virus infection: a systematic review of diagnostic test accuracy. Bull World Health Organ. E-pub: 25 May 2016. doi: http://dx.doi.org/10.2471/BLT.16.178301

49. Ioos S, Mallet H-P, Goffart IL, Gauthier V, Cardoso T, Herida M. Current Zika virus epidemiology and recent epidemics. Med Mal Infect. 2014;44(7):302-7.
Records identified through database searching (n = 2776)
MEDLINE – 1171
EMBASE - 1048
CINAHL - 102
WHOGL - 64
Cochrane CCTR - 10
Cochrane CDSR - 3
Cochrane DARE - 0

Records screened after duplicates removed (n = 2316)

Records excluded (n = 2174)

Full-text articles assessed for eligibility (n = 142)

Full-text articles excluded, with reasons (irrelevance to subject, review articles) (n = 124)

Studies included in qualitative synthesis (n = 18)

Studies included in quantitative synthesis (meta-analysis) (n = 0)
| Characteristics of ZIKV infection in mothers, fetuses and newborns | Publications | Study designs | Countries | Key findings | Other information |
|---|---|---|---|---|---|
| Clinical manifestations of ZIKV maternal, fetal and newborn infection | McCarthy, M., 2016 Ventura, C.V., et al., 2016 Ventura, C.V., et al., 2016b Villamil-Gómez, W.E., et al., 2016 Thomas, D.L., et al., 2016 Schuler-Faccini, L., et al., 2016 Reyna-Villasamil, E., et al., 2016 Oliveira Melo, A., et al., 2016 Mlakar, J., et al., 2016 Meaney-Delman, D., et al., 2016 Kleber de Oliveira, W., et al., 2016 Calvet, G., et al., 2016 Brasil Martínes, R., et al., 2016 Brasil, Patrícia, et al. 2016 Besnard M, et al., 2014 de Paula Freitas, B., et al. 2016 | Retrospective cohort Case series Case series Case report Case report Retrospective cohort Case report Case report Case series Case report Case series Retros. + Prosp. Cohort Case series Case series Prospective cohort Case series Case series | Brazil Brazil Brazil Colombia Puerto Rico Brazil Venezuela Brazil Brazil USA Brazil Brazil Brazil French Polynesia Brazil | Cutaneous rash, maculopapular rash, fever, arthralgia, itch, myalgia, nausea or vomiting, bleeding, respiratory findings, conjunctivitis, malaise, headache, abdominal pain, chills, retroocular pain, edema in lower limbs, hemiparesis, asthenia, jaundice, lumbar pain | Besnard M, et al., 2014 reported mild pruritic rash without fever and mild fever (37.5 – 38 °C) |
| Not reported or vague | Cauchemez, S., et al., 2016 Oliveira Melo, A., et al., 2016 | Retrospective cohort Case reports | French Polynesia Brazil | No rash, fever or other infection Stated as ‘suffered from symptoms related to Zika virus infection’ |  |
|----------------------|-------------------------------------------------------------|---------------------------------|------------------------|--------------------------------------------------------------------------------|---|
| Asymptomatic         | Sarno, M., et al., 2016                                     | Case report                     | Brazil                 | No symptoms shown, first indication of abnormal pregnancy was at ultrasound finding of intrauterine growth retardation (18th weeks) | Not reported (NR) |
| Trimester of infection | Ventura, C.V., et al., 2016 Ventura, C.V., et al., 2016b Sarno, M., et al., 2016 Villamil-Gómez, W.E., et al., 2016 Thomas, D.L., et al., 2016 Schuler-Faccini, L., et al., 2016 Reyna-Villasmil, E., et al., 2016 Mlakar, J., et al., 2016 Meaney-Delman, D., et al., 2016 Calvet, G., et al., 2016 Brasil Martines, R., et al., 2016 Besnard M, et al., 2014 de Paula Freitas, Bruno, et al. 2016 | Case series Case report Case report Case report Case report Retrospective cohort Case report Case report Case series Case series Case series Case series | Brazil Brazil Brazil Colombia Puerto Rico Brazil Venezuela Brazil USA Brazil Brazil French Polynesia Brazil | 50 First trimester 22 Second trimester 25 Third trimester 1 Post-partum Cauchemez, S., et al., 2016 did not report trimester infection |
| **Effects on pregnancy complications (maternal)** | Reyna-Villasmil, E., et al., 2016  
Meaney-Delman, D., et al., 2016  
Brasil Martines, R., et al., 2016  
Brasil, Patrícia, et al. 2016 | Case report  
Case series  
Case series  
Prospective cohort | Venezuela  
USA  
Brazil | GBS; decreased muscle movements and difficulty speaking/swallowing, myalgia, fever, and rash and conjunctivitis for 10 days. Neurological examination showed logical alteration of cranial nerves and speech, decreased muscle strength and respiratory failure  
4 miscarriages (1st trimester)  
2 stillbirths (fetal deaths after 30 weeks of gestation) | NR |
| **Effects on pregnancy complications (fetus/newborn)** | All publications except:  
Reyna-Villasmil, E., et al., 2016  
Thomas, D.L., et al., 2016 | Case report  
Case report | Venezuela  
Puerto Rico | Microcephaly, hydraencephaly, macular alterations, optic abnormalities, intra-ocular calcification, cataracts, cerebral (intracranial) calcification, ascites and subcutaneous edema, coarse calcification, cerebellar involvement, severe arthrogryposis, severe CNS affection and gross intrauterine growth retardation, ventriculomegaly | Brasil Martines, R., et al., 2016 reported 2 fetal deaths  
Brasil, Patrícia, et al. 2016 reported 2 fetal deaths |
| **Fetus alterations frequencies/rate and absolute risk** | Kleber de Oliveira, W., et al., 2016  
Cauchemez, S., et al., 2016  
Ventura, C.V., et al., 2016b | Retros. + Prosp. cohort  
Retrospective cohort  
Case report | Brazil  
French Polynesia  
Brazil | Microcephaly had a highest prevalence in Brazilian states of Pernambuco  
Risk of microcephaly | NR |
(estimated 1%) 95 cases (34 – 191) per 10000 women (1st trimester) corresponding to a risk ratio of 53.4 (95% CI 6.5–1061.2 Severe ocular abnormalities when the infection occurs in the 1st or 2nd trimester of pregnancy

