While Zika virus (ZIKV) has faded from the news, close to three billion people who have never been infected with the Asian lineage of ZIKV live in Aedes aegypti-endemic areas. Despite the high level of investment in ZIKV research and diagnostics, recent reviews and journal supplements have identified a spectrum of outstanding questions from almost every discipline of ZIKV-related research.

In 2016, WHO began a major global initiative to facilitate cross-study analyses of ZIKV-related studies of pregnant women and their children through both the creation of standardized protocols for cohort and case-control studies and through the creation of the ZIKV Individual Participant Data (IPD) Consortium. The ZIKV IPD Consortium is a global collaboration of ZIKV researchers that have agreed to pool de-identified, participant-level data to clarify persistent questions in ZIKV epidemiology and to provide more accurate information about the absolute risk of adverse ZIKV-related fetal, infant, and child outcomes. The largest cohorts of pregnant women began as the outbreak was ending, resulting in a smaller than expected number of ZIKV-infections. The ZIKV IPD Consortium will conduct and individual participant data meta-analysis (IPD-MA) to leverage existing data to better inform women and couples planning a pregnancy on the longer-term consequences of fetal exposure that are not observable at birth or during the first year.

The ZIKV IPD-MA Protocol is available from BMJ Open, here. The objectives of the ZIKV IPD Consortium-led IPD-MA are to:

1. Estimate the absolute and relative risks of fetal infection with ZIKV; miscarriage (<20 weeks gestation), fetal loss (≥ 20 weeks gestation), microcephaly, and other manifestations of CZS and later developmental delays.

2. Identify factors that modify women’s risk of adverse ZIKV-related fetal, infant, and child outcomes and infants’ risk of infection (e.g. gestational age at time of infection, clinical or subclinical illness, concurrent or prior arbovirus exposure, other congenital infections, and other posited effect measure modifiers).

3. Use information on the relative importance of different effect measure modifiers identified in Objective 2 to decompose the total effect of ZIKV infection during pregnancy on adverse fetal, infant, and child outcomes into 1) the direct effect of ZIKV; 2) the indirect effect of ZIKV as mediated by the effect measure modifier of interest (e.g. DENV, CHIKV, or STORCH pathogens); and 3) the effect of the interaction between ZIKV and the mediator of interest.

4. Develop and validate a risk prediction tool to identify pregnant women at a high risk of an adverse ZIKV-related outcome and to inform couples planning a pregnancy, healthcare providers, and/or resource mobilization (e.g. vector control strategies; antenatal care; open access to contraception).

Many cohort studies that were launched at the height of the epidemic were limited to symptomatic pregnant women or only followed children that presented with CZS or other ZIKV-related outcomes that are observable at birth. While a number of important developmental outcomes can only be measured after two years of age, most cohorts were only funded to collect data until two years of age. The ZIKV IPD leverages limited
case data from smaller studies launched early in the outbreak and limited long-term follow-up data from the few studies following children beyond age three.

![Figure 1. Distribution of monthly Zika virus cases and Zika virus-related longitudinal studies of pregnant women and their infants and children. Vertical axis shows the total number of monthly reported ZIKV cases for countries/regions listed (6 month moving average using data extracted from PLISA website). Each of the 42 colored circles represents a participating study with color corresponding to country/region and circle size corresponding to the number of pregnant women enrolled in the study. The horizontal colored lines indicate the time period during which a participating study recruited pregnant women.](image)

The translation of IPD-MA findings into clinical practice will be informed by a multi-country qualitative study to ascertain the preferences of women of reproductive age for sharing de-identified data for the IPD-MA and for learning about their risk of ZIKV-associated adverse fetal, infant, or child outcomes in the presence of significant uncertainty.

**Geographic location**
As of April 2020, 45 cohort studies and active surveillance sites from 25 countries and territories have agreed to contribute de-identified data to the ZIKV IPD Consortium IPD-MA. Participating studies come from Africa, Asia, Europe, and North and South America.

**Main deliverables**
Clinical risk prediction tool that uses existing participant-level data to provide guidance for individuals and couples planning a pregnancy during a ZIKV outbreak

Open Access Manuscripts that respond to outstanding questions in ZIKV epidemiology

Open Access Manuscripts that explore community preferences for learning about the risks of ZIKV-related adverse fetal, infant, and child outcomes in the presence of uncertainty

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Lausanne University Hospital, Switzerland
London School of Hygiene and Tropical Medicine, England
McGill University, Canada
National Centre for Infectious Diseases, Singapore
National Institute of Allergy and Infectious Diseases (NIAID), USA
New York City Department of Health and Mental Hygiene, USA
Pan American Health Organization, USA
St. George’s University, Grenada
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