The spread of mosquito-borne viruses in modern times

Title

The spread of mosquito-borne viruses in modern times: a spatio-temporal analysis of dengue and chikungunya

Authors

Rossi, G.[1*#], Karki, S.[1], Smith, R.L.[1], Brown, W.M.[1], Ruiz, M. O.[1]

[1] Department of Pathobiology, College of Veterinary Medicine, University of Illinois at Urbana-Champaign, 2001 S Lincoln Ave, 61802 Urbana (IL), USA

[*]Current address: Royal (Dick) School of Veterinary Medicine, University of Edinburgh, Easter Bush Campus, Midlothian EH25 9RG, UK

[#]Corresponding author: g.rossi@ed.ac.uk

Abstract

Since the 1970s, mosquito-borne pathogens have spread to previously disease-free areas, as well as causing increased illness in endemic areas. In particular, dengue and chikungunya viruses, transmitted primarily by *Aedes aegypti* and secondarily by *Aedes albopictus* mosquitoes, represent a threat for up to a third of the world's population, and are a growing public health concern.

In this study, we assess the spatial and temporal factors related to the occurrences of historic dengue and chikungunya outbreaks in 76 nations focused geographically on the Indian Ocean, with outbreak data from 1959 to 2009. First, we describe the historical spatial and temporal patterns of outbreaks of dengue and chikungunya in the focal nations. Second, we use a boosted regression tree approach to assess the statistical relationships of nations' concurrent outbreak occurrences and annual occurrences with their spatial proximity to prior infections and climatic and socio-economic characteristics.

We demonstrate that higher population density and shorter distances among nations with outbreaks are the dominant factors that characterize both dengue and chikungunya outbreaks. In conclusion, our analysis provides crucial insights, which can be applied to improve nations' surveillance and preparedness for future vector-borne disease epidemics.

Keywords

Vector-borne diseases; Dengue virus; Chikungunya virus; Indian Ocean; Boosted regression trees

1. Introduction

The spread of mosquito-borne pathogens to new areas has increased markedly since the 1970s along with an overall increase in cases of illnesses. Two diseases that saw a dramatic expansion during this period are those associated with the dengue and chikungunya viruses. Both viruses are transmitted by *Aedes aegypti* mosquitoes with secondary transmission by *Aedes albopictus*, and the two diseases share an intertwined history and ecology (Manore et al., 2014; Carey, 1971).

Dengue virus (DENV) cases have been increasing steadily for decades, as the area of endemic transmission has expanded. At the time of this writing, more than 1/3 of the world's population was at risk of illness from dengue virus (DENV), with recent estimates of 390 million human infections annually (Bhatt et al., 2013; Gurugama et al., 2010; Monath, 1994). DENV infections were first reported in 1780, and contributed to large concurrent epidemics in port cities of Asia, Africa and North America in the late 1700s - coinciding with an increase in global commerce (Gubler, 1998). After a more recent surge in cases during the years of World War II, cases of dengue declined thanks to intensive efforts to reduce the *Aedes aegypti* mosquitoes, only to expand dramatically after 1980 (Murray et al., 2013). DENV has four distinct serotypes (DENV-1 – DENV-4), and some of the recent increase in cases has taken place as these serotypes expanded and mixed globally (Messina et al., 2014).

Chikungunya virus (CHIKV) was not identified until 1952 near the border of Tanzania and Mozambique (Lahariya and Pradhan, 2006), but it was likely circulating globally earlier than the 1950s, with cases of illness sometimes being confused with those caused by DENV. Even today, reported cases without laboratory confirmation can lead to misclassification (Roth et al., 2014; Halstead, 1980; Carey, 1971). After the early 1970s, there was little evidence of chikungunya epidemics until a dramatic reemergence in the Indian Ocean region in 2005. During this period millions of cases were recorded within a short period of time, with peaks of 47,000 new cases in a single week

(Higgs, 2006), and a very high attack rate in some locales – including some 244,000 cases among the approximately 800,000 residents of the island of Reunion (Simon et al., 2008). This expansion coincided with a viral mutation of CHIKV that resulted in more efficient transmission by *Aedes albopictus* mosquitoes and an increase in virulence (Kucharz and Cebula-Byrska, 2012). In 2007 it reached Europe, when a temperate region in Italy reported locally transmitted CHIKV following introduction by travelers from the Indian Ocean (Chevillon et al., 2008; Simon et al., 2008). CHIKV cases were later observed in southern France, and in 2017, after a decade without local cases, Italy again saw invasion and subsequent local transmission of CHIKV (Amraoui and Failloux, 2016; Marano et al. 2017). CHIKV also spread to the Americas following the outbreak in the Indian Ocean, with nearly 1.7 million cases reported in this region between December 2013 and September 2015 (Cassadou et al., 2014; Petersen and Powers, 2016; Roth et al., 2014).

Zika virus, also transmitted primarily by *Aedes aegypti*, more recently entered global awareness. It caused an extraordinary epidemic in Brazil, after first being reported in the spring of 2015, with thousands more cases in the Americas since then (Esposito and Fonseca, 2016; Faria et al. 2017). The most recent large Zika outbreaks followed its expansion to the Yap Islands in the Pacific Ocean in 2007 and subsequent spread to other parts of Southeast Asia and the Pacific (Chang et al., 2016; Weaver et al., 2016).

Here, we focused on historical outbreaks of illness from DENV and CHIKV. Some general principles guide the processes that result in expansion of mosquito-borne pathogens, but the precise mechanisms behind the emergence, as well as the spatial and temporal dynamics of mosquito-borne diseases (MBDs) spread, can vary considerably (Wood et al., 2017). By comparing the patterns of two viruses with similar ecological niches, we expect to gain insight into general characteristics that promote their expansion. Zika has a similar transmission pattern as chikungunya and dengue, but it lacks the long historic record of global circulation, and we thus did not include it in this study. We did

not consider malaria, which is transmitted by different mosquito species and is not a viral disease.

MBDs are found primarily in tropical or sub-tropical regions, and areas where they have emerged and reemerge in recent years are typified by suitable vector habitat, large, diverse wildlife populations, and increasing human population density (Jones et al., 2008). On the other hand, socioeconomic factors such as lifestyle, poor infrastructure, and poor sanitation are also likely to facilitate their diffusion (Moreno-Madriñán and Turell, 2017). More recently, the movement of both mosquitoes and infected hosts has been enhanced by globalization and increased air traffic (Brown et al., 2012; Tatem et al., 2012). In addition, MBDs have the potential to increase with climate change and the accompanying changes in wet-dry periods (Donat et al., 2016; Naish et al., 2014; Patz et al., 1996; Tjaden et al., 2017). Other factors that can play a critical role for MBD transmission are the evolution of virulence and the increased resistance of mosquitoes to insecticides (Maciel-de-Freitas et al., 2014; Greenwood et al., 2008, Moncayo et al., 2004). Finally, emergence can be driven by poor housing conditions found in crowded urban and sub-urban settlements, lack of mosquito control, and invasion of vectors into new areas along with deforestation and development of new agricultural enterprises (Ali et al., 2017; Dash et al., 2013; Moreno-Madriñán and Turell, 2017; Petersen and Powers 2016; Schrag and Wiener, 1995).

We compared factors driving the historic emergence of dengue and chikungunya viruses after World War II. On the one hand, we had the expectation that similarities between the two would exist because of their similar transmission cycles. On the other hand, we recognize that the two viruses are in different families, with DENV belonging to the flaviviriridae and CHIKV to the alphaviridae, and while their spatial distribution does have overlap, the temporal patterns of the two are distinct. The *Aedes albopictus* mosquitoes from multiple regions are quite competent in transmission of CHIKV, and generally are more competent in transmission of CHIKV than DENV. *Aedes albopictus* has a broader range across climatic conditions than *Aedes aegypti* (Brady et al. 2014; Turell et al., 1992). Now, it has

established itself globally, so the possibility of outbreaks in more temperate conditions, though still generally low, is higher for CHIKV (Kucharz and Cebula-Byrska, 2012; Bonizzoni et al., 2013; Manni et al., 2017). By comparing the exogenous factors associated with outbreaks of the two viruses across a significant time period, we expect to reveal general patterns of emergence that can help explain these two specific examples of expanding MBDs, and provide insights about the potential for expansion of other mosquito-borne viruses.

The objectives of this analysis are twofold. First, we described the spatial and temporal patterns of outbreaks of illness from DENV and CHIKV after the end of World War II in 76 nations centered on continents that border the Indian Ocean. Second, we have assessed the characteristics of these nations relative to their temporally concurrent outbreaks (or endemic status) of dengue and of chikungunya. By doing so, we provided a basis for comparison of the biological and social factors that might influence the spread of both the vector mosquitoes and the viruses, during a period of increasing cases from 1965 to 2009.

