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Emerging Problems in Infectious Diseases

Zika virus infection, associated microcephaly, and low yellow fever vaccination coverage in Brazil: is there any causal link?

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Abstract

Introduction: Since the end of 2014, Zika virus (ZIKV) infection has been rapidly spreading in Brazil.

Methodology: To analyze the possible association of yellow fever vaccine with a protective effect against ZIKV-related microcephaly, the following spatial analyses were performed, using Brazilian municipalities as units: i) yellow fever vaccination coverage in Brazilian municipalities in individuals aged 15-49; ii) reported cases of microcephaly by municipality; and iii) confirmed cases of microcephaly related to ZIKV, by municipality. SaTScan software was used to identify clusters of municipalities for high risk of microcephaly.

Results: There were seven significant high risk clusters of confirmed microcephaly cases, with four of them located in the Northeast where yellow fever vaccination rates were the lowest. The clusters harbored only 2.9% of the total population of Brazil, but 15.2% of confirmed cases of microcephaly.

Conclusion: We hypothesize that pregnant women in regions with high yellow fever vaccination coverage may pose their offspring to lower risk for development of microcephaly. There is an urgent need for systematic studies to confirm the possible link between low yellow fever vaccination coverage, Zika virus infection and microcephaly.

Key words: Zika; Brazil; epidemiology.

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Introduction

Since the end of 2014, Zika virus (ZIKV) infection has been rapidly spreading in Brazil, especially in the Northeast region of the country [1-4]. In June 2015, the Brazilian Ministry of Health (MoH) identified the first cases of neurological syndromes in patients with a history of exanthematic disease in endemic regions for arboviruses (ZIKV, DENV and Chikungunya virus) [5,6], and since September 2015 the number of notified cases of microcephaly has increased steadily [2]. As a consequence, MoH instructed the Federal States to report all cases of neurological syndromes and microcephaly [7]. By March 2016, a total of 6,381 suspected microcephaly cases were reported, and 854 confirmed; many of them occurred in infants born to women living in areas of ZIKV transmission. Transmission of ZIKV was confirmed in 22 of Brazil's 26 states including the Federal District.

ZIKV and yellow fever virus, in its urban transmission cycle, both share the same mosquito vector, *Aedes* mosquitoes. Yellow fever is an acute vector-borne short term viral disease. Despite the availability of an effective vaccine, there is still active transmission in many countries [8]. In Brazil, autochthonous cases of sylvatic yellow fever regularly occur in small clusters, transmitted by other mosquito species. In 2015, 7 autochthonous cases of yellow fever were reported [9]. Consequently, yellow fever vaccination is recommended for residents and for travelers directed to 18 of the 27 Federal States [10]. In the 9 remaining States, mostly located on the coastline along the Atlantic Ocean, transmission risk is

considered very low to negligible, and vaccination of the general population is not recommended [11]. However, there is no consensus on expanding vaccination to the entire country [12].

Considering the close relation of other arboviruses with ZIKV, such as the yellow fever virus, it might be speculated that yellow fever vaccine to some extent may provide a protective effect against severe disease and sequelae caused by ZIKV infection, such as microcephaly.

