COMMENTARY

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Investigating Zika-Microcephaly's 'Crash'

INTRODUCTION

Pandemic Zika-microcephaly (Brazil in 2015) was attributed to a virus never previously clinically diagnosed to cause human illness in the Americas. The genome and morphology of Zika are nearly indistinguishable from those of its *flavivirus* cousin, dengue, itself long endemic to Brazil. The millions of prior cases of dengue had evinced no association with microcephaly. In 2015, Brazil had no clinical laboratory Zika testing or bedside Zika diagnoses. The separate claim of a microcephaly "cluster" was made without comparison data or uniform diagnostic criteria.[1] The novel claim of Zika causing microcephaly was not subject to the required rigor of scientific inquiry and peer review; nonetheless stringent interventions by government actors and the World Health Organization (WHO) accrued. Despite dire predictions of 1 million additional microcephalic births in the tropics worldwide yearly thereafter,[2] Zika microcephaly never recurred in Brazil or elsewhere. In the interim, there has been no critical review of the underlying theory itself. This commentary defines that 2015 event as a "crash" and is structured for analysis and learning, just as is done with aircraft crash investigation reports.

ZIKA VIRUS

Tropical mosquito-borne flaviviruses include dengue, yellow fever, Japanese encephalitis, and the monkey virus named for Uganda's Zika Forest in 1947. Dengue and Zika are transmitted by *Aedes aegypti*. There was no human disease outbreak to bring Zika to the attention of physicians within its first 60 years.

First Alleged Outbreak

In 2007, residents of Yap (Micronesia) experienced aches and fever, which was a laboratory-confirmed dengue-recurrence. The Centers for Disease Control and Prevention (CDC) made a post hoc determination of Zika, while acknowledging its dengue cross-reactivity. Duffy et al[3] claimed, based on retrospective questionnaires and circularity of logic: a "*clinical illness . .(was) . . probably attributable to Zika virus*", asserting that Yap's clinicians had noted some differences from dengue. There were no fatalities or birth defects.

MICROCEPHALY STANDARDS

Microcephaly is a nonspecific clinical finding of occipitofrontal circumference three standard deviations below the mean. Prior to 2016, Brazil had used only a −2 standard deviation cutoff to determine microcephaly (eliciting a rate 17 times more frequent).[4]

The main actors in Brazil included Dr Kleber Luz, pediatrician, Natal; Dr Carlos Brito, general practitioner, Recife; Drs Gúbio Soares Campos and Silvia Sardi, married virologist team, Bahia; Drs Ana and Vanessa van der Linden (Mota), neuropediatricians, Recife; and Dr Claudia Duarte dos Santos, virologist, Curitiba.

THE ZIKA-MICROCEPHALY TIMELINE

Zika: A Human Illness?

Drs Luz and Brito formed a group, CHIKV-The Mission, in September 2014, hoping to announce the discovery of Chikungunya virus infection in Brazil.[5]

In spring 2015, Dr Luz asserted that his patients with mild clinical dengue were infected with the Zika virus, despite no laboratory confirmation and the impossibility of clinically distinguishing dengue and Zika.[6]

There were no published articles in the literature guiding clinicians on how to distinguish dengue from Zika. There is nothing in the record anywhere that documents what precisely Dr Luz found clinically different from mild dengue.

Soon after, Drs Soares Campos and Sardi announced that they had, via reverse transcription polymerase chain reaction (RT-PCR), identified Zika virus in 7 out of 24 samples collected from patients who had reported mild allergy symptoms. They used PCR primers for Zika virus that were not approved for clinical use in Brazil.[5,7]

Drs Soares Campos and Sardi leaked their findings to the press before the tests were independently confirmed. There

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was no raging illness, yet they posed as heroes: "*We decided to benefit the public more, rather than . . . writing a scientific paper and publishing it*."[5]

Within a month, Bahia state's health ministry officially contradicted Drs Soares Campos and Sardi's assertion. The ministry tested 500 patients from the same cohort and reported that none of the group tested positive for Zika; further, half of them tested positive for dengue, and more tested positive for parvovirus, rubella, and measles than those Drs Soares Campos and Sardi claimed to have tested positive for Zika.[7]

However, Drs Soares Campos and Sardi, celebrated as "the discoverers of Zika," were rewarded with academic tenure.

Dr Luz had reached out to Dr Duarte dos Santos to "find Zika"; however, Dr Duarte dos Santos could not find laboratory confirmation for Zika in any of Dr Luz's samples.[5] In June 2015, Dr Luz published a paper announcing the first lab-confirmed discovery of indigenous Zika in Brazil, with Dr Duarte dos Santos as coauthor.[8]

Impact of the Zika Leak

The physicians involved in the 2015 Zika claim intentionally leaked their assertions to the press and readily gave interviews in which they expressed no doubt. This ensured their message became the narrative fixed in the public's mind. Dr Brito asserted similar circularity: "We investigated 1,100 [dengue] patients. Of this total, 81% met clinical criteria for Zika (sic)."[9]

The careful findings released by expert peers that refuted these assertions did not receive the same exposure. National politicians worried only about the public narrative.

