Is Zika the cause of Microcephaly? Status Report November 4, 2016

Yaneer Bar-Yam*, Raphael Parens*, Alfredo J. Morales*

**New England Complex Systems Institute, Cambridge MA 02139*

(Dated: November 4, 2016)

We summarize current evidence on the prevalence of Zika and microcephaly in Brazil and Colombia and conclude that the expectation of a large number of microcephaly cases outside of Brazil has not been realized. The ratio of microcephaly to Zika cases is inconsistent between Colombia and Brazil and between Brazilian states, where the majority of cases are confined to the northeast region. At the rate of microcephaly in Colombia, if all pregnancies in the Brazilian state of Pernambuco were infected by Zika, we estimate there would only be 100 cases of microcephaly in a year, whereas the number of confirmed cases is 386. Other causes and co-factors of microcephaly must be considered, including the pesticide pyriproxyfen which has been added to drinking water in some regions of Brazil since the fall of 2014 and is cross-reactive with retinoic acid which is known to cause microcephaly. Even without confirmation, the continued increase of microcephaly cases in Brazil by 100 per month warrants urgent policy action to stop the use of pyriproxyfen.

A dramatic increase in microcephaly cases in northeast Brazil in the latter half of 2015 led to a search for the cause and its prevention [1]. Attention has focused on a Zika virus outbreak which started at the beginning of that year, leading to the inference that the microcephaly cases arose from early pregnancy infections [3]. Moreover, Zika infections have been directly linked to a few cases of microcephaly [4]. Declared a public health emergency, the Zika virus spread throughout South and Central America. This wave of infection was expected to be followed by a wave of microcephaly birth defects, comparable to the cases in Brazil. Here we review the information available to date and conclude that the data is inconsistent with a direct causal link between Zika and most of the microcephaly cases reported. In particular, Colombia reported a large number of Zika infections, but it has only seen a small number of Zika-associated microcephaly cases (see Fig. 1). The number of Zika infections reported in Brazil is roughly 200,000 while that in Colombia is 90,000. The number of confirmed microcephaly cases in Brazil now exceeds 2,000, while the number in Colombia linked to Zika is only 57. Other countries have reported a comparatively small number of cases ranging from a few to a few tens of cases [1] (see Table I). Moreover, despite many cases of Zika in other parts of Brazil, the majority of microcephaly cases have been confined to the northeast region, which has a population of approximately 50 million, comparable