| Postpartum clinical presentations (maternal) | Besnard M, et al., 2014 | Case report | French Polynesia | Post-delivery mild pruritic rash, mild fever (37.5–38 °C) and myalgia | NR |
|---|---|---|---|---|---|
| Postpartum clinical presentations (childbirth) | Brasil Martines, R., et al., 2016 Besnard M, et al., 2014 | Case report | Case report | Brazil French Polynesia | NR |
| Other tests | McCarthy, M., 2016 Ventura, C.V., et al., 2016 Ventura, C.V., et al., 2016b Sarno, M., et al., 2016 Villamil-Gómez, W.E., et al., 2016 Reyna-Villasril, E., et al., 2016 Mlakar, J., et al., 2016 | Retrospective cohort Case series Case series Case reports Case report Case report Case report Case report Case series Case series | Brazil Brazil Brazil Brazil Colombia Venezuela Brazil Brazil Brazil | Negative serology for: toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, or HIV, HTLV, HSV 1 &2, Rheumatoid fever, HBV, VDRL, EBV), Tests for dengue virus, chikungunya virus, Toxoplasmosis, rubella virus, cytomegalovirus, herpes | Ventura, C.V., et al. 2016 and Sarno, M., et al., 2016 had positive IgG and negative IgM ELISA results for toxoplasmosis, rubella virus and cytomegalovirus Villamil-Gómez, W.E., et al., 2016 reported 1 positive |
| Authors                        | Study Type          | Country | Diagnoses                                                                 |
|-------------------------------|---------------------|---------|---------------------------------------------------------------------------|
| Calvet, G., et al., 2016       | Prospective cohort Case series | Brazil | simplex virus, HIV, Treponema pallidum, and parvovirus B19, syphilis       |
| Brasil Martines, R., et al., 2016 |                     | Brazil | (isolating Escherichia coli) trichomonas trophozoites and 3 positives for toxoplasma IgG and 1 for Rubella |
| Brasil, Patrícia, et al. 2016 |                     | Brazil | Brasil, Patrícia, et al. 2016 reported Immunity to rubella and cytomegalovirus |
| de Paula Freitas, B., et al. 2016 |                     | Brazil | Besnard M, et al., 2014 reported dengue negative test result              |
Table 2. Methodological quality assessment for case reports using the National Institute of Health (NIH) Tool

| Study ID | Ventura C.V 2016 | Ventura C.V 2016b | Sarno M 2016 | Villamil Gomez W.E 2016 | Thomas D. L 2016 | Reyna-Villasmil 2016 | Oliveira Melo 2016 | Mlakar 2016 | Meaney-Delman 2016 | Calvet G 2016 | Brasil Martines 2016 | Besnard M 2014 | de Paula Freitas 2016 |
|----------|------------------|-------------------|--------------|--------------------------|------------------|----------------------|-------------------|------------|---------------------|----------------|----------------------|----------------|-------------------|
| 1. Was the study question or objective clearly stated? | YES | YES | YES | YES | YES | YES | NO | YES | YES | YES | YES | YES | YES |
| 2. Was the study population clearly and fully described, including a case definition? | NO | YES | YES | NO | YES | NO | YES | YES | YES | YES | NO | YES | YES |
| 3. Were the cases consecutive? | YES | YES | NA | YES | NO | NA | YES | NA | YES | YES | YES | YES | YES |
| 4. Were the subjects comparable? | YES | YES | NA | YES | NO | NA | YES | NA | YES | YES | YES | YES | YES |
| 5. Was the exposure clearly described? | YES | YES | YES | YES | YES | YES | YES | YES | YES | YES | NO | YES | YES |
| 6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? | YES | YES | YES | YES | YES | YES | YES | YES | YES | YES | YES | YES | NO |
|                         | NO | YES | YES | YES | CD | YES | CD | YES | CD | YES | NO | NO | NA |
|-------------------------|----|-----|-----|-----|----|-----|----|-----|----|-----|----|----|----|
| 7. Was the length of follow-up adequate? |    |     |     |     |    |     |    |     |    |     |    |    |    |
| 8. Were the statistical methods well-described? |    |     |     |     |    |     |    |     |    |     |    |    |    |
| 9. Were the results well-described?             |    |     |     |     |    |     |    |     |    |     |    |    |    |
| Quality Rating (Good, Fair, or Poor)           |    |     |     |     |    |     |    |     |    |     |    |    |    |
| Letter to editor | FAIR | GOOD | GOOD | GOOD | Letter to editor | POOR | Selective reporting | GOOD | Letter to editor | FAIR | GOOD | FAIR | GOOD | FAIR | GOOD | GOOD | GOOD |
| Study ID                | McCarthy, M 2016 (retrospective cohort study) | Schuler-Faccini 2016 (retrospective cohort study) | Kleber de Oliveira 2016 (retrospective cohort study) | Cauchemez S 2016 (retrospective cohort study) | Brasil Patricia 2016 (prospective cohort study) |
|------------------------|---------------------------------------------|-------------------------------------------------|-------------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| **Representativeness of exposed cohort** |                                             |                                                 |                                                 |                                               |                                               |
| Truly representative of the average woman (*) | Not population based (Gotten from a teaching hospital in Salvador, one state) | * (infants born in eight states of Brazil’s states reported to the registry) | * (infants born in three states of Brazil’s states reported to the registry) | * (datasets from the French Polynesia Zika virus outbreak) | Not population based (Gotten from centers in Rio de Janeiro, one state) |
| Somewhat representative of the average woman (*) |                                             |                                                 |                                                 |                                               |                                               |
| **Selected group of users** |                                             |                                                 |                                                 |                                               |                                               |
| No description of the derivation of the cohort |                                             |                                                 |                                                 |                                               |                                               |
| **Selection of non-exposed cohort** |                                             |                                                 |                                                 |                                               |                                               |
| Drawn from the same community as the exposed cohort (*) | No non-exposed cohort | No non-exposed cohort | Only one cohort of exposed individuals | Only one cohort of exposed individuals | Only one cohort of exposed individuals |
| Drawn from a different source |                                             |                                                 |                                                 |                                               |                                               |
| No description of the derivation of the non-exposed cohort |                                             |                                                 |                                                 |                                               |                                               |
| **Ascertainment of exposure** |                                             |                                                 |                                                 |                                               |                                               |
| Secure records (e.g., surgical records) (*) | No description | No description | * (Registry) | * (Serological and surveillance data) | * (data gotten from clinical and US data) |
| Structured interview (*) |                                             |                                                 |                                                 |                                               |                                               |
| Written self-report |                                             |                                                 |                                                 |                                               |                                               |
| No description |                                             |                                                 |                                                 |                                               |                                               |
| **Demonstration that outcome of interest not present at study start** |                                             |                                                 |                                                 |                                               |                                               |
| Yes (*) | * (Yes, MCP or familial history was excluded) | No | No | No | * (Yes. No women had had diagnoses of fetal malformations in the current pregnancy before enrollment) |
| No |                                             |                                                 |                                                 |                                               |                                               |
| **Comparability of cohorts on the basis of the design or analysis** |                                             |                                                 |                                                 |                                               |                                               |
| Only one cohort of exposed individuals | Only one cohort of exposed individuals | Only one cohort of exposed individuals | Only one cohort of exposed individuals | Only one cohort of exposed individuals | Only one cohort of exposed individuals |
| Study controls for gestational age and/or birth weight (*) | Study controls for any additional factor (*) | Assessment of outcome | Independent blind assessment (*) | Record linkage (*) | Self-report | Follow-up long enough for outcomes to occur | Yes (*) | No | Adequacy of follow-up of cohorts | Complete follow-up – all subjects accounted for (*) | Subjects lost to follow-up unlikely to introduce bias or description provided of those lost (*) | No statement | Adequacy of follow-up of cohorts | Complete follow-up – all subjects accounted for (*) | Subjects lost to follow-up unlikely to introduce bias or description provided of those lost (*) | No statement | Total number of stars | 1 star | 4 stars | 4 stars | 5 stars | 5 stars |
|---------------------------------------------------------|-------------------------------------------------|---------------------|---------------------------------|-------------------|------------|---------------------------------------------|---------|---|----------------------------------------|-----------------------------------------------|-------------------------------------------------|-----------|----------------------------------------|-----------------------------------------------|-------------------------------------------------|-----------|------------------|------------------|------------------|------------------|------------------|------------------|
| **No description**                                     | * (Record (registry) linkage implied)           | * (Record linkage)  | * (Record linkage from datasets) | * (Record linkage and self-report as they were followed up weekly by telephone) |
| **No**                                                  | * (Yes, for mothers of infants with MCP\# born during August to October 2015) | * (Yes, from January 1, 2015–January 7, 2016) | * (Yes, over a 23-month study period) | * (Yes, women were followed up from September 2015 through February 2016) |
| **Not reported**                                        | * (all subjects accounted for)                  | Not reported         | * (All subjects accounted for)   | * (all subjects accounted for) |

