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Communication

# The Zika Virus Individual Participant Data Consortium: A Global Initiative to Estimate the Effects of Exposure to Zika Virus during Pregnancy on Adverse Fetal, Infant, and Child Health Outcomes

Zika Virus Individual Participant Data Consortium

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**Abstract:** This commentary describes the creation of the Zika Virus Individual Participant Data Consortium, a global collaboration to address outstanding questions in Zika virus (ZIKV) epidemiology through conducting an individual participant data meta-analysis (IPD-MA). The aims of the IPD-MA are to (1) estimate the absolute and relative risks of miscarriage, fetal loss, and short- and long-term sequelae of fetal exposure; (2) identify and quantify the relative importance of different sources of heterogeneity (e.g., immune profiles, concurrent flavivirus infection) for the risk of adverse fetal, infant, and child outcomes among infants exposed to ZIKV in utero; and (3) develop and validate a prognostic model for the early identification of high-risk pregnancies and inform communication between health care providers and their patients and public health interventions (e.g., vector control strategies, antenatal care, and family planning programs). By leveraging data from a diversity of populations across the world, the IPD-MA will provide a more precise estimate of the risk of adverse ZIKV-related outcomes within clinically relevant subgroups and a quantitative assessment of the generalizability of these estimates across populations and settings. The ZIKV IPD Consortium effort is indicative of the growing recognition that data sharing is a central component of global health security and outbreak response.

**Keywords:** Zika virus; individual participant data meta-analysis; data sharing; emerging pathogen; prognostic model; prediction model; congenital Zika syndrome; microcephaly

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While the world has turned to face COVID-19, recent epidemics are re-emerging [1,2]. Even as vector control is sidelined to confront the current crisis [3], close to 3 billion Zika virus (ZIKV) naïve people live in *Aedes-aegypti* endemic areas in Asia and Africa [4]. Despite the advances in ZIKV research, researchers are only now beginning to characterize the longer-term sequelae of fetal ZIKV exposure [5,6]. Identification of factors that affect the risk of fetal infection and adverse pregnancy, birth, and pediatric developmental outcomes is central to quantifying the burden of disease related to ongoing and future ZIKV transmission and critical for the development of diagnostic assays, vaccines, appropriate early intervention strategies, and targeted preventive measures.

In February 2017, a group of researchers formed the ZIKV Individual Participant Data (IPD) Consortium to conduct an individual participant data meta-analysis (IPD-MA) of ZIKV-related longitudinal studies of pregnant women and their children. The ZIKV IPD Consortium initiative arose from a meeting of international organizations and Ministries of Health in June 2016 to coordinate and harmonize ZIKV-related research efforts [7]. IPD-MA is the synthesis and analysis of participant-level data across related studies and provides a number of statistical and clinical advantages over aggregate data meta-analysis [8]. The research objectives of the ZIKV IPD Consortium IPD-MA are to (1) estimate the absolute and relative risks of miscarriage, fetal loss, and short- and long-term sequelae of fetal Zika

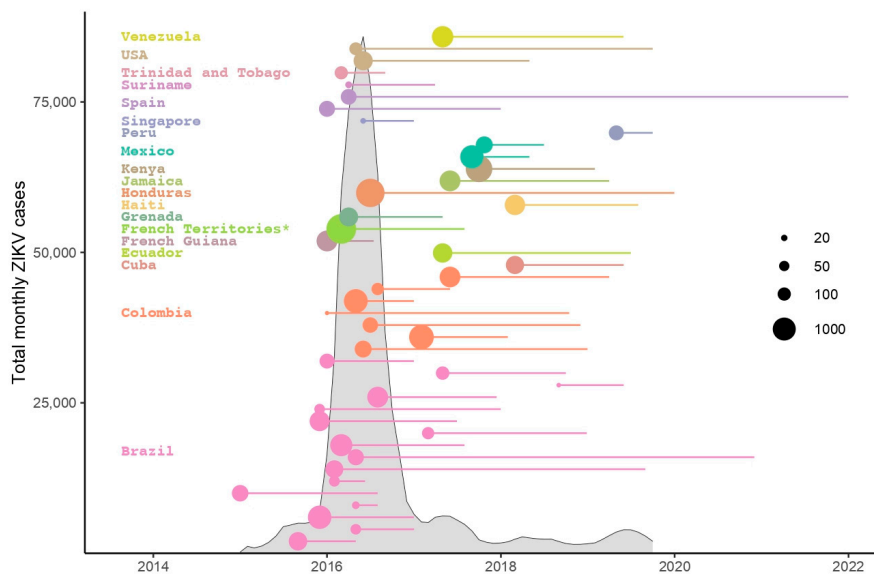
exposure for women that experience symptomatic and asymptomatic ZIKV infection during pregnancy; (2) identify and quantify the relative importance of different sources of heterogeneity in the risk of adverse fetal, infant, and child outcomes among infants exposed to ZIKV in utero; and (3) develop and validate a prognostic prediction model [9] to identify high risk pregnancies and inform communication between health care providers and their patients and to optimize mobilization of resources (e.g., vector control strategies, antenatal care, and family planning programs). The IPD-MA will include data from longitudinal studies or country-level active surveillance systems that measure ZIKV exposure and infection during pregnancy and subsequent fetal, infant, and/or child outcomes. The full protocol for the IPD-MA is available from *BMJ Open* (<https://bmjopen.bmj.com/content/9/6/e026092>).

