



## Zika and the Risk of Microcephaly

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**Z**ika virus (ZIKV) infection during pregnancy has been linked to birth defects,<sup>1</sup> yet the magnitude of risk remains uncertain. Investigators studying the 2013–2014 Zika outbreak in French

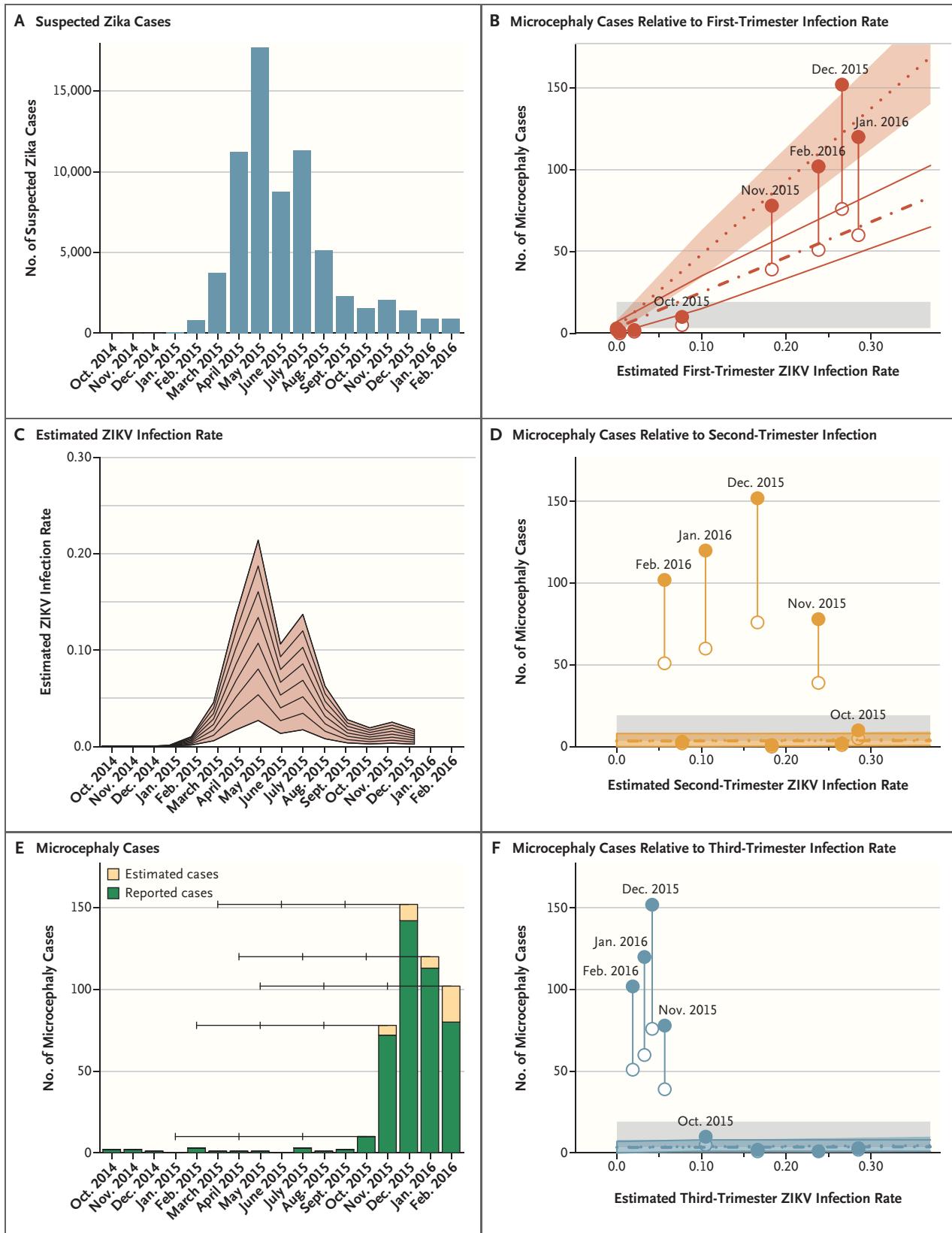
Polynesia estimated that the risk of microcephaly due to ZIKV infection in the first trimester of pregnancy was 0.95% (95% confidence interval, 0.34 to 1.91), on the basis of eight microcephaly cases identified retrospectively in a population of approximately 270,000 people with an estimated rate of ZIKV infection of 66%.<sup>2</sup>