*MCP - microcephaly*
| No | MEDLINE | Results |
|----|---------|---------|
| 1  | exp Flavivirus/ | 16541 |
| 2  | exp Flavivirus Infections/ | 20393 |
| 3  | (zika or flavivi* or "flavi vi** or dengue or (encephalitis adj3 (japan* or "st louis" or "tick borne")).mp. | 34755 |
| 4  | or/1-3 | 35485 |
| 5  | Chikungunya Virus/ | 1534 |
| 6  | Chikungunya Fever/ | 584 |
| 7  | chikungunya.mp. | 2689 |
| 8  | Arboviruses/ | 3169 |
| 9  | arbovirus*.mp. | 8293 |
| 10 | or/5-9 | 10400 |
| 11 | or/4,10 | 42307 |
| 12 | exp "Congenital, Hereditary, and Neonatal Diseases and Abnormalities"/ | 1E+06 |
| 13 | exp "Embryonic and Fetal Development"/ | 229585 |
| 14 | exp Embryonic Structures/ | 391915 |
| 15 | exp Nerve Growth Factors/ | 41137 |
| 16 | Cephalometry/ | 24107 |
| 17 | Maternal Exposure/ | 6172 |
| 18 | exp Pregnancy/ | 784084 |
| 19 | Pregnant Women/ | 21837 |
| 20 | Prenatal Care/ | 63551 |
| 21 | exp Prenatal Diagnosis/ | 2E+06 |
| 22 | or/12-21 | 1607 |
| 23 | 11 and 22 | 266351 |
| 24 | (microcephal* or microlissencephal* or anencephal* or ((congenital or brain or cerebral or "white matter" or nerv* or neur*) adj3 (malformation* or abnormalit* or defect* or calcification or development* or growth))).mp. | 31460 |
| 25 | (cephalometr* or (head adj3 (circumference* or size))).mp. | 1E+06 |
| 26 | (prenatal or antenatal or fetus or fetal or foetus or foetal or gestation* or intrauter* or pregnan* or "expectant mother*").mp. | 376522 |
| 27 | embryo*.mp. | 10082 |
| 28 | stillbirth*.mp. | 34460 |
| 30 | or/24-29 | 2E+06 |
| 31 | 11 and 30 | 1811 |
| 32 | 31 not medline.st. | 124 |
| 33 | exp Nervous System Malformations/cn, em, ep, et [Congenital, Embryology, Epidemiology, Etiology] | 7727 |
| 34 | TORCH.mp. | 930 |
| 35 | Toxoplasma/ | 11353 |
| 36 | exp Toxoplasmosis/ | 17866 |
| 37 | exp Viruses/ | 673651 |
| 38 | exp Virus Diseases/ | 783448 |
| 39 | Aedes/ | 11697 |
| 40 | or/34-39 | 1E+06 |
| 41 | 33 and 40 | 243 |
| No | EMBASE | Results |
|----|--------|---------|
| #1 | 'flavivirus'/exp | 23321 |
| #2 | 'flavivirus infection'/exp | 22456 |
| #3 | zika OR flavivi* OR 'flavi vi*' OR dengue OR encephalitis NEAR/3 (japan* OR 'st louis' OR 'tick borne') OR 'west nile fever*' OR 'yellow fever*' | 40882 |
| #4 | 'chikungunya virus'/de | 2271 |
| #5 | 'chikungunya'/de | 1519 |
| #6 | chikungunya | 3625 |
| #7 | 'arbovirus'/de | 4180 |
| #8 | arbovirus* | 7688 |
| #9 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 | 50455 |
| #10 | 'congenital malformation'/exp | 713508 |
| #11 | 'prenatal development'/exp | 201031 |
| #12 | 'embryo (anatomy)'/exp | 213844 |
| #13 | 'neurotrophic factor'/exp | 60485 |
| #14 | 'cephalometry'/de | 20598 |
| #15 | 'pregnancy'/exp | 649044 |
| #16 | 'expectant mother'/de | 288 |
| #17 | 'prenatal care'/exp | 120829 |
| #18 | 'prenatal diagnosis'/exp | 87727 |
| #19 | microcephal* OR microlissencephal* OR anencephal* OR (congenital OR brain OR cerebral OR 'white matter' OR nerv* OR neur*) NEAR/3 (malformation* OR abnormalit* OR defect* OR calcification OR development* OR growth) | 535932 |
| #20 | cephalometr* OR head NEAR/3 (circumference* OR size) | 33737 |
| #21 | prenatal OR antenatal OR fetus OR fetal OR foetus OR foetal OR gestation* OR intruter* OR pregnant* OR 'expectant mother*' OR stillbirth* | 1212384 |
| #22 | embryo* | 515358 |
| #23 | neurotroph* | 53990 |
| #24 | #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 | 2536003 |
| #25 | #9 AND #24 | 2579 |
| #26 | 'nervous system malformation'/exp/congenital disorder',etiology','epidemiology' | 18065 |
| #27 | torch | 1438 |
| #28 | 'toxoplasma'/exp | 16001 |
| #29 | 'toxoplasmosis'/de | 19821 |
| #30 | 'virus'/exp | 893164 |
| #31 | 'virus infection'/exp | 964171 |
| #32 | 'aedes'/exp | 13176 |
| #33 | #27 OR #28 OR #29 OR #30 OR #31 OR #32 | 1492147 |
| #34 | #26 AND #33 | 513 |
| #35 | #25 OR #34 | 3081 |
| #36 | #35 AND [humans]/lim NOT ([animals]/lim NOT #32) | 1307 |
| No | CENTRAL                                                                 | Results |
|----|------------------------------------------------------------------------|---------|
| #1 | MeSH descriptor: [Flavivirus] explode all trees                         | 124     |
| #2 | MeSH descriptor: [Flavivirus Infections] explode all trees              | 241     |
| #3 | *zika or flavivi* or "flavi vi*" or dengue or (encephalitis near/3 (japan* or "st louis" or "tick borne")) or "west nile fever*" or "yellow fever*:ti,ab,kw | 536     |
| #4 | #1 or #2 or #3                                                          | 536     |
| #5 | MeSH descriptor: [Chikungunya virus] this term only                      | 4       |
| #6 | MeSH descriptor: [Chikungunya Fever] this term only                     | 2       |
| #7 | chikungunya:ti,ab,kw                                                  | 14      |
| #8 | MeSH descriptor: [Arboviruses] this term only                           | 1       |
| #9 | arbovirus*:ti,ab,kw                                                   | 6       |
| #10| #5 or #6 or #7 or #8 or #9                                              | 20      |
| #11| #4 or #10                                                               | 553     |
| #12| MeSH descriptor: [Congenital, Hereditary, and Neonatal Diseases and Abnormalities] explode all trees | 15296   |
| #13| MeSH descriptor: [Embryonic and Fetal Development] explode all trees    | 3554    |
| #14| MeSH descriptor: [Embryonic Structures] explode all trees              | 2655    |
| #15| MeSH descriptor: [Cephalometry] this term only                         | 592     |
| #16| MeSH descriptor: [Maternal Exposure] this term only                     | 46      |
| #17| MeSH descriptor: [Prenatal Care] this term only                         | 1197    |
| #18| MeSH descriptor: [Prenatal Diagnosis] explode all trees                | 1021    |
| #19| (microcephal* or microloissecephal* or anencephal* or ((congenital or brain or cerebral or "white matter" or nerv* or neur*) near/3 (malformation* or abnormality* or defect* or calcification or development* or growth))):ti,ab,kw | 3633    |
| #20| (cephalometr* or (head near/3 (circumference* or size))):ti,ab,kw      | 1385    |
| #21| (prenatal or antenatal or fetus or fetal or foetal or gestation* or intrauter* or pregnant* or "expectant mother*" or stillbirth*):ti,ab,kw | 37768   |
| #22| embryo*:ti,ab,kw                                                       | 3817    |
| #23| neurotroph*:ti,ab,kw                                                  | 587     |
| #24| #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 | 55078   |
| #25| #11 and #24                                                            | 13      |
| #26| MeSH descriptor: [Nervous System Malformations] explode all trees and with qualifier(s): [Etiology - ET]| 9       |
| #27| #25 or #26                                                             | 22      |

