American Society of Tropical Medicine and Hygiene
2023 Annual Meeting | Chicago, Illinois, United States

World Health Organization

human reproduction programme hrp 50
research for impact
UNDP·UNFPA·UNICEF·WHO·WORLD BANK

WHO Zika Virus Infection Individual Participant Data (ZIKV IPD) Meta-Analysis

Phase 1: preliminary findings from a Consortium-wide initiative

The Zika virus individual participant data Consortium

Zika virus (ZIKV) infection during pregnancy is a known cause of microcephaly and other congenital and developmental anomalies. To better understand the relationship between ZIKV infection during pregnancy and adverse fetal, infant, or child outcomes, international leaders in ZIKV research established the ZIKV Individual Participant Data (IPD) Consortium in 2017.

Phase 1 objective was to estimate the absolute and relative risk of fetal infection, fetal loss (≥ 20 weeks gestation), and microcephaly for women who did and did not experience ZIKV infection during pregnancy, as well as the absolute risk of congenital zika syndrome for women who experienced ZIKV infection during pregnancy.

Method: We conducted 1- and 2-stage meta-analyses (MA) on data from 18 cohorts to determine absolute and relative risk. Data were imputed using the R package mice. Estimations were drawn from 50 imputed datasets. Additionally, we conducted a Bayesian analysis for a comparative assessment of the results. ZIKV positivity was determined based on two criteria: the study's own definition and a standardized definition outlined by Ximenes et al. 2019, which classified evidence as negative, limited, moderate, or robust.

64 identified studies and letter of agreement obtained for inclusion in this IPD-MA. We systematically searched Medline and Embase on 8 July 2018, without language restrictions and expanded our search by consulting with experts in the field, contacting health ministries and authorities such as the World Health Organization (WHO), and setting up a monthly PubMed alert to identify new studies.

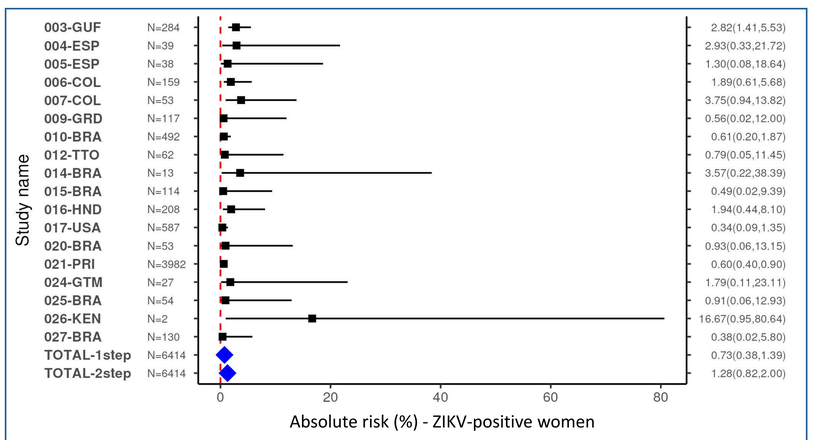
18 datasets out of 64 included in this preliminary analysis (Phase 1) following bias assessment. Data were harmonized to the WHO CRF.

11 **Countries:** Brazil, Colombia, French Guiana, Grenada, Guatemala, Honduras, Kenya, Puerto Rico, Spain, Trinidad and Tobago, USA.

Maternal characteristics using zika infection by study definition	ZIKV neg (N=2427)	ZIKV pos (N=5965)	ZIKV status Missing (N=706)	Overall (N=9093)
Age (years)				
Median [Q1, Q3]	27 [23, 32]	27 [22, 31]	25[21, 31]	27 [22, 32]
Missing	128 (5%)	4860 (82%)	48 (7%)	5036 (55%)
Gestational age at zika infection (weeks)				
Median [Q1, Q3]	39 [38, 40]	39 [38, 39]	39 [38,40]	39 [38, 40]
Missing	-	-	-	-
Maternal zika infection by Ximenes definition				
Negative	636 (26%)	0 (0%)	33 (5%)	669 (7%)
Limited	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Moderate	15 (1%)	2693 (45%)	3 (0%)	2711 (30%)
Robust	1 (0%)	2501 (45%)	1 (0%)	2503 (28%)
Missing	1774 (73%)	771 (13%)	664 (94.8%)	3209 (35%)