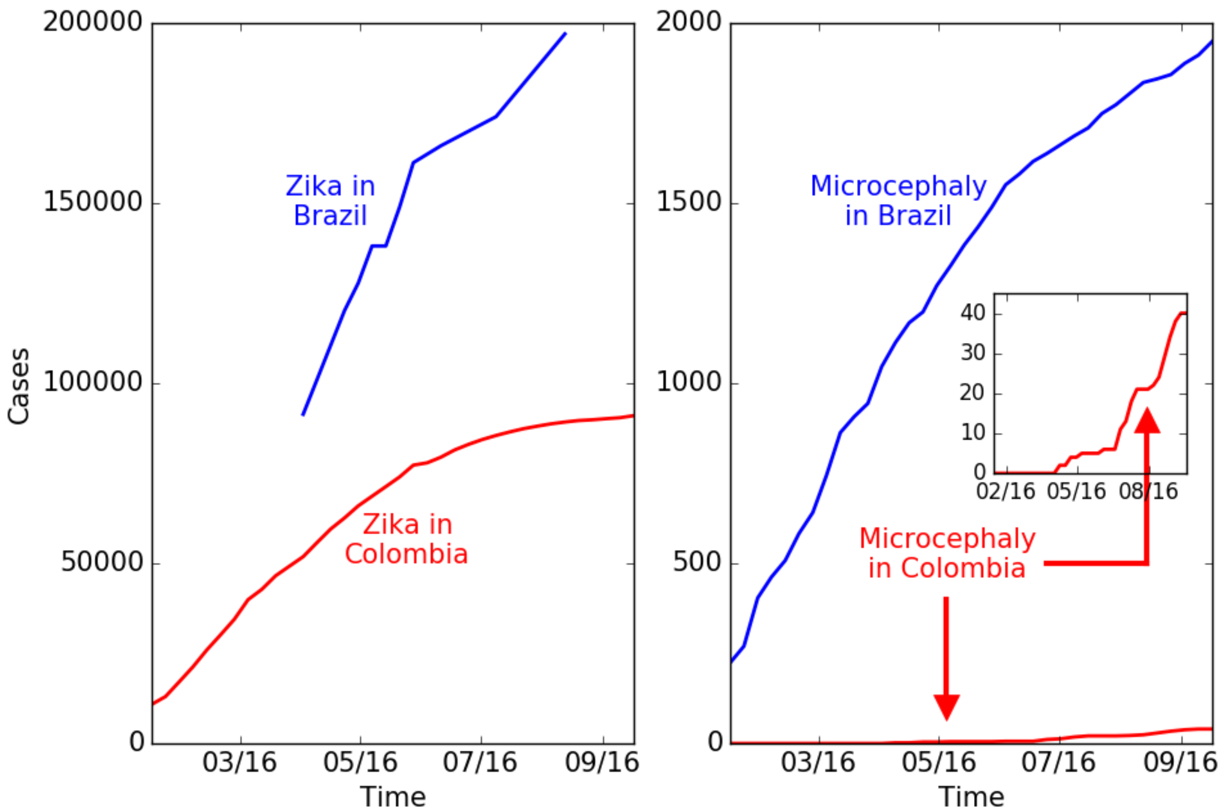

FIG. 1: Reported cases of microcephaly and Zika in Brazil and Colombia. A. Cumulative reported cases of Zika in Brazil and Colombia. B. Total microcephaly cases reported in Brazil and Zika associated microcephaly cases reported in Colombia. The number of Zika cases in Colombia is lower by a factor of 2, while the number of microcephaly is lower by a factor of 50. (Brazil reports total microcephaly numbers and does not distinguish those linked to Zika. Colombia reports only Zika-linked microcephaly cases. The historical background rate of microcephaly in Colombia is 140 per year.)

to that of Colombia. While questions remain about reliability of tests and reporting, the extent of the inconsistencies is difficult to account for. Overall, the discrepancies suggest other causes or co-factors, rather than Zika itself, are the primary source of microcephaly in Brazil.

The Colombian outbreak of Zika began in August of 2015 and the number of infections increased rapidly in early 2016. Fig. 2 shows reported cases of microcephaly linked to Zika infections (red dots). These are compared with cases predicted based on the number of Zika-infected pregnancies [5] and two models of Zika as a cause of microcephaly that originate in studies of an outbreak in French Polynesia [6]. A few cases are expected to be present just based upon the background rate of microcephaly of 2 in 10,000 births. While a number of cases of Zika and microcephaly were reported beginning early in 2016, until June 11, 2016 the number of these cases had not risen above the expected background rate of birth defects that would have occurred in those infected

Country/Territory	Zika-related Microcephaly Cases	Probable Location of Infection
Brazil	2063	Brazil
Cabo Verde	9	Cabo Verde
Canada	1	Undetermined
Costa Rica	1	Costa Rica
Colombia	47	Colombia
Dominican Republic	10	Dominican Republic
El Salvador	4	El Salvador
French Guiana	10	French Guiana
French Polynesia	8	French Polynesia
Grenada	1	Grenada
Guatemala	15	Guatemala
Haiti	1	Haiti
Honduras	1	Honduras
Marshall Islands	1	Marshall Islands
Martinique	12	Martinique
Panama	5	Panama
Paraguay	2	Paraguay
Puerto Rico	2	Puerto Rico
Slovenia	1	Brazil
Spain	2	Colombia, Venezuela
Suriname	1	Suriname
Thailand	2	Thailand
United States of America	28	Undetermined

