Expected Duration of Adverse Pregnancy Outcomes after Zika Epidemic

Rosalind M. Eggo, Adam J. Kucharski

Evidence is increasing that Zika virus–related adverse outcomes can occur throughout pregnancy. Mathematical modeling analysis using reported outcome data suggests that surveillance for these outcomes should begin as soon as an outbreak is detected and should continue for 40 weeks after the outbreak ends.

Quantifying the risk for adverse pregnancy outcomes (APOs) after Zika virus infection is of critical public health importance. Recent studies have suggested that risk for microcephaly is concentrated in pregnancies in which infection occurs during the first trimester (*1*,*2*). However, microcephaly is at the severe end of the APO spectrum and might have a different risk profile from other outcomes: brain abnormality and malformation, eye anomalies, neural tube defects, arthrogryposis, congenital deafness, and others (*3*). In particular, estimates of APOs after symptomatic confirmed Zika virus infection suggest risk for fetal injury throughout pregnancy (*3*,*4*). Thus, a better understanding of the likely duration and risk for APOs after Zika virus outbreaks is urgently needed (*2*). We used surveillance and clinical data to estimate the timing and number of expected APO events after observed Zika outbreaks in 9 regions of Brazil during April 2015–July 2017.

The Study

To quantify APO risk, we used data from a study that recruited 345 pregnant women with rash in the previous 5 days, of whom 134 tested positive for Zika virus infection (*4*). Excluding 9 losses to follow-up, we followed a cohort of 125 women during pregnancy; surviving infants were examined for APOs. A total of 58 APOs occurred in this group; microcephaly was infrequent (4 [6.9%] of 58) but severe (*4*).

We fitted a logistic model to individual-level data for the 125 followed-up women to estimate the proportion of APOs after symptomatic Zika virus infection at each week of gestation (Figure 1, panel A). Although the fitted linear model suggested a decline in risk over time, the model did not perform significantly better than a model with constant risk for APO at any gestational age (online Technical Appendix, https://wwwnc.cdc.gov/EID/article/24/1/17-0482-Techapp1.pdf). For comparison, we also considered a theoretical risk profile in which APO risk occurs only during the first trimester (Figure 1, panel A).

We used these risk profiles to estimate the period through which an elevated rate of APOs would be expected after the 2015–2016 Zika epidemic in 9 regions of Brazil (Figure 1, panels B–J). We superimposed the timing of confirmed microcephaly cases in each region to assess the relationship between observed microcephaly and expected duration of elevated APO risk but did not fit explicitly to microcephaly incidence data. If risk were assumed to occur only during the first trimester, the period of APOs would be shorter than the duration of observed microcephaly events. In contrast, the predicted durations of APOs based on risk throughout pregnancy were more consistent with the observed distribution of microcephaly in these regions.

To examine the potential duration and risk for Zika-associated APOs more generally, we also predicted the pattern of APOs under 3 hypothetical epidemic scenarios: single outbreak, multipeaked epidemic, and endemic transmission (Figure 2). For each epidemic scenario, the model suggested that the duration of elevated risk was much longer than the duration of cases if APOs could occur from infection in any gestational week. This observation means that in areas where seasonal outbreaks of Zika occur, the risk for APOs might not return to baseline levels between epidemics, and Zika-specific interventions based on timing of pregnancy might be less effective (*7*).

Our findings are subject to several limitations. First, we based the estimation of APO risk by gestation period on a cohort study of symptomatic infection with rash, which does not occur with all Zika virus infections (*8*). However, recent evidence suggests the risk for APOs is similar for symptomatic and asymptomatic infection (*9*). We included pregnancy loss during the first trimester (miscarriage) as an APO, but excluding these 5 cases did not alter the findings (online Technical Appendix, Sensitivity Analysis on Inclusion of Miscarriages section). Moreover, evidence suggests that APOs might not be detectable at birth but appear later, which would underestimate the frequency of APOs (*10*).

