Changes in the dynamics of dengue incidence in South and Central America are possibly due to cross-population immunity after Zika virus epidemics

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Abstract
Objective: We tested the hypothesis that Zika virus (ZIKV) immunity may protect against dengue virus (DENV) infection, disease severity, or human amplification, based on analysis of epidemiological data from our long-term surveillance study (2009 – 2016) in the city of Salvador, Brazil that indicated a substantial reduction in the frequency of laboratory-confirmed dengue cases following the Zika outbreak.

Methods: To assess whether similar patterns were observed across the Americas, we did a broader explorative investigation of historical series (2004 to 2019) of suspected cases of dengue fever, covering 20 DENV-endemic South and Central American countries. We used segmented linear regressions of single group interrupted time series (ITS) analysis to evaluate whether the Zika epidemic had a statistical effect on the trends of annual dengue incidence.

Results: We observed in our 16-year historical series that in all countries, the incidence of dengue exhibited periodic oscillations over time, with a general trend of statistically significant increase during the pre-Zika period overall and for 11 of the 20 countries. Following the peak of the first population exposure to ZIKV in the Americas, in 2016, the overall rate of reported dengue cases in 2017 and 2018 in the countries under study sharply dropped (P<0.05) and was the lowest reported since 2005. Individually in each country, a statistically significant reduction in the annual dengue incidence beginning in 2016 or in 2017-2018 occurred in 13 of the 20 studied countries. However, in 2019, reports of suspected dengue cases increased across the Americas. In Brazil, Dominican Republic, Guatemala, and Honduras, dengue incidence was >5 times higher in 2019 than in 2017 and 2018, and, in 2019, they had the greater dengue incidence than in all previous years throughout the historical series.

Conclusions: The widespread decline in suspected dengue cases recorded in 2017 and 2018 lends further support to our previous epidemiological hypothesis of ZIKV induced cross-species immunity to DENV. However, the cross-protection appears to be transient (around 2 years). Long-term, prospective follow-ups of dengue reports are needed to confirm (or refute) these findings, which could have significant public health implications, in particular regarding

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/TMI.13526
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DENV vaccine development and application.

**Keywords:** dengue virus, Zika virus, herd immunity, cross-protection, The Americas

**Introduction**

Dengue virus (DENV) and Zika virus (ZIKV) are mosquito-transmitted flaviviruses. DENV (serotypes 1-4) has been endemic in the Americas for decades, with expanding geographical range and incidence. Since ZIKV emerged and spread throughout the Americas starting in 2015 (1,2), interest has grown in the potential impact of the immunological cross-reactivity elicited by ZIKV and DENV in sequential infections, given their genetic and antigenic similarities (3).

In 2017, we analyzed our primary epidemiological data from a long-term (2009 – 2016) surveillance study to detect dengue cases among acute febrile illness in the city of Salvador (population ≈2.9 million), Brazil, which is endemic for all four DENV serotypes, and which in 2015, was seriously affected by a Zika epidemic (4). Estimates indicate that over 60% of Salvador’s inhabitants have been infected by ZIKV (5,6). The results of our analysis showed a substantial reduction in dengue case detection after the Zika epidemic, suggesting that ZIKV immunity, acquired by a large proportion of the local population, afforded protection from DENV infections (4). In contrast, the Zika epidemic was closely followed by one caused by chikungunya virus, with the same human-amplified, *Aedes aegypti-*transmitted cycle, indicating that improved vector control or avoidance did not explain the dengue decline (7,8).

Here, we present results of a broader explorative investigation of historical series (2004 to 2019) of suspected cases of dengue fever, covering DENV-endemic South and Central American countries that have undergone Zika epidemics, to assess whether they also presented a subsequent decline in dengue incidence.