As of August 2020, 52 cohort studies and country-level active surveillance system sites from 28 countries and territories have agreed to contribute de-identified data to the ZIKV IPD Consortium IPD-MA. The use of participant-level data from diverse geographies and populations will allow the team to better identify the clinical, virological, environmental, and individual-level factors that predict severe ZIKV-related fetal effects or adverse neurocognitive or neurodevelopmental outcomes in the child, several of which can only be measured after two years of age [10]. For example, the diversity of populations will help researchers understand differences in the sequelae of fetal exposure between populations with a high prevalence of recent prior exposure to other arboviruses and those where ZIKV occurs alone, while accounting for yellow fever immunization. Figure 1 shows the distribution of ZIKV cases at the global level, extracted from the PAHO PLISA Health Information Platform for the Americas [11]. Each circle represents a longitudinal study or country-level active surveillance system with circle size corresponding to the number of pregnant women enrolled and the line indicating the time period during which studies recruited pregnant women. As indicated in the graph, the number of new ZIKV cases has decreased dramatically since 2018, and several of the larger studies began towards the end of the epidemic in the Americas. Utilizing available data will be especially important since few studies have been able to secure funding for the follow-up needed to understand the spectrum and incidence of longer-term consequences of fetal exposure to ZIKV.

The global response to ZIKV has been characterized by unprecedented levels of collaboration between countries, research organizations, universities, and surveillance systems [12]. The ZIKV IPD Consortium effort is indicative of the growing recognition that data sharing is a central component of global health security and outbreak response. Ideally, cross-study and cross-system data synthesis and analysis would take place in real time during an epidemic. To make that possible, the governance and systems for data and sample sharing need to be in place before the next major outbreak. Statistical methods for valid synthesis and analysis of large combined datasets in an IPD-MA need to be adapted to inform the public health response to emerging pathogens [13], especially when there is no reference standard that can be used to evaluate the relative accuracy of different diagnostic assays [14–16].

Women living in and travelling to countries with ongoing or recent ZIKV transmission face a tremendous burden from the fear and uncertainty around the risks associated with ZIKV infections during pregnancy, guidance from public health authorities to avoid or delay pregnancy, and the lack of economic and social support for the challenges of raising infants with congenital Zika syndrome (CZS) and other ZIKV-related disabilities and developmental delays [17,18]. Research study participants have the added burden of intensive follow-up that may require frequent blood draws and long commutes. While there is currently no vaccine or prophylaxis to prevent or mitigate the effects of ZIKV infection during pregnancy, leveraging data across studies to improve precision and developing the statistical methods needed to improve the accuracy and quantify the uncertainty of the information conveyed to families and health systems are ethical imperatives.

Despite the persistent threat of ZIKV infection to pregnant women and women of reproductive age worldwide, investment in critical areas of ZIKV research is waning. Leveraging existing investments through collaboration will accelerate the development of effective prevention, harm reduction, and control strategies. Best practices and lessons learned from the research response to ZIKV can be used to improve the coordination and speed of the global research response to emerging pathogens.



**Figure 1.** Distribution of monthly Zika virus (ZIKV) 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 of raw data extracted from PAHO PLISA Health Information Platform for the Americas, 2 November 2019). 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. Ten studies missing information on number of pregnant women enrolled are excluded from the graph. \* French Territories include Guadeloupe, Martinique, and French Guiana.

Global travel, trade, urbanization, and climate change have all facilitated the development of novel hosts [19] and extended the range of existing hosts [20], fundamentally altering the geographic range of vector-borne diseases. Innovations in research response are central to ensuring that global health security systems keep pace. The synthesis of participant-level data across studies with the ZIKV IPD Consortium IPD-MA is a first step. Employing prospective harmonization and real-time collaborative analyses that utilize participant-level data to inform epidemic response is the way forward.

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