### CINAHL

| Search ID# | CINAHL                                                                 | Results |
|------------|------------------------------------------------------------------------|---------|
| S34        | S26 OR S33                                                             | 200     |
| S33        | S27 AND S32                                                            | 15      |
| S32        | S28 OR S29 OR S30 OR S31                                               | 145712  |
| S31        | (MH "Virus Diseases+")                                               | 137287  |
| S30        | (MH "Viruses+")                                                       | 29364   |
| S29        | (MH "Toxoplasmosis+")                                                 | 875     |
| S28        | TORCH                                                                  | 261     |
| S27        | (MH "Nervous System Abnormalities+/EM/EP/ET")                          | 781     |
| S26        | S11 AND S25                                                            | 185     |
| S25        | S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 | 382515  |
| S24        | (prenatal or antenatal or fetus or fetal or foetal or gestation* or intrauter* or pregnant* or "expectant mother*" or stillbirth*) | 176976  |
| S23        | (cephalometr* or (head N3 (circumference* or size)))                  | 4217    |
| No | Title | Reason for exclusion |
|----|-------|----------------------|
| 1  | Brasil, L.M., et al., Web platform using digital image processing and geographic information system tools: a Brazilian case study on dengue. Biomedical Engineering Online, 2015. 14: p. 69. | No primary data, paper discusses prevention strategy for dengue mosquitos which can be applied to ZIKV infection. |
| 2  | Grabowski, J.M., et al., Changes in the Proteome of Langat-Infected Ixodes scapularis ISE6 Cells: Metabolic Pathways Associated with Flavivirus Infection. PLoS Neglected Tropical Diseases [electronic resource], 2016. 10(2): p. e0004180. | Not related to review objective. |
| 3  | Gulland, A., WHO strengthens Zika travel advice to pregnant women. BMJ, 2016. 352: p. i1460. | No primary data, news comment/summary about WHO press conference on the ZIKV meeting |
| 4  | Goorhuis, A., et al., Zika virus and the risk of imported infection in returned travelers: Implications for clinical care. Travel Medicine & Infectious Disease, 2016. 14(1): p. 13-5. | No primary data, case reports on male and female seniors of >50 years with imported ZIKV infection from Suriname |
| 5  | Cover photo. Bulletin of the World Health Organization, 2016. 94(3): p. 162-162 1/9p. | No primary data, a commentary. |
| 6  | Brito, C., Zika virus: A new chapter in the history of medicine. Acta Medica Portuguesa, 2015. 28(6): p. 679-680. | No primary data, a narrative summary. |
| 7  | Petersen, E., et al., Rapid Spread of Zika Virus in The Americas - Implications for Public Health Preparedness for Mass Gatherings at the 2016 Brazil Olympic Games. International Journal of Infectious Diseases, 2016. 44: p. 11-5. | No primary data, opinion paper which discusses implications for ZIKV infection in mass gatherings like the Olympics. |
| 8  | Torjesen, I., Zika virus outbreaks prompt warnings to pregnant women. BMJ, 2016. 352: p. i500. | No primary data, news release |
| No. | Reference                                                                 | Description                                                                                     |
|-----|----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| 9   | Chang, C., et al., The Zika outbreak of the 21st century. Journal of Autoimmunity, 2016. 68: p. 1-13. | No primary data, extensive narrative review on spread, mode of transmission, pathogenesis, prevention and treatment for ZIKV infection |
| 10  | Yakob, L. and T. Walker, Zika virus outbreak in the Americas: The need for novel mosquito control methods. The Lancet Global Health, 2016. 4(3): p. e148-e149. | No primary data, a lancet commentary                                                              |
| 11  | Heymann, D.L., et al., Zika virus and microcephaly: why is this situation a PHEIC? Lancet, 2016. 387(10020): p. 719-21. | No primary data, a commentary on ZIKV infection as PHEIC                                            |
| 12  | Roa, M., Zika virus outbreak: reproductive health and rights in Latin America, 2016, Lancet: Philadelphia, Pennsylvania. p. 843-843 2/3p. | No primary data, an opinion article                                                               |
| 13  | Azevedo, A., Brazil's scientists scramble to solve the Zika puzzle. 2016, World Health Organization. p. 165-166 2p. | No primary data, news interview of Azevedo et al. who is currently following 300 women suspected to have ZIKV infection |
| 14  | Heukelbach, J., et al., Zika virus outbreak in Brazil. Journal of Infection in Developing Countries, 2016. 10(2): p. 116-20. | No primary data, a review                                                                        |
| 15  | Elachola, H., et al., A crucial time for public health preparedness: Zika virus and the 2016 Olympics, Umrah, and Hajj, Lancet, 2016. 387(10019): p. 630-2. | No primary data, a narrative review extending ZIKV effects to preparedness for international events |
| 16  | Higgs, S., Zika Virus: Emergence and Emergency. Vector-Borne and Zoonotic Diseases, 2016. 16(2): p. 75-76. | No primary data, an editorial comment on ZIKV infection                                              |
| 17  | Lucey, D.R., Time for global action on Zika virus epidemic. BMJ: British Medical Journal, 2016. 352(8044): p. i781-i781 1p. | No primary data, an editorial                                                                    |
| 18  | McCarthy, M., CDC updates Zika virus guidance to protect pregnant women. BMJ, 2016. 352: p. i786. | No primary data, a news release                                                                   |
| 19  | Mor, G., Placental Inflammatory Response to Zika Virus may Affect Fetal Brain Development. American Journal of Reproductive Immunology, 2016. 75(4): p. 421-2. | No primary data, a narrative review on postulated effects of ZIKV infection in neonates via placental transmission |
| 20  | Samarasekera, U. and M. Triunfol, Concern over Zika virus grips the world. The Lancet, 2016. 387(10018): p. 521-524. | No primary data, a review                                                                        |
| 21  | Burke, R.M., et al., Zika virus infection during pregnancy: What, where, and why? British Journal of General Practice, 2016. 66(644): p. 122-123. | No primary data, an editorial reporting on history, spread and advice for prevention of ZKV infection |
| 22  | Byass, P. and A. Wilder-Smith, Utilising additional sources of information on microcephaly. 2016, Lancet: Philadelphia, Pennsylvania. p. 940-941 2p. | No primary data, a narrative summary on possible sources of information for microcephaly associated with ZIKV infection |
| 23  | Siqueira, W.L., et al., Zika virus infection spread through saliva - a truth or myth? Pesquisa Odontologica Brasileira = Brazilian Oral Research, 2016. 30(1): p. e46. | No primary data, an opinion article                                                               |
| 24  | MacFadden, D.R. and I.I. Bogoch, Zika virus infection. CMAJ: Canadian Medical Association Journal, 2016. 188(5): p. 367-367 1p. | No primary data, a fact sheet                                                                    |