Second, the data were from patients recruited in Rio de Janeiro, whereas we considered potential risk across all regions of Brazil. Although the cohort was large and APO data detailed, numbers of exposed women in each gestational

Affiliation: London School of Hygiene & Tropical Medicine, London, UK

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week were low, leading to large CIs on the risk profile (Figure 1, panel A). We therefore used a linear model to estimate the risk at each gestational week because data were insufficient to fit a more complex risk function. The range of data (6–39 weeks' gestation) also constrained our estimates.

Third, publicly available epidemiologic reports from Brazil recorded microcephaly cases, rather than all forms of APO. We qualitatively compared these microcephaly reports with our estimates for the duration of risk for APOs, but the risk for microcephaly by gestational week might differ from the overall risk for APOs. Different regions are likely to have differing baseline levels of APOs in the absence of Zika virus infection; we therefore focused our analysis on the risk for APOs associated with Zika virus

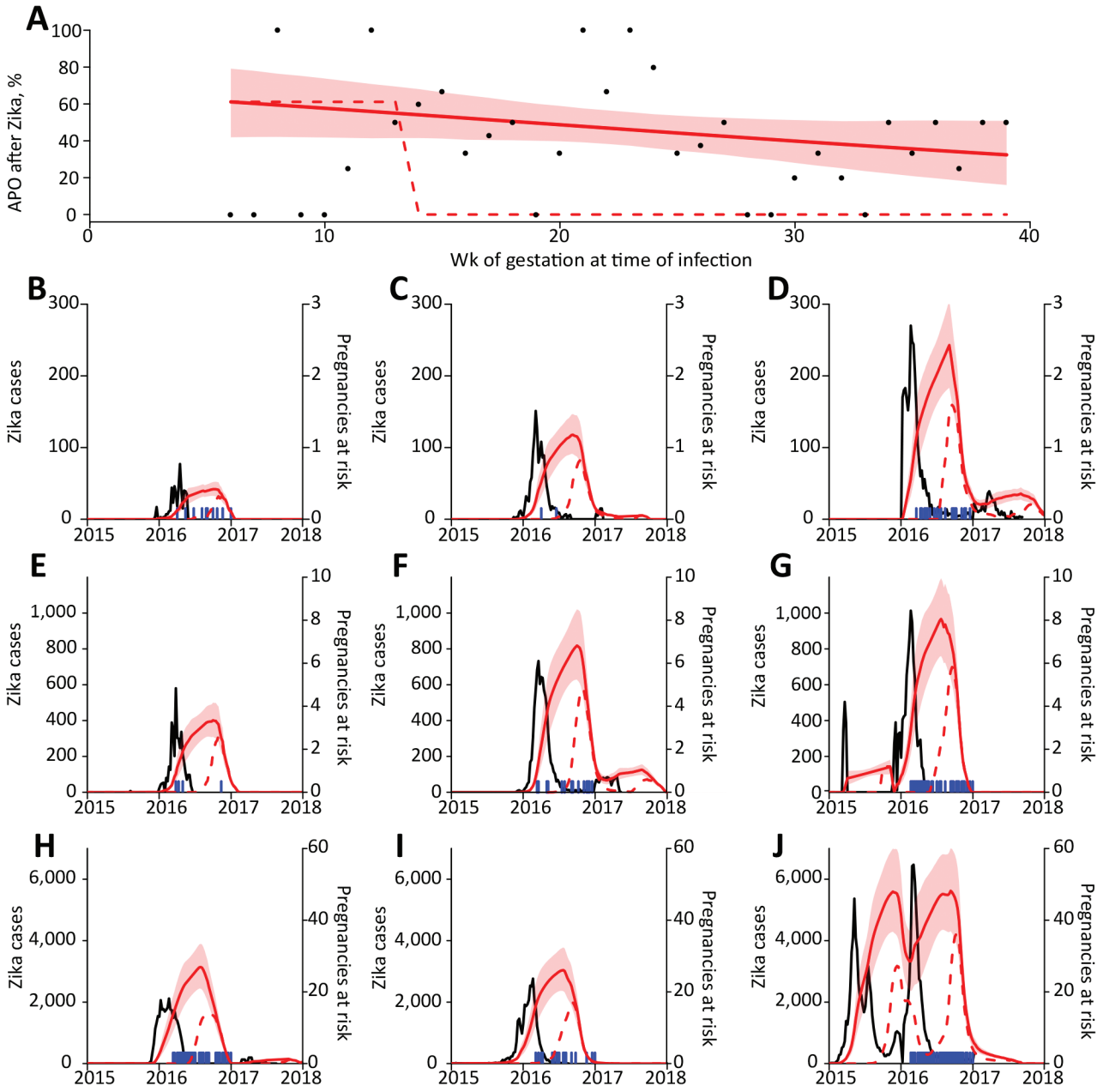

Figure 1. Relationship between Zika virus infection and expected related APOs per 1,000 pregnancies in Brazil during April 2015–July 2017. A) Percentage of APOs (fetal loss at any gestational age, stillbirth, neonatal abnormality) given symptomatic PCR-confirmed Zika virus infection. Points show weekly proportion with APO (*4*); red line indicates fit to data with a generalized linear model, and shading indicates 95% CIs; dashed line indicates fixed risk in first trimester only (*5*). B–J) Blue lines indicate suspected Zika cases in different regions; red lines indicate expected number of births with Zika-associated APO in subsequent weeks based on the 2 risk distributions in panel A. Shaded regions indicate 95% CIs. Model assumes 17% of Zika virus infections are reported (*5*,*6*). APO, adverse pregnancy outcome.