**Methods**

We selected 20 American countries that report suspected cases of dengue fever to the Pan American Health Organization (PAHO) and WHO and had a minimum incidence of 10 suspected dengue cases per 100,000 population per year, between 2004 and 2015. This criterion was very inclusive, allowing selection of countries that had periods of low DENV transmission, while excluding countries where dengue does not represent a continuous public health problem (such as Argentina, Chile, and Uruguay), or where the available data on dengue reporting seemed unreliable. The countries selected were Bolivia, Brazil, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Honduras, Martinique, Mexico, Nicaragua, Panama, Paraguay, Peru, Puerto Rico, and Venezuela. In Brazil, Colombia, El Salvador, Guatemala, Honduras, Martinique, Mexico, Puerto Rico and Venezuela, the first reports of Zika suspected cases occurred in 2015, but the epidemics peaked in 2016. For other countries (Costa Rica, Dominican Republic, Ecuador, French Guiana, Guadeloupe, and Nicaragua), 2016 was the year in which Zika suspected cases were first reported and also the year when the cases peaked (9,10). In 2017, the number of reported Zika cases dropped sharply in these 15 countries, suggesting that Zika epidemics did not last much longer than one year.

Exceptions occurred in Panama, which had the first suspected cases of Zika in 2015 and the disease peak in 2016, but which continued to report a high number of cases during the following years; Bolivia and Peru, which had the first suspected cases of Zika in 2016, the greatest number of cases in 2017, and continued to have a large number of cases in the following years; and Guyana and Paraguay, which had the first suspected cases of Zika in 2015, but with the
number of reported Zika cases very small (maximum of 33 in 2016 for Guyana and maximum of 145 in 2018 for Paraguay) (9). Because 17 of the 20 studied countries had autochthonous ZIKV transmission peaking in 2016, we assumed that this year was the year with the greatest ZIKV transmission in South and Central Americas.

For each country, we obtained data from the public PAHO website on the annual number of suspected dengue and Zika reported cases and on the annual estimated population, for the period between 2004 and 2019 (9). Updated data on dengue case reports for the 52 epidemiological weeks of 2019 were obtained on January 30th and revised on July 27th, 2020. The incidence of suspected dengue cases per 100,000 inhabitants was calculated annually and used to describe the pattern of dengue occurrence in a historical sequence. We present the annual incidence of suspected dengue cases over time for all countries under investigation together and, in addition, the annual incidence of dengue in each country. We did not calculate standardized incidences based on age distribution because our goal was not to compare the annual incidences between countries, but rather within each of them.

Then, we used segmented linear regression of single group interrupted time series (ITS) analysis (11) to assess, in statistical terms, the effect of the Zika epidemic on the trends of annual dengue incidence throughout the historical series. ITS model is a quasi-experimental design used to evaluate the effectiveness of population-based health interventions, when the particular outcome of interest is used to establish a baseline trend, which is interrupted by an intervention at a known point in time (12). We assumed the Zika epidemic as a proxy of an “intervention” that might have changed dengue dynamics.

For this analysis, we divided the historical series in three periods: the pre-Zika epidemic period (2004-2015); the period of the Zika epidemic effect over DENV transmission (2016-2018); and the period after the Zika epidemic effect, which included the last study year of 2019. This last period was defined because empirical observation has shown that dengue transmission has resumed in 2019. It was not included in the ITS analysis since it was too short for time trend analysis.

The year of 2016, when ZIKV transmission in the South and Central Americas was at the highest level, was defined as the breaking point for the historical series. For all the countries together and for each one of them, we estimated the linear trend of dengue incidence for the periods before (2004-2015) and during the Zika epidemic effect (2016-2018), and the immediate step change in its level in the year (2016) of the Zika epidemic (the “intervention”). We set as a statistically significant trend a two-tailed alpha of 0.05. To adjust for the data autocorrelation, we used the Prais – Winsten Estimator (11) and added robust variance in the model. For the period after the Zika epidemic effect (year of 2019), we performed only a descriptive analysis.

Results

We observed in our 16-year historical series that the incidence of dengue exhibited periodic oscillations over time. However, before the peak of ZIKV transmission in the South and Central America, in the period between 2004 and 2015, the overall annual incidence of dengue for the 20 countries together presented a statistically significant trend of linear increase (Figure 1). In 2016, the year of the most intensive Zika epidemics in the region, the overall dengue incidence level did not substantially change compared to the prior period (P >0.05), but it was followed by a sharp and statistically significant drop in the incidence trend (P <0.05) during 2017 and 2018. The overall incidence of reported dengue cases in 2017 and 2018 for the 20 countries under study was the lowest reported since 2005 (Figure 1).

