Determining the rate and week of infection of Zika caused microcephaly from Colombian and Brazilian data; Status Report August 1, 2016

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The epidemic of Zika in Colombia was expected to result in many cases of microcephaly. However, until epidemiological week 23 (June 11) there were only 6 reported cases. The number of cases increased to 21 in weeks 24-27, which appears to confirm expectations about Zika as a cause of microcephaly, though the most recent weeks 28 and 29 are below the expected trend. Here we consider available data on Zika and microcephaly, and construct a comparison with models of the time period of infection during pregnancy that results in microcephaly in Colombia and in the state of Bahia, Brazil. We find that the reports from Colombia until June 11 are consistent with only background cases, while subsequent reports tracked a model in which only first trimester infections result in microcephaly. The data from Bahia is also consistent with first trimester infections causing microcephaly. Using a rate of 1% microcephaly cases for Zika infections in the first trimester (inferred from cases in French Polynesia) leads to a prediction of 200 total microcephaly cases for Colombia. However, the data from Bahia suggests a much higher rate of microcephaly, implying over 10,000 cases. Other Brazilian states have inconsistent and even higher rates according to reported cases. Any interpretation of rates, however, is sensitive to the reliability of Zika infection reports. Recently, inconsistencies in observed number of microcephaly cases across Brazil have led to questions about whether there are other factors involved in the conditions that cause microcephaly. While our analysis of the comparison of Brazil and Colombia raises similar questions, underreporting of Zika cases in Brazil makes it difficult to draw any conclusions. We note the conclusion that microcephaly is caused by infections in the first trimester of pregnancy should not be interpreted to imply that there are no consequences of later pregnancy infections.

In April, the CDC declared Zika the cause of microcephaly in Brazil [1] with over 1,500 confirmed cases [2]. Outside of Brazil a similar number of cases have not been seen thus far. In Colombia cases of Zika have been identified in August, 2015, and the outbreak grew rapidly from October. Colombian health authorities [3] reported 6 confirmed cases of microcephaly with Zika infections as of June 11, 2016, a number that stayed the same over three weeks (over the same period the WHO has been reporting 7 cases [2]). The number increased by 5, 2, 5, 2, -1, 1 (-1 is a correction) in weeks ending June 18, 25, July 2, 9, 16, 23, 2016 for a total of 21 cases (reporting as of July 29, 2016). Colombia is not reporting the number of microcephaly cases that are not linked to Zika. Here we show that until June 11, the cases can be accounted for by background rates, while the new cases are consistent with a model in which only first trimester pregnancy infections cause microcephaly [4, 5], though the last two weeks are below the trend (see Fig. 1).

A study published on June 15, 2016 in the New England Journal of Medicine [6] reports results of women infected until March 28, whose pregnancies were observed until May 2, 2016. The study tracked 1,850 women, whose date of infection with Zika is known relative to the start of the pregnancy. Of these, 532, 702, and 616 were infected in the first, second and third trimesters respectively. 16%, 29% and 93% (85, 204, and 583) of the pregnancies concluded. No cases of microcephaly were observed. The total number of pregnancies with Zika infections is much larger, with 11,944 cases with Zika symptoms being observed in clinical settings. At the time of the article, no cases of microcephaly occurred in all of these nearly 12,000 pregnancies. However, the report cites 4 cases of microcephaly with Zika in the general population that did not report any Zika symptoms, these cases being reported prior to April 28. This implies that there are many more unreported, symptomless, cases of Zika infection. Since there is less than 1 in 12,000 incidence of Zika until this point in the epidemic, there should be at least four times as many infected individuals that do not have symptoms in order for there to be 4 microcephaly with Zika cases, for a total of $5 \times 12,000$ or 60,000 Zika cases. There is other evidence for underreporting of Zika. For example, the incidence among women is twice that of men. Women at home may be infected at a higher rate, or reporting is focused on women because of the concern about maternal effects.