Fetal Loss

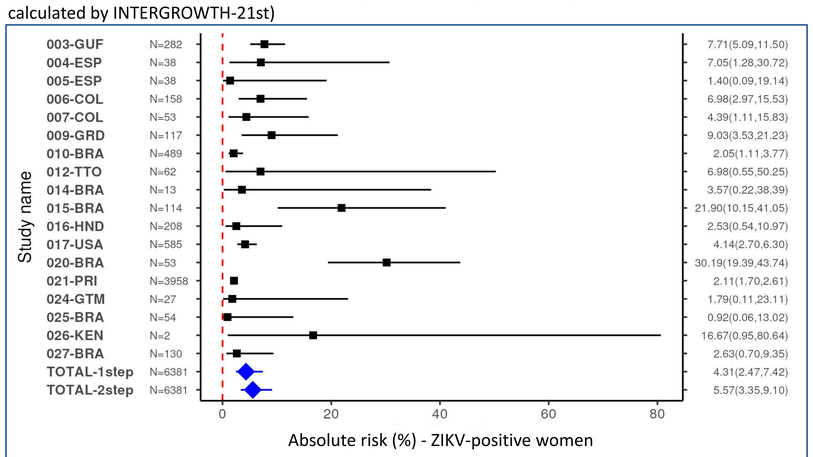
(20 weeks gestation or more)



In the one-stage MA, the absolute risk (AR) of fetal loss for ZIKV-positive women was 0.73% (0.38%, 1.39%), while for ZIKV-negative women it was 0.31% (0.40%, 2.57%). The relative risk (RR) was 2.17% (0.62%, 7.51%). Using the standardized definition for ZIKV positivity in women within the Bayesian framework, the AR for ZIKV-positive was 0.74 (0.18, 1.88), and 0.59% (0.23%, 1.39%) for ZIKV-negative women AR. The RR was 1.22 (0.27, 3.97).

Microcephaly at birth

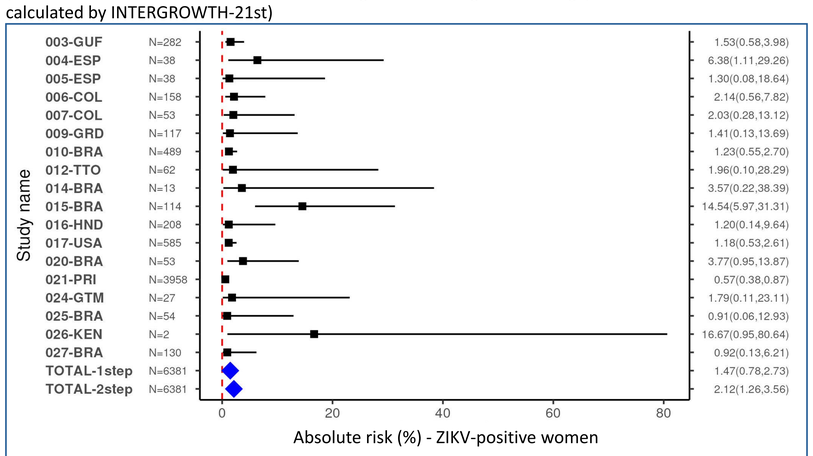
(more than 2 standard deviations below average for sex and gestational age, in accordance with values calculated by INTERGROWTH-21st)



In the one-stage MA, the absolute risk (AR) of microcephaly at birth for newborns of ZIKV-positive women was 4.31% (2.47%, 7.42%), while for ZIKV-negative women it was 1.26% (0.40%, 3.97%). The relative risk (RR) was 1.56% (0.73%, 3.36%). Using the standardized definition for ZIKV positivity in women within the Bayesian framework, the AR for ZIKV-positive women was 4.64% (1.40%, 11.05%) and 1.50% (0.62%, 3.25%) for ZIKV-negative women. The RR was 3.08% (0.88%, 8.71%).

Severe Microcephaly at birth

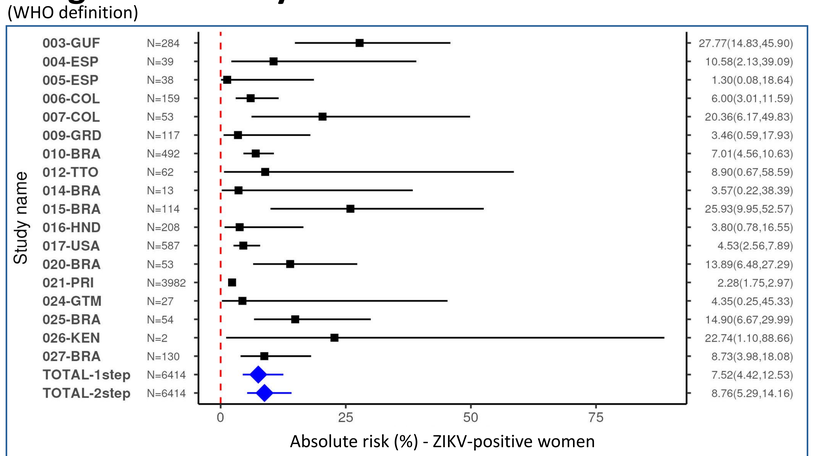
(more than 3 standard deviations below average for sex and gestational age, in accordance with values calculated by INTERGROWTH-21st)



