

A basic study of the association of dengue, yellow fever and Zika with global warming and their vector-level transmission interactions

Estudio básico sobre la relación del dengue, fiebre amarilla y Zika con el calentamiento global y sus interacciones de transmisión a nivel de vector

Polwatta Gallage Tharindu^{1*} 

1 Tropical Ecosystem Research Network (TERN), Sri Lanka.



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* Corresponding author email:
g.tharindu@yahoo.com

ABSTRACT

Dengue, yellow fever and Zika are high-priority vector-borne viral infections responsible for large numbers of cases and deaths, as well as considerable economic burdens, among nations in tropical and subtropical regions. Global warming is believed to greatly affect the transmission dynamics of these diseases and, because the three viruses share the same population of transmission vectors in a given region, it is thought that the transmission dynamics of one disease can affect the others. However, to date, these interactions remains little studied. The aim of this study was to evaluate the association of disease transmission pattern with temperature anomalies and transmission dynamics, and the interactions of the three diseases using incidences as a proxy for transmission patterns, employing correlation analysis. A significant positive correlation was observed between dengue incidence and temperature anomalies, while a significant negative correlation was observed between yellow fever and temperature anomalies. In the regions considered, a significant negative correlation was observed between the incidence of yellow fever and dengue. Zika did not exhibit significant correlations with temperature anomalies or any other disease. Based on the observations made, it can be concluded that global warming could greatly affect the global transmission dynamics of both dengue and yellow fever, while the patterns of yellow fever transmission could also affect long term dengue transmission patterns.

Keywords: *Dengue, yellow fever, Zika, climate change, interactions*

RESUMEN

El dengue, la fiebre amarilla y el Zika son infecciones virales transmitidas por vectores de alta prioridad que son responsables de un gran número de casos, muertes y cargas económicas en los países de las regiones tropicales y subtropicales. Se sospecha que el calentamiento global afecta en gran medida la dinámica de transmisión de estas enfermedades, y como estos tres virus comparten la misma población de vectores de transmisión en una región, la dinámica de transmisión de una enfermedad puede afectar a otras. Estas interacciones se han estudiado poco hasta ahora. Este estudio evaluó la asociación del patrón de transmisión de la enfermedad con anomalías de temperatura y las interacciones de la dinámica de transmisión de tres enfermedades utilizando incidencias como proxy de los patrones de transmisión, mediante el uso de análisis de correlación. En el estudio se observó una correlación positiva significativa entre la incidencia del dengue y las anomalías de temperatura. Se observó una correlación negativa significativa entre la fiebre amarilla y las anomalías de temperatura. En las regiones consideradas se observó una correlación negativa significativa entre la incidencia de fiebre amarilla y dengue. El Zika no mostró correlaciones significativas con anomalías de temperatura o cualquier otra enfermedad. De acuerdo con las observaciones, se puede concluir que el calentamiento global podría afectar considerablemente la dinámica de transmisión global del dengue y la fiebre amarilla. Los patrones de transmisión de la fiebre amarilla también podrían afectar los patrones de transmisión del dengue a largo plazo.

Palabras clave: *dengue, fiebre amarilla, Zika, cambio climático, interacciones*



Introduction

According to World Health Organization (WHO) criteria, dengue, yellow fever and Zika are three high priority vector-borne viral infections, generally found in tropical and subtropical regions of the world. Respectively, they are caused by the dengue virus (DENV 1-4), yellow fever virus (YFV), and Zika virus (ZIKV), which belong to the *Flaviviridae* family and are transmitted by *Aedes albopictus* and *Aedes aegypti* mosquitoes (Barrett and Monath, 2003, Musso and Gubler, 2016, Ross, 2010). According to WHO models, 390 million incidences of dengue (WHO, 2021) and 84 000~170 000 incidences of yellow fever (WHO, 2019) are expected annually. Despite the fact that Zika is no longer believed to be posing a threat at outbreak level, 1.3 billion people are estimated to be at risk of exposure to Zika by 2050, due to temperature increases resulting from global warming and climate change (Ryan *et al.*, 2021). In common with Zika, the threats from dengue and yellow fever are also expected to be amplified, both numerically and spatially, by 2050 due to the effects of climate change (Campbell *et al.*, 2015, Gaythorpe *et al.*, 2020). This could be related to the life cycle ecology of vectors, associated with global warming and climate change, which are known to trigger natural disasters such as floods that favor vector propagation (Iwamura *et al.*, 2020). Such higher case numbers and increased mortality rates would impose a massive economic and resource burden upon many of the world's nations.

Given that the subtropical and tropical regions of the world are directly at risk from these diseases, a better understanding of the epidemiological dynamics of these three diseases is vital, in order to enable this challenge to be met successfully.

Furthermore, because these three viruses share the same transmission vector species and the same vector population in a region, and an individual vector mosquito can only host one type of virus and transmit the disease within the same human host population, the transmission of one disease can be statistically associated with the other two diseases at vector level, even though infections might not be correlated clinically. However, these aspects have still not been properly explored. Therefore, in this study our first goal was to assess the association of incidences of each disease with temperature anomalies associated with climate change. Then, we used incidences of each of the three diseases as surrogates to assess the interaction between the transmission dynamics of dengue, yellow fever and Zika, at the vector eco-epidemiological level.