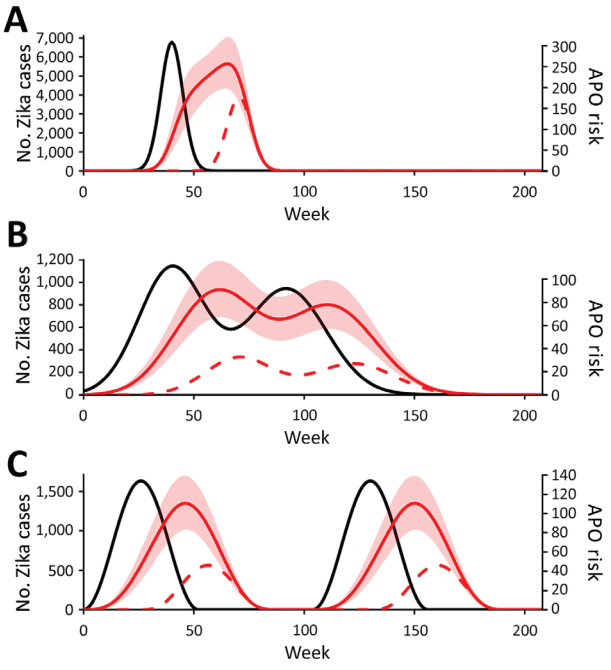

Figure 2. Expected temporal distribution of Zika virus–related adverse pregnancy outcomes under different hypothetical outbreak scenarios, Brazil, April 2015–July 2017. Black lines indicate Zika cases; red lines indicate risk (APOs/1,000 births) for Zika-associated APO in subsequent weeks based on the 2 risk distributions in panel A. Dashed lines indicate timing of outbreaks: A) short, single-peaked outbreak; B) double-peaked outbreak; C) biennial epidemics (i.e., a seasonal endemic state). A population size of 1 million, reporting of 17% of Zika infections, and a 50% attack rate during a 4-year period were assumed. APO, adverse pregnancy outcome.

infection. Why some areas of Latin America have reported more cases of microcephaly than others remains unclear (*11*). There may be unmeasured cofactors that alter the risk for APO on Zika virus infection (*12*). Another factor could be differences in the proportion of Zika cases reported, which could lead to variation in incidence of APOs. We assumed 17% of Zika infections were reported (*6*,*8*); if the proportion reported was larger, it would mean fewer women were infected during the epidemic, and hence fewer would be expected APOs (online Technical Appendix, Sensitivity Analysis on Fraction of Cases Reported section).

Finally, Brazil made Zika notifiable in November 2015, which might have increased reporting (*13*). In addition, the Zika incidence data varied markedly by region, which may be due to true differences in outbreak dynamics or to differences in reporting of cases (Figure 1). Although variability in weekly Zika incidence data would alter the precise relationship between Zika cases and population-level rate of APO, the general shape and duration of enhanced risk estimated in the model remains the same (online Technical Appendix, Sensitivity Analysis on Fraction of Cases Reported section).