2. Materials and methods

2.1. Dengue and chikungunya outbreaks dataset

We developed an outbreak occurrence dataset that included an indication of outbreaks (or continuing endemic status) of dengue and chikungunya for each year from 1952 to 2009. For the sake of simplicity and ease of communication, we refer henceforth to the event of interest as an "outbreak" and use it to denote the observed presence of locally acquired CHIKV or DENV in a country in a year. Our definition did not consider the size of outbreaks, and reports of one to three cases were not included. A nation with hyper-endemic condition of ongoing annual dengue disease cases was considered in outbreak status from that point on. We also did not distinguish among dengue serotypes, because those data are very rare, especially in the older records.

The study region comprised 76 nations stretching from Africa to Australia, generally focused on the Indian Ocean (See Supplementary material: Appendix A and Figure 1). The status of each nation for each year was determined by a two-stage review of literature, supplemented by records from the regional offices of the World Health Organization and review of health data from national health ministries, when accessible. The first stage of the review was a search in the National Center for Biotechnology Information PubMed citations database on terms that showed papers about the history of the presence of chikungunya or dengue cases globally. This returned 63 documents. A second review focused specifically on searches that included the names (including prior names when those changed) of the 76 nations of interest and resulted in 84 additional papers. The review emphasized tables and maps that indicated places where dengue or chikungunya were reported. Finally, we consulted the World Health Organization regional data records for the African, Eastern Mediterranean, the South-East Asian and the Western Pacific regions and used these to both review and supplement the material from the literature. The outcome of interest indicated whether a given nation recorded an outbreak of illness in a given year or not. For the complete list of the evaluated documents and the datasets used, see Supplementary material: Appendix A.

2.2. Statistical Analysis

We first evaluated the pattern of outbreaks by place, time, and the annual co-occurrence across nations using graphs and GIS mapping (Esri, ArcGIS). We then developed two groups of statistical models, with outbreaks from DENV and CHIKV analysed separately: 1) the co-occurrence of outbreaks in pairs of nations (co-occurrence models), and 2) the outbreaks relative to factors associated with each nation (nation-specific models). The statistical analyses focused on the years from 1965 to 2009, when data on the selected covariates were available consistently for all of the nations under consideration. The co-occurrence model was designed to reveal the factors driving the spatio-temporal patterns of the two viruses through an assessment of characteristics between countries that had co-

occurrences of outbreaks of the viruses in a given year. To develop the co-occurrence models, we divided the binary yearly outbreaks time series into nine 5-year periods, from 1965 to 2009, and in each time period we calculated the number of years outbreaks co-occurred in each possible pair of countries during that 5-year period (from a minimum of 0, to a maximum of 5). The nation-specific models, on the other hand, aimed to determine the factors best able to predict the number of outbreaks of dengue and chikungunya across the observed region based on characteristics of the nations across time. For this analysis, we considered the yearly occurrence of outbreaks in each country during the entire observation period.

Boosted regression tree (BRT) methods were used to fit all models. The boosting technique uses a machine learning algorithm to produce a final prediction model that is an ensemble of individual regression trees in a stage wise fashion: the original data are fitted with a first regression tree, and then the residuals of that first model become the input data on which the second tree is fitted, and so on (Conley et al., 2014). One important feature of this type of model is that data are weighted repeatedly in each re-fitting on the previous tree residuals. In this way, the misclassified points in previous trees, have more weight than values that were classified correctly in the following fit. The learning rate controls the contribution of each tree to the final model (Conley et al., 2014). For the co-occurrences model we used a BRT model with a 10 fold cross-validation, with the BRT model parameters of learning rate, tree complexity, and bag fraction set as suggested by Elith et al. (2008). Boosted regression uses cross validation to minimize over-fitting by determining when adding additional trees no longer improves predictive performance, and selecting that optimum number of trees. Because the co-occurrences data were counts, we specified a Poisson type of model for the dependent variable, as done by Ashby et al. (2017). Each of the 5-year periods was treated as a separate model.

In the nation-specific model, the BRT approach was used as described above, but the form of the model was logistic regression, in which the probability that an outbreak of disease occurred in

nation *i* and year *y* (with corresponding covariates $Z_{i,y}$) corresponded to $P(DEN_{i,y}=1|Z_{i,y})$ or $P(CHIK_{i,y}=1|Z_{i,y})$ and was modelled with a logit function. To develop the nation-specific models, the dataset was divided in two parts: a first training part included data for 26 out of the 76 nations. The other 50 nations were used to test the model results. We repeated this procedure 50 times, in order to reduce the stochastic effect due to the nations' selection. The nation-specific models were evaluated against the observed data using point biserial correlation (Bahn and McGill, 2013), Test COR, between the observed values and the predicted probability ("polycor" package, R Core Team 2016), and the Bernoulli deviance (i.e. Test dev) that measured the residual deviance between the predicted values of the model and the observed values of the test data ('dismo' package, Hijmans et al., 2013). All BRT models were fitted in R using the 'gbm' and 'dismo' libraries (Hijmans et al., 2013; Ridgeway, 2013).

2.2.1. Covariates for the co-occurrence models

For the co-occurrence models, all covariates measured factors that compared nation pairs (Table 1). With the exception of the data for geographical and historical factors, which did not vary over time, we calculated the 5-year period averages for each of the other factors to fit the same time-step as the co-occurrence measures. Population counts and density, gross domestic product (GDP), and climatic data were all originally found at the year/country resolution.

First, we considered geographical and historical factors using data retrieved from the French research centre CEPII dataset (Meyer and Zignago, 2011). These factors were invariant through time including: the *geographical distance* between each pair (DIS) calculated as the distance between capital cities; *contiguity* (CON), a binary variable coded as 1 if two countries shared a border, 0 otherwise; *common colonizer* or *formerly part of the same country* (CCO), a binary variable set to 1 if the two countries were under the rule of the same colonizing nation or had been part of the same country in the past, 0 otherwise; *common language* (CLA), a binary variable set to 1 if the two countries have a common language among the two most commonly spoken, 0 otherwise.

196 Second, we considered climatic factors. We first retrieved the yearly average temperature
197 (TEM) and precipitation (PRE) for each nation from the Climate Data API (World Bank). To compare
198 the countries with respect to these factors, we computed a climate similarity index *CLI*. This was
199 simply the Euclidean distance between countries in a space where TEM and PRE were the dimensions,
200 following Tatem et al. (2006). In order to properly balance the effect of the two, both TEM and PRE
201 were rescaled to a 0–1 range.

202 Third, we used the Gross Domestic Product as a measure of wealth of each nation to calculate
203 the difference between each pair of countries (DWE). Finally, we incorporated two demographic
204 variables: human population density (DEN) and migration flow (MIG). To compare the pairwise effect
205 of density, we used a gravity model variable (DEG) based on distance and density (Cauchemez et al.,
206 2014). Specifically the index between countries *i* and *j* was calculated as:

207 $$DEG_{ij} = \frac{DEN_i \, x \, DEN_j}{DIS_{ij}^2} \quad . \qquad (1)$$

208 Net migration data were already in the form of bilateral flows (Abel 2013; Abel and Sander
209 2014), between the nation pairs. Because the original data for 1960-1999 (Abel 2013) were an estimate
210 of the net migratory flows for 10-year-periods between each pair of countries, we halved the 10-year
211 periods values between 1965 and 1989. We were able to keep the original flow values, estimated over
212 5-year periods from 1990 to 2009 (Abel and Sander 2014).

213 *2.2.2 Covariates for the nation-specific models*

214 The nation-specific models included eight covariates measured for each nation over time. First,
215 we collated the DEN, TEM, PRE, and GDP for each nation as described above, maintaining the
216 original yearly values. As a measure of international migration, we used the yearly total of incoming
217 and outgoing flows (MIG_i and MIG_o, respectively). To obtain those yearly values, we divided all nation
218 pairs' 10-year or 5-year flows by ten and five, respectively, and then summed all the incoming and

outgoing yearly migration values in which the 76 nations included in this study were listed both as an origin and a destination.

In order to address the temporal autocorrelation of disease outbreaks we introduced two indices, each computed separately for dengue and chikungunya. The first was a binary covariate that indicated whether the nation was exposed to an outbreak in the previous year, *PRY* (equal to 1 for year T if an outbreak was observed in year T-1, 0 otherwise). The second index was used to quantify the external "force of infection" (ESI), based on other nations' previous year outbreak status. For this index, we followed Cauchemez et al. (2014) using a gravity model approach. In particular, for nation *i* and year *y* the index was calculated as:

$$ESI_{i,y} = \sum_{j \neq i}^{T} \left(\frac{V_{j,y-1} \times DEN_{j,y-1} \times DEN_{i,y-1}}{DIS_{ij}^2} \right), \quad (2)$$

in which $V_{j,y-1}$, $DEN_{j,y-1}$, and $DIS_{j,y-1}$ correspond to the outbreak status of the previous year in all nations $j \in \mathbf{T} \neq i$, population density (#individuals per squared km), and between-country distance (in km; see Table 1), respectively.