TABLE I: Countries and territories that have reported microcephaly and/or central nervous system (CNS) malformation cases potentially associated with Zika virus infection [2].

with Zika, even if Zika were not a cause [7]. After that date, cases initially tracked a trajectory matching a model of 1% of pregnancies infected in the first trimester developing microcephaly [8]. However, the number of cases subsequently plateaued and increased in stages but more slowly than expected from the model. As of epidemiological week 42, a total of 56 cases have been reported [9], 11 of which can be explained as background cases unrelated to Zika. This is well short of the 155 total cases predicted from 1% of first trimester pregnancies along with the background rate. It is also far less than the over $2,000$ cases reported in Brazil. Based on this data, approximately 0.25% of first trimester infections (less than 0.1% of infected pregnancies) in Colombia have resulted in microcephaly. The coincidence of increased microcephaly cases with the timing of births infected in the first trimester suggests Zika is responsible for a limited number of microcephaly cases. This is consistent with other reports that link Zika with cases of microcephaly, as has also been shown with a few other viral infections, but is not consistent with Zika being the cause of the majority of cases reported in Brazil.

Based on the analysis of Fig. 2 we can conclude that the cases of Zika-caused microcephaly occur only due to infections in the first trimester. We can therefore compare reports of Zika infections with microcephaly reports 33 weeks later to identify the potential causal relationship between Zika and microcephaly in different states of Brazil. Zika and microcephaly cases reported in six Brazilian states in 2016 are shown in Fig. 3 along with an indicator of the time difference of 33 weeks. We see that the ratio between Zika and microcephaly reports varies between 1 and almost 10^{-3} (note the logarithmic scale). That it is possible to have a ratio of about 1 is surprising if one views Zika as a cause of microcephaly. The Zika cases are not specifically pregnancies so the number of pregnancies with Zika infections should be much less than the number of Zika cases. To estimate the number of Zika infected pregnancies in the first trimester at a particular time we would multiply the number of reported cases by an underreporting factor of 5 [7] to obtain an estimate of the actual number of cases, and multiply by the fraction of the population that is pregnant in the first trimester at any time, 0.37% (birthrate per day times 90), so the number of susceptible pregnancy Zika infections would be about 1.8% of the number of Zika cases. This number is smaller than the number of microcephaly cases in several states. As an upper bound on the number of Zika induced microcephaly cases we can take the estimated incidence from Colombia of less than 0.1% of pregnancies and calculate the number of cases that would be present if everyone was infected by Zika. For Pernambuco, with a population of 9.3 million and an approximate birth rate of 15 per 1,000, the number of microcephaly cases would be approximately 140, less than the actual number 386. Moreover, the inconsistency among the states of the numbers is independent of any calculation of the rates of the number of susceptible pregnancies. All calculations are sensitive

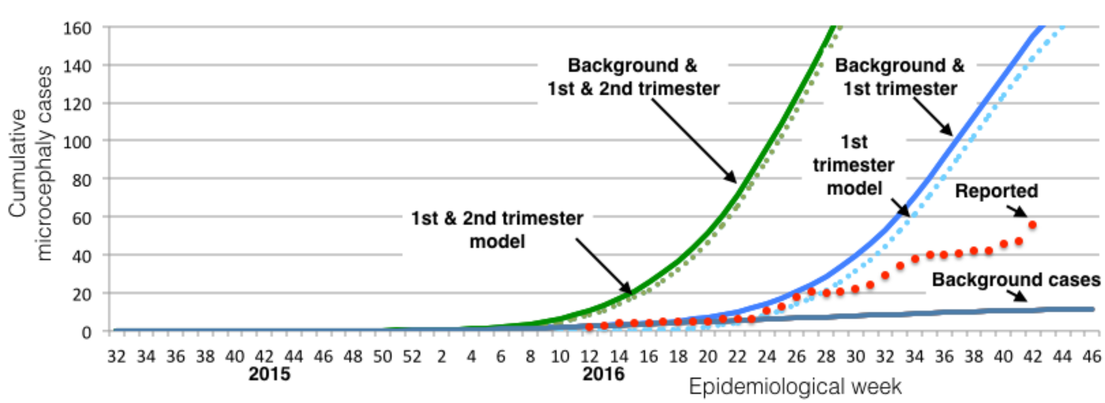

FIG. 2: Predicted trajectories of microcephaly cases based on two models of Zika infection susceptibility. Red dots represent reported cases. The models are based upon a study of cases in French Polynesia, and the reported number of cases in Brazil suggests that the rate in the models is significantly lower than the rate in northeast Brazil.

