

Research Article

Is the Zika Virus the Cause of Microcephaly Epidemic in Brazil? Epidemiological Data Suggest a Negative Answer

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Abstract

In Brazil thousands of cases of congenital microcephaly appeared "simultaneously" with the spread of an epidemic of Zika virus infections. As consequence the World Health Organization, launched an international alarm under the hypothesis that the Zika virus was the cause of the epidemic of microcephaly. If an infection caused by this virus is the cause of the many observed congenital malformations, we should expect to find a time interval of 7-9 months between the mother infection and the birth of a malformed child. On the contrary, the peak incidence of the malformation took place *three–four months before* the maximum spread of the virus. Moreover the large majority of the children with microcephaly were born exclusively in the North-Eastern states of Brazil while the Zika virus rapidly spread throughout the rest of the country. Therefore from an epidemiological point of view, the "causal link" between the two events appears to be largely unproven.

BACKGROUND

In the year "July 2015-June 2016" in Brazil thousands of cases of congenital microcephaly appeared "simultaneously" with the spread of an epidemic of Zika virus infections.

Following several alarms initially launched by the Brazilian Health Authorities [1-3], and rapidly magnified by the media, on February 1, 2016 the president of "Public Health Emergency of International Concern" [4], in Brazil: in practice the temporal coincidence was assumed as the proof of a causal link between the two events. This WHO declaration was completely (and in large measure passively) accepted by the scientific community [5-7], and this fact produced a general belief that a world-wide health disaster (the Zika virus is present in a geographic area where two billion people live) was not only possible but already existent. The WHO declaration has also had enormous environmental and economic consequences for the human community.

After more than two years it is nowadays possible to ask if epidemiological data confirm or disprove the hypothesis of a causal link between Zika virus and microcephaly epidemics.

METHODS

We tried to critically summarize the available scientific literature and the innumerable contributions of Health Authorities and of "Experts" trying to reconstruct the epidemiology of the

two Brazilian epidemics, spread of Zika virus infections and congenital microcephaly, in order to understand if the hypothesis of the causal link between them was justified.

To reconstruct the temporal trend of the epidemiological curve of the spread of virus Zika infections we have official data only relative to the whole country [8]. The report begins in January in spite of the fact that it is well known that the virus was largely present in Brazil in the year 2015 [9,10]. This probably happens because suitable laboratory investigations were not yet sufficiently available in 2015.

To reconstruct the epidemiological curve of microcephaly in Brazil, we have available the epidemiological bulletins [11]. It must be noted that, for several reasons, these bulletins do not allow the correct description of the real epidemiological curve.

First of all the bulletins describe the progression of the epidemiological situation beginning from November 2015 [8], while other official data certify that in April of the same year a huge number of congenital microcephaly had been already registered in the North-East part of Brazil [12].

Moreover in each bulletin a huge number of cases still "Under Investigation (UI)" "is always cumulatively reported: in the North - Eastern part of Brazil: UI cases were 2960 in January and still 1580 in December of 2016.

Finally the bulletins do not take in account the fact that the number of confirmed cases has certainly been influenced by the three changes of the definition of microcephaly performed by the Health Authorities in Brazil [13].

Making simple reasonable hypotheses but with rather complex numerical procedures we could “correct” most of the cited defects of the data in the official bulletins, but the results would not significantly influence the conclusions of the present paper. Therefore, in reconstructing the epidemiological curves of microcephaly, we used the figures of “confirmed” cases as they appear in the official bulletins, without “corrections”.

RESULTS

Zika virus epidemic

Literature suggests that, well before it was first isolated (April 2015) and since the last months of 2015, the Zika virus was already present in Brazil [9], especially in the North-Eastern states of the country: from there, in the course of the year 2015, the virus invaded the whole Brazil and starting from the beginning of 2016 the infective epidemic of the virus was mainly active in the opposite part of the country [8].