The Microcephaly Claim

In August 2015, Dr Vanessa van der Linden examined a fraternal twin with microcephaly, intuiting a mystery-virus causation that somehow hadn't affected his normal brother.[10]

She and her mother, Dr Ana van der Linden, soon after asserted a microcephaly cluster in Recife, contacted local pediatricians, and solicited cases quickly—a self-fulfilling prophecy.

In October 2015, they connected with Dr Brito, who queried 26 mothers of microcephalic infants, attributing every fever or rash during pregnancy to Zika.[5] No questionnaires were provided to mothers of normal infants.

At once, Recife's media reported Zika-microcephaly, a stunning triple declaration that:

1. Microcephaly was epidemic.
2. Pregnant women had had Zika.
3. Zika caused microcephaly.

These declarations left unspoken Dr Brito's investigatory biases, nonexistent Zika-testing, and deficient microcephaly data analysis.

Two days after this latest media leak, Dr Brito chaired a medical meeting (boycotted by local institutional scientists)[5] to endorse the reported Zika-microcephaly connection, intensifying the growing public panic. Brazil's microcephaly "cases" exploded (Figure), with the greatest impact locally, reaching a 100:1 rate of overdiagnosis.[11]

In November, Dr Brito announced, "I have no doubt that we are now opening a new chapter in the history of medicine."[12]

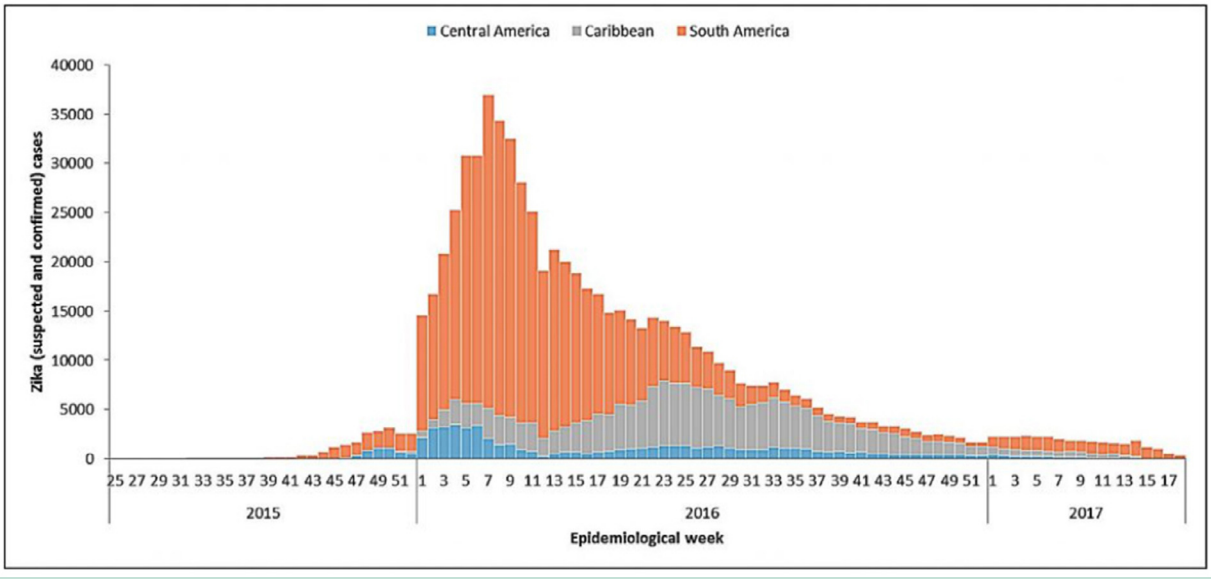

Figure 1 Distribution of suspected and confirmed Zika cases by epidemiological week and sub-region. Region of the Americas, 2016–2017.

Acquiescence to Panic

On October 27, 2015, the Pernambuco state addressed a possible microcephaly increase without attributing any one cause. Former Brazilian president Dilma Rousseff, more aggressive, engaged 225,000 military troops to combat mosquitoes. In February 2016, the WHO declared Zika a public health emergency of international concern (PHEIC), advising against travel (eg, to the Rio Olympics).

Whereupon Zika-Microcephaly Vanished

Beginning in 2016, as Brazil's clinical Zika-testing capability and coordinated microcephaly standards came into existence, Zika and microcephaly clusters both suddenly disappeared. No medical, scientific, media, or public authority has yet retracted any aspect of the Zika-microcephaly theory, even now 6 years after the double-disappearance that essentially contradicts it.

ANALYSIS OF A CRASH

The 2015 Zika-microcephaly crash was characterized by total disregard for the scientific method. It is impossible to avoid the conclusion that there was an intentional effort to present conjecture as scientific fact. The effort to "discover" something new was unrelenting and succeeded fully, sadly rewarding this lack of respect for the scientific method. Rushing to the press cannot be ascribed to a legitimate good-faith reason in the self-admitted absence of a fatal disease.