Conclusions

Our results suggest that if fetal injury from Zika virus infection can occur across a range of gestational ages, APOs after a Zika outbreak could occur for a long time after the outbreak subsided. This duration is longer than if the risk is assumed to be in the first trimester only (*2*,*14*). Combined with epidemiologic reports of APOs collected in Brazil, which show an increase in microcephaly rate at a time inconsistent with first trimester–only risk, evidence is mounting to recommend extended surveillance for APOs and to include a spectrum of outcomes, not only microcephaly (*10*,*15*).

Our results suggest that when Zika outbreaks are identified, surveillance and planning for infection-associated APOs might need to focus on a longer period than previously thought. In addition to the potential for APOs several months after an epidemic, the risk period may begin soon after the outbreak is detected. Further studies are crucial to refine the risk for APO during gestation and to ensure pregnant women can be correctly informed of their risk, so that population-level surveillance can be effectively implemented.

Dr. Eggo is a mathematical modeler working on infectious disease dynamics and control at the London School of Hygiene & Tropical Medicine. Her research interests include severe outcomes of infection and the health inequities and inequalities that can result.

Dr. Kucharski is a mathematical modeler focused on outbreak disease dynamics at the London School of Hygiene & Tropical Medicine. His research interests include new emerging infections and immunity from individual infection history.

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Address for correspondence: Rosalind M. Eggo, London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK; email: r.eggo@lshtm.ac.uk

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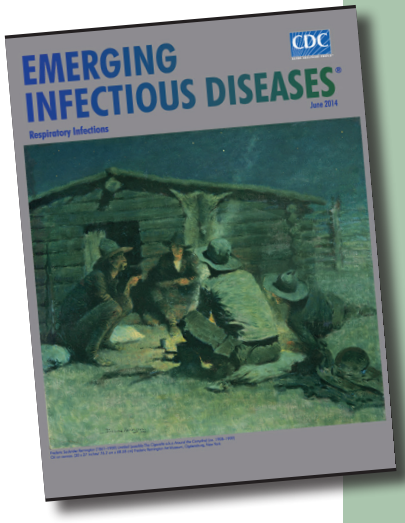
Zika Virus

Zika [zēkˈə] Virus



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Zika virus is a mosquito-borne, positive-sense, single-stranded RNA virus in the family *Flaviviridae*, genus *Flavivirus* that causes a mild, acute febrile illness similar to dengue. In 1947, scientists researching yellow fever placed a rhesus macaque in a cage in the Zika Forest (*zika* meaning "overgrown" in the Luganda language), near the East African Virus Research Institute in Entebbe, Uganda. A fever developed in the monkey, and researchers isolated from its serum a transmissible agent that was first described as Zika virus in 1952. It was subsequently isolated from a human in Nigeria in 1954. From its discovery until 2007, confirmed cases of Zika virus infection from Africa and Southeast Asia were rare. In 2007, however, a major epidemic occurred in Yap Island, Micronesia. More recently, epidemics have occurred in Polynesia, Easter Island, the Cook Islands, and New Caledonia.

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Article DOI: https://doi.org/10.3201/eid2401.170482

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Technical Appendix

Data

Data were drawn from Brasil et al. (*1*) (Technical Appendix Table 1). We included cases of fetal loss in the first trimester (miscarriage) in the analysis but include sensitivity analysis on this in the Sensitivity Analysis on Inclusion of Miscarriages section.

Zika Incidence

Time series of the weekly number of Zika cases in each region were initially drawn from the supplement of Ferguson et al. (*2*) and then updated with more recent values by the same methods, i.e., transcribed from situation reports in each affected region. Data from Bahia are updated in line with surveillance reports. All values are provided in a public github repository (https://github.com/rozeggo/microcephaly_Brazil).

Analysis Code

All code for the analyses conducted here are provided in https://github.com/rozeggo/microcephaly_Brazil.