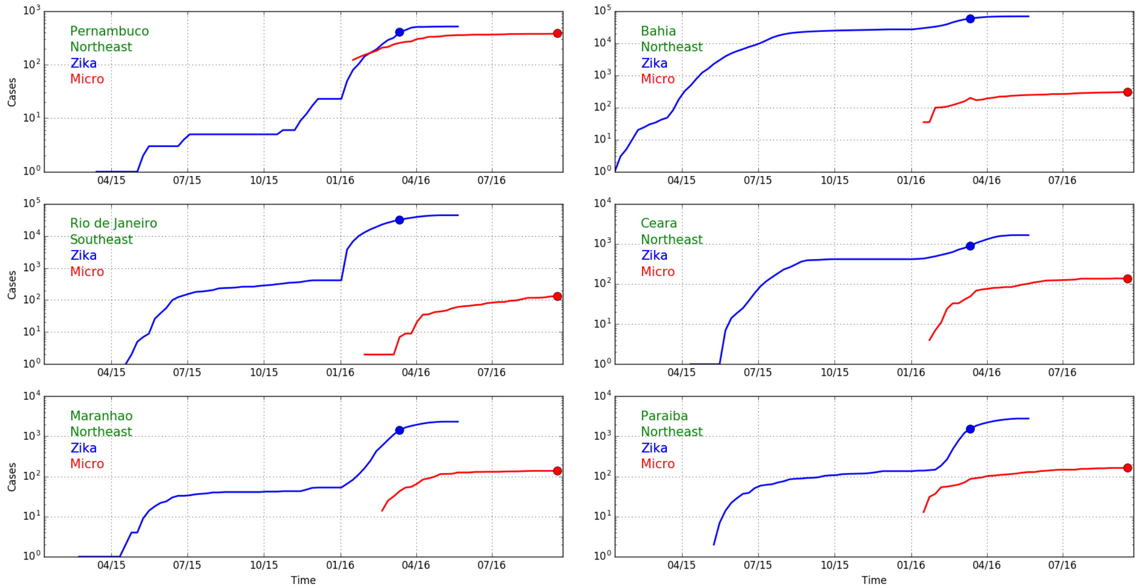

FIG. 3: Cumulative Zika (blue) and microcephaly (red) cases over time in five northeast Brazilian states and the state with the largest number of cases elsewhere, Rio de Janeiro (log scale). Blue and red dots are separated by 33 weeks, the expected delay between first trimester infections and expected microcephaly births caused by them. The differences in ratios in different states (Fig. 5) suggests that Zika is not the cause of microcephaly.

to the possibility that reporting is poor and inconsistent across states and countries. However, given the public health emergency that would promote careful reporting, and given the difference between rates of microcephaly in Colombia and Brazil, other explanations for the inconsistency within Brazil must be considered.

Expanding the discussion to all states of Brazil, Fig. 4 shows confirmed cases of Zika (blue) and microcephaly (red) for Brazilian states. The widely-varying relative proportion of Zika and microcephaly is apparent in the multipliers used to show the microcephaly data on the same vertical scale. Figure 5 shows the ratio between Zika and microcephaly cases as a function of time (including the 33 week delay) for all Brazilian states. As the figure shows, ratios vary widely across the country, but are higher than the small proportion of cases reported in Colombia. Table 1 shows the ratio of microcephaly cases to Zika cases reported 33 weeks previously for all Brazilian states, including current cases and the maximum over the year. In the northeastern states, only Bahia is reporting a number of cases consistent with Zika as a primary cause of microcephaly. Interestingly Rio de Janeiro, the only state outside the northeast that has more than 100 cases, is also consistent with Bahia (though the ratio was higher earlier in times). Other states outside the northeast have too few cases to reliably compare.

