



Infectious Diseases

Spatial quantification of the world population potentially exposed to Zika virus

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Abstract

Background: Zika virus is an emerging Flaviviridae virus, which has spread rapidly in the last few years. It has raised concern because it has been associated with fetus microcephaly when pregnant women are infected. The main vector is the mosquito *Aedes aegypti*, distributed in tropical areas.

Methods: Niche modelling techniques were used to estimate the potential distribution area of *A. aegypti*. This was overlapped with human population density, determining areas of potential transmission risk worldwide. Afterwards, we quantified the population at risk according to risk level.

Results: The vector transmission risk is distributed mainly in Asia and Oceania on the shores of the Indian Ocean. In America, the risk concentrates in the Atlantic coast of South America and in the Caribbean Sea shores in Central and North America. In Africa, the major risk is concentrated in the Pacific and Atlantic coasts of Central and South Africa. The world population under high and very high risk levels includes 2.261 billion people.

Conclusions: These results illustrate Zika virus risk at the global level and provide maps to target the prevention and control measures especially in areas with higher risk, in countries with less sanitation and poorer resources. Many countries without previous vector reports could become active transmission zones in the future, so vector surveillance should be implemented or reinforced in these areas.

Key words: ZIKV, *Aedes aegypti*, viral contagion risk, vectorial transmission, vector niche modelling, exposure level

Key Messages

- Zika virus (ZIKV) could be transmitted to 43.9% of the world population.
- Around 30.4% of the global human population could be under high or very high risk of ZIKV.
- Our model of the spatial distribution of *Aedes aegypti* includes tropical and subtropical areas from 35° north latitude to 35° south latitude in four continents.
- Some countries have more than 90% of their population under risk of being affected by ZIKV.

Introduction

The Zika virus (ZIKV) has generated global alarm. ZIKV is part of the family Flaviviridae; it was discovered in monkeys in 1947, and human cases were reported in Asia and Africa in the 1960s.¹ This virus is transmitted mainly by the bite of the mosquito *Aedes aegypti*, which has a global distribution.² *Aedes albopictus* is also a possible vector in laboratory experiments.³ *Aedes aegypti* has adapted efficiently to urban areas and feeds mostly indoors on humans, unlike *A. albopictus*, which is abundant in peridomestic habitats and feeds on a wide range of hosts, mainly mammals.⁴ ZIKV has been isolated from several species of mosquitoes,^{5–7} but their vector status remains to be investigated. ZIKV is maintained in a zoonotic cycle between arboreal *Aedes* spp. mosquitoes and non-human primates in African and Asian forests.⁷ The reports of ZIKV have increased since 2007, reaching a peak in 2015.^{8–10} The mechanisms of transmission involved, in addition to direct contact with the vectors, include blood transfusion, perinatal transmission and sexual intercourse.^{11–16} Human infection with ZIKV can present mild fever, rash, headache, joint pain, muscle pain, malaise and conjunctivitis in adult patients; in pregnant women, the fetus has a high risk of microcephaly.^{17–19}

Kraemer *et al.*²⁰ studied the distribution of the *A. aegypti* worldwide and identified the most suitable areas as tropical climate zones; Messina *et al.*²¹ recently mapped the global environmental suitability of ZIKV using niche modelling techniques with the global database of Kraemer *et al.*²⁰, proving its utility and corroborating the previous results. The risk of infection due to ZIKV has not yet been determined in a spatially explicit way, associating the presence of the mosquitoes and the human population. The probability of establishment and spread of an infectious disease depend in many ways on human factors such as sanitation, socio-economic condition (poverty) and access to health services, among others.^{22,23} The aim of our study was to assess the potential risk of ZIKV vector transmission at the global level, considering *A. aegypti* as the main vector, and to quantify the number of people exposed to contact with this vector.

Methods

Modelling of the vector distribution

We generated a potential environmental niche model for the vector, using the maximum entropy technique with MaxEnt Software V3.3.3k^{24,25}; linking spatially explicit environmental layers and records of the species, it extrapolates the sites where a species should be present. We used the elevation layer and 19 bioclimatic layers of the WorldClim project, both at 2.5 arc minute spatial resolution worldwide (approximately 5 km*5km cells). The occurrences of *A. aegypti* were taken from the Global Biodiversity Information Facility species database,²⁶ MosquitoMap²⁷ and Dryad.²⁰ The combined database included 20 203 occurrences.

The preliminary distribution of *A. aegypti* was modelled initially using all variables (19 bioclimatic plus elevation) with 15 replicates and 500 iterations each, using the cross-validation technique, calculating the variables' importance in the model. Using R 3.2.2 software, we evaluated the normality of the data with the Shapiro-Wilk test^{28,29}; then we determined the level of correlation between pairs of variables in the presence points using the absolute correlation coefficient.³⁰ The variables were selected according to their importance in the preliminary distribution model, taking into account that their correlation index had to be low (less than ± 0.7). The final model was generated using the cross-validation technique with 100 replicates and 500 iterations each, including seven selected variables, corresponding to a 95% confidence model generated from the replicates. Its adjustment was measured by the area under the curve metric (AUC).