We also aimed to understand the particular importance of the two indices, PRY and ESI, relative to the ability of the model to predict the occurrence of the dengue and chikungunya outbreaks for a given year. Thus, we ran the following five models for each disease with the exclusion of PRY (models 2 and 4) and/or ESI (models 3 and 4) as described below:

1. The complete model (C) included all eight covariates (DEN, TEM, PRE, GDP, MIG_i, MIG_o, PRY, ESI);
2. The second model (W) included seven covariates and excluded the external force of infection (DEN, TEM, PRE, GDP, MIG_i, MIG_o, PRY);

3. The third model (E) excluded the nation's previous state (*PRY)* but included the external force of infection (DEN, TEM, PRE, GDP, MIG_i, MIG_o, ESI);

4. The fourth model (N) excluded both types of prior states, internal and external (DEN, TEM, PRE, GDP, MIG_i, MIG_o);

5. Finally, the fifth model consisted of a simplified (S) model, developed by starting from the complete model (C) and then dropping the non-influential covariates following Elith et al. (2008).

3. Results

Dengue outbreaks were recorded in 38 of the 76 nations under consideration during the study period from 1952 to 2009, and there were between 1 and 45 years of co-occurrence among nation pairs during that period. Outbreaks occurred in East and Southeast Asian nations throughout the entire period, but only Singapore and Thailand had outbreaks in all 45 years. South and Central Asian countries experienced dengue outbreaks consistently in the period from 1962 to 1972, then again starting in 1988 and continuing to the present (Figure 1). Sri Lanka had the most years of outbreaks for the South Asian region, for a total of 32 years. Only a few African nations had outbreaks, with only Nigeria, Djibouti, Somalia, and the Seychelles with four or more years of outbreaks.

Chikungunya outbreaks were recorded in 34 of the 76 nations during the period from 1952 to 2009, and there were from 1 to 5 years of co-occurrence during the 45-year study period. The five nations with 9 or more years of outbreaks recorded included Indonesia, Malaysia, Thailand, South Africa, and India, but African nations were represented in higher proportion than other regions and compared to dengue in most of the period (Figure 1). South Africa, Reunion, and Democratic Republic of the Congo were the three African nations with the highest number of years of outbreaks, with 10, 5,

and 5 years, respectively.

3.1. Co-occurrence models

The dengue co-occurrence models were stable, and the percentage of the explained deviance obtained with the 10-fold cross validation was between 40% and 80%, with the highest explained deviance in models for the periods from 1975-1979 and from 1995-1999 (Figure 2). The most important covariate was the gravity index (DEG), whereby nations that were closer together geographically and had higher population density had more instances of dengue co-occurrence (Figure 2). This result was consistent across all time periods, but the effect size declined over time. As expected, the partial dependencies plots (Supplementary material: Appendix B) showed that DEG generally had a positive effect on the number of co-occurrences. The geographical distance (DIS) and GDP difference (DWE) both were important in the dengue model. For DIS, the effect was negative at distances greater than 5,000 km, but was variable when closer than that. For DWE, the effect was positive for differences close to zero, but when differences were large; co-occurrence was variable.

The results of the co-occurrence models for chikungunya outbreaks indicated that the most important covariates were DIS, DEG and climatic distance (CLI). This model was not stable over time, however, with the explained CV deviance less than 40% in all but the final time period (2005 – 2009), and with the period 1990-1994 without any co-occurrences (Figure 3). The partial dependencies plots (Supplementary material: Appendix B) reflect this instability as well, showing very different patterns for each covariate, depending on the 5-year period. We thus developed eight annual models for a period restricted to 2002 to 2009. As with the first chikungunya model, the most important covariates were DEG, DIS and CLI, with DEG being especially important in the years with the most outbreak activity. As seen with the first chikungunya analysis, the stability of the analysis increased when the annual number of outbreak observations increased (Figure 4).

3.2. Nation specific models

For all five versions of the nation specific models for dengue, no single model outperformed the others if we take into account only the area under the receiver operating characteristic curve (AUC) of the cross validation (Figure 5, A). However, by considering the AUC that resulted from the independent test, models W and N were notably weaker. These two weak models did not include the external force of infection from other countries (ESI), while the weakest model, N, had neither ESI nor PRY (Figure 5, B). In agreement with this result, the same two models produced the lowest correlated result relative to the observed dengue outbreaks occurrence values (Figure 6, A). Among all models, the complete model produced the best results.

The chikungunya nation-specific models produced similar results to the dengue models (Figure 5, C and D). However, the prediction power was lower (Figure 6, B). As for DEN, the complete model was the best for the chikungunya analysis, but this result was not as clear as for dengue. For both of the complete models, the ESI index, measuring the external force of infection, had the highest relative contribution (Figure 7, A and B), while the other covariates played a relatively minor role.

The simplified (S) version of the nation-specific models automatically withdrew the less influencing covariates from the complete model. In the case of dengue, PRY was withdrawn 38 of 50 times, followed by TEM (16), DEN (15), MIG_i (11), GDP (10), MIG_o (3), and PRE (2). ESI was never withdrawn. Similarly, in the S models for chikungunya, ESI was never withdrawn, while PRY was withdrawn 40 times, followed by TEM (25), GDP (23), DEN (17), MIG_o (15), MIG_i (11), and PRE (3). Those numbers were reflected in the relative contribution provided by each covariate in the complete model (Figure 7).

4. Discussion and Conclusions

The main objectives of this work were to: (i) show how dengue and chikungnuya spread across

311 the Indian Ocean region during the time period following World War II, and (ii) provide an estimate of
312 which factors might have facilitated this spread. From the analysis of outbreak co-occurrences, we
313 learned that dengue and chikungunya outbreaks were more likely to take place between pairs of nations
314 that were relatively close to each other and had high population densities (DEG). This factor, based on
315 the gravity model concept, had considerably more importance than simple contiguity. Considering
316 chikungunya during the years from 2002 to 2009, DIS had higher relative importance than DEG during
317 the years when fewer nations reported outbreaks, but DEG and DIS had about the same level of
318 importance during years when more nations had outbreaks. This indicates that in the years when
319 chikungunya was less widespread, proximity to another nation with an outbreak was a risk factor, but
320 during years with higher levels of outbreaks, having both high population density and being nearer to
321 other nations with high population density increased risk.

322 The external force of infection index (ESI), used in the nation-specific models, was a similar
323 measure to DEG, but it also included the effect of the number of proximate nations with outbreaks in
324 the prior year. Compared to DEG, ESI was much more clearly important relative to the other variables
325 considered for both dengue and chikungunya annual outbreaks, and was even more important than the
326 information about an outbreak within the same nation in the previous year (PRY*)*. Because this index
327 was built with information about both population density and distance, it might act as a proxy for non-
328 observed variables, such as the number of travellers or shipped goods. In fact, while travelling can
329 move infectious individuals and spread pathogens to favourable landscapes, shipping can move both
330 infected people and vectors residing within containers, on ships, or in other transport equipment (Tatem
331 et al., 2006). Given the absence of these types of data, we also used historical/anthropological
332 variables, such as the common language, and common colonizer as covariates. The rationale behind
333 this choice was that countries with languages in common or that were part of the same nation in the
334 past might have more connections, or that this would be a facilitation for the movement of people and

goods. However, these variables did not prove important for any of our models. A more direct measure of movement of goods would have improved our ability to assess this, but our analysis went back to the 1960s, and unfortunately, reliable, comprehensive datasets on flight connections, passenger numbers, shipping volumes and boat routes were not available for the entire study period. These types of data may be a further step for analysis of the more recent years, and could add more depth and precision in the analysis of that time period.

Our regression analyses spanned 45 years, from 1965 to 2009. Data on the subsequent years (to 2011) were available for the presence/absence of dengue and chikungunya, however not all covariates were available (migration) or available in the same format (temperature and precipitation). Thus, we elected not to run different models at different points in time, as the comparison of the same factors through time was one of the key features of this work. For the same reason, we did not consider such data as the number of flying passengers, which can be found online for recent periods only. The choice of considering 5-years long periods in the co-occurrence model was very important for the analysis, because we minimized the time periods in which it was not possible to run the models due to no outbreak co-occurrences, as would have happened by considering a year-to-year time series. As indicated by the results, when the number of co-occurrences was low, the analysis lost power.

The precise definition of an outbreak year required subjective judgement, while the variability of surveillance consistency and the changing contemporary interest by the research community would have influenced the amount of information available for our review. By focusing systematically on only the 76 nations in question and having three members of the team come to conclusions both independently and through discussion, we reduced this problem. Moreover, given the above described issues, by considering the binary time series per country (presence/absence of dengue and chikungunya), our data gain temporal and spatial homogeneity, as the case reporting rates were very different at different points in time, and in different countries characterized by widely different

surveillance practices and level of research effort. On the one hand, this assumption might lead to bias because we neglected the number of cases, but on the other hand we gained in consistency across time, and that was a fundamental point of the analysis.