In summary, since the Zika virus spread from Brazil to Colombia, the international community

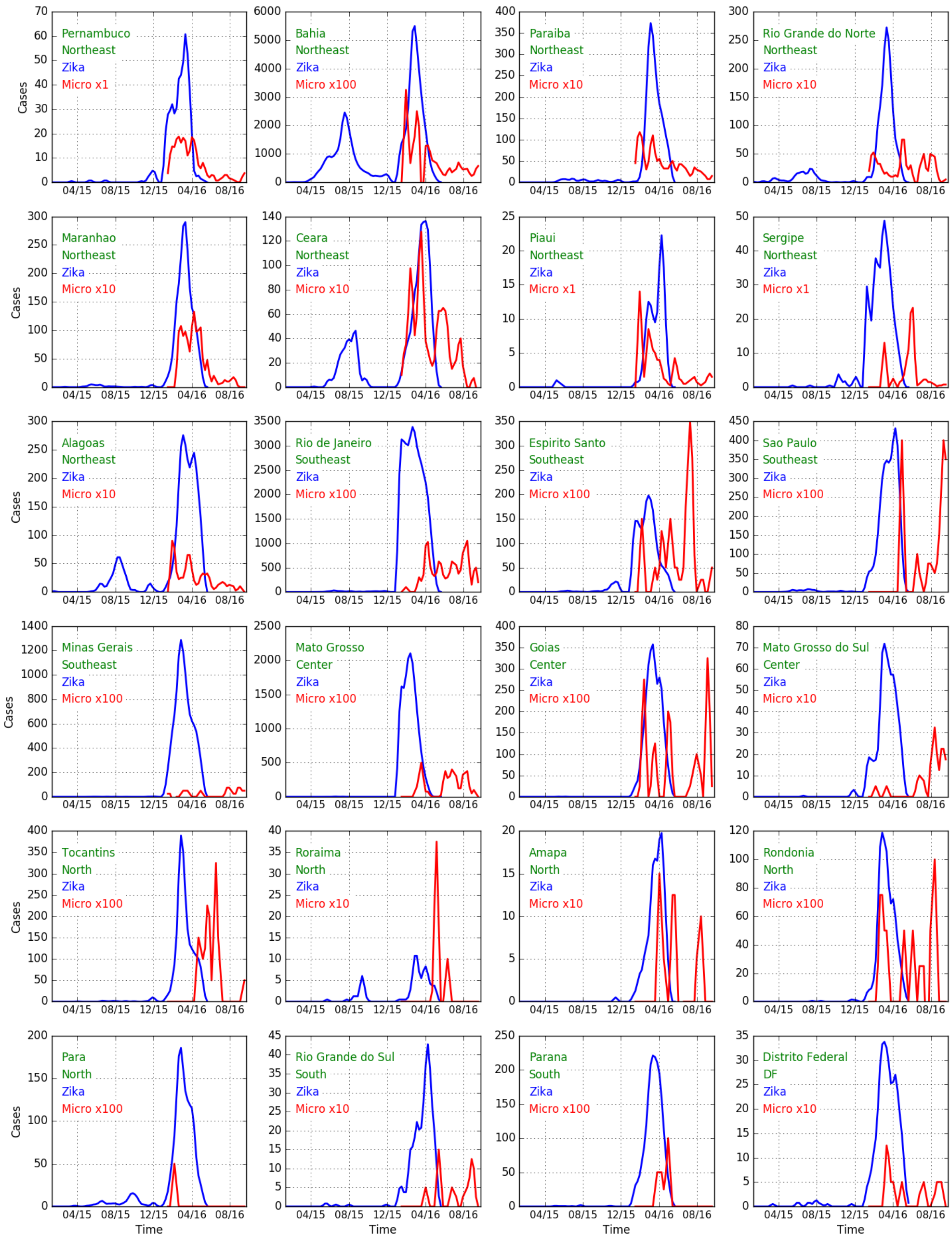

FIG. 4: Weekly Zika (blue) and microcephaly (red) reports over time in each Brazilian state. Note the multipliers for the microcephaly numbers. If Zika is the cause of the cases of microcephaly a delay of about 33 weeks should be seen between peaks of the former and latter. This appears to be the case for Bahia, Ceara, and Alagoas for early peaks of Zika and later peaks of microcephaly. We note that if seasonal use of insecticides coincides with outbreaks, then the cause may also be those insecticides (see text). The coincidence of peaks of one and the other is coincidental due seasonal effects. A filter, $\{0.25, 0.5, 0.25\}$, has been applied to smooth the data.