| 25  | Ayres, C.F.J., Identification of Zika virus vectors and implications for control. The Lancet Infectious Diseases, 2016. 16(3): p. 278-279. | No primary data, a narrative summary on the possibility of vectors other than A. aegypti for ZIKV spread |
| 26  | McCarthy, M., Zika virus outbreak prompts US to issue travel alert to pregnant women. BMJ, 2016. 352: p. i306. | No primary data, a news release                                                                   |
| 27  | Vouga, M., et al., CDC guidelines for pregnant women during the Zika virus outbreak. 2016, Lancet: Philadelphia, Pennsylvania. p. 843-844 2p. | No primary data, a review providing suggestions on when to perform amniocentesis                  |
| 28  | Vogel, G., A race to explain Brazil's spike in birth defects : Evidence points toward the fast-spreading Zika virus as the cause of microcephaly. Science, 2016. 351(6269): p. 110-111. | No primary data, a news release                                                                   |
| 29  | Dyer, O., SIXTY SECONDS ON . . . ZIKA VIRUS. BMJ: British Medical Journal, 2016. 352(8042): p. 129-129 1/2p. | No primary data, a news release                                                                   |
| 30  | Dyer, O., Jamaica advises women to avoid pregnancy as Zika virus approaches. BMJ, 2016. 352: p. i383. | No primary data, a news report                                                                  |
| No. | Citation                                                                                           | Primary Data | Summary                                                                                     |
|-----|---------------------------------------------------------------------------------------------------|--------------|--------------------------------------------------------------------------------------------|
| 31  | Stratton, S.J., Zika Virus Association with Microcephaly: The Power for Population Statistics to Identify Public Health Emergencies. Prehospital & Disaster Medicine, 2016. 31(2): p. 119-20. | No primary data | Viewpoint article on the importance of epidemiology                                         |
| 32  | Mayor, S., Zika infection in pregnancy is linked to range of fetal abnormalities, data indicate. BMJ, 2016. 352: p. 11362. | Primary data | This study provides primary data on the same cohort of women in one of the studies included in the review (Brasil P. et al), to avoid repetition we excluded it |
| 33  | Millichap, J.G., Zika Virus Infection and Microcephaly. Pediatric Neurology Briefs, 2016. 30(1): p. 8. | Primary data | This study provides primary data on the same cohort of women in one of the studies included in the review (Schuler Faccini et al.) To prevent double reporting we excluded it. |
| 34  | Kelvin, A.A., et al., ZIKATracker: A mobile App for reporting cases of ZIKV worldwide. Journal of Infection in Developing Countries, 2016. 10(2): p. 113-5. | No primary data | Report on the development of a mobile application to report ZIKV infected cases.            |
| 35  | Ginier, M., et al., Zika without symptoms in returning travellers: What are the implications? Travel Medicine and Infectious Disease, 2016. 14(1): p. 16-20. | No primary data | Case report in a non-pregnant woman                                                        |
| 36  | Carneiro, L.A.M. and L.H. Travassos, Autophagy and viral diseases transmitted by Aedes aegypti and Aedes albopictus. Microbes and Infection, 2016. 18(3): p. 169-171. | No primary data | Review                                                                                      |
| 37  | Iacobucci, G., Zika highlights need for ethical framework for developing vaccines for pregnant women. BMJ, 2016. 352: p. i1155. | No primary data | News release/comment on an article about vaccination for pregnant women and Zika (Omer 2016) |
| 38  | Malone, R.W., et al., Zika Virus: Medical Countermeasure Development Challenges. PLoS Neglected Tropical Diseases [electronic resource], 2016. 10(3): p. e0004530. | No primary data | Epidemiological, survey, narrative review and analysis on spread, countries affected, projections. A review which analyzes information concerning the ZIKV outbreak in South America, Central America, and the Caribbean and the status of relevant medical countermeasures (MCM) available for treating or preventing Zika virus infection and disease. |
| 39  | Attar, N., ZIKA virus circulates in new regions. Nature Reviews Microbiology, 2016. 14(2): p. 62. | No primary data | Narrative summary on Zika spread                                                             |
| 40  | Rodriguez-Morales, A.J., Zika and microcephaly in Latin America: An emerging threat for pregnant travelers? Travel Medicine & Infectious Disease, 2016. 14(1): p. 5-6 2p. | No primary data | Editorial                                                                                     |
| 41  | Cofre, F., [Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg?]. Revista Chilena de Infectologia, 2016. 33(1): p. 96. | Foreign language article | Reporting 2 cases. This is a translated version of the Oliveira Melo et al. article, therefore it is not an actual report. |
| 42  | Barreto, M.L., et al., Zika virus and microcephaly in Brazil: a scientific agenda. Lancet, 2016. 387(10022): p. 919-21. | No primary data | The study refers to a review by Soares et al and suggests an action plan for the government relative to ZIKV infection |
| 43  | Victora, C.G., et al., Microcephaly in Brazil: How to interpret reported numbers? The Lancet, 2016. 387(10019): p. 621-624. | No primary data | Review                                                                                      |
| 44  | Wong, S.S.Y., R.W.S. Poon, and S.C.Y. Wong, Zika virus infection-the next wave after dengue? Journal of the Formosan Medical Association, 2016(Wong S.S.Y., samsonsy@hku.hk) Department of Microbiology, Research Centre for Infection and Immunology, Faculty of Medicine, The University of Hong Kong, Hong Kong). | No primary data | Paper provides detailed information on ZIKV infection                                          |
| 45  | Von Eije, K.J., et al., Imported Zika virus infection in the Netherlands. Nederlands Tijdschrift voor Geneeskunde, 2016. 160(8). | No primary data | News commentary in foreign language article                                                   |
| 46  | Villa, R., Zika, or the burden of uncertainty. Clinica Terapeutica, 2016. 167(1): p. 7-9. | No primary data | Editorial                                                                                     |
| 48  | Teixeira, M.G., et al., The Epidemic of Zika Virus—Related Microcephaly in Brazil: Detection, Control, Etiology, and Future Scenarios. American Journal of Public Health, 2016. 106(4): p. 601-605 5p. | No primary data | Description of the epidemiology of ZIKV                                                       |
| 49  | Talan, J., Epidemiologists Are Tracking Possible Links Between Zika Virus, Microcephaly, and Guillain—Barre Syndrome. Neurology Today, 2016. 16(4): p. 1-23 7p. | No primary data | News item                                                                                     |
Staples, J.E., et al., Interim Guidelines for the Evaluation and Testing of Infants with Possible Congenital Zika Virus Infection - United States, 2016. MMWR - Morbidity & Mortality Weekly Report, 2016. 65(3): p. 63-7.