The WHO DengueNet was originally considered as a primary source of information for dengue outbreaks, but while it is a valuable resource to determine the status of dengue in a nation, completeness is inconsistent globally (Ruberto et al., 2015). Endemic status was another difficulty. While it is not difficult to identify a clear outbreak, such as chikungunya in Reunion Island in 2006 or Kolkata in 1963, identifying endemic dengue in light of both undercounting of cases and neglect of data can be problematic. India provides an important example: from the late 1980's on, our assessment was that India had dengue outbreak status every year, even though the years from 1997 to 2000 had relatively low numbers of reported cases compared to the years before and after (Chakravarti et al., 2012). We made this assessment because the total reported cases during those low years were still in the high hundreds of cases and the number of reported cases was most likely consistently under reported (Bhatt et al., 2013). This also illustrates a limitation on the designation of the “nation” as the observational unit. India’s outbreaks took place over a dispersed population, and variability in such a large, ecologically diverse and highly populated nation could be as important as between smaller nations, or even more. Another issue we had regarded but were not able to account for were the four different serotypes of DENV: only more recently have government reports and published literature included these consistently, but most often our sources did not report the serotype involved in each outbreak. Thus, we could not develop individual outbreak data or analyse the four serotypes separately.

Dengue infections have continued to increase globally since the end year of our analysis in 2009, and today, the WHO considers at least 100 countries globally to have endemic transmission (WHO 2017). Chikungunya has likewise expanded since 2009 (Petersen and Powers 2016). Our analysis approach was appropriate for conditions of newly emerging or intermittent outbreaks, but

more detailed data are needed to determine the dynamics of the spread of dengue in recent years. In the absence of more complete and refined surveillance data on vector-borne diseases, the processes that lead to expansion of MBDs will remain incomplete.

The development of the covariates also required decisions and assumptions. For example, we built the two indexes (DEG and ESI) using the population density instead of the rough number of individuals. Our reasoning was twofold. First, the nations of interest had a wide population and area size range, so the number of individuals might not be very representative of actual crowding. Second, we detected a higher correlation between population and migration flows (0.67, $p < 10^{-3}$), than between density and migration flows (0.23, $p < 10^{-3}$). Thus, we chose the latter, population density, in order to reduce potential multicollinearity effects. For similar reasons, we chose the distance between capitals instead of the distance between the centre of each country, because the capital city might be more representative of the population distribution in heterogeneous countries. On the other hand, the two distances were very similar (correlation 0.99, $p < 10^{-2}$), and early exploratory models run with both showed no difference. The choice of using boosted regression tree technique was very important as well. Thanks to this technique, we could use different types of covariates with no need to transform them. Also, the interpretation of BRT results is generally very intuitive, and models include the potential interactions of covariates, without having explicitly to account for them, such as in classical logistic regression. Finally, machine learning techniques such as BRT can be easily re-applied to similar datasets, and their use is expanding in the epidemiological context.

In conclusion, our results highlighted trends found in both dengue and chikungunya outbreaks in the Indian Ocean region. In particular, the density of populations and less distance between outbreaks were dominant factors in the occurrence of those diseases, as found generally for emerging infectious diseases (Jones et al., 2008). We also found that outbreaks in neighbouring countries provided a good prediction of local outbreaks for both diseases. The relative importance of these

factors may reflect the higher probability of both vectors or infected people moving between countries as well the propensity for nearby nations to have similar climatic conditions. Even with increased global movement of people and goods, the ideas behind the gravity indexes were clearly important. In a similar vein, Cauchemez et al. (2014) found that distance between countries was a better predictor of chikungunya spread in the Caribbean than air transportation. Our analysis also highlighted how the boosted regression trees (BRT) approach can be used for both paired variables in the co-occurrence model as well as for the prediction model by nations.

The incorporation of data from available sources and further analyses in this direction will help the scientific community in reaching a comprehensive picture about the global spread of vector-borne diseases. This will help Ministries of Health, the WHO, and other agencies to more effectively allocate resources (i.e. financial, research, workforce) to prioritize those situations where conditions make outbreaks most likely in order to limit the diffusion of these epidemics.

Acknowledgements

The authors thank Stephanie Mundis who provided valuable help in carrying out the first review of the papers.

References:

1. Abel, G. J. 2013. Estimating global migration flow tables using place of birth data. Demographic Research 28: 505-546.
2. Abel, G. J., and N. Sander. 2014. Quantifying Global International Migration Flows. Science 343: 1520-1522.
3. Ali, S., O. Gugliemini, S. Harber, A. Harrison, L. Houle, J. Ivory, S. Kersten, R. Khan, J. Kim, C. LeBoa, E. Nez-Whitfield, J. O'Marr, E. Rothenberg, R. M. Segnitz, S. Sila, A. Verwillow, M. Vogt, A. Yang, and E. A. Mordecai. 2017. Environmental and Social Change Drive the Explosive Emergence of Zika Virus in the Americas. PLoS neglected tropical diseases 11: e0005135.
4. Amraoui F., A. B. Failloux. 2016. Chikungunya: an unexpected emergence in Europe. Current Opinions in Virology 21:146–150. doi:10.1016/j.coviro.2016.09.014.
5. Ashby, J., M. J. Moreno-Madriñán, C. T. Yiannoutsos, and A. Stanforth. 2017. Niche Modeling of Dengue Fever Using Remotely Sensed Environmental Factors and Boosted Regression Trees. *Remote Sensing 9:* 328. doi: 10.3390/rs9040328
6. Bahn V, B. J. McGill. 2013. Testing the predictive performance of distribution models. Oikos 122:321–331. doi:10.1111/j.1600-0706.2012.00299.x.
7. Bastian, M., S. Heymann, M. Jacomy. 2009. Gephi: an open source software for exploring and manipulating networks. In: International AAAI Conference on Weblogs and Social Media, San Jose, California. ISWSM.
8. Bhatt, S., P. W. Gething, O. J. Brady, J. P. Messina, A. W. Farlow, C. L. Moyes, J. M. Drake, J. S. Brownstein, A. G. Hoen, O. Sankoh, M. F. Myers, D. B. George, T. Jaenisch, G. R. Wint, C. P. Simmons, T. W. Scott, J. J. Farrar, and S. I. Hay. 2013. The global distribution and burden of dengue. Nature 496: 504-507.
9. Bonizzoni, M., G. Gasperi, X. Chen, and A. A. James. 2013. The invasive mosquito species Aedes albopictus: current knowledge and future perspectives. Trends in parasitology 29: 460-468.
10. Brady, O. J., N. Golding, D. M. Pigott, M. U. Kraemer, J. P. Messina, R. C. Reiner, Jr., T. W. Scott, D. L. Smith, P. W. Gething, and S. I. Hay. 2014. Global temperature constraints on *Aedes aegypti* and *Ae. albopictus* persistence and competence for dengue virus transmission. Parasites & vectors 7: 338.
11. Brown, E. B., A. Adkin, A. R. Fooks, B. Stephenson, J. M. Medlock, and E. L. Snary. 2012.

Assessing the risks of West Nile virus-infected mosquitoes from transatlantic aircraft: implications for disease emergence in the United Kingdom. Vector borne and zoonotic diseases 12: 310-320.

12. Carey, D. E. 1971. Chikungunya and dengue: a case of mistaken identity? Journal of the History of Medicine 26: 243-262.
13. Cassadou, S., S. Boucau, M. Petit-Sinturel, P. Huc, I. Leparc-Goffart, and M. Ledrans. 2014. Emergence of chikungunya fever on the French side of Saint Martin island, October to December 2013. Euro surveillance: bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin 19.
14. Cauchemez, S., M. Ledrans, C. Poletto, P. Quenel, H. de Valk, V. Colizza, and P. Y. Boelle. 2014. Local and regional spread of chikungunya fever in the Americas. Eurosurveillance 19: 15-23.
15. Chakravarti, A., R. Arora, and C. Luxemburger. 2012. Fifty years of dengue in India. Trans.R.Soc.Trop.Med.Hyg. 106: 273-282.
16. Chang, C., K. Ortiz, A. Ansari, and M. E. Gershwin. 2016. The Zika outbreak of the 21st century. Journal of autoimmunity 68: 1-13.
17. Chevillon, C., L. Briant, F. Renaud, and C. Devaux. 2008. The Chikungunya threat: an ecological and evolutionary perspective. Trends in microbiology 16: 80-88.
18. Conley, A. K., D. O. Fuller, N. Haddad, A. N. Hassan, A. M. Gad, and J. C. Beier. 2014. Modeling the distribution of the West Nile and Rift Valley Fever vector Culex pipiens in arid and semi-arid regions of the Middle East and North Africa. Parasites & vectors 7.
19. Dash, A. P., R. Bhatia, T. Sunyoto, and D. T. Mourya. 2013. Emerging and re-emerging arboviral diseases in Southeast Asia. Journal of vector borne diseases 50: 77-84.
20. Donat, M. G., A. L. Lowry, L. V. Alexander, P. A. O'Gorman, and N. Maher. 2016. More extreme precipitation in the world's dry and wet regions. Nature Climate Change 6: 508-+.
21. Elith, J., J. R. Leathwick, and T. Hastie. 2008. A working guide to boosted regression trees. Journal of Animal Ecology 77: 802-813.
22. Esposito D. L. A., B. A. L. Da Fonseca. 2016. Zika and chikungunya infections in Brazil: Reviewing the epidemic and treatment options. Revista da Sociedade Brasileira de Medicina Tropical 49:535–536. doi:10.1590/0037-8682-0428-2016.
23. Faria N. R., J. Quick, I. M. Claro, J. Thézé, J. G. de Jesus, M. Giovanetti, et al. 2017. Establishment and cryptic transmission of Zika virus in Brazil and the Americas. Nature 546:406.