In the current outbreak, thousands of cases of infants with suspected microcephaly or other developmental anomalies of the central nervous system that may be associated with ZIKV infection have been reported in Brazil. To estimate the magnitude of the risk of microcephaly in Brazil, we analyzed data from Bahia (see Panel A of the figure). Serosurvey data from Yap Island, Feder-

ated States of Micronesia (where there was an outbreak in 2007), and French Polynesia indicate that reported Zika cases represent only a small fraction of the number of ZIKV infections that actually occur. The infection rate in Bahia cannot be reliably inferred from currently available data, so we assumed that it could range from 10 to 80% on the basis of estimates from Yap and French Polynesia (66 to 73%) and reports from non-outbreak ZIKV serosurveys (6 to 40%) (see the Supplementary Appendix, available with the full text of this article at NEJM.org). We apportioned this risk across 2015 according to the temporal distribution of reported cases (see Panel C of the figure), assumed that all pregnant

women were equally susceptible to infection (regardless of the gestational age of their fetuses), and assessed the association of infection risk with microcephaly cases reported in the Brazilian Live Births Information System between July 2015 and February 2016 (as of March 21, 2016, accounting for a reporting delay and assuming that all reported births occurred at full term) (see Panel E of the figure).

Considering different infection-rate scenarios (from 10 to 80%), possible overreporting (0% or 100%), and an uncertain baseline microcephaly rate (2 to 12 cases per 10,000 births), we found a strong association between the risk of microcephaly and infection risk in the first trimester and a negligible association in the second and third trimesters, in keeping with the associations found in population-level estimates for French Polynesia (see the Supplementary



**Facing page: Relationship between Trimester-Specific ZIKV Infection Risk and Microcephaly in Bahia, Brazil.**

Panel A shows the approximate number of suspected Zika cases reported in Bahia by month. Panels B, D, and F are described below. Panel C shows the estimated ZIKV infection rate, assuming an overall infection rate of 10 to 80%. Panel E shows the numbers of microcephaly cases in Bahia, including reported cases (green) and estimated additional cases (yellow), accounting for reporting delays (see the Supplementary Appendix). Horizontal lines indicate the approximate gestational period by trimester for births in October 2015 through February 2016 (under the assumption that the pregnancies reached full term). In Panels B, D, and F, the solid points represent the total number of microcephaly cases for each birth cohort (July 2015 through February 2016) in Bahia (adjusted for reporting delays) relative to the estimated infection rate for the first (Panel B), second (Panel D), and third (Panel F) trimesters if the overall 2015 infection rate was 50%. The open points represent 50% of this value (reflecting potential overreporting), and the gray area represents expected baseline microcephaly rates of 2 to 12 cases per 10,000 births. Model-fitted estimates and 95% credible intervals for microcephaly cases are shown for data with (dotted line) and without (dashed line) overreporting.

Appendix). The estimated baseline risk of microcephaly was low, approximately 2 per 10,000 births (see Panels B, D, and F of the figure, and the Supplementary Appendix), but the estimated risk due to infection in the first trimester ranged from 0.88% (95% credible interval, 0.80 to 0.97), when we assumed an 80% overall ZIKV infection rate and 100% overreporting of microcephaly cases, to 13.2% (95% credible interval, 12.0 to 14.4), when we assumed a 10% ZIKV infection rate and no overreporting.

The lower end of this range is similar to the approximate 1% risk estimated for French Polynesia, especially if infection rates in Bahia were high (40% or more with overreporting, 70% or more

without overreporting). It is also possible that the French Polynesia estimate is an underestimate; it is from a single outbreak, and microcephaly cases were identified retrospectively. Furthermore, higher risks of microcephaly have been documented for some other viruses.<sup>2</sup> Both estimates are consistent with the lack of reported microcephaly cases in Yap: if microcephaly risk due to ZIKV infection during the first trimester was 0.88 to 13.2%, then zero to four microcephaly cases would have been expected.

There are uncertainties and limitations with all current estimates of microcephaly risk associated with ZIKV infection. First, available data are very limited, especially in recently affected areas such as Bahia, where infection rates are unknown and microcephaly cases are still being reported and evaluated. The limited information on ZIKV infection rates is compounded by difficulty in the clinical confirmation of microcephaly, as evidenced by low confirmation rates in the independent, temporary microcephaly reporting system established by Brazil in late 2015. Carefully designed serosurveys and data from other locations can help in refining these estimates.