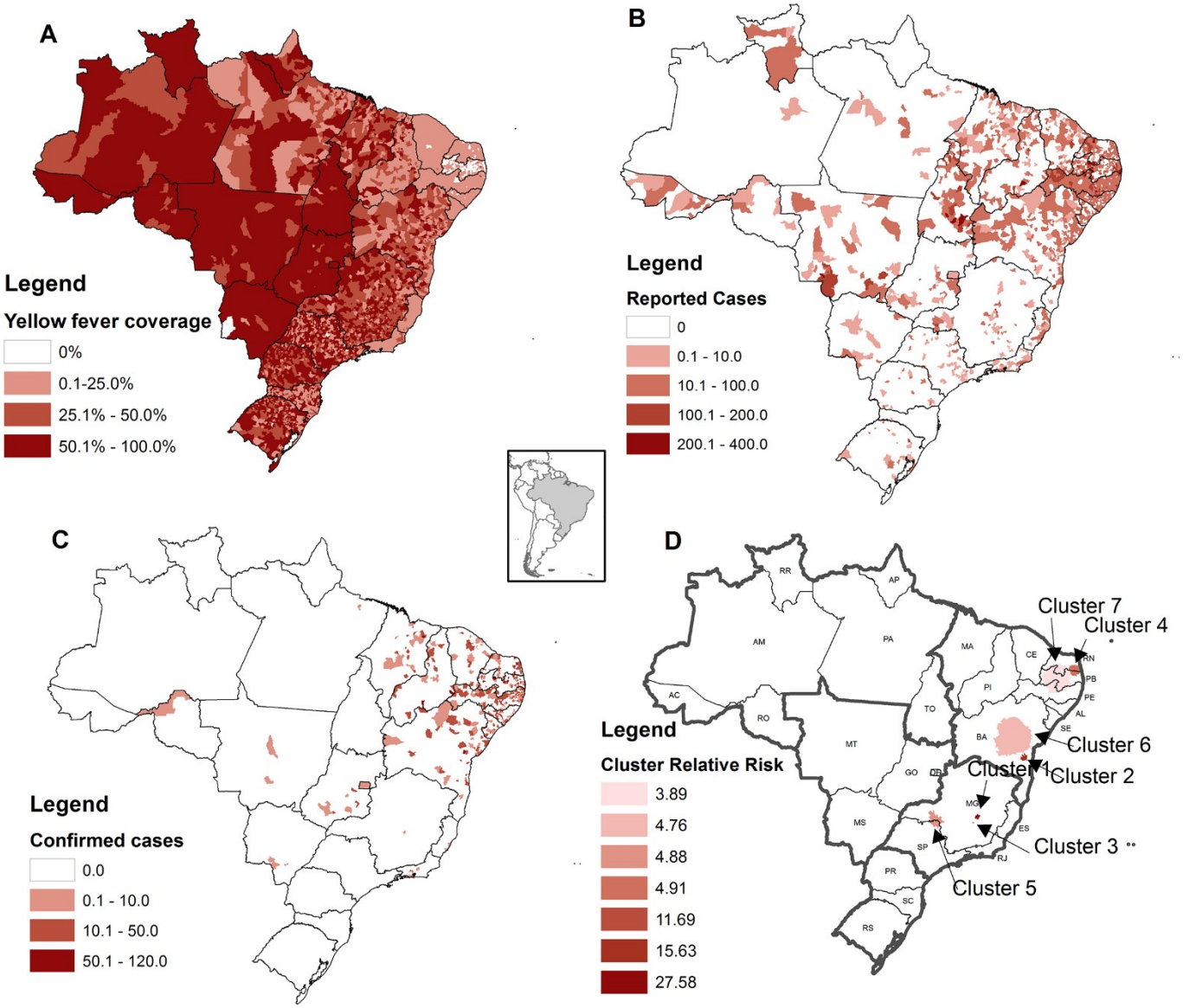
Methods

Brazil is a country of continental dimensions, with a population of approximately 205 million inhabitants and 5,570 municipalities, with major parts of its territory considered as risk areas for yellow fever transmission.

Three different descriptive spatial analyses were performed, using the Brazilian municipalities as units of analysis: 1. yellow fever vaccination coverage in Brazilian municipalities in individuals aged 15-49 years; 2. reported cases of microcephaly by municipality; and 3. confirmed cases of microcephaly related to ZIKV, by municipality.

Spatial scan statistic analysis was performed, using SaTScan software package version 9.4.2 (Harvard Medical School, Boston, USA), to identify significant clusters of Brazilian municipalities for high risk of

Figure 1. (**A**) Yellow fever vaccination coverage in individuals aged 15-49 in Brazil; (**B**) reported cases of microcephaly between October 2015 and March 2016; (**C**) confirmed cases of microcephaly between October 2015 and March 2016; (**D**) clusters of confirmed cases of microcephaly associated with ZIKV; arrows indicate location of clusters. Observation units are the 5,570 municipalities of Brazil.



microcephaly. SaTScan uses a flexible geographic scanning window and includes different sets of neighboring areas. These clusters were identified using pure spatial analysis with a radius assuming 50% of the population at risk. Vaccination coverage data by municipality are freely available and were obtained from the Informatics Department of the Unified Health System - DATASUS (http://tabnet.datasus.gov.br). Notified and confirmed cases of microcephaly were provided by the Brazilian MoH.

Results

Data showed that in the Northeast of the country - the region most heavily affected by Zika-related microcephaly – yellow fever vaccination coverage was the lowest (Figure 1A-C). We identified seven significant clusters at high risk for confirmed microcephaly cases, consisting of three or more municipalities (Figure 1D). Four out of these clusters were located in the Northeast of the country. The most extensive cluster consisted of 176 municipalities in Pernambuco (PE), Paraíba (PB) and Rio Grande do Norte (RN) states (Figure 1D), followed by another major cluster consisting of 110 municipalities in Bahia State (BA). There was also another isolated small cluster in Bahia State. An additional cluster in the northeast of the country includes Rio Grande do Norte (RN) and Paraíba (PB) States (59 municipalities). The remaining three clusters were smaller and located in other areas of the country, namely in Minas Gerais (MG) and São Paulo (SP) States. All clusters harbored only 2.9% of the total population of Brazil, but 15.2% of confirmed cases of microcephaly ($p < 0.001$). During the last 15 years, all 333 yellow fever cases occurred in areas where yellow fever vaccination is recommended.

Conclusion

Our analysis indicates that pregnant women in regions with high yellow fever vaccination coverage may pose their offspring to lower risk to develop microcephaly.

In fact, vaccination against Japanese encephalitis, dengue fever and yellow fever may produce cross-reactive antibodies. Antibody cross-reactivity is known to occur between different flavivírus infections, such as yellow fever, Japanese encephalitis, and dengue fever [13,14], and in a historical study, a volunteer infected with ZIKV virus produced antibodies against both yellow fever virus and ZIKV [15].

We are aware that this is a small descriptive study, and that our ecological data are prone to confounders and bias (such as environmental factors that may influence the spread of Zika virus in yellow fever-endemic areas). Therefore, no causal relationship can be established, and we emphasize an urgent need for systematic studies to confirm the possible link between low yellow fever vaccine coverage and microcephaly. Our data also suggest that a vaccine based on the existing yellow fever vaccine should be considered. Additional systematic studies are needed, such as a cohort study investigating yellow fever antibody titres in populations at risk. Adequately designed laboratory-based investigations and studies on animals need to be performed to investigate the possible protective effect of yellow fever vaccination against subsequent infection with Zika virus, and thus microcephaly.

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Conflict of interests: No conflict of interests is declared.