Analyzing the situation of each country (Figure 2), we observed that the incidence trend was generally increasing between 2004 and 2015, and was statistically significant in 11 (Bolivia, Brazil, Colombia, Dominican Republic, El
Salvador, Guatemala, Honduras, Mexico, Nicaragua, Paraguay, Peru) of the 20 countries until the unusual decline in 2017 and 2018. In 2016, the year of the ZIKV transmission peak in the region, there was an immediate and statistically significant decrease in the incidence of dengue in seven countries (Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Puerto Rico, and Venezuela) (P <0.05 for each country). In contrast, two countries (Nicaragua and Panama) presented a statistically significant increase in dengue incidence. In 2017 and 2018, a statistically significant decrease in the trend of the annual dengue incidence was observed for 10 (Bolivia, Brazil, Colombia, Costa Rica, Dominican Republic, Ecuador, Guatemala, Honduras, Mexico, and Nicaragua) of the 20 countries (p <0.05). In El Salvador, Puerto Rico and Venezuela, there was no statistically significant downward trend during 2017 and 2018, but the incidence of dengue remained low during these years. Altogether, 13 countries had a statistically significant decline in dengue incidence in 2016 and/or through 2017 and 2018.

Of the other seven countries, five (French Guiana, Guadeloupe, Guyana, Martinique, and Paraguay) remained with relatively low levels of dengue incidence in 2017 and 2018, but no statistically significant decline trend was observed after Zika epidemics. Peru was unique in that the Zika epidemics peaked later, in 2017. Thus, the breaking point used in the ITS analysis may have not been appropriate. For a sensitivity analysis, we modified the ITS analysis for Peru, establishing 2017 as the breaking point in the historical series, and found a statistically significant trend for both linear increase in dengue incidence between 2004 and 2016, and a statistically significant downward trend after 2017 (supplementary figure). The only country presenting a different pattern was Panama, where levels of dengue incidence remained relatively high between 2017 and 2019, after a statistically significant increase in 2016.

In Martinique, Brazil and Guatemala, dengue incidence in 2017 and 2018 was the lowest since 2004, 2005 and 2011 respectively; in Costa Rica, Dominican Republic, El Salvador, French Guiana, Guyana, Honduras, Puerto Rico, and Venezuela the incidence in 2017 or 2018 was the lowest ever recorded in the historical series. In Puerto Rico, dengue decline began earlier, in 2014, and has remained low ever since, making this the longest sequence of years of low dengue incidence in the period between 2004 and 2019. The same happened in Venezuela, which had lower levels of dengue incidence since 2016.

However, in 2019, the overall incidence of suspected dengue cases reported in the 20 countries under study increased about 5 times compared to 2017 and 2018 and was the greatest ever recorded in the historical series (Figure 1). In Brazil, Dominican Republic, El Salvador, Guadeloupe, Guatemala, Guyana, Honduras, Martinique and Puerto Rico, dengue incidence increases varied from 5- to 58.8- fold compared to the 2017 or 2018 records (although incidences remained relatively low for Guadeloupe, Guyana, Martinique and Puerto Rico). In addition, Brazil, Dominican Republic, Guatemala, Honduras, and Nicaragua had a greater dengue incidence in 2019 than in all previous years throughout the historical series (Figure 2). Other countries presenting a massive increase in dengue incidence in 2019 were Colombia and Mexico. Conversely, other countries did not face a dengue reemergence in 2019 and maintained low incidence levels (Bolivia, Costa Rica, Ecuador, French Guiana, Paraguay, Peru, Puerto Rico, and Venezuela; the last two maintain their dengue incidence as among the smallest of their historical series as previously mentioned).

Discussion

Although laboratory-based evidence indicates that immunological cross-reaction between DENV and ZIKV does exist (13,14), the discussion remains ongoing because some studies support cross-protection (15,16), while others indicate that it may raise disease severity through immune enhancement (17–20); others have shown no effect of cross-

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immunity (21,22). Thus, epidemiological studies are critical to elucidate the clinical effect of DENV and ZIKV cross-immunity. Our results on dengue dynamics from 2004 to 2019 demonstrate an unusual, widespread and statistically significant decline in the incidence of suspected dengue cases reported to PAHO and WHO in 2017 and 2018 in 13 of 20 countries of the South and Central America, just following ZIKV spread through the continent in 2016. These findings lend further support to our previous epidemiological hypothesis (4) that population immunity to ZIKV may yield cross-protection against DENV in sequential infections, and therefore plays a role in the dynamics of dengue incidence. This hypothesis was also underlined by PAHO/WHO experts (23) in the context of discussions of possible explanatory hypotheses for the general pattern of decrease in dengue across the Americas in 2017.