Available official data concerning documented Zika virus infections are only relative to the whole country (Figure 1). These data describe a “bell shaped” curve beginning somewhere in 2015, reaching its maximum around March 2016 and slowly ending before the end of the year.

The epidemic of congenital microcephaly

The dimension of the epidemic is huge: according to the Brazilian Ministry of Health, 2,775 cases of congenital microcephaly have been confirmed by clinical, radiological, and/or laboratory methods (928 were confirmed by laboratory criteria, RT-PCR or serological test) [8].

The epidemic of microcephaly began before September 2015 (58 cases of microcephaly were already present in the hospitals of the state of Pernambuco between September and October) [13,14], reached its peak between November 2015 and January 2016, and came to an end in March 2016 (Figure 2). The fact that in the 18 months since then only sporadic cases have been reported in Brazil seems to exclude the hypothesis of an epidemic characterized by a seasonal trend, which is recurring in certain periods of the year due to climatic factors or linked to the biology of *Aedes Aegypti*, the insect responsible for the virus spread.

The geographic localization of the microcephaly epidemic is highly important (Figure 3). It can be seen that in Brazil almost all the malformations (more than 90% of the cases) have been registered in the North-Eastern states (a quarter of the country), vice-versa only a limited number of cases were reported in the Western or Southern states of the country where in 2016 Zika virus infection had its highest incidence.

Moreover, it must be said that in none of the over 80 countries of the tropical belt of the planet in which the Zika virus continuously causes infective epidemics an increase in the incidence of congenital microcephaly, comparable to the one observed in Brazil, has ever been reported.

DISCUSSION AND CONCLUSIONS

Before discussing the over reported epidemiological data it is worthwhile to consider the meaning of the numerous scientific reports dealing with newborns bearing congenital microcephaly in whose brain the Zika virus was isolated: In most of these cases the mother reported an episode of severely symptomatic viral infection in the early phase of their pregnancy. It is well known [15], which Zika virus infection is completely asymptomatic in about 80% of cases and with very mild clinical symptoms in about 20% of infected people: therefore pregnant women with clearly symptomatic infection belong to the less than 1% of infected persons. The cited publications seem therefore to demonstrate