Modelling of potential transmission risk for the population due to contact with the vector

We used the Population Density Grid, v3 of 2000, with 2.5 arc minute spatial resolution for the world (<http://sedac.ciesin.columbia.edu/data/set/gpw-v3-population-density>) generated by the Socioeconomic Data and Application Center (SEDAC) of NASA.³¹

We used a geographic information system (GIS) to link the probability of presence of the vector with the exposed

population. First, we reclassified the probability of presence of the vector, to convert the MaxEnt resulting grid with continuous information into a new discrete grid with levels of presence probability null, low, medium and high, using four equal intervals to assign the thresholds for each level. To evaluate the population at risk, the population density grid was classified in four levels: null (0–1 inhabitants/km²), low (>1–10 inhabitants/km²), medium (>10–100 inhabitants/km²) and high (more than 100 inhabitants/km²), assigning a value to each category (null = 0; low = 1; medium = 2; high = 3). The new discrete grids were multiplied using the Raster Calculator tool (Figure 1). With this product, we estimated the potential ZIKV transmission risk in levels from Null to Very high (Figure 1). Finally, we performed a geographic identification of the zones with major risk of transmission.

Quantification of the exposed human population

The levels of transmission risk were overlapped with a grid of population count by square kilometre. The population grid used was the Global Rural-Urban Mapping Project, Version 1 (GRUMPv1) of NASA.³² This corresponds to an estimate of the population in the year 2000, with a spatial resolution of 30 arc minutes (1 km). The number of inhabitants was counted by country according to level of exposure.

Results

Modelling the vector distribution

The final model had an AUC of 0.746 ± 0.016. None of the included variables had an absolute correlation index greater than 0.7 (Figure 2 and Supplementary Material 2, available as Supplementary Data at IJE online). The most important variables were the mean annual temperature, annual temperature range and precipitation of the wettest month, with 56.3%,

16.6% and 16.6% importance, respectively; these three variables contributed 89.5% to the probability of presence of the vector and 56.6% of the permutation importance in the model (Figure 2). The most suitable conditions for *A. aegypti* corresponded to high temperatures, with a peak between 18° and 22°C; with low variation of the temperature amplitude, less than 20°C annual range of temperature; and high levels of precipitation, increasing asymptotically, reaching a peak at 600-mm precipitation in the wettest month (Figure 3). The spatial distribution of this mosquito includes tropical and subtropical areas from 35° north latitude to 35° south latitude in four continents, according to the model (Figure 4a).

In America, the insect would develop essentially in the Atlantic coast, with greater probability of presence in Brazil, Colombia and Venezuela. In Argentina, it would be present only in the extreme north-east areas. Peru and Bolivia would have areas with high probability of presence, mainly in Amazonia. Chile would have low probability of presence of the vector in the north and north-central areas, with high probability in Easter Island. In Central America, the mosquito could be distributed in all its countries, principally on the Caribbean Sea coast. In North America, it would be present in Mexico and the USA, mainly on the Caribbean Sea shores. The probability of presence is very low for the Pacific coast (Figure 4b).

Aedes aegypti predicted distribution in Africa is limited by the Sahara Desert; it would be present from 12° north latitude to 12° south latitude, occupying Central Africa. It would be abundant in both Atlantic and Indian Ocean shores, and present in Madagascar (Figure 4c).

In Asia, it would be present in several countries including India, Burma, Thailand and Cambodia; the Himalayan massif appears as the most important geographic barrier to its dispersion, blocking their passage to north and north-east Asia (Figure 4d).

The insect is predicted to be present in all the islands of Oceania, concentrating in the Philippines, Indonesia and

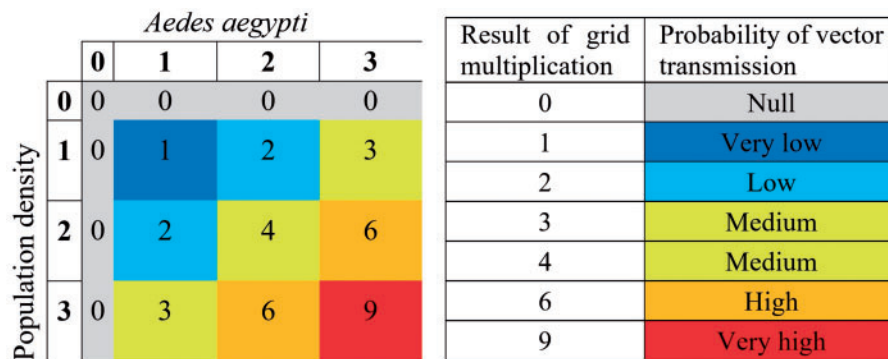


Figure 1. Schemes of the raster multiplication process and risk level generation. Left: Double entry matrix generating a linkage grid between the probability of presence of the vector and the population density. The values 0 to 3 represent the four reclassified levels of each variable. Right: Probability of vector transmission according to the result of the grid multiplication, and corresponding risk levels.