To interpret the microcephaly reports, we consider a study in French Polynesia [7], which provided evidence that 1 in 100 pregnancies exposed in the first trimester, or alternatively 0.5 in 100 of all pregnancies exposed in the first and second trimester, resulted in microcephaly. This study was based upon a small number of cases and ultrasound detection rather than births. Nevertheless, it provides a benchmark for microcephaly per Zika exposure, which is two orders of magnitude larger than the minimum reported background rate for microcephaly, 2 in 10,000 [8]. We note that the Zika induced cases should be considered to be in addition to the background cases, which are due to other causes.

We construct a model of the Zika infected pregnancies by considering each pregnancy to have a uniform probability

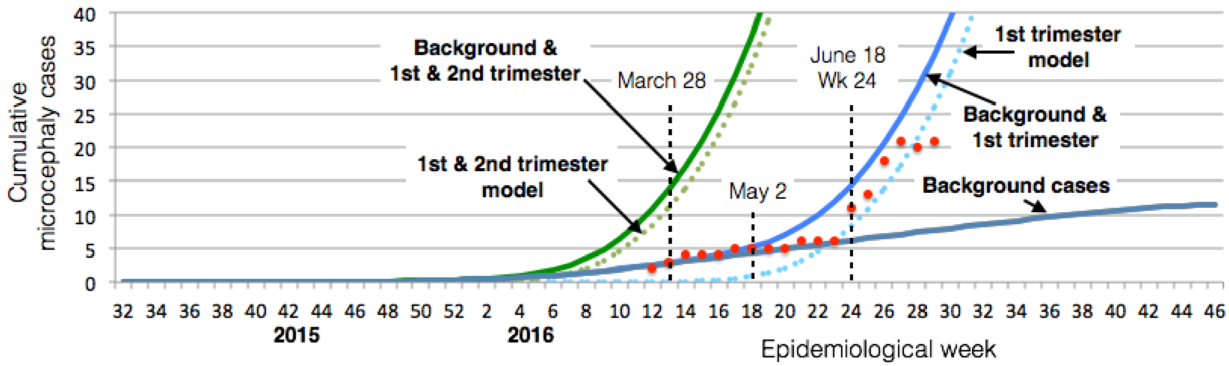

FIG. 1: *Comparison of reported cases in Colombia with background and Zika causal models*—We show the reported cases of Zika and microcephaly (red dots) with background cases of microcephaly coincident with Zika infections at a rate of 2 per 10,000 births (gray), and two models of Zika induced microcephaly obtained from the study in French Polynesia [7]. The first assumes that pregnancies infected in the first trimester have a 1:100 rate of microcephaly, the second assumes that pregnancies infected in the first and second trimester have a 1:200 rate of microcephaly. The data is consistent with just background cases until the report of epidemiological week 24, ending June 18. The data in weeks 24 through 27 is reasonably consistent with the first trimester model, suggesting we should see a much larger number of cases from pregnancies infected in the first trimester over the following weeks. Weeks 28 and 29 have fallen from that trend leading to a shortfall compared to the model of about 10 cases. The model of first and second trimester exposures appears to be ruled out. We note that the French Polynesia study was based primarily upon cases detected by ultrasound, which are not reported in Colombia aside from one case [6]. It is unclear why ultrasound based observations of microcephaly in Colombia have not been more widely reported if many births are pending.

of infection across 39 weeks. This enables us to estimate the total number of Zika infected pregnancy births, as well as the number that are born after exposure in the first trimester, or in the first and second trimesters. The total number of cases should be a combination of Zika exposure and background cases.

For background cases, any birth has the minimum probability of 2 in 10,000 of microcephaly. If a Zika infection occurred anytime during pregnancy it would be a Zika and microcephaly case at birth. Using the Zika reports by week until March 28 [6], we calculate 4,310 births till May 2, based upon a uniform distribution of infection dates and standard birth distribution [9]. Multiplying by 5 to include the non-symptomatic cases, we have a minimum of 21,550 births, or 4 microcephaly with Zika births. Until June 13 the number of pregnancies infected by Zika till March 28 that have given birth are $6145 \times 5 = 30,725$. We can use this to estimate the number of background cases using the rate of 2 in 10,000, which gives 6.