24. Greenwood, B. M., D. A. Fidock, D. E. Kyle, S. H. Kappe, P. L. Alonso, F. H. Collins, and P. E. Duffy. 2008. Malaria: progress, perils, and prospects for eradication. The Journal of clinical investigation 118: 1266-1276.
25. Gubler, D. J. 1998. Dengue and dengue hemorrhagic fever. Clinical microbiology reviews 11: 480-496.
26. Gurugama, P., P. Garg, J. Perera, A. Wijewickrama, and S. L. Seneviratne. 2010. Dengue viral infections. Indian journal of dermatology 55: 68-78.
27. Halstead, S. B. 1980. Dengue haemorrhagic fever--a public health problem and a field for research. Bulletin of the World Health Organization 58: 1-21.
28. Higgs, S. 2006. The 2005-2006 Chikungunya epidemic in the Indian Ocean. Vector borne and zoonotic diseases 6: 115-116.
29. Hijmans, R., S. Phillips, J. Leathwick, and J. Elith. 2014. Package 'dismo'. 2011.
30. Jones, K. E., N. G. Patel, M. A. Levy, A. Storeygard, D. Balk, J. L. Gittleman, and P. Daszak. 2008. Global trends in emerging infectious diseases. Nature 451: 990-993.
31. Kucharz, E. J., and I. Cebula-Byrska. 2012. Chikungunya fever. European journal of internal medicine 23: 325-329.
32. Lahariya, C., and S. K. Pradhan. 2006. Emergence of chikungunya virus in Indian subcontinent after 32 years: A review. Journal of vector borne diseases 43: 151-160.
33. Maciel-de-Freitas, R., F. C. Avendanho, R. Santos, G. Sylvestre, S. C. Araujo, J. B. Lima, A. J. Martins, G. E. Coelho, and D. Valle. 2014. Undesirable consequences of insecticide resistance following Aedes aegypti control activities due to a dengue outbreak. PloS one 9: e92424.
34. Mackenzie, J. S., and D. T. Williams. 2009. The zoonotic flaviviruses of southern, south-eastern and eastern Asia, and Australasia: the potential for emergent viruses. Zoonoses and public health 56: 338-356.
35. Manni, M., C. R. Guglielmino, F. Scolari, A. Vega-Rua, A. B. Failloux, P. Somboon, A. Lisa, G. Savini, M. Bonizzoni, L. M. Gomulski, A. R. Malacrida, and G. Gasperi. 2017. Genetic evidence for a worldwide chaotic dispersion pattern of the arbovirus vector, Aedes albopictus. PLoS Neglected Tropical Diseases 11: e0005332.
36. Marano, G., S. Pupella, I. Pati, F. Masiello, M. Franchini, S. Vaglio, C. Velati, and G. M. Liumbruno. 2017. Ten years since the last Chikungunya virus outbreak in Italy: history repeats itself. Blood transfusion = Trasfusione del sangue 15: 489-490.
37. Mayer, T., and S. Zignago. 2011. Notes on CEPII's distances measures: The GeoDist database.
38. Messina, J. P., O. J. Brady, T. W. Scott, C. Zou, D. M. Pigott, K. A. Duda, S. Bhatt, L.

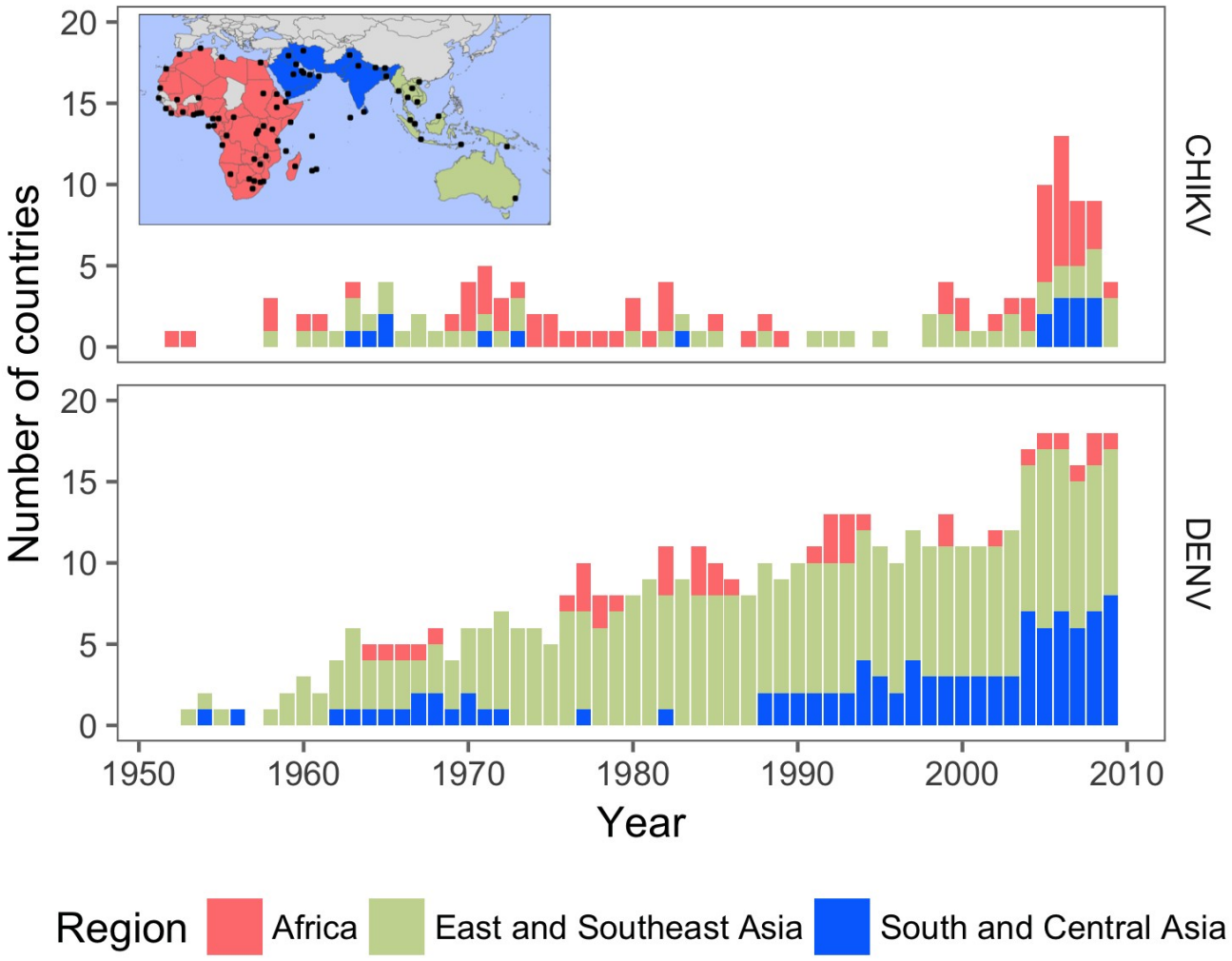
Katzelnick, R. E. Howes, K. E. Battle, C. P. Simmons, and S. I. Hay. 2014. Global spread of dengue virus types: mapping the 70 year history. Trends in microbiology 22: 138-146.