Comparison of Fitted Model and Constant Risk

We estimated the adverse pregnancy outcome (APO) risk function by fitting a linear model with binomial link function to the individual-level APO data using the R package "*mgcv*" and function "glm()." In the model, the intercept was estimated to be 0.6685 (SE 0.5163), and the estimated coefficient for risk for APO by week of gestation was –0.0360 (SE 0.0215). Although it has previously been suggested that there is a higher risk for Zika-associated adverse

outcomes earlier in pregnancy, the performance of the linear model was not substantially better than a simpler model that assumed a constant risk across the whole pregnancy period (model with linear term had Akaike Information Criterion, AIC = 173.76; model with constant risk had AIC = 174.64).

Using Case Data to Estimate Pregnancies with APO

We first calculated total number of reported cases, *C*, during the epidemic:

$$C = \sum_{t} c_t$$

where c_t is the number of cases reported in week *t*. We combined this value with the assumed proportion of cases that were reported, *r*, and the population size *N* to calculate the overall attack rate, *A*, for the population:

$$A = \frac{C}{rN}$$

In our main analysis, we assumed *r* = 0.17, based on the estimated number of case-women who attended health care facilities (C = 30,000), population size (N = 275,000) and postepidemic seroprevalence (A = 0.66) in the 2013–14 Zika outbreak in French Polynesia (*3*,*4*), but tested this assumption in a sensitivity analysis (see Sensitivity Analysis on Fraction of Cases Reported section.

To estimate weekly expected number of pregnancies with APO, we estimated the probability that someone would have been infected during their pregnancy. For a woman who was 6 weeks pregnant in week *t* of the outbreak (we did not consider the earlier period of pregnancy because no APO data were available for this (Figure 1, panel A), the risk for APO, a_t, at *t* weeks was:

$$a_t = \sum_{j=t}^{t+39-6} \frac{c_t}{C} f(j - t + 6)$$

where *f(x)* denotes the risk for APO given infection in gestation week *x*, and we assume a gestation period of 39 weeks. These women would therefore be expected to give birth in week *t*+39–6. Finally we scaled the risk by the number of pregnant women expected each week;

because the birth rate was 14 per 1,000 in 2015 (*5*), we would expect (14 × N)/(52 × 1,000) births per week.

The calculations in the simulation study were performed in the same way, except with simulated trajectories for the number of cases over time.

Sensitivity Analysis on Fraction of Cases Reported

To determine the effect on our estimates of assuming 17% of Zika cases are reported, we also examined the findings when we assumed 40% of Zika cases are reported (Technical Appendix Figure 1). The overall number of pregnancies at risk for APO is lower, the time period of elevated risk is the same, and therefore the overall public health message is unchanged by this assumption (Technical Appendix Figure 2).

Sensitivity Analysis on Inclusion of Miscarriages

To test the effect of first trimester fetal loss (miscarriage in Brasil et al. [*1*]) we refitted the model with those 5 events excluded, and show the same results as in the main paper (Technical Appendix Table 2, Technical Appendix Figure 3). There is little effect on estimates: intercept = 0.2427 (SE 0.5538), week coefficient = –0.0206 (SE 0.0226).

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Technical Appendix Table 1. Pregnancy and Zika virus APO data that include first-trimester fetal loss (miscarriage), Brazil, April 2015–July 2017