Recent studies have revealed associations between symptomatic ZIKV infection during all trimesters and adverse pregnancy outcomes<sup>3</sup> and potential peak risk during gestational weeks 14 to 17.<sup>4</sup> How these outcomes relate to the clear association between first-trimester risk and microcephaly at the population level in French Polynesia and Bahia is uncertain. On the population level, the temporal relationship is confounded by variation in infection

risk, gestational age, and fetal outcome assessment. Here we assumed that all births were full term; although fetal loss and early termination have been documented, the delay between the Zika outbreak and microcephaly cases in French Polynesia and Bahia indicates that the majority of cases were associated with first-trimester infection risk in pregnancies that were at or near full term.

Meanwhile, our understanding of the biology of ZIKV infection in pregnancy is based on clinically described cases in pregnant women with symptomatic infection. We therefore have little knowledge of the effects of mild or asymptomatic ZIKV infections or ZIKV infections in early pregnancy, when women may be unaware of the pregnancy. The risk of adverse events may be higher in symptomatic infections, but mild infections are probably more common and thus may also contribute substantially to the overall burden.

Furthermore, microcephaly is only one possible adverse outcome among a spectrum of conditions that may be part of congenital Zika syndrome. A population-level increase in central nervous system anomalies has been observed in both French Polynesia and Brazil. More data are needed to refine gestational age-specific risk estimates for microcephaly and these other outcomes related to ZIKV infection, especially to assess population-level infection rates and the effects of congenital Zika syndrome at all gestational ages in relation to both symptomatic and asymptomatic infection.

Although much remains unknown about the effects of ZIKV

infection during pregnancy, population-level data from French Polynesia and Bahia reveal a clear association between first-trimester ZIKV infection and microcephaly risk. The pattern was probably similar in other

 **An audio interview with Dr. Eric Rubin is available at NEJM.org** parts of northeastern Brazil, where Zika outbreaks in early 2015 were followed by microcephaly outbreaks in late 2015. If the risk of infection and adverse outcomes is similar in the other geographic areas where ZIKV has since spread, many more cases of microcephaly and other adverse outcomes are likely to occur. In light of the growing evidence, it is prudent to take precautions to

avoid ZIKV infection during pregnancy<sup>5</sup> and for health care systems to prepare for an increased burden of adverse pregnancy outcomes in the coming years.

The findings and conclusions in this article are those of the authors and do not necessarily reflect the official position of the Centers for Disease Control and Prevention. All data are publicly available, and JAGS code (see the Supplementary Appendix) is available from Dr. Johansson upon request.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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## Biomarker Tests for Molecularly Targeted Therapies — The Key to Unlocking Precision Medicine

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As the promise and the pitfalls of precision medicine gain increasing attention,<sup>1,2</sup> enthusiasm about the field has been heightened by a rapid reduction in the cost of high-throughput genomic sequencing and a dramatic increase in the identification of potential molecular targets for therapy. Biomarker tests for molecularly targeted therapies can help physicians to select the most effective therapy for a patient's condition and avoid treatments that could be ineffective or harmful. If precision medicine is to reach its potential, such biomarker tests will have to be developed in a timely fashion.

Some observers, however, have expressed concern that these rap-

id developments have caused genomic data to accumulate at a rate that exceeds our ability to adequately capture, fully analyze, and properly interpret them. The medical armamentarium available to physicians seeking to tailor therapies to their patients' conditions is expanding in parallel. Annual spending on molecularly targeted therapies for oncology in the United States now exceeds \$10 billion, outpacing spending on conventional chemotherapies. In 2015 alone, the Food and Drug Administration approved 18 new agents for cancer, nearly all of which were based on the principles of precision medicine.

The degree to which physicians will be able to apply genom-

ic information in selecting therapy that improves clinical care remains to be seen and will probably vary over the near term.<sup>3,4</sup> The processes of identifying and validating biomarker tests and of developing and evaluating targeted therapies are complex. Potentially useful tests have not been adopted into clinical practice rapidly, in part because we lack common evidentiary standards for regulatory, clinical, coverage, and reimbursement decisions. Furthermore, clinical implementation will require the consistent collection and sharing of data on biomarker tests, treatments, and patient outcomes.<sup>5</sup>

The Institute of Medicine (IOM) has convened several ex-