No primary data, an interim guideline for health care providers in the US developed by CDC

Sikka, V., et al., The emergence of zika virus as a global health security threat: A review and a consensus statement of the INDUSEM Joint working Group (JWG). Journal of Global Infectious Diseases, 2016. 8(1): p. 3-15.

No primary data, a detailed narrative review

Saxena, S.K., et al., Zika virus outbreak: an overview of the experimental therapeutics and treatment. VirusDisease, 2016(Saxena S.K., shailen@ccmb.res.in; Elahi A.; Gadugu S.; Prasad A.K.) CSIR-Centre for Cellular and Molecular Biology (CCMB), Hyderabad, India): p. 1-5.

No primary data, an overview on experimental treatments associated with the ZIKV outbreak

Rubin, E.J., M.F. Greene, and L.R. Baden, Zika Virus and Microcephaly. The New England journal of medicine, 2016. 374(10): p. 984-985.

No primary data, a narrative review providing narrative information, the review also suggests no link between microcephaly and ZIKV infection

Rodriguez-Morales, A.J., A.C. Bandeira, and C. Franco-Paredes, The expanding spectrum of modes of transmission of Zika virus: A global concern. Annals of Clinical Microbiology and Antimicrobials, 2016. 15(1).

No primary data, an editorial

Petersen, E.E., et al., Interim Guidelines for Pregnant Women During a Zika Virus Outbreak - United States, 2016. MMWR - Morbidity & Mortality Weekly Report, 2016. 65(2): p. 30-3.

No primary data, CDC recommendations for travelling pregnant women

Paixão, E.S. and L.C. Rodrigues, What we need to know about Zika virus. British Journal of Hospital Medicine (17508460), 2016. 77(3): p. 124-125

No primary data, an editorial

Paixao, E.S., et al., History, Epidemiology, and Clinical Manifestations of Zika: A Systematic Review. American Journal of Public Health, 2016. 106(4): p. 606-12.

No primary data, a systematic review on general ZIKV infection with no isolated data for pregnant women.

Oster, A.M., et al., Interim Guidelines for Prevention of Sexual Transmission of Zika Virus - United States, 2016. MMWR - Morbidity & Mortality Weekly Report, 2016. 65(5): p. 120-1.

No primary data, CDC guidelines for prevention of sexual transmission

Omer, S.B. and R.H. Beigi, Pregnancy in the Time of Zika: Addressing Barriers for Developing Vaccines and Other Measures for Pregnant Women. JAMA, 2016. 315(12): p. 1227-8.

No primary data, study reports on the barriers for vaccine development for pregnant women

Olsen, B. and A. Lundkvist, [In Process Citation]. Lakartidningen, 2016. 113.

No primary data, there were no cases of ZIKV infected pregnancies

Oduyebo, T., et al., Update: Interim Guidelines for Health Care Providers Caring for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure -- United States, 2016. MMWR: Morbidity & Mortality Weekly Report, 2016. 65(5): p. 122-127 6p.