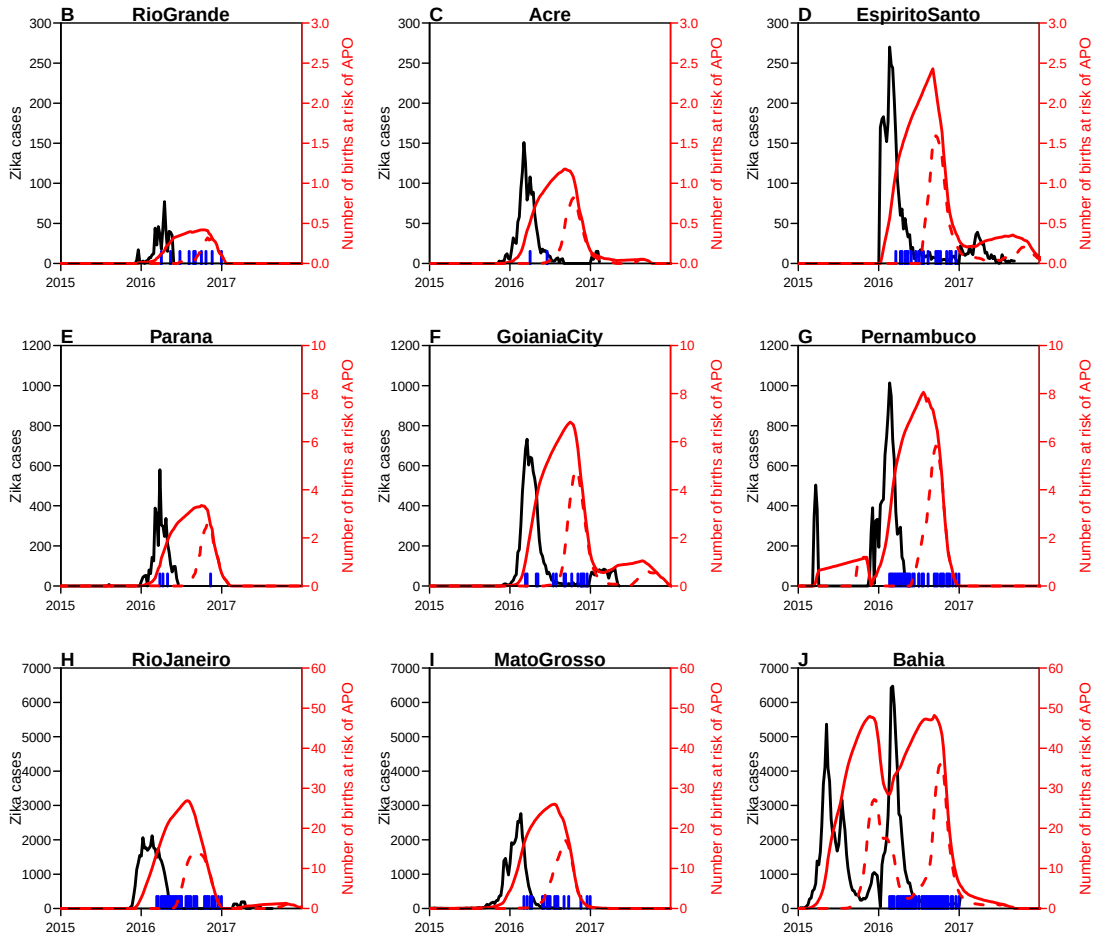
Week of gestation	APO negative	APO positive	Total pregnancies
6	1	2	3
7	1	0	1
8	0	2	2
9	1	1	2
10	2	1	3
11	3	2	5
12	0	2	2
13	1	1	2
14	2	3	5
15	1	2	3
16	2	1	3
17	4	3	7
18	3	3	6
19	4	0	4
20	2	1	3
21	0	4	4
22	2	4	6
23	0	4	4
24	1	4	5
25	4	2	6
26	5	3	8
27	3	3	6
28	2	0	2
29	2	0	2
30	4	1	5
31	2	1	3
32	4	1	5
33	1	0	1
34	2	2	4
35	2	1	3
36	1	1	2
37	3	1	4
38	1	1	2
39	1	1	2
Total	67	58	125

*Data are from Brasil et al. (*1*). APO, adverse pregnancy outcome.