39. Monath, T. P. 1994. Dengue: the risk to developed and developing countries. Proceedings of the National Academy of Sciences of the United States of America 91: 2395-2400.
40. Moncayo, A. C., Z. Fernandez, D. Ortiz, M. Diallo, A. Sall, S. Hartman, C. T. Davis, L. Coffey, C. C. Mathiot, R. B. Tesh, and S. C. Weaver. 2004. Dengue emergence and adaptation to peridomestic mosquitoes. Emerging infectious diseases 10: 1790-1796.
41. Moreno-Madriñán, M. J., M. Turell. 2017. Factors of concern regarding Zika and other *Aedes aegypti*-Transmitted viruses in the United States. Journal of Medical Entomology 54: 251-257. doi: 10.1093/jme/tjw212.
42. Naish S., P. Dale, J. S. Mackenzie, J. McBride, K. Mengersen, S. Tong. 2014. Climate change and dengue: a critical and systematic review of quantitative modelling approaches. BMC Infectious Diseases 14:167. doi:10.1186/1471-2334-14-167.
43. Patz, J. A., P. R. Epstein, T. A. Burke, and J. M. Balbus. 1996. Global climate change and emerging infectious diseases. JAMA: the journal of the American Medical Association 275: 217-223.
44. Petersen, L. R., and A. M. Powers. 2016. Chikungunya: epidemiology. F1000Research 5.
45. Ridgeway, G. 2007. Generalized Boosted Models: A guide to the gbm package. Update 1: 2007.
46. Roth, A., A. Mercier, C. Lepers, D. Hoy, S. Duituturaga, E. Benyon, L. Guillaumot, and Y. Souares. 2014. Concurrent outbreaks of dengue, chikungunya and Zika virus infections - an unprecedented epidemic wave of mosquito-borne viruses in the Pacific 2012-2014. Euro surveillance: bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin 19.
47. Ruberto, I., E. Marques, D. S. Burke, and W. G. Van Panhuis. 2015. The availability and consistency of dengue surveillance data provided online by the World Health Organization. PLoS neglected tropical diseases 9: e0003511.
48. Schrag, S. J., and P. Wiener. 1995. Emerging infectious disease: what are the relative roles of ecology and evolution? Trends in ecology & evolution 10: 319-324.
49. Simon, F., H. Savini, and P. Parola. 2008. Chikungunya: a paradigm of emergence and globalization of vector-borne diseases. The Medical clinics of North America 92: 1323-1343, ix.
50. Tatem, A. J., S. I. Hay, and D. J. Rogers. 2006. Global traffic and disease vector dispersal. Proceedings of the National Academy of Sciences of the United States of America 103: 6242-

6247.

51. Tatem, A. J., Z. Huang, A. Das, Q. Qi, J. Roth, and Y. Qiu. 2012. Air travel and vector-borne disease movement. Parasitology 139: 1816-1830.
52. Tjaden N. B., J. E. Suk, D. Fischer, S. M. Thomas, C. Beierkuhnlein, J. C. Semenza. 2017 Modelling the effects of global climate change on Chikungunya transmission in the 21st century. Scientific Reports 7:3813. doi:10.1038/s41598-017-03566-3.
53. Turell, M. J., J. R. Beaman, and R. F. Tammariello. 1992. Susceptibility of selected strains of *Aedes aegypti* and *Aedes albopictus* (Diptera: Culicidae) to chikungunya virus. Journal Medical Entomology 29: 49–53. doi: 10.1093/jmedent/29.1.49
54. Weaver, S. C. 2014. Arrival of chikungunya virus in the new world: prospects for spread and impact on public health. PLoS neglected tropical diseases 8: e2921.
55. Weaver, S. C., F. Costa, M. A. Garcia-Blanco, A. I. Ko, G. S. Ribeiro, G. Saade, P. Y. Shi, and N. Vasilakis. 2016. Zika virus: History, emergence, biology, and prospects for control. Antiviral research 130: 69-80.
56. Wood, C. L., A. McInturff, H. S. Young, D. Kim, and K. D. Lafferty. 2017. Human infectious disease burdens decrease with urbanization but not with biodiversity. Philosophical transactions of the Royal Society of London. Series B, Biological sciences 372.
57. World Health, O. 2017. Dengue and severe dengue: Fact sheet. *In* WHO [ed.], http://www.who.int/mediacentre/factsheets/fs117/en/.

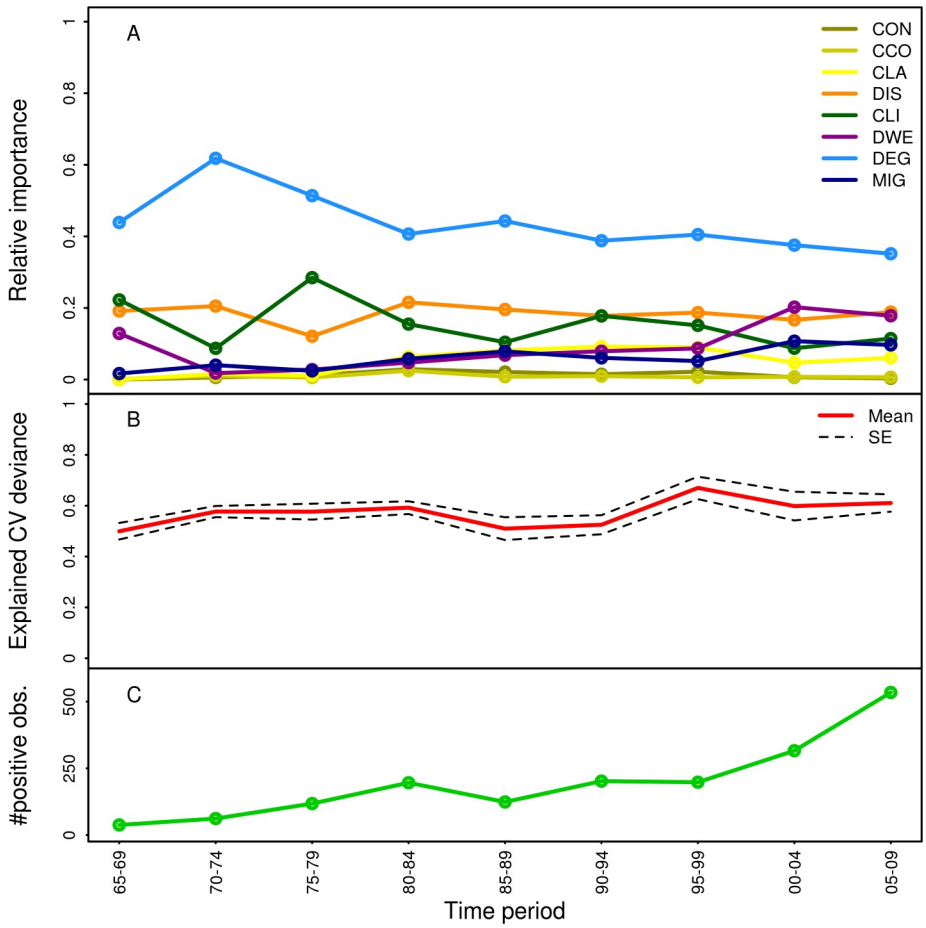
573 **Tables and figures captions**



575 **Figure 1**: The 76 nations included in the study, the capital cities used for distance metrics (map in the
576 top-left box) and the number of nations with an outbreak of chikungunya (top panel) and dengue
577 (bottom panel) for the years from 1952 to 2009. The green portion of the bars are nations in Oceania,
578 and in East and Southeast Asia, blue bars are in South and Central Asia and red bars are in Africa.

579

580



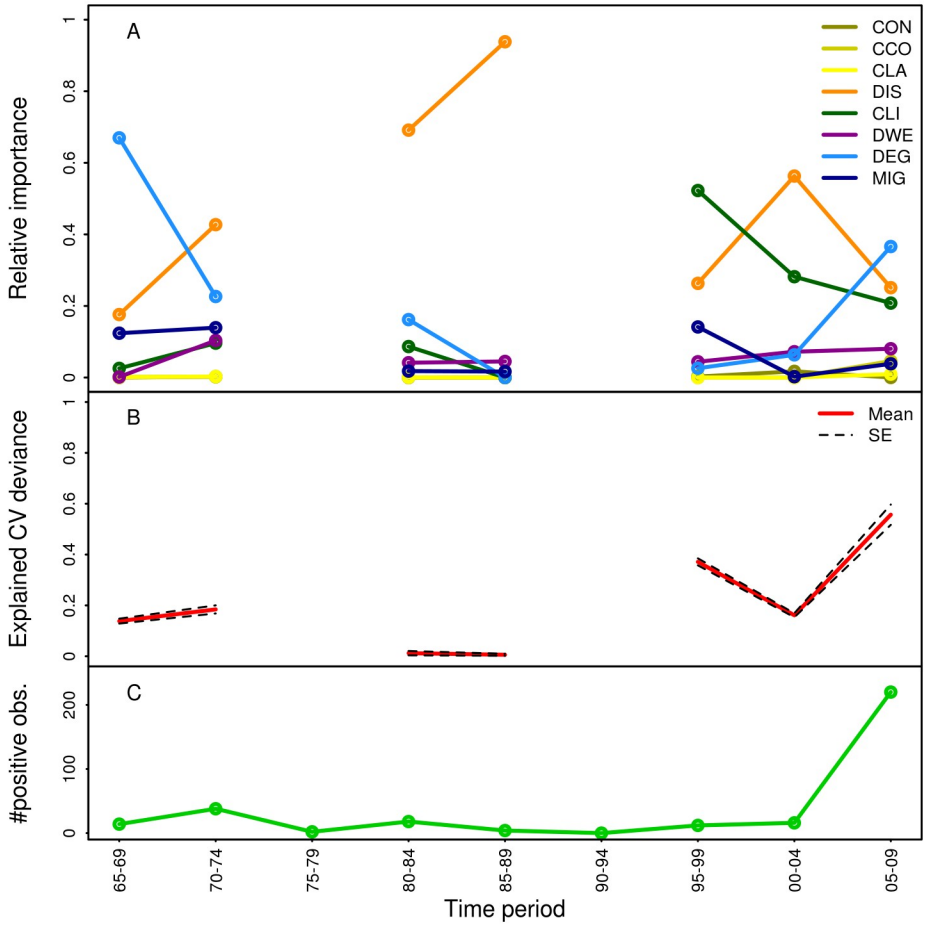
581 **Figure 2**: Analysis of the co-occurrences of dengue virus outbreaks within the Indian Ocean region
582 from 1965 to 2009. A) The different relative importance of the considered covariates (CON, territory
583 contiguity; CCO, common colonizer/part of the same country in the past; CLA, common language;
584 DIS, geographical distance; CLI, climatic distance; DWE,GDP/wealth distance; DEG, density gravity
585 index; MIG, migration), B) the fraction of the explained deviance by the 10-fold Cross Validation (CV)
586 process(mean, red solid line, and standard error, black dashed line), and C) the number of positive co-
587 occurrences in each 5-year period.