No primary data, CDC guideline updates for clinicians

Mohamad Idris, F., Zika – A pandemic in progress? Malaysian Journal of Medical Sciences, 2016. 23(2): p. 70-72.

No primary data, the study narratively discusses Aedes agent of ZIKV infection and the possibility of adaptation to other Aedes vectors

Miranda-Filho, D.d.B., et al., Initial Description of the Presumed Congenital Zika Syndrome. American Journal of Public Health, 2016. 106(4): p. 598-600.

No primary data, an overview which describes the concept of presumed congenital Zika syndrome

Mende, A., Zika virus in South America: Travel guidelines for pregnant women. Pharmazeutische Zeitung, 2015. 160(49).

No primary data, foreign language guideline to travelers relative to ZIKV infection

McDonnell, P.J., Playing 'hide and Zika'. Ophthalmology Times, 2016. 41(4): p. 6-6 2/3p.

No primary data, an editorial

Maurice, J., WHO reveals its shopping list for weapons against Zika. The Lancet, 2016. 387(10020): p. 733.

No primary data, the article describes WHO action plan to stem ZIKV spread, tests, drugs and vaccines in the pipeline
67 Martines, R.B., et al., Notes from the Field: Evidence of Zika Virus Infection in Brain and Placental Tissues from Two Congenitally Infected Newborns and Two Fetal Losses - Brazil, 2015. MMWR - Morbidity & Mortality Weekly Report, 2016. 65(6): p. 159-60.

To avoid double reporting, we excluded this study. This CDC report provides data on the same cohort mentioned in CDC MWR report. It discusses evidence of a link between Zika virus infection and microcephaly and fetal demise through detection of viral RNA and antigens in brain tissues from infants with microcephaly and placental tissues from early miscarriages.

68 Marrs, C., et al., Zika Virus and Pregnancy: A Review of the Literature and Clinical Considerations. American Journal of Perinatology, 2016(Marrs C., carolinemarrs@gmail.com; Olson G.; Saade G.; Hankins G.; Wen T.) Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, The University of Texas Medical Branch, Galveston, Texas).

No primary data, a narrative review which discusses Zika virus in pregnancy.

69 Lupton, K., Zika virus disease: a public health emergency of international concern. British Journal of Nursing, 2016. 25(4): p. 198-202.

No primary data, the study provides a narrative summary of signs, symptoms, prevention, treatment and travel advice all related to ZIKV infection.

70 Lucey, D.R. and L.O. Gostin, The Emerging Zika Pandemic: Enhancing Preparedness. JAMA, 2016. 315(9): p. 865-6.

No primary data, a viewpoint article which provides tips on preparation strategies relative to ZIKV infection.

71 Lucey, D.R., Time for global action on Zika virus epidemic: Our response to infectious disease epidemics must be faster and smarter. BMJ (Online), 2016. 352((Lucey D.R., DRL23@Georgetown.edu) Department of Medicine, Infectious Diseases, Georgetown University Medical Center, Washington, United States).

No primary data, an editorial summary.

72 Lockwood, C.J., Zika virus and microcephaly. Contemporary OB/GYN, 2016. 61(2): p. 6-9 3p.

No primary data, an opinion article discussing the magnitude of ZIKV infection threat and the MCP-ZIKV link.

73 Li, J.D. and D.X. Li, [Epidemiological characteristics of Zika virus disease]. Chung-Hua Liu Hsing Ping Hsueh Tsa Chih Chinese Journal of Epidemiology, 2016. 37(3): p. 329-34.

No primary data, an epidemiologic systematic review in Chinese.

74 Laoprasopwattana, K., et al., Chikungunya and dengue virus infections during pregnancy: seroprevalence, seroincidence and maternal-fetal transmission, southern Thailand, 2009-2010. Epidemiology & Infection, 2016. 144(2): p. 381-8.

No primary data, a report on chikungunya and dengue virus infection, no co-infection with Zika was reported.

75 Krader, C.G., Zika virus and Chikungunya in the U.S.--Syphilis infections incease in newborns. Dermatology Times, 2016. 37(3): p. 10-18 2p.

No primary data, a news article on ZIKV infection.

76 Korhonen, E.M., et al., Zika virus infection in a traveller returning from the Maldives, June 2015. Euro Surveillance: Bulletin European sur les Maladies Transmissibles = European Communicable Disease Bulletin, 2016. 21(2): p. 14.

No primary data, a case report on the history of ZIKV infection in a male patient. Initially negative, 2 weeks later he had a low dengue viral seropositivity attributed to cross reactivity between flaviviruses.

77 Hills, S.L., et al., Transmission of Zika Virus Through Sexual Contact with Travelers to Areas of Ongoing Transmission - Continental United States, 2016. MMWR - Morbidity & Mortality Weekly Report, 2016. 65(8): p. 215-6.

No primary data, case reports on only males and no pregnant cases.

78 Hibbeler, B., Zika virus infections: Risk for pregnant women. Deutsches Arzteblatt International, 2016. 113(4): p. A137.

No primary data, a news article on ZIKV infection.

79 Hennigan, T., Brazil struggles to cope with Zika epidemic. BMJ (Online), 2016. 352(Hennigan T., hennigantom@gmail.com) São Paulo, Brazil).

No primary data, a news report.

80 Hasson, M., K.L. Kahl, and T. Nhu, Vision-threatening abnormalities possible in infants with presumed Zika virus-associated microcephaly. Ocular Surgery News, 2016. 34(5): p. 25-25 1/3p.

Duplicate of de Paula Freitas et al, one of the included studies. We excluded this study to prevent double reporting.

81 Gulland, A., Genetically modified mosquitos may be used in fight against Zika. BMJ: British Medical Journal, 2016. 352(8046): p. 298-299 2p.

No primary data, a news report.

82 Godlee, F., Zika, and rapid diagnostic tests for malaria. BMJ (Online), 2016. 352((Godlee F., fgodlee@bmj.com) BMJ, United States).

No primary data, a news report.

83 Gatherer, D. and A. Kohl, Zika virus: a previously slow pandemic spreads rapidly through the Americas. Journal of General Virology, 2016. 97(2): p. 269-73.

No primary data, a narrative review which discusses phylogenetic links with ZIKV infection.
Galindo-Fraga, A., et al., Zika Virus: A New Epidemic on Our Doorstep. Revista de Investigacion Clinica, 2015. 67(6): p. 329-32.

Fleming-Dutra, K.E., et al., Update: Interim Guidelines for Health Care Providers Caring for Infants and Children with Possible Zika Virus Infection - United States, February 2016. MMWR - Morbidity & Mortality Weekly Report, 2016. 65(7): p. 182-7.