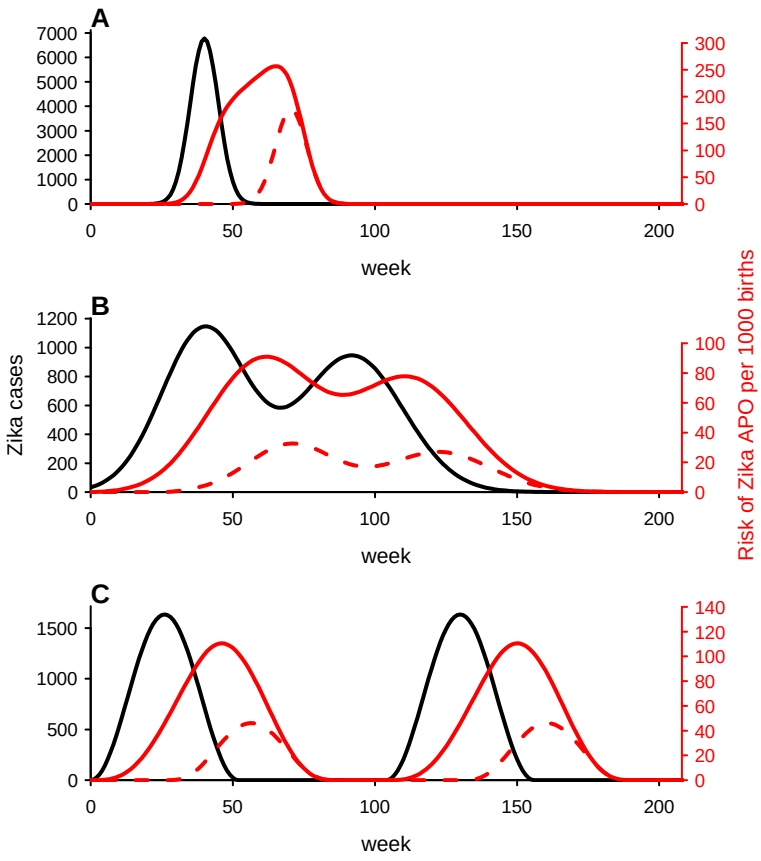
Technical Appendix Table 2. Pregnancy and Zika virus APO data that exclude first-trimester fetal loss (miscarriage), Brazil, April 2015–July 2017

Week of gestation	APO negative	APO positive	Total pregnancies
6	1	0	1
7	1	0	1
8	0	2	2
9	1	0	1
10	2	0	2
11	3	1	4
12	0	2	2
13	1	1	2
14	2	3	5
15	1	2	3
16	2	1	3
17	4	3	7
18	3	3	6
19	4	0	4
20	2	1	3
21	0	4	4
22	2	4	6
23	0	4	4
24	1	4	5
25	4	2	6
26	5	3	8
27	3	3	6
28	2	0	2
29	2	0	2
30	4	1	5
31	2	1	3
32	4	1	5
33	1	0	1
34	2	2	4
35	2	1	3
36	1	1	2
37	3	1	4
38	1	1	2
39	1	1	2
Total	67	53	120