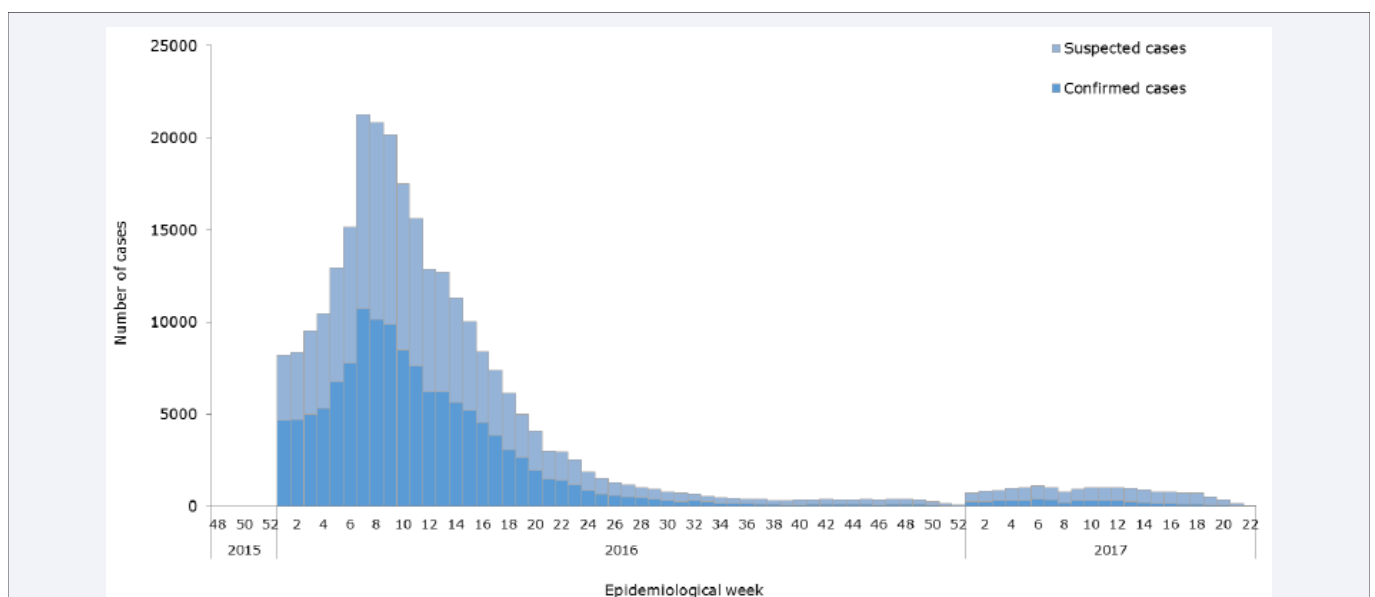


Figure 1 Suspected and confirmed Zika cases in Brazil (data from: PAN WHO, 29 June 2017).

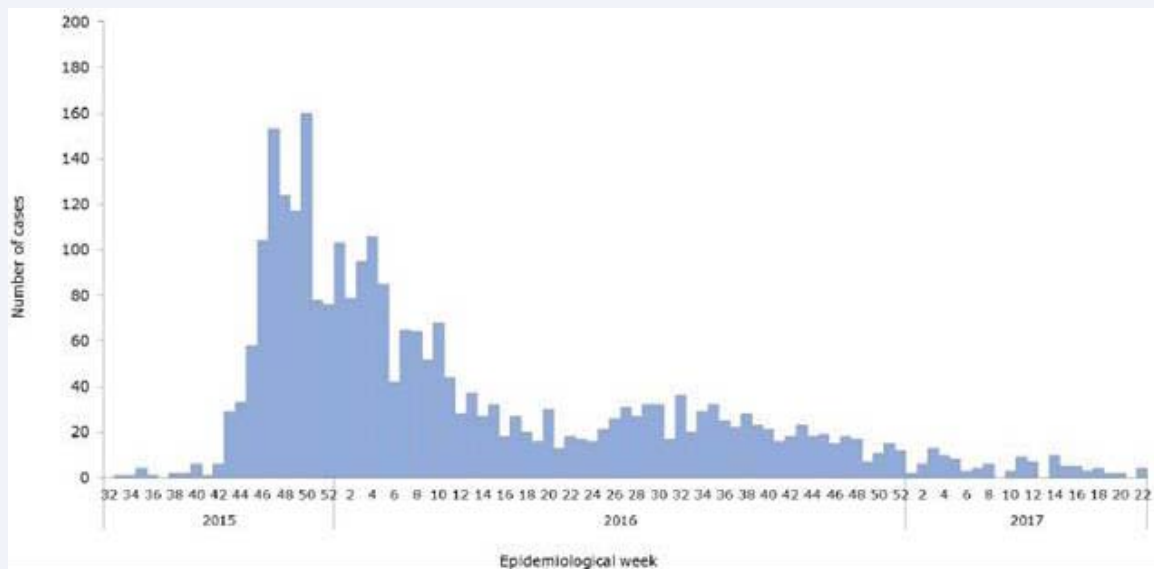


Figure 2 Total confirmed cases of congenital syndrome, Brazil. EW 32 of 2015 to EW 22 of 2017 (data from: PAN WHO, 29 June 2017).