We strongly believed that our study would establish a basic but solid statistical platform through which to initiate further multidisciplinary research with regard to the parasitology and entomology of disease dynamics, leading to an improved understanding of the disease epidemiology, and better disease management in the future.

Materials and method

Data collection: The annual dengue, yellow fever and Zika incidences in 195 countries, from 1990 to 2019, were obtained from the Global Health Data Exchange Global Burden of Disease Study 2019 (GBD 2019) data resources. Annual global average temperature anomalies data from 1990 to 2019 were obtained from the NOAA Global Climate Time Series data platform (NOAA, 2021).

Normality testing: Data for all the variables (global and regional incidences, as well as temperature anomalies) were tested for normality using the Shapiro-Wilk normality test (Shapiro and Wilk, 1965).

Associations between each disease and temperature anomalies: For preliminary visualization of correlations between each disease and temperature anomalies, scatterplots were developed. Based on non-normal outcomes of the Shapiro-Wilk normality test for sample variables, Spearman's rank correlation coefficient assessment was conducted in order to quantify correlations between each disease and temperature anomalies, at a 95% significance level (Daniel, 1990).

Associations between each disease within a given region: Based on non-normal outcomes of the Shapiro-Wilk normality test for sample variables, Spearman's rank correlation coefficient assessment was conducted for dengue, yellow fever and Zika incidences data in Africa, Central America and South America, in order to quantify interactions between dengue and yellow fever, dengue and Zika, and Zika and yellow fever.

Results and discussion

Associations between each disease and temperature anomalies:

Incidences of dengue infection appeared to increase along with increases in temperature anomalies. However, incidences of yellow fever appeared to decrease against increasing temperature anomalies. In the case of Zika virus infections, incidences appeared to be positively correlated to increasing temperature anomalies (Fig. 1).

Based on Spearman's rank correlation coefficient, a significant monotonic positive correlation ($\rho = 0.878$) was observed between dengue incidences and temperature anomalies ($p\text{-value } (1.921e-10) < 0.05$) at a 95% significance level. Between yellow fever incidences and temperature anomalies, a significant monotonic negative correlation ($\rho = -0.881$) was observed ($p\text{-value } (1.3e-10) < 0.05$) at a 95% significance level. Even though a positive correlation between Zika virus incidences and temperature anomalies was visually apparent in the graphs, no negative or positive significant monotonic correlation was quantitatively proven between Zika virus incidences and temperature anomalies ($p\text{-value } (0.0968) > 0.05$), at a 95% significance level. Therefore, it appears that Zika transmission prefers a fixed range of

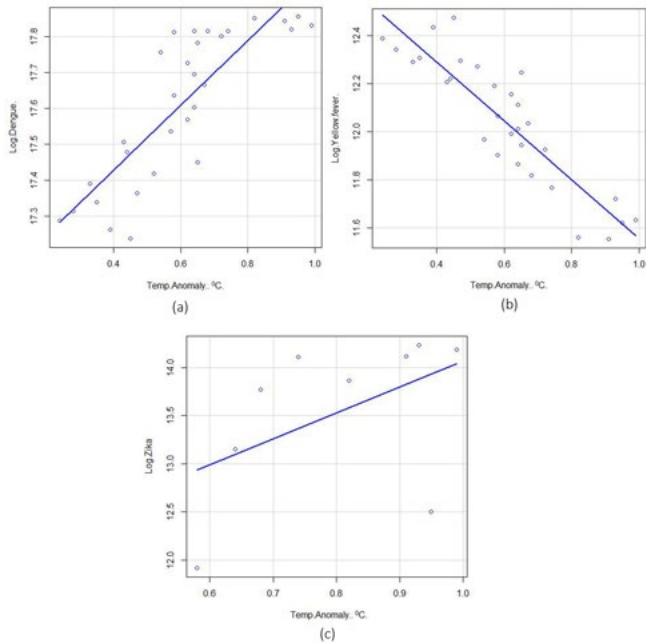


Figure 1. Global annual incidences vs. temperature anomalies (a) Dengue (b) Yellow fever and (c) Zika virus infections (in log scales). (On the NOAA platform, temperature anomalies for each year had been calculated by deducting the 20th century average temperature value [reference value] from the annual average temperature of each year between 1990 and 2019.)

temperature (including higher temperatures), rather than broader fluctuations or anomalies.

However, the decline in yellow fever incidences over time may also be associated with the effective vaccination initiatives undertaken in order to combat yellow fever over the past few decades.

Due to the endemic nature of Zika transmission and because only a couple of large scale outbreaks have occurred, limited to a couple of regions, the amount of data available with which to statistically associate Zika with temperature anomalies remains low. This lack of sufficient temporal data on Zika may be the reason for there being no apparent significant correlation between

Zika and temperature anomalies based on the above statistical analysis. However, literature proposing a significant positive correlation between Zika and global warming could be based on projection models developed using existing patterns.