588

589

590

591



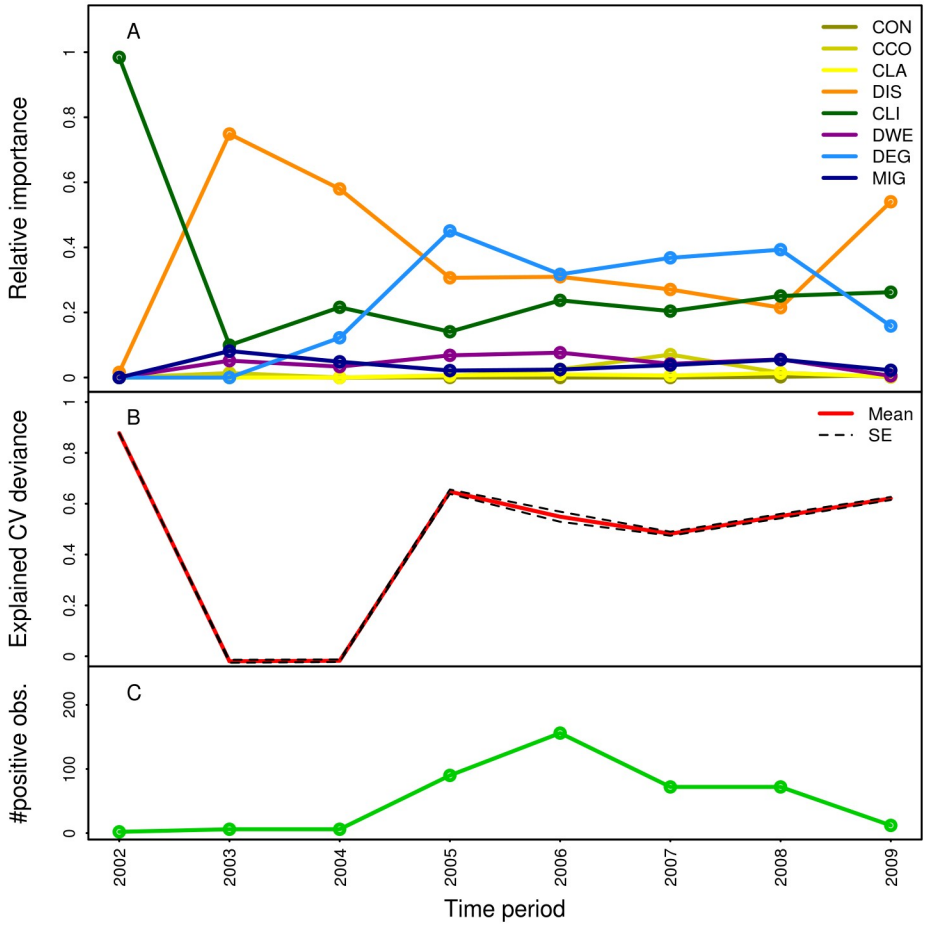
592 **Figure 3**: Analysis of the co-occurrences of chikungunya virus outbreaks within the Indian Ocean
593 region from 1965 to 2009. A) The different relative importance of the considered covariates (CON,
594 territory contiguity; CCO, common colonizer/part of the same country in the past; CLA, common
595 language; DIS, geographical distance; CLI, climatic distance; DWE,GDP/wealth distance; DEG,
596 density gravity index; MIG, migration), B) the fraction of the explained deviance by the 10-fold Cross
597 Validation (CV) process(mean, red solid line, and standard error, black dashed line), and C) the number
598 of positive co-occurrences in each 5-year period.

599

600

601

602

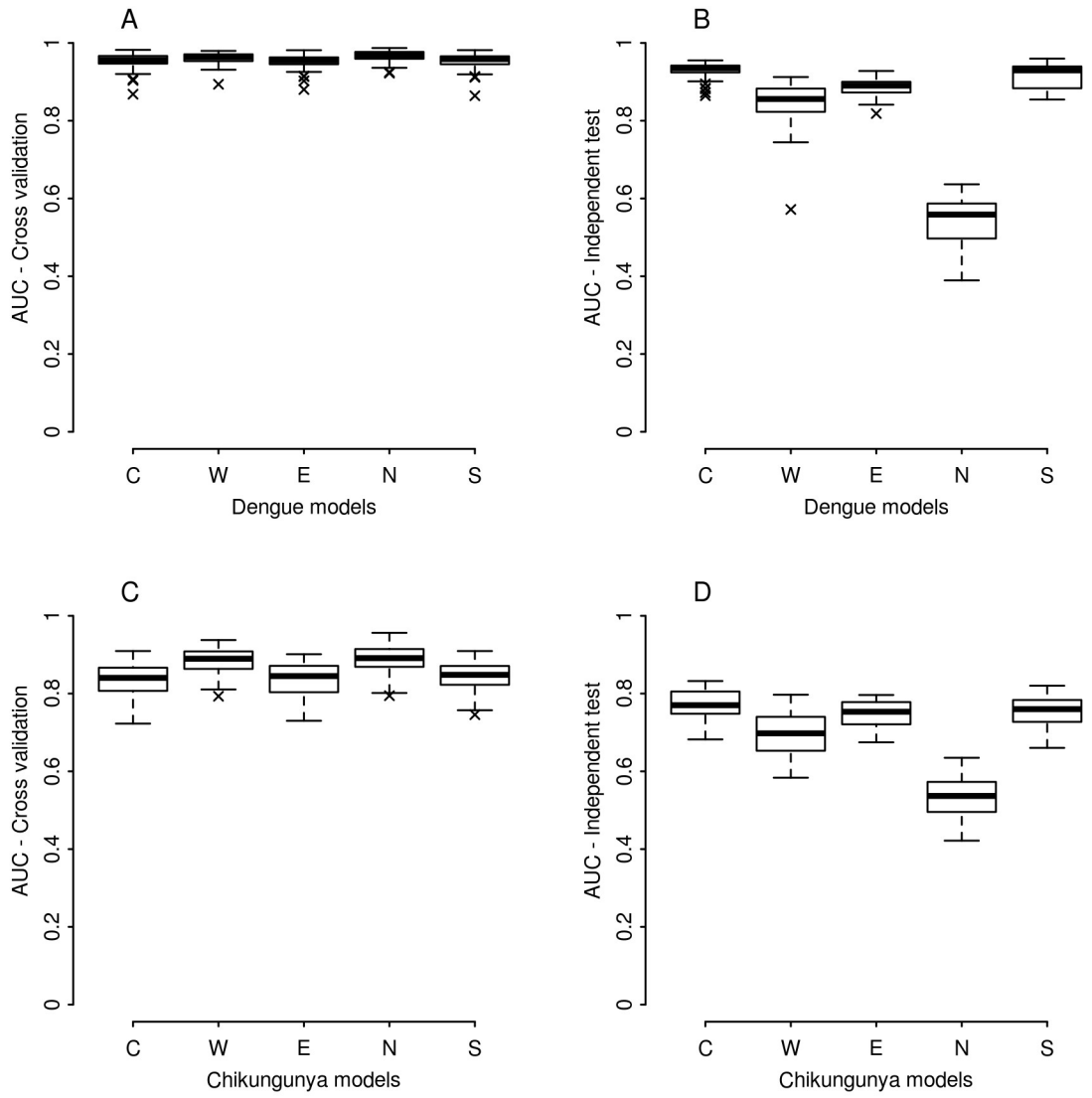


603 **Figure 4**: Analysis of the co-occurrences of chikungunya virus outbreaks within the Indian Ocean
604 region in years from 2002 to 2009. A) The different relative importance of the considered covariates
605 (CON, territory contiguity; CCO, common colonizer/part of the same country in the past; CLA,
606 common language; DIS, geographical distance; CLI, climatic distance; DWE,GDP/wealth distance;
607 DEG, density gravity index; MIG, migration), B) the fraction of the explained deviance by the 10-fold
608 Cross Validation (CV) process(mean, red solid line, and standard error, black dashed line), and C) the
609 number of positive co-occurrences in each 5-year period.

610

611

612



613 **Figure 5**: The Area under the receiver operating characteristic curve (AUC) in the analysed models:
614 complete (C), no external force of infection (W), no within-country previous status (E), no past
615 outbreak information (N), and simplified model (S). AUC in the cross-validation (CV, panels A and C),
616 and in the independent nation-specific test (panels B and D) for the five dengue (panels A and B), and
617 chikungunya (panels C and D) models. Boxplots represent the distribution of values for the 50
618 independent runs of the models, each time randomly selecting countries to be included in the training
619 dataset.

620

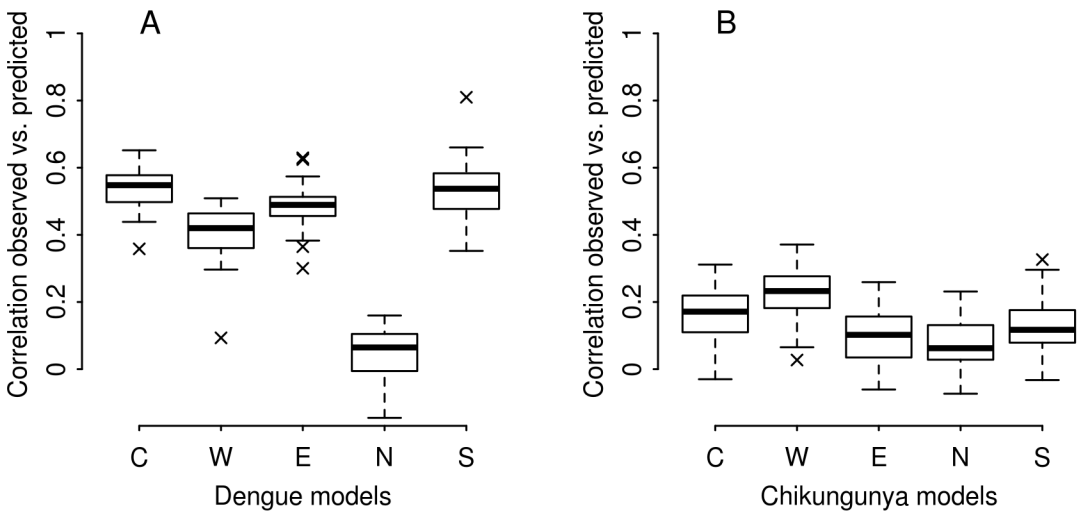
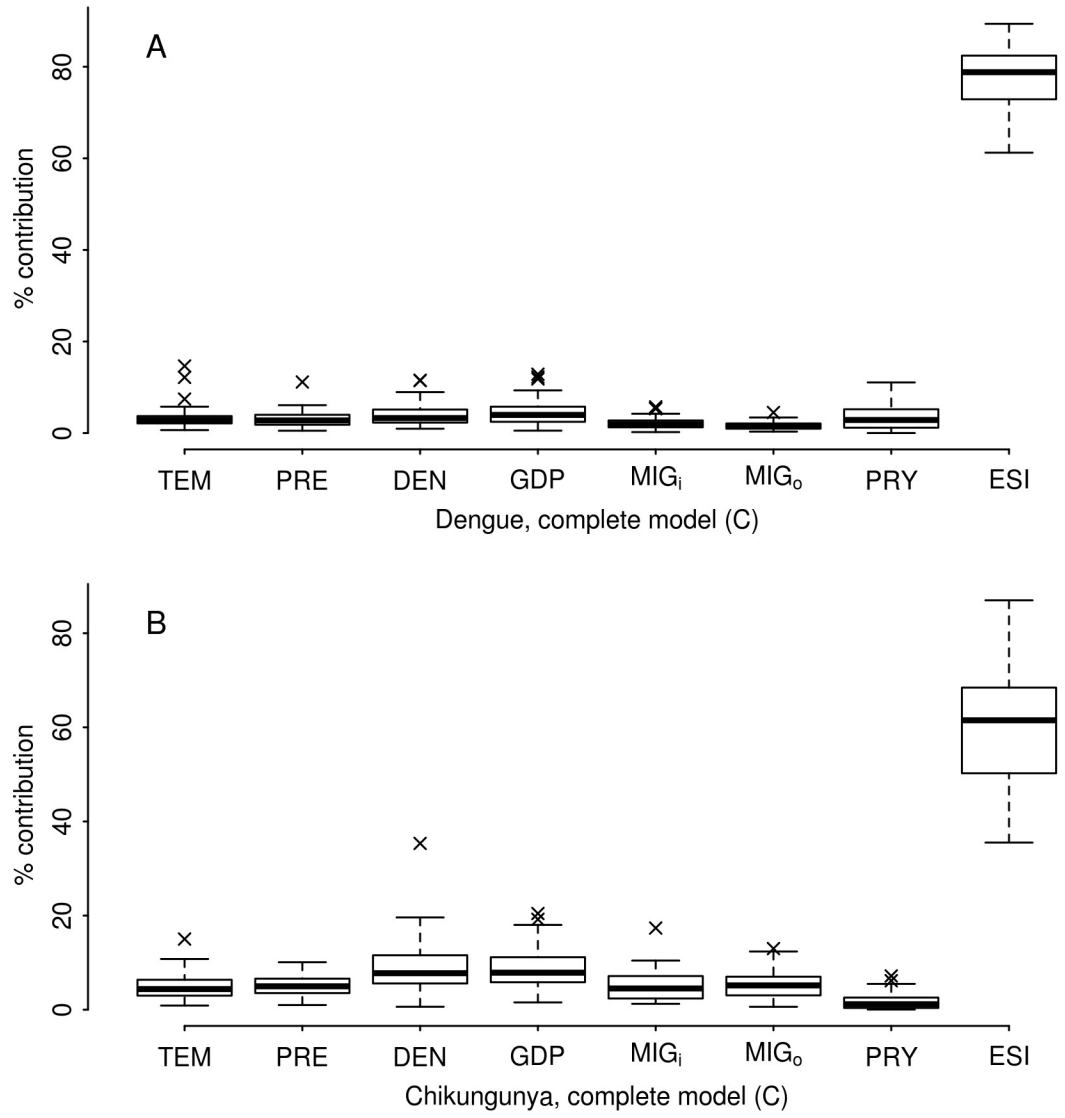


Figure 6: Point biserial correlation between the predicted and observed outbreaks occurrences values for the five dengue (panel A), and chikungunya (panel B) models: complete (C), no external force of infection (W), no within-country previous status (E), no past outbreak information (N), and simplified model (S). Boxplots represent the distribution of values for the 50 independent runs of the models, each time randomly selecting countries to be included in the training dataset.



627 **Figure 7**: Covariates contributions for the complete dengue (A) and chikungunya (B) models. Boxplots
628 represent the distribution of values for the 50 independent runs of the models, each time randomly
629 selecting countries to be included in the training dataset.

630

Co-variate data				
Factor	**Class**	**Units**	**Years**	**Source**
Mean temperature (TEM)	Climatic	°C	1901-2012	Climate Data API (https://datahelpdesk.worldbank.org/knowledge-base/articles/902061-climate-data-api)
Mean precipitation (PRE)	Climatic	mm	1901-2012	Climate Data API (https://datahelpdesk.worldbank.org/knowledge-base/articles/902061-climate-data-api)
Population (POP)	Demographic	#individuals	1966-2014	Data WorldBank (http://databank.worldbank.org/data/reports.aspx?source=world-development-indicators)
Mean pop. Density (DEN)	Demographic	#ind./km^2	1966-2014	Data WorldBank (http://databank.worldbank.org/data/reports.aspx?source=world-development-indicators)
Gross domestic product (GDP)	Economic	2005 USD	1960-2014	Data WorldBank (http://databank.worldbank.org/data/reports.aspx?source=world-development-indicators)
Migration (MIG)	Demographic	#individuals	1960-2009	Estimation in Abel 2013 and Abel 2014
Distance (DIS)	Geographical	km	-	CEPII (http://www.cepii.fr/)
Contiguity (CON)	Geographical	binary	-	CEPII (http://www.cepii.fr/)
Colonial/Language similarity (CCO/CLA)	Historic	binary	-	CEPII (http://www.cepii.fr/)

631

632 **Table 1**: Description and source of the selected covariates data.