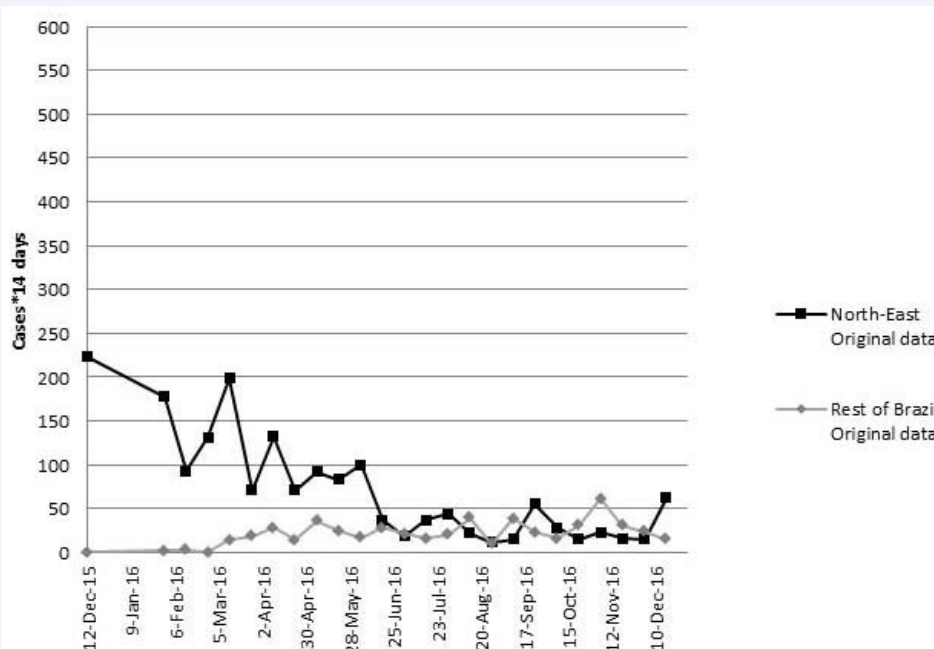


Figure 3 Epidemic curves (interval between points= two weeks) of microcephaly in the North - East states (black lines) and in the rest of Brasil (grey lines) according to "confirmed" cases reported in the official bulletins [3].

that the Zika virus, like many other viral or non viral infective agents can cause malformations in early infected pregnant women. The paper of Cordeiro [13], which deals with about half of the cases admitted to Pernambuco hospitals in September - October 2015 is difficult to evaluate because it is not population based and does not provide clinical information about the pregnancy of the mothers. In summary the small number and the quality (poor from epidemiological point of view) of the reports dealing with cases with documented association Zika virus - congenital microcephaly cannot be taken as a valid explanation of the Brazilian huge epidemic of malformations we are describing.

As shown before, the Brazilian epidemic of Zika virus infection probably begun in 2014, slowly spread in the course of 2015, reaching a peak of diffusion around March 2016.

If we are to believe that an infection caused by this virus is the cause of the many observed congenital malformations, we should expect to find a time interval of 7-9 months between the mother infection and the birth of a malformed child. From the moment that, obviously, the higher the number of infected persons the greater the probability for a mother to be contaminated, in practical terms we should expect to find the peak of microcephaly incidence *several months after* the maximal diffusion of the

virus. On the contrary, as shown before, the peak incidence of the malformation takes place *three–four months before* the maximum spread of the virus: if the hypothesis of the causal link between Zika and microcephaly is true, why the virus resulted maximally dangerous for pregnant women at the beginning of the epidemic when its circulation was low and almost innocuous at the moment of its maximal diffusion? A question which has not a simple explanation.

More difficult is to answer the next question: if the cause of microcephaly is the Zika virus, an infective agent which rapidly spread from Bahia-Pernambuco to the rest of the country, why the large majority of the almost three thousands children with microcephaly were born exclusively in the North-Eastern states of Brazil?

In summary the analysis of available data demonstrates that the two epidemics, Zika virus infections and congenital microcephaly, are not “simultaneous” and not coincident in their geographical location: therefore, from an epidemiological point of view, the “causal link” between the two events appears to be largely unproven.

We think that the Brazilian and International Health Authorities and the scientific medical community should try to answer the over reported questions or suggest alternative explanations for the etiology of the epidemic of microcephaly in Brazil.

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