Figure 1 shows the background and the two models of Zika caused microcephaly: for first trimester only infections and for first and second trimester infections. These are compared with the recent data reported from Colombia. The background rate model is consistent with the data until June 11. The additional weekly reports since then are reasonably consistent with the first trimester model, perhaps with some additional delay. The delay may indicate that infections in the final one or two weeks of the first trimester do not result in microcephaly. Uncertainties in the reporting process limit our ability to reach a precise conclusion. The analysis thus far suggests a Zika induced microcephaly rate that is consistent between French Polynesia and Colombia, though the number of reported cases in the last two weeks in Colombia is low by perhaps 10 cases. This analysis does not address the possibility of other birth defects due to Zika infections during other stages of pregnancy.

We also analyzed data available for the state of Bahia in Brazil (Fig. 2), which includes both case counts for Zika and microcephaly, unlike many other states in Brazil including Pernambuco which only reported microcephaly. The results are consistent with a much higher rate of microcephaly than that reported in French Polynesia or Colombia. We compare with three numbers, the number of confirmed cases, 263, the number of suspected cases, 1154, and the number confirmed as having both Zika and microcephaly, 38. The first two are reported for Bahia, while the last is taken from the national ratio of confirmed Zika and microcephaly cases as a fraction of confirmed microcephaly cases, 14.4%.

According to the data that is available, the fraction of first trimester pregnancies exposed to Zika that have confirmed microcephaly is 63%, the number of suspected cases is 289% of first trimester Zika exposed pregnancies (which in principle is not inconsistent with a first trimester model of confirmed microcephaly cases), and the fraction of pregnancies exposed to Zika that are confirmed to have both Zika and microcephaly is 9.5%. All of these values are significantly larger than the 1% rate obtained from French Polynesia and used above to model Colombia. We note that the population of Bahia is about 10 million, 1/5 of the population of Colombia. The relative reliability of

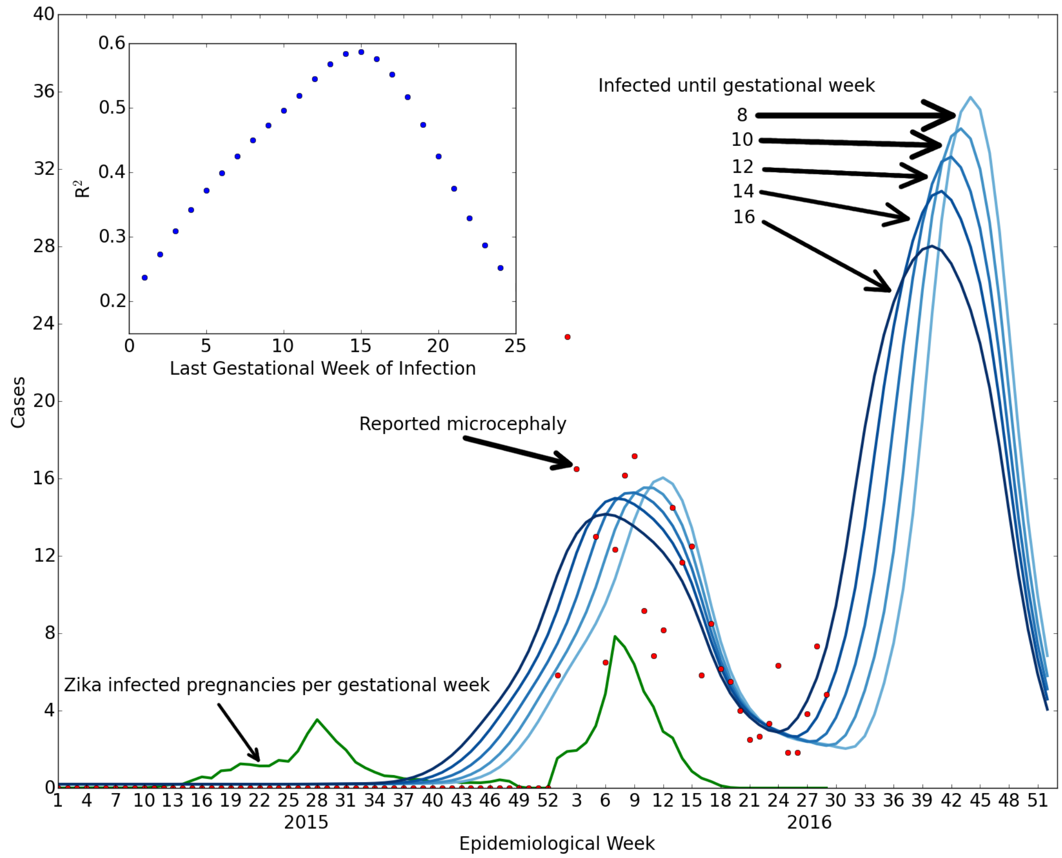

FIG. 2: *Comparison of Zika and microcephaly cases in Bahia, Brazil*—We compare reported microcephaly cases with or without symptoms of Zika (red dots) with the projected number of cases for susceptibility up to week 8, 10, 12, 14, 16 (shades of darker blue) with microcephaly for 84%, 71%, 63%, 56%, 49% of the Zika pregnancies (optimized fit) based upon the reported number of Zika infections (green shows estimated Zika infected pregnancies per week of gestation). The left green peak gives rise to the central red/blue peak due to the delay between first trimester infection and the births. The inset shows the goodness of fit for different numbers of weeks in which infections cause microcephaly. The best fit overall occurs for susceptibility up to 16 weeks, but the initial rise is more consistent with 8 weeks, suggesting that the Zika induced microcephaly cases are likely due to infections approximately during the second month of pregnancy rather than the first trimester as a whole.

Zika case reporting is unclear. In order for the microcephaly fraction to correspond to the 1% first trimester model of French Polynesia, the number of Zika cases would have to be underreported in Bahia by a factor of 63. For other Brazilian states that report both Zika and microcephaly counts there are inconsistent results including even higher levels of microcephaly to reported Zika cases (Fig. 3 and Table 1). We note that a previously published report on the total of Zika and microcephaly cases across all states, in effect, inappropriately linked Zika in Bahia with microcephaly in Pernambuco [10]. Whether the Zika reporting rate is responsible for the discrepancy between Brazilian rates and Colombian rates is yet to be determined. A large discrepancy would be a necessary if Zika is consistently causing a certain percentage of microcephaly. Our results are dominated by the analysis of Zika reporting in 2015, and reporting became mandatory only in 2016. In any case, the analysis shown in Fig. 2 suggests that the second peak of the Zika epidemic is shortly going to give rise to a new set of microcephaly cases.

When considering the implication of the Brazilian microcephaly count for the Colombian ones, it may be important to recognize that the models we used in Fig. 1 consider all Zika induced microcephaly cases as being confirmed to have Zika infections. If the confirmation rate is similar to the 14.4% found in Brazil, we would multiply the number of confirmed Zika induced microcephaly cases by a factor of $7 = 1/14.4\%$ to obtain the total number of Zika induced microcephaly cases. We would then have to increase the rate of microcephaly by this factor, which would make the Colombian results inconsistent with the French Polynesian results (raising the question as to why many more cases, approximately 50 instead of 8, were not observed there), but somewhat more consistent with the much higher microcephaly rates in Bahia. The additional cases (of order 100) should also be observed in microcephaly cases above background, but without evidence of Zika infection. Reports of confirmed microcephaly cases not linked to Zika are not being published, though we might consider the possibility that they have been included in the 92 cases that