Associations between each disease within a given region:

In the context of correlations between diseases within Africa, a significant monotonic negative correlation ($\rho = -0.8358176$) was observed between yellow fever incidences and dengue incidences (p-value (0.000008418) < 0.05) at a 95% significance level. Similarly, a significant monotonic negative correlation ($\rho = -0.8278087$) was observed between yellow fever incidences and dengue incidences (p-value (0.000009166) < 0.05) at a 95% significance level in the regions of Central America and South America.

However, no significant correlations were observed between yellow fever and Zika incidences in both regions (Africa; p-value (0.08333) > 0.05, the Americas; p-value (0.6777) > 0.05), at a 95% significance level. Similarly, no significant correlations were observed between dengue and Zika incidences in both regions (Africa; p-value (0.75) > 0.05, the Americas; p-value (0.81) > 0.05), at a 95% significance level.

When the incidence pattern of the three diseases within each region is considered as a surrogate for transmission pattern, it appears that the transmission pattern of dengue might be affected by the transmission pattern of yellow fever within the same population, since they share the same vector population within the region. In other words, if dengue transmission is high as a result of the majority of the *Aedes aegypti* mosquitoes in the population being infected with dengue, it might reduce the availability of *Aedes aegypti* mosquitoes for yellow fever transmission, and vice versa.

Furthermore, a successful vaccination program has been implemented against yellow fever for almost

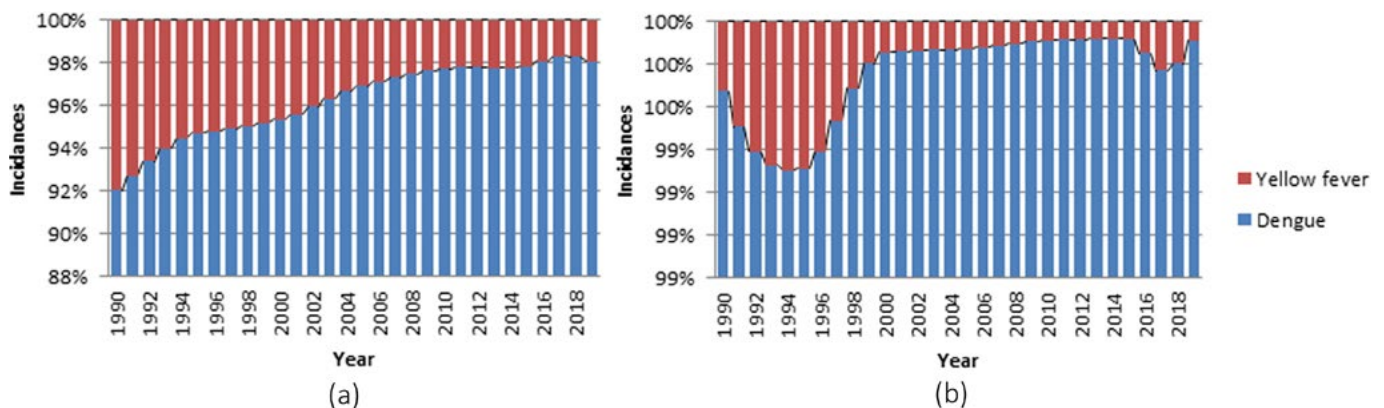


Figure 2. Annual percentage of dengue vs. yellow fever (out of total annual cases of dengue, yellow fever and Zika) (a) African region, (b) Central America and South America region.



seven decades (Ishikawa *et al.*, 2014). Viral reserves within infected human hosts play a significant role in the continuity of the viral transmission cycle, from an epidemiological perspective, since humans play a role in part of the lifecycle of the virus as a host (serial correlation of previous cases to present cases). When this reserve is reduced due to successful vaccine intervention, reduction in the incidence of yellow fever within a region is the result. While this is a positive outcome in terms of yellow fever transmission, at the same time it may serve to improve the availability of vectors for dengue transmission, by eliminating competition, leading to an increase in dengue transmission over time (Fig. 2).

As we have already mentioned, the lack of sufficient data on Zika may be the reason for there being no apparent significant correlation between Zika and the other two diseases (dengue and yellow fever), based on the above statistical analysis.

However, using the abovementioned surrogate analysis for baseline details, in order to determine transmission association dynamics, it is recommended that further work be conducted through a parasitological and entomological multidisciplinary approach, with an experimental design, in order to confirm the presence of virus in vectors at different stages in their lifecycles and measure the ratios of vectors carrying each virus within the vector population of a given region.

Conclusions

Based on the above statistics, it is concluded that global warming and associated climate change can affect the global transmission dynamics of dengue and yellow fever. However, due to absence of data and its endemic nature, the effect of climate change on Zika virus transmission cannot be determined at this time.

Regarding associations between dengue, yellow fever and Zika transmission among the same host population, it is concluded that transmission patterns of yellow fever can significantly affect dengue transmission patterns. However, once again, lack of data means that the interaction of Zika outbreaks with the existing transmission dynamics of dengue and yellow fever within the same host population, using the same vector population, remains undetermined.

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