Likewise, epidemiological investigations have evaluated the role of DENV and ZIKV cross-immunity in the opposite direction (i.e. the effect of prior DENV immunity on the incidence of ZIKV infection and disease) and have proved that prior DENV infection cross-protects against ZIKV. In Brazil, a cohort study found that pre-existing high antibody titers to DENV reduced the risk of both ZIKV infection and symptoms (6). A similar observation was made in a pediatric Nicaraguan cohort, which showed that prior DENV immunity reduced the risk of symptomatic ZIKV infection (24). In addition, in a case-control investigation, mothers of neonates with congenital Zika syndrome (CZS) had lower DENV seroprevalence and a smaller number of DENV-neutralized serotypes than control mothers whose children were born without CZS (25). Altogether, the accumulated epidemiological evidence points to a bidirectional cross-protection between DENV and ZIKV.

However, the dengue resurgence in the Americas in 2019 indicates that ZIKV immunity likely provides only short-term cross-protection against DENV infections (≈2-3 years), which might be expected based on what is known regarding heterotypic DENV cross-immunity. Since DENV cross-immunity generally does not persist for more than 12-36 months (26) the protective capacity offered by ZIKV immunity against DENV should also be short and related to the level of antibody titers, as observed in sequential dengue strain infections (19,27,28). Therefore, a drop in cross-protective immunity is likely one of the fuels behind the increase in the incidence of suspected dengue cases reported in 2019. Alternative or contributing factors that may help explain the rise or maintenance of low levels of dengue incidence among the countries in 2019 include population susceptibility to specific DENV serotypes, circulating DENV serotypes, vector abundance, and vector control measures. There is evidence for example that DENV serotype 2, which did not cause epidemics in Brazil since the late 2000s (29,30), re-emerged as the main serotype detected in 2019. Simultaneous circulation of the four DENV serotypes, which may increase the risk of DENV infections, was also detected in Brazil, Guatemala, Mexico, and Peru in 2019 (9). Except for Peru, which faced the Zika epidemic later, in 2017, all other countries had large increases in dengue incidence in 2019. Thus, differences in the timing of when the Zika epidemics reached each country and the extent of the epidemics may also have played a role in the dynamics of dengue transmission.

Of note, based on reported data on dengue cases from Brazil and Colombia, Borchering et al. (31) simulated dengue incidence under multiple assumptions of DENV-ZIKV interactions and found not only a dengue incidence reduction due to ZIKV cross-protection, but also a subsequent dengue resurgence after a short period of low dengue occurrence. The mechanism of cross protection that our data indicate could be prevention of infection, a reduction in apparent disease, and/or a reduction in viremia, resulting in inefficient amplification and transmission. Accurate, longitudinal DENV serological data from the 2015-2019 time period are needed to distinguish these possibilities. Unfortunately, such data are very scarce due to inherent cross-reactions among flaviviruses in most serologic assays.

Although other factors, such as population immunity against dengue strains and enhanced vector control
programs, can be important modifiers of the dynamic of dengue, they do not appear to provide sufficient explanation for the widespread decline in dengue between 2017 and 2018. In particular, we note that there were no significant changes in vector surveillance systems that co-occurred in the different countries we considered (23). In Brazil, for instance, environmental education and vector control have never prevented arbovirus transmission (32) and the prevalence of DENV immunity for each serotype has not been enough to prevent widespread transmission and repeated large outbreaks from 2009 till 2016 (33). Even if vector control or educational efforts to improve vector avoidance improved after the Zika epidemic, the increase in chikungunya cases in Salvador, Brazil immediately after the Zika outbreak refutes a major role for these efforts in the dengue reduction (7,8).