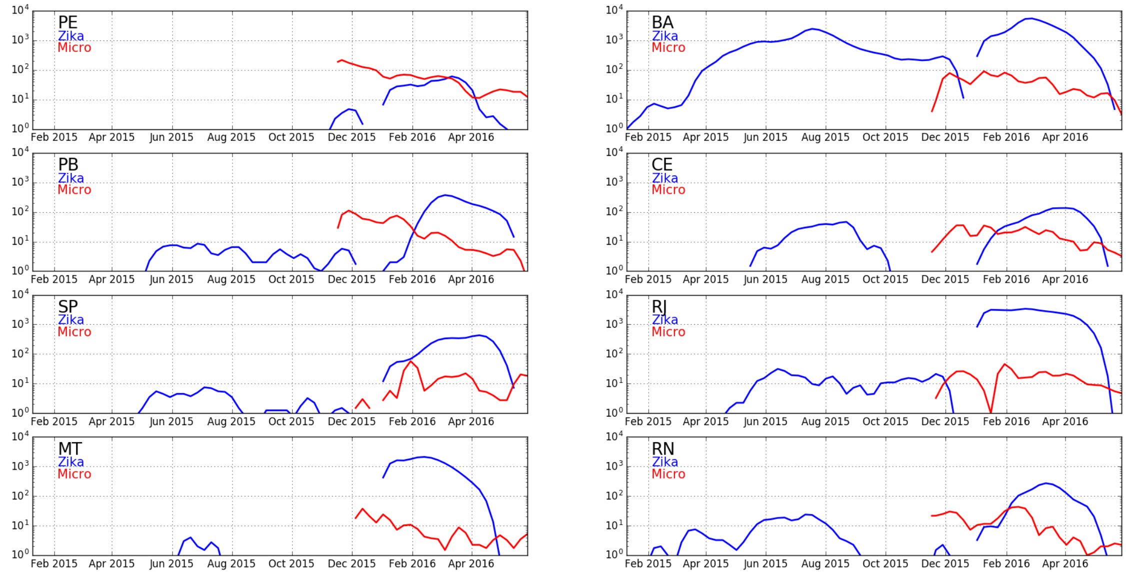

FIG. 3: *Plots of Zika and microcephaly cases in Brazil*—Plots (log scale) are shown for eight states of Brazil: Pernambuco (PE), Bahia (BA), Paraiba (PB), Ceará (CE), São Paulo (SP), Rio de Janeiro (RJ), Mato Grosso (MT), and Rio Grande do Norte (RN). Bahia has the highest counts of Zika relative to microcephaly six months later when births of pregnancies exposed in the first trimester are expected.