There was no cluster analysis by experts prior to public announcement of microcephaly. There has been little coverage of 2016's data-reconstruction study's contradicting the original "epidemic."[13] Clinical laboratory confirmation of Zika was an erstwhile scientific impossibility. The neuropediatricians did not use a uniform standard for classifying microcephaly. Conflicts of interest and severe biases abounded, and flouting of basic scientific procedures that all physicians know are important, all went unchallenged. The paper published by Dr Luz is not credible on any level. There remains no paper clinically distinguishing Zika from dengue.

After national officials panicked, there was no pushback from WHO experts who had months to query the "science" and observe the phenomenon's absence elsewhere.

Public health officials in other nations chose to amplify the panic rather than independently uphold the scientific method (eg, Morens and Fauci[14]). Many advised a birth moratorium until a vaccine.

RECOMMENDATIONS

Science by assertion is not science. The level of mere assertion in the Zika-microcephaly crash, beginning with the 2009 paper in the *New England Journal of Medicine*,[3] is unacceptably high. Allowing assertion to displace science will permanently damage the credibility of physicians.

1. The medical community must officially declare that there is no scientific basis to claim that Zika microcephaly ever existed and that it is not an emerging or ongoing threat to pregnant women.
2. The 2009 *New England Journal of Medicine* paper must carry at minimum an "expression of concern," given the unsupportable assertion within regarding the clinical presentation of Yap patients as distinct from dengue.
3. The WHO must recommit to the scientific method prior to pushing the panic button.
4. Medical schools and residency programs must redouble efforts to encourage individual skepticism of even peer-reviewed journal papers and encourage their involvement in initiatives such as PubPeer.
5. The medical community must have a high index of suspicion toward "first-ever" discoveries that circumvent the peer-review process.
6. We must not forget the nearly billion young reproductive families in the tropics who live in fear of a single mosquito bite irrevocably damaging the cherished life within. They deserve closure.
7. We should question why the Zika science researchers themselves have not heretofore announced such doubts.

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References

1. Schuler-Faccini Lavinia, et al. Possible Association Between Zika Virus Infection and Microcephaly — Brazil, 2015. *Morbidity and Mortality Weekly Report* 2016;65(3):59–62.
2. Campos Coelho Antonio Victor, Crovella Sergio. Microcephaly Prevalence in Infants Born to Zika Virus-Infected Women: A Systematic Review and Meta-Analysis. *International Journal of Molecular Sciences* 2017;18(1714).
3. Duffy MR, Chen TH, Hancock WT, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* 2009;360:2536–43. https://doi.org/10.1056/NEJMoa0805715.
4. Gomes Victora Cesar, et al. Microcephaly in Brazil: how to interpret reported numbers? *The Lancet* 2016;387(10019):621–4. https://doi.org/10.1016/S0140-6736(16)00273-7.
5. Diniz D. *Zika: From the Brazilian backlands to global threat*. London, UK: Zed Books; 2017.
6. BRAGA LIZ. How a Small Team of Doctors Convinced the World to Stop Ignoring Zika. *NEWSWEEK MAGAZINE* 2016(02/29/16).
7. Costa Júnior J. Satélite: diagnósticos de casos de Zika na Bahia podem estar errados. *Correio*. Available at: https://www.correio24horas.com.br/noticia/nid/satelite-diagnosticos-de-casos-de-zika-na-bahia-podem-estar-errados/. Accessed March 10, 2022.
8. dos Santos Claudia Nunes Duarte, Luz Kleber, et al., https://doi.org/10.1590/0074-02760150192. First report of autochthonous transmission of Zika virus in Brazil. Mem Inst Oswaldo Cruz. 2015;110:569−572. Mem Inst Oswaldo Cruz, Rio de Janeiro, Vol. 110(4): 569−572, June 2015 5. https://doi.org/10.1590/0074-02760150192
9. Leite C. Zika/Microcefalia: 'É um novo capítulo na história da medicina'. *Jornal do Comercio*. Available at: https://jc.ne10.uol.com.br/canal/cidades/saude/noticia/2015/11/29/zikamicrocefalia-e-um-novo-capitulo-na-historia-da-medicina-210170.php. Accessed March 10, 2022.

10. Johnson Reed, Jelmayer Rogerio. The Brazilian Doctors Who Sounded the Alarm on Zika and Microcephaly. *Wall Street Journal* 2016(January 28).
11. Belluz Julia. Beware overblown Zika estimates. So far, most reports of birth defects have not been confirmed. *Vox* 2016(February 2).
12. Ministério da Saúde, Secretaria de Vigilância em Saúde. *Vírus Zika no Brasil: a resposta do SUS*. Brasília, Brazil: Ministério da Saúde; 2017:54.
13. Soares de Araújo JS, Regis CT, Grigório Silva Gomes R, et al. Microcephaly in north-east Brazil: a retrospective study on neonates born between 2012 and 2015. *Bull World Health Organ* 2016;94(11):835–40. https://doi.org/10.2471/BLT.16.170639.
14. Morens DM, Fauci AS. Pandemic Zika: A formidable challenge to medicine and public health. *J Infect Dis* 2017;216(suppl 10):S857–9. https://doi.org/10.1093/infdis/jix383.