Our study has several limitations. First, it was based on secondary data, and the reported number of dengue cases may not reflect the true picture for each country. It is possible that Zika and dengue cases had been misdiagnosed and misreported between them, because they co-circulated in the Americas since 2014-2015 and they share clinical similarities that may hamper an accurate clinical suspicion. Even serologically confirmed cases may have been wrongly classified due to anti-DENV and anti-ZIKV cross-reactive immune response. Thus, it is possible that countries which did not record a large Zika epidemic, such as Guyana and Paraguay, and that theoretically could serve as “imperfect controls” where dengue incidence were not expect to change, might actually have had an unrecognized Zika epidemic that could help explain the non-statistically significant decline in dengue incidence in 2017 and 2018. Second, the period elapsed since ZIKV spread is still too short to determine long-term effects on the dengue incidence pattern. In addition, because in some countries (e.g., Colombia, French Guiana, Guadeloupe, Guyana, Martinique, Puerto Rico, and Venezuela) dengue incidence began to decline before the Zika outbreak, other factors not considered in this study may have played an important role in the observed dynamics of dengue transmission. In Venezuela, for example, the ongoing political and socioeconomic crisis may have negatively impacted the quality of the dengue surveillance system, which might have impaired the accuracy of the analyzed data on dengue case reports.

Yet, the coincidental large reduction in dengue incidence following ZIKV spread in the Americas, together with current epidemiological and immunological knowledge on the interactions between these flaviviruses, suggests the existence of ZIKV cross-species immunity to DENV. Prospective cohort studies to determine dengue incidence among subjects exposed and non-exposed to ZIKV are urgently needed to confirm (or refute) these findings, which could have significant public health implications, in particular with regard to DENV and ZIKV vaccine development and application.

Acknowledgment
We thank the staff of the arboviral surveillance systems from South and Central America for their effort in detecting and reporting cases suspected of arboviral infections, and the Pan American Health Organization and the World Health Organization for providing public access to the number of reported cases suspected of dengue and Zika. We also thank the Brazilian National Council for Scientific and Technological Development; the Bahia Foundation for Research Support; the Coordination for the Improvement of Higher Education Personnel, Brazilian Ministry of Education; the Department of Science and Technology, Secretariat of Science, Technology and Strategic Inputs, Brazilian Ministry of Health; the Oswaldo Cruz Foundation; and the Federal University of Bahia for providing fund support and scholarships for our arboviral research group.
References


Figure legends

Figure 1. Overall incidence of reported cases of dengue per 100,000 population from 2004 to 2019, in 20 DENV-endemic South and Central American countries.

Note: The solid blue lines represent the regression estimations for the pre-Zika epidemic period (2004-2015) and the period of the Zika epidemic effect over DENV transmission (2016-2018). The blue asterisks indicate statistically significant regression estimations for linear trend. The vertical black dotted line indicates the start for the period of Zika epidemic effect and the vertical red dotted line indicates the immediate step change in the incidence level in 2016, year of the greater ZIKV transmission in the Americas (proxy of an “intervention”). The red asterisks indicate a statistically significant step change in the incidence level in 2016.

Figure 2. Historical series of the incidence of reported cases of dengue per 100,000 population from 2004 to 2019, for 20 DENV-endemic South and Central American countries.

Note: The solid blue lines represent the regression estimations for the pre-Zika epidemic period (2004-2015) and the period of the Zika epidemic effect over DENV transmission (2016-2018). The blue asterisks indicate statistically significant regression estimations for linear trend. The vertical black dotted line indicates the start for the period of Zika epidemic effect and the vertical red dotted line indicates the immediate step change in the incidence level in 2016, year of the greater ZIKV transmission in the Americas (proxy of an “intervention”). The red asterisks indicate a statistically significant step change in the incidence level in 2016.

Supplementary figure. Incidence of reported cases of dengue per 100,000 population from 2004 to 2019 for Peru.

Note: The solid blue lines represent the regression estimations for the pre-Zika epidemic period (2004-2016) and the period of the Zika epidemic effect over DENV transmission (2017-2019). The blue asterisks indicate statistically significant regression estimations for linear trend. The vertical black dotted line indicates the start for the period of Zika epidemic effect and the vertical red dotted line indicates the immediate step change in the incidence level in 2017, year of the greater ZIKV transmission in Peru (proxy of an “intervention”).
Dengue incidence per 100,000 population

Legend

- 2016, year of the Zika epidemic peak
- Annual incidence
- Linear trend, statistically significant (P<0.05)
- Step change in level not statistically significant (P>0.05)
Legend
- 2016, year of the Zika epidemic peak
- Annual incidence
- Linear trend, not statistically significant (P>0.05)
- Linear trend, statistically significant (P<0.05)
- Step change in level not statistically significant (P>0.05)
- Step change in level statistically significant (P<0.05)