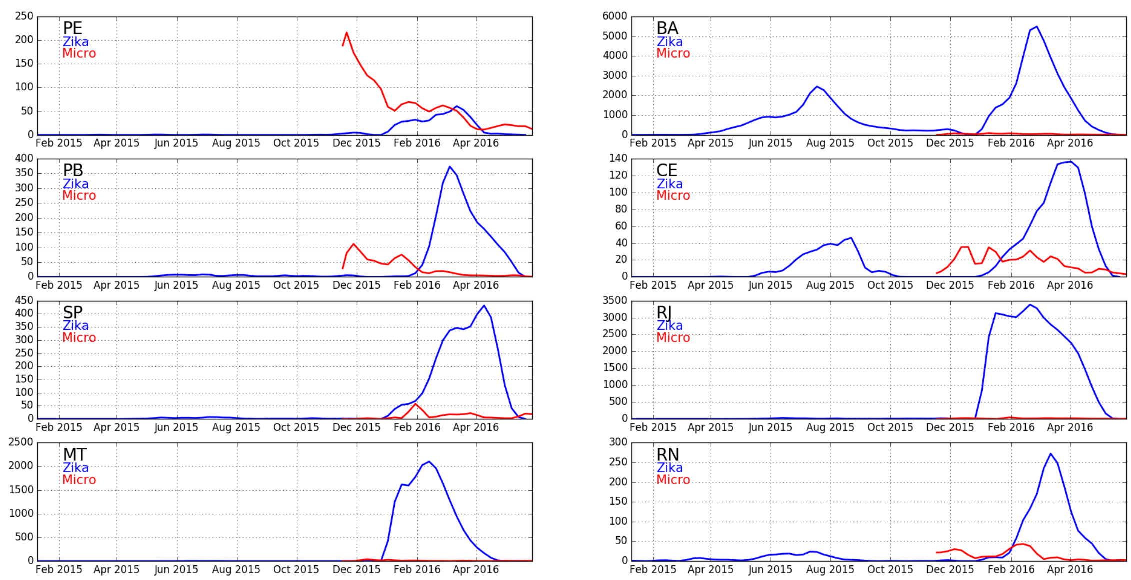

FIG. 4: Same as Fig. 3, but using a linear scale.

were "discarded" when investigating the Zika and microcephaly cases [3]. However, the total number of expected background microcephaly cases, with or without coincidental Zika infections, is 82 cases by the end of July (140 per year). Subtracting out the ones that are coincidental Zika infections leaves only about 20 for additional Zika caused microcephaly cases, which is not enough. More speculatively, they might be included in the 207 cases that are "under investigation."

Using the existing models we can project the number of cases to be expected in Colombia. If we use the estimated rate of microcephaly induced by Zika of 1 in 100 pregnancies exposed in the first trimester [7], there should be 200 microcephaly cases arising from Zika exposure of pregnancies infected until March 28. However, only about 1 in 7 of these will also have confirmed Zika infections if this fraction follows the pattern in Brazil. On the other hand, if we

State	Confirmed Zika & microcephaly	Confirmed microcephaly	Suspected microcephaly
Bahia (BA)	9.5%	63%	289%
Rio de Janeiro (RJ)	318%	>1000%	>1000%
Ceará (CE)	349%	>1000%	>1000%
Rio Grande do Norte (RN)	644%	>1000%	>1000%
Paraíba (PB)	>1000%	>1000%	>1000%
Pernambuco (PE)	>1000%	>1000%	>1000%
São Paulo (SP)	>1000%	>1000%	>1000%
Mato Grosso (MT)	>1000%	>1000%	>1000%

TABLE I: *Rate of microcephaly in pregnant women infected with Zika during the first gestational trimester for the eight Brazilian states with the largest numbers of microcephaly cases*—The rate of Zika induced microcephaly according to the available data is very large, suggesting only a small fraction of Zika cases were reported.

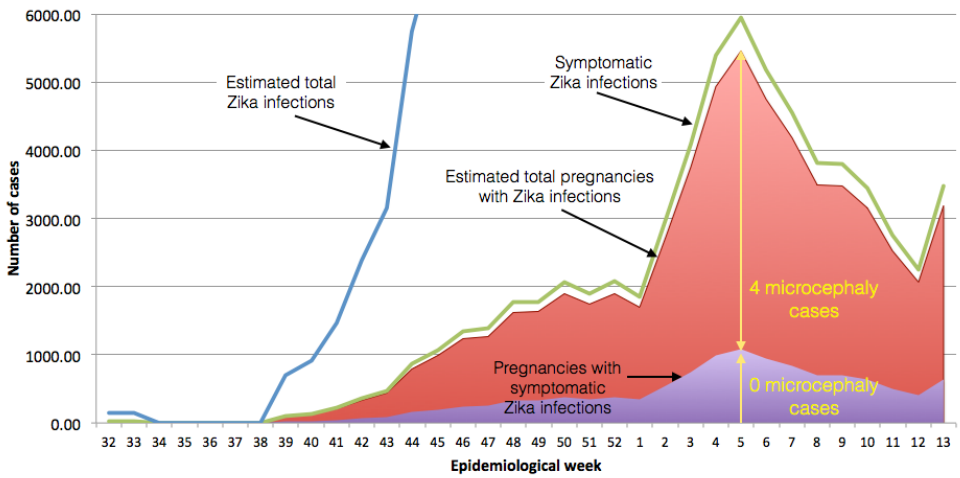

FIG. 5: *Population of Zika infected pregnancies*—To model the Colombian Zika and microcephaly epidemic, the reported number of symptomatic cases per week until March 28 (green line) [6] is normalized by the number of pregnancies (11,944, shaded purple) and multiplied by 5 to obtain the total number of symptomatic and usymptomatic cases (red shading) due to the observation of 4 Zika and microcephaly cases that don't have Zika symptoms. While we don't use it directly, the total number of Zika infections can be estimated (blue line) by similarly multiplying the number of reported cases correcting for the bias in reporting between women and men assuming the infection rate is comparable. Other assumptions about the total number of cases do not affect the results reported here.