In the one-stage MA, the absolute risk (AR) of microcephaly at birth for newborns of ZIKV-positive women was 1.47% (0.78%, 2.73%), while for ZIKV-negative women it was 0.20% (0.04%, 1.14%). The relative risk (RR) was 3.78% (1.33%, 10.75%). Using the standardized definition for ZIKV positivity in women within the Bayesian framework, the AR for ZIKV-positive women was 4.64% (1.40%, 11.05%) and 1.50% (0.62%, 3.25%) for ZIKV-negative women. The RR was 3.08% (0.88%, 8.71%).

Congenital Zika Syndrome

(WHO definition)



In the one-stage MA, the absolute risk (AR) of congenital zika syndrome for newborns of ZIKV-positive women was 7.52% (4.42%, 12.53%). Using the standardized definition for ZIKV positivity in women within the Bayesian framework, the AR for ZIKV-positive women was 9.27% [3.41%, 26.12%].

Discussion

In this comprehensive Phase-1 IPD-MA, we investigated the absolute and relative risks of fetal and infant outcomes among women who either were or were not infected with ZIKV during pregnancy. We observed significant heterogeneity in both absolute and relative risks across studies and examined factors that might influence the relationship between ZIKV infection during pregnancy and its impact on fetal and infant outcomes. One potential reason for the marked heterogeneity across studies for all outcomes might be the differences in defining maternal ZIKV status and how outcomes are categorized. Future research should focus on examining more outcomes within a larger, more consistent dataset.

As we progress to Phase 2 of our IPD-MA, the primary aim of the subsequent phase will be to create and validate predictive models. These models will be designed to estimate the risk of fetal and infant outcomes in pregnant women with ZIKV infection, aligning with Objectives 2, 3, and 4 of the ZIKV IPD-MA protocol.

Authors: The 'Zika virus individual participant data Consortium' consists of 160 collaborators, encompassing experts from diverse fields. They convene weekly to discuss data harmonization, exposure aspects, outcomes, and result interpretation. A full list of contributors can be found at https://www.dropbox.com/scl/fi/3kxkdnsubozgz7lgx6c9s/Authorship-list-2023.pdf?rlkey=567qqbzfzzp1ozx5cyh3hxc6v&dl=0.
Corresponding author: Ronaldo Silva (rosilva@who.int)

Funding: The development of the IPD-MA protocol was supported by a Wellcome Trust grant to the WHO Department of Reproductive Health and Research Human Reproduction Programme, grant number 206532/Z/17/Z. The WHO Health Emergencies Programme and the Global Arbovirus Initiative also supported this work.

Selected References:
1. Wilder-Smith A, Wei Y, Araújo TVB, et al. Understanding the relation between Zika virus infection during pregnancy and adverse fetal, infant and child outcomes: a protocol for a systematic review and individual participant data meta-analysis of longitudinal studies of pregnant women and their infants and children. *BMJ Open* 2019; **9**(6): e026092.
2. World Health Organisation. 2016. Screening, assessment and management of neonates and infants with complications associated with Zika virus exposure in utero. WHO/ZIKV/MOC/16.3/Rev3.
2. 3. Carabali M, Maxwell L, Levis B, et al. Heterogeneity of Zika virus exposure and outcome ascertainment across cohorts of pregnant women, their infants and their children: a metadata survey. *BMJ Open* 2022; **12**(11): e064362.
4. Ximenes RAA, Miranda-Filho DB, Brickley EB, et al. Zika virus infection in pregnancy: Establishing a case definition for clinical research on pregnant women with rash in an active transmission setting. *PLoS Negl Trop Dis* 2019; **13**(10): e0007763.
5. Campbell H, de Jong VMT, Maxwell L, et al. Measurement error in meta-analysis (MEMA)-A Bayesian framework for continuous outcome data subject to non-differential measurement error. *Res Synth Methods*. 2021;12(6):796-815. doi:10.1002/jrsm.1515