Fauci, A.S. and D.M. Morens, Zika Virus in the Americas--Yet Another Arbovirus Threat. New England Journal of Medicine, 2016. 374(7): p. 601-604.

Evans, G., Zika Questions Abound, but Standard Precautions Will Stop it. Hospital Infection Control & Prevention, 2016. 43(3): p. 25-29.

Dyer, O., Zika virus spreads across Americas as concerns mount over birth defects. BMJ (Clinical research ed.), 2015. 351((Dyer O.) Montreal): p. h6983.

Dhimal, M., et al., Zika Virus: Yet Another Emerging Threat to Nepal. Journal of Nepal Health Research Council, 2015. 13(31): p. 248-51.

Check Hayden, E., Spectre of Ebola haunts Zika response. Nature, 2016. 531(7592): p. 19.

Bell, B.P., C.A. Boyle, and L.R. Petersen, Preventing Zika Virus Infections in Pregnant Women: An Urgent Public Health Priority. American Journal of Public Health, 2016. 106(4): p. 589-90.

Basarab, M., et al., Zika virus. BMJ (Online), 2016. 352((Basarab M.; Bowman C.; Cropley I., iancropley@nhs.net) Department of Infectious Diseases, Royal Free London NHS Foundation Trust, London, United Kingdom).

Ahmad, S.S.Y., T.N. Amin, and A. Ustianowski, Zika virus: Management of infection and risk. BMJ (Online), 2016. 352((Ahmad S.S.Y.; Ustianowski A., Andrew.Ustianowski@pat.nhs.uk) Northwest Regional Infectious Diseases Unit, North Manchester General Hospital, Pennine Acute Hospitals Trust, Manchester, United Kingdom).

Pyriproxyfen, Zika and Microcephaly. Positive Health, 2016(229): p. 11-11.

Zika Virus, Microcephaly, Guillain-Barré, Genetically Modified Mosquitos and Potential Vaccine Damage. Positive Health, 2016(229): p. 12-12.

Zika: A clinical guide. 2016, BMJ Publishing Group. p. 366-366.

LATEST FREE ZIKA VIRUS RESOURCES FROM BMJ. BMJ: British Medical Journal, 2016(8045): p. 262-262.

Zika Virus: what you need to know. Midwifery Matters, 2016(148): p. 3-3.

Advice on Zika virus. Primary Health Care, 2016. 26(2): p. 7-7.
| No. | Reference | Type of Document | Description |
|-----|-----------|------------------|-------------|
| 104 | Science committee calls on government to build Zika virus evidence base. Emergency Nurse, 2016. 23(10): p. 6-6 1/4p. | No primary data, a news article on ZIKV infection |
| 105 | Zika 101: Prime threat for the pregnant. Hospital Employee Health, 2016. 35(3): p. 32-34 3p. | No primary data, a CDC educational report for the public related to ZIKV infection |
| 106 | Public health authorities race to contain fast-moving Zika outbreak. ED Management, 2016. 28(4): p. 37-41 5p. | No primary data |
| 107 | NEWS ROUND-UP. Community Practitioner, 2016. 89(3): p. 6-7 2p. | No primary data, a news release discussing WHO prediction of ZIKV affecting 4 million |
| 108 | Zika virus: A new global threat for 2016. The Lancet, 2016. 387(10014): p. 96. | No primary data, the study discusses the history of ZIKV infection |
| 109 | The next steps on Zika. Nature, 2016. 530(7588): p. 5. | No primary data, the study provides suggestions on actions to take relative to ZIKV infection |
| 110 | Resources and latest news about zika virus disease available from ECDC. Eurosurveillance, 2016. 21(5). | No primary data, an editorial summarizing ZIKV related information |
| 111 | European Commission Horizon 2020 programme call for vaccine development research into malaria and neglected infectious diseases, including Zika virus. Eurosurveillance, 2016. 21(6). | No primary data, an editorial calling for proposals on research and vaccinations related to ZIKV infection |
| 112 | Zika virus in the dock. The Lancet Infectious Diseases, 2016. 16(3): p. 265. | No primary data, the study provides narrative information relative to general ZIKV infection |
| 113 | Zika virus infection: global update on epidemiology and potentially associated clinical manifestations. Weekly Epidemiological Record, 2016. 91(7): p. 73-81. | No primary data, a narrative review and update on general epidemiology and potential clinical manifestations for ZIKV infection |
| 114 | Healthcare staff encouraged to warn patients of the risks of the Zika virus. Nursing Standard, 2016. 30(24): p. 9. | No primary data, a news report discussing links to Zika virus infection, guidance for primary care and clinicians |
| 115 | Zika virus. Nursing Standard, 2016. 30(24): p. 17. | No primary data, clinical updates on ZIKV infection |
| 116 | Musso, D. and D. Baud, Zika virus: Time to move from case reports to case control. The Lancet Infectious Diseases, 2016((Musso D., dmusso@ilm.pf) Unit of Emerging Infectious Diseases, Institut Louis Malardé, PO Box 30, 98713 Papeete, Tahiti, French Polynesia) | No primary data, the study advocates a move from case studies to case-control all in the context of ZIKV infection |
| 117 | Epidemiological report of week 8 monitoring cases of microcephaly in Brazil. | No primary data in the foreign language article |
| 118 | Protocol for surveillance and response to the occurrence of microcephaly related to zika virus infection. | No primary data in the foreign language article |
| 119 | Technical report: possible change in the epidemiological pattern of microcephaly in Pernambuco. | No primary data in the foreign language article |
| 120 | Clinical and epidemiological protocol for investigating cases of microcephaly in the state of Pernambuco. | No primary data in the foreign language article |
| 121 | Zika virus: information to the public. | No primary data in the foreign language article |
| 122 | Brazilian Ministry of Health. 12 January 2016: Weekly epidemiological update on suspected microcephaly cases (Novos casos suspeitos de microcefalia são divulgados pelo Ministério da Saúde) (12 January 2016) Available at: http://portalsaude.saude.gov.br/index.php/cidadao/princluirapid/agencia-saude/21677-novos-casos-suspeitos-de-microcefalia-sao-divulgados-pelo-ministerio-da-saude –accessed January 26th, 2016. | No primary data in the foreign language article |
| 123 | Hazin, A. N., Poretti, A., Cruz, D. D. C. S., Tenorio, M., van der Linden, A., Pena, L. J., ... & Martelli, C. M. T. (2016). Computed tomographic findings in microcephaly associated with Zika virus. New England Journal of Medicine. | No primary data |
| 124 | Petersen, L. R., Jamieson, D. J., Powers, A. M., & Honein, M. A. (2016). Zika Virus. New England Journal of Medicine. | No primary data |