use the estimates from Bahia for microcephaly rates, then the number of cases of Zika and microcephaly should rise to 2,400, and the number of total microcephaly cases to over 10,000. The total per week would have to rise accordingly to much larger numbers.

The seemingly large discrepancy between microcephaly counts in Colombia and Bahia echoes discrepancies between different parts of Brazil that recently [11] led to questions about whether there are additional factors that affect the microcephaly rates (see also [12–14]).

Details about the construction of the model for Zika caused microcephaly are provided in Figs. 5-7. A similar model has previously been applied to a single municipality of Bahia [14], without discussion of comparisons with other areas.

In summary, it is unclear from available data whether the model of Zika as the sole cause of microcephaly can consistently account for the cases across different countries and regions of Brazil. In the most recently reported 29th epidemiological week, of the 21 confirmed microcephaly and Zika cases in Colombia, only about 13 cases can be attributed to Zika infections and 8 cases to the background due to other causes (Fig 1). The number of cases in Brazil is much higher and the estimated rates per pregnancy are much higher. The main uncertainty in the comparative analysis to date of the rate of Zika induced microcephaly in Brazil is the reliability of Zika case number reporting. The reporting of cases in upcoming weeks in Colombia and in Brazil, where a new wave of microcephaly is expected, will provide additional information.

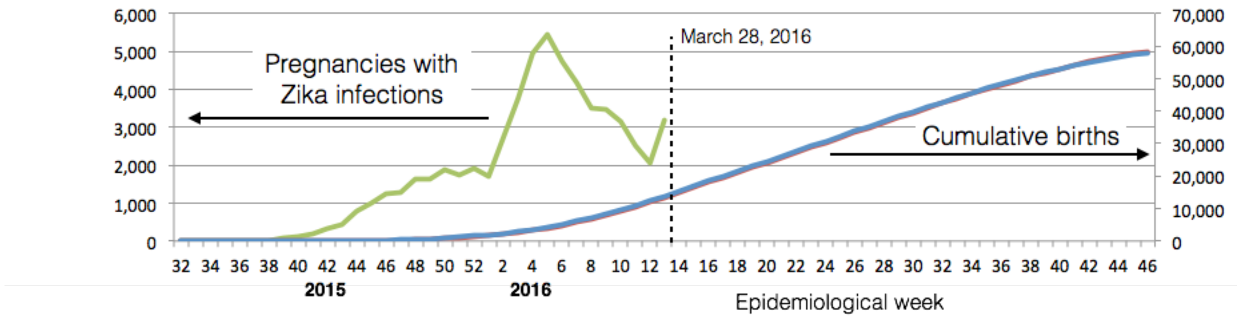

FIG. 6: For the estimated number of Zika infected pregnancies (green), assuming infections are uniformly distributed across 39 weeks of pregnancy, we obtain the number of Zika infected births per week, either by assuming births occur at the entry to the 40th week (red) or by assuming a distribution of births from week 35 through 43 by fractions [15]: $\{0.015, 0.027, 0.065, 0.135, 0.257, 0.316, 0.163, 0.02, 0.001\}$. The inclusion of early births has a significant effect at early times.