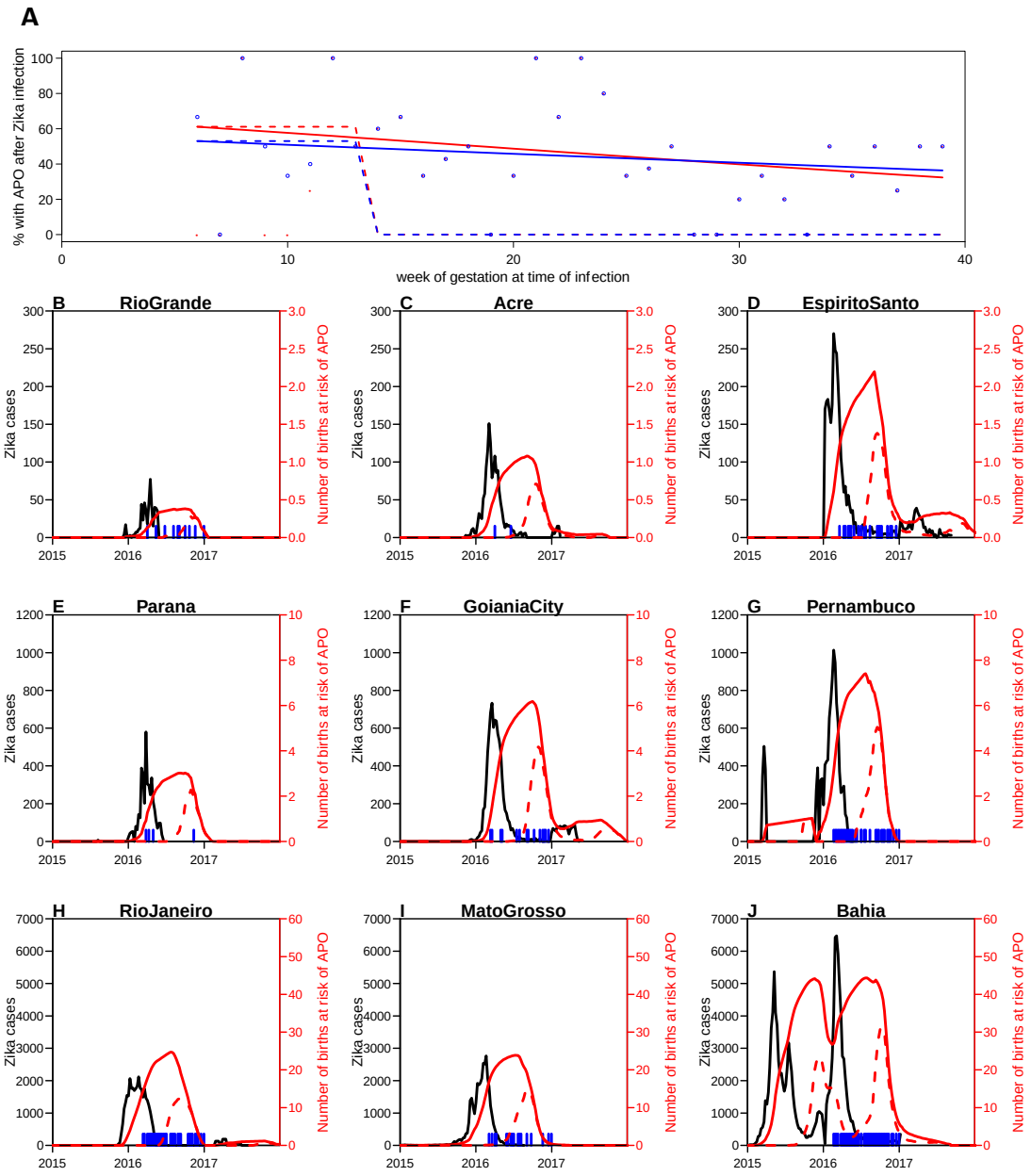
***Data are from Brasil et al. (*1*). APO, adverse pregnancy outcome.**



Technical Appendix Figure 1. Model-derived number and duration of adverse pregnancy outcomes (APOs) assuming 40% of Zika cases are reported, Brazil, April 2015–July 2017. Red line shows expected number of Zika-associated APO births from the fitted model (Figure 1, panel A main text), with 95% CI given by the shaded region for an assumption of 40% of Zika cases reported. Dashed line shows fixed risk in first trimester only. Black line shows suspected Zika cases in different regions. We assume 40% of Zika infections are reported in this sensitivity analysis. Blue ticks mark weeks in which microcephaly cases were reported in each region.



Technical Appendix Figure 2. Expected temporal distribution of adverse pregnancy outcomes (APOs) under different hypothetical outbreak scenarios, Brazil, April 2015–July 2017. Black line shows Zika cases (left axis); red shows expected proportion of births with Zika-associated APO in subsequent weeks based on the 2 risk distributions in A (right axis). A) Short, single-peaked outbreak. B) Double-peaked outbreak. C) Biennial epidemics (i.e., a seasonal endemic state). We assume a population size of 1 million, that 40% of Zika infections are reported, and a 50% attack rate during a 4-year period. APO, adverse pregnancy outcome.



Technical Appendix Figure 3. A) Comparison of findings with and without miscarriage (fetal loss in first trimester) as an adverse pregnancy outcome (APO), Brazil, April 2015–July 2017. Red line shows fit to data including miscarriages and blue excludes those APOs, with 95% CI given by the shaded region. Dashed line shows fixed risk in first trimester only. B–J) Black line shows suspected Zika cases in different regions; red lines show expected number of births with Zika-associated APO in subsequent weeks based on the blue fitted risk distribution in Technical Appendix Figure 3, panel A. Blue ticks mark weeks in which microcephaly cases were reported in each region.