

Is Zika the cause of Microcephaly? Status Report June 22, 2016

Yaneer Bar-Yam*, Dan Evans[‡], Raphael Parens*, Alfredo J. Morales* and Fred Nijhout[†]

*New England Complex Systems Institute, Cambridge MA 02139, [‡]Jincumbilly, NSW Australia, [†]Department of Biology, Duke University, Durham, NC 27708

(Dated: June 23, 2016)

In April, the CDC declared Zika the cause of microcephaly in Brazil [1], but questions remain, as outside of Brazil a similar number of cases have not been seen. In Colombia cases of Zika have been identified in August, 2015, and the outbreak grew rapidly from October. As of June 15 2016, the WHO reports 7 Zika associated microcephaly cases in Colombia in contrast to over 1,500 confirmed cases in Brazil [2]. Population size cannot account for the difference as the 48 million population of Colombia is one fifth the 200 million population of Brazil, and the Brazilian cases are highly concentrated in part of the country, particularly Pernambuco with a population of 9.3 million. The main explanation for the absence of cases is that the epidemic in Colombia has not yet led to many births of women exposed in the first or second trimesters. However, the timing of such births is immanent and the available data is beginning to allow for interpretation that questions the conclusion that Zika is the cause of the microcephaly.

The best available information about the Colombia epidemic is from preliminary results of a study published on June 15, 2016 in the New England Journal of Medicine [3]. It reports results of women infected until March 28, whose pregnancies were followed until May 2, 2016. The study identifies 1,850 women that are being tracked, whose date of infection with Zika is known, and 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 have 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. No cases of microcephaly occurred in all of these 12,000 pregnancies.

To interpret these results, we consider a study in French Polynesia [4] 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 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 [5].

Accordingly, as of May 2 in Colombia the tracked cohort should have just less than one case (0.85) in the first model and $0.5 \times (85 + 204) = 1.4$ cases in the second model. This suggests that the cohort is at the limit of number of pregnancies without microcephaly.

From the larger population of pregnancies with Zika symptoms we cannot draw as direct conclusions. If we were to assume that the population is similar to the tracked cohort we would expect $(11,944/1,850) = 6.5$ times as many cases. Under these circumstances we could rule out the possibility of Zika as a cause of mi-

crocephaly by an order of magnitude less than the benchmark. It is unlikely the general population cases are the same as the cohort, which was likely chosen from early cases of exposure.

We note, however, that 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 cases of Zika infection that are not reported. 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. Either women are infected at a higher rate, or reporting is focused on women because of the concern about maternal effects.

Combining the symptomless and symptomatic individuals we would expect $5 \times 6.5 = 33$ times as many cases as the cohort, i.e. 22 and 37 cases in the two exposure models. This would seem to rule out Zika as a cause of microcephaly.

We can, however, consider the alternative that Zika is not the cause of microcephaly. 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 [3], we calculate 4,310 births till May 2 based upon a uniform distribution of infection dates and standard birth distribution [6]. 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 $6145 \times 5 = 30,725$. Estimating the number of pregnant Zika infections beyond March 28 at the same rate of that week, we have 7,100 symptomatic pregnant Zika births or 35,500 births of Zika infections. This would give the observed 7 reported microcephaly and Zika cases reported to date.

This gives a consistent interpretation that there is no direct link between Zika and microcephaly except for random co-occurrence. We note that the base rate of microcephaly in the absence of Zika is 140 per year in Colombia, which is consistent with the approximately 50 microcephaly cases in the first 4 months of 2016, only 4 of which have been connected to Zika. When interpreting Zika as the cause, background cases must be subtracted.

An alternative cause of microcephaly in Brazil could be the pesticide pyriproxyfen, which is cross-reactive with retinoic acid, which causes microcephaly, and is being used in drinking water [7–9].

*The number of births reported is difficult to reconcile with the Zika incidence data in the paper, reported numbers are used here.

-
- [1] S. A. Rasmussen, et al., *NEJM* 374.20, 1981-1987 (2016) <http://www.nejm.org/doi/full/10.1056/NEJMs1604338>
 - [2] Situation report 16 June 2016, *WHO* (June 16, 2016), <http://apps.who.int/iris/bitstream/10665/242439/1/zikasitrep-16Jun2016-eng.pdf?ua=1>.
 - [3] O. Pacheco, et al, *NEJM* (June 15, 2016), <http://www.nejm.org/doi/full/10.1056/NEJMoa1604037#t=article>.
 - [4] S. Cauchemez, et al, *Lancet* 387, 10033, p21252132 (21 May 2016), [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(16\)00651-6/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)00651-6/fulltext).
 - [5] Facts about Microcephaly, CDC, <http://www.cdc.gov/ncbddd/birthdefects/microcephaly.html>.
 - [6] Length of pregnancy by week, *Spacefem.com* <http://spacefem.com/pregnant/charts/duedate3.php>.
 - [7] D. Evans, et al, *arXiv:1604.03834* (April 13, 2016), <http://necsi.edu/research/social/pandemics/pyriproxyfen>.
 - [8] Pyriproxyfen and microcephaly *SWETOX* (March, 2016), <http://swetox.se/wp-content/uploads/2016/03/ppf-zika.pdf>.
 - [9] Report from physicians *Red Universitaria de Ambiente y Salud* (Feb. 3, 2016), http://www.reduas.com.ar/wp-content/uploads/downloads/2016/02/Informe-Zika-de-Reduas_TRAD.pdf.