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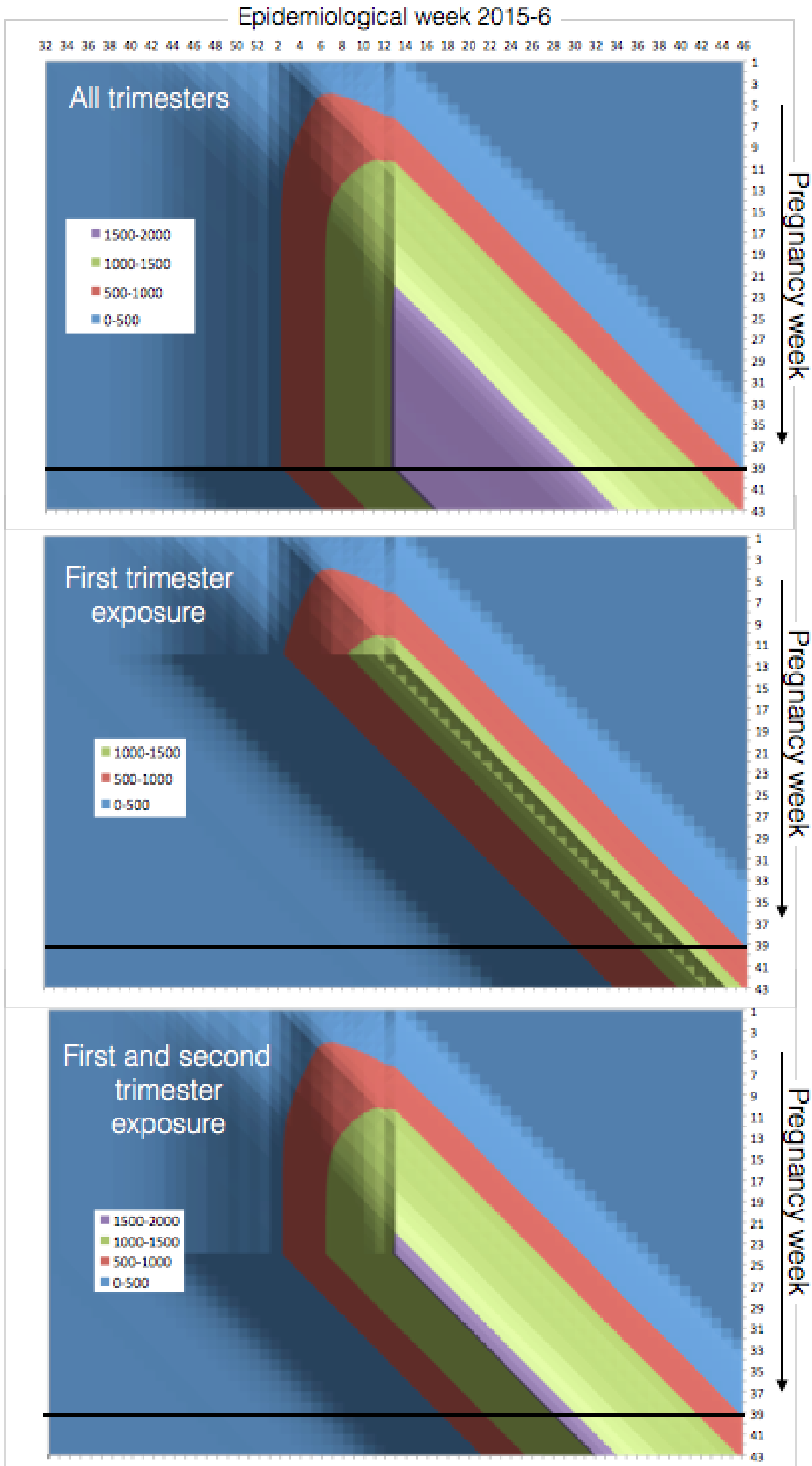

FIG. 7: The number of pregnancies during a particular week (vertical axis) present during a particular epidemiological week (horizontal axis). Using a uniform exposure by week of pregnancy assumption, we show the total number of pregnancies (top) the number of pregnancies exposed in the first trimester (middle) and the number of pregnancies exposed in either the first or second trimester (bottom). The number of births in each category is approximately the number that cross the 39/40 week boundary (horizontal black line), but is more accurately given by weighting them according to the distribution of births from week 35 through 43.