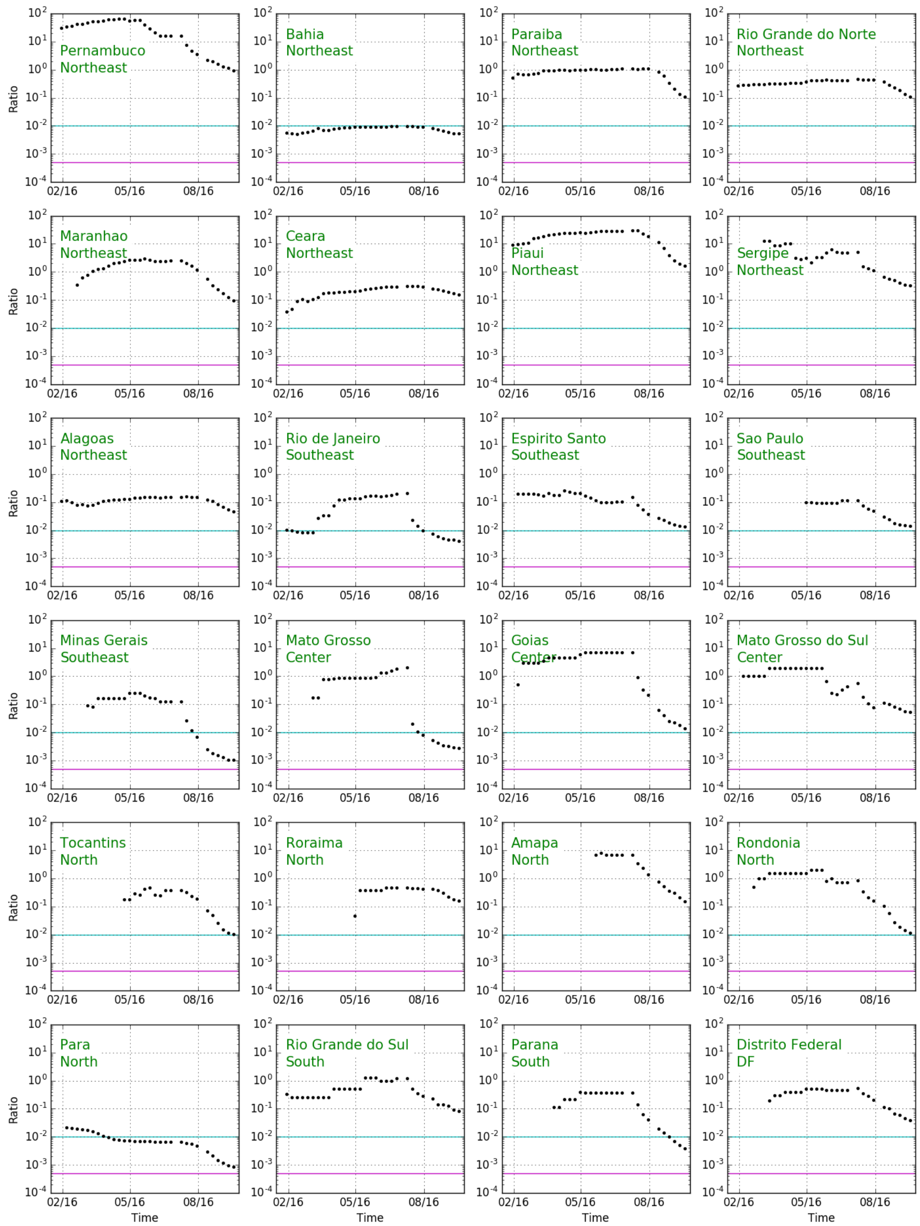

FIG. 5: Ratio of microcephaly cases to Zika cases 33 weeks earlier as a function of time for all Brazilian states. The horizontal green line represents a ratio of 1% and the purple horizontal line represents a ratio of 0.05%. To obtain the number of microcephaly cases per first trimester Zika infected pregnancy (rather than all Zika cases) we would have to include both unreported Zika cases and multiply by the proportion of pregnancies, multiplying the ratio by a factor of 25. Differences between rates would remain.

has been waiting to see if an accompanying spread of microcephaly would also occur. After months of uncertainty, the data now indicates that Colombia will not be seeing a comparably large number of Zika-related birth defects. This discrepancy suggests a need to reexamine conditions in Brazil, particularly in the northeastern states which saw the majority of microcephaly cases. If Zika alone

Region	State	Current Zika	Current Microcephaly	Current Ratio	Maximum Zika	Maximum Microcephaly	Maximum Ratio
Northeast	Pernambuco	408	386	0.95	5	334	67
Northeast	Bahia	59560	312	0.0052	27290	268	0.0098
Northeast	Paraiba	1547	166	0.11	140	155	1.1
Northeast	Rio Grande do Norte	1295	138	0.11	264	123	0.47
Northeast	Maranhao	1419	138	0.097	43	126	2.9
Northeast	Ceara	906	137	0.15	431	136	0.32
Northeast	Piaui	59	99	1.7	3	89	30
Northeast	Sergipe	384	123	0.32	2	26	13
Northeast	Alagoas	1766	84	0.048	504	79	0.16
Southeast	Rio de Janeiro	31542	130	0.0041	412	87	0.21
Southeast	Espirito Santo	1727	23	0.013	23	6	0.26
Southeast	Sao Paulo	1779	26	0.015	88	10	0.11
Southeast	Minas Gerais	7539	8	0.0011	12	3	0.25
Center	Mato Grosso	16680	47	0.0028	17	35	2.1
Center	Goias	1721	24	0.014	2	14	7.0
Center	Mato Grosso do Sul	370	20	0.054	1	2	2.0
North	Tocantins	1712	18	0.011	23	11	0.48
North	Roraima	62	10	0.16	21	10	0.48
North	Amapa	59	9	0.15	1	8	8
North	Rondonia	599	7	0.012	2	4	2.0
North	Para	1139	1	0.00088	47	1	0.021
South	Rio Grande do Sul	123	10	0.081	4	5	1.3
South	Parana	1014	4	0.0039	10	4	0.40
DF	Distrito Federal	201	8	0.040	11	6	0.55

TABLE II: Ratio of microcephaly cases to Zika cases reported 33 weeks previously for all Brazilian states, including current cases and the maximum over the year.

is not enough to cause large numbers of birth defects, some other factor or factors unique to Brazil are present. Recently several reports have suggested that co-factors are responsible [10–12]. A cofactor would be one in which Zika is the cause, but the presence of some other environmentally present substance increases the susceptibility. However, it is also possible that even without Zika infections another cause is responsible if its presence began at about the same time. One possibility is the pesticide pyriproxyfen, which has been largely dismissed as a potential cause despite being insufficiently researched [4].

Pyriproxyfen is a larvicide that interferes with the development of mosquitos, and it has been suggested that it might also interfere with human development [13, 14]. Pyriproxyfen is cross-reactive with retinoic acid which is known to cause microcephaly [15]. The pesticide has been applied to drinking water in some regions of Brazil since the fall of 2014, which is consistent with the start of the microcephaly epidemic in the summer of 2015. It has not been used in drinking water in Colombia. While pyriproxyfen is approved for application to drinking water, its large-scale implementation in Brazil is unprecedented.

While the total number of microcephaly cases remains low in Colombia and other countries, cases in Brazil continue to rise at the rate of 100 affected births per month (see Figure 1). Since pyriproxyfen may be playing a role in Brazil's disproportionate increase of birth defects, rapid policy action is needed to replace its use as a pesticide until its effects can be more thoroughly studied.

---

[1] Zika cases and congenital syndrome associated with Zika virus reported by countries and territories in the Americas, 2015-2016, Cummulative cases, World Health Organization (October 20, 2016), `http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=36621&lang=en`.

[2] Zika situation report, World Health Organization (October 27, 2106), `http://www.who.int/emergencies/zika-virus/situation-report/27-october-2016/en/`.

[3] S. A. Rasmussen, et al., *NEJM* 374.20, 1981-1987 (2016) `http://www.nejm.org/doi/full/10.1056/NEJMsr1604338`

[4] Raphael Parens, Yaneer Bar-Yam, Zika and other potential causes of microcephaly in Brazil: Status March 8, 2016, NECSI (2016), `http://necsi.edu/research/social/pandemics/zikacauses.html`.

[5] O. Pacheco, *et al*, *NEJM* (June 15, 2016), `http://www.nejm.org/doi/full/10.1056/NEJMoa1604037#t=article`.

[6] S. Cauchemez, et al, Lancet 387, 10033, p21252132 (21 May 2016), `http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)00651-6/fulltext`.

[7] Yaneer Bar-Yam, Dan Evans, Raphael Parens, Alfredo J. Morales, Fred Nijhout, Is Zika the cause of Microcephaly? Status Report June 22, 2016, New England Complex Systems Institute (June 22, 2016)

http://necsi.edu/research/social/pandemics/statusreport.

[8] Yaneer Bar-Yam, Raphael Parens, Alfredo J. Morales, Fred Nijhout, Is Zika the cause of Microcephaly? Status Report June 27, 2016, NECSI (June 27, 2016) http://necsi.edu/research/social/pandemics/statusreport2.

[9] Boletin Epidemiologico Semanal (BES), Instituto Nacional de Salud (October 22, 2016), http://www.ins.gov.co/boletin-epidemiologico/Paginas/default.aspx.

[10] D. Butler, Brazil asks whether Zika acts alone to cause birth defects, Nature (July 25, 2016), http://www.nature.com/news/brazil-asks-whether-zika-acts-alone-to-cause-birth-defects-1.20309#/.

[11] D. Phillips, N. Miroff, Scientists are bewildered by Zika's path across Latin America, Washington Post (October 25, 2016), https://www.washingtonpost.com/world/the_americas/scientists-are-bewildered-by-zikas-path-across-latin-america/2016/10/25/5e3a992c-9614-11e6-9cae-2a3574e296a6_story.html.

[12] D, McNeil Jr., J. Cobb, Colombia is hit hard by Zika, but not by Microcephaly, The New York Times (October 31, 2016), http://www.nytimes.com/2016/11/01/health/colombia-zika-microcephaly.html?_r=0.

[13] Dan Evans, Fred Nijhout, Raphael Parens, Alfredo J. Morales, Yaneer Bar-Yam, A possible link between pyriproxyfen and microcephaly, NECSI (2016), http://necsi.edu/research/social/pandemics/pyriproxyfen.

[14] Report from physicians in the crop-sprayed villages, Red Universitaria de Ambiente y Salud (February 3, 2016), http://www.reduas.com.ar/wp-content/uploads/downloads/2016/02/Informe-Zika-de-Reduas_TRAD.pdf.

[15] Pyriproxifen and microcephaly, SWETOX (March, 2016), http://swetox.se/wp-content/uploads/2016/03/ppf-zika.pdf.