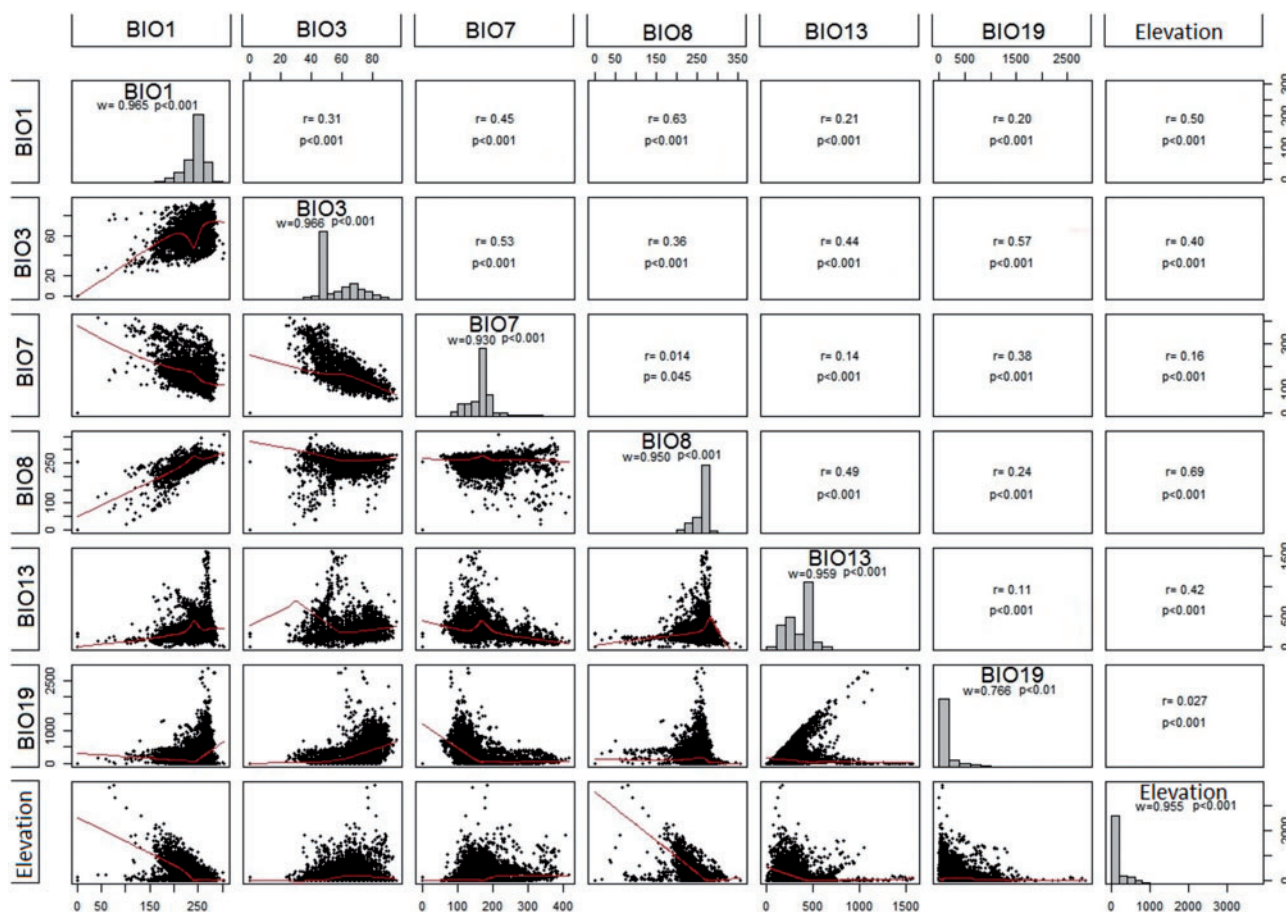


Figure 2. Correlation panel of *Aedes aegypti* suitability model variables. The panel shows only the selected variables in the final model. The upper right boxes show the absolute correlation index (r) and its p -value. The diagonal boxes show histograms of each variable and the Shapiro-Wilk test result of each variable (w), with its p -value. The lower left boxes show the scatter plot of correlation between pairs of variables.

Papua New Guinea. The north-eastern Australian coast has high probability of presence of this mosquito (Figure 4d).

Europe has no considerable chance of presence of the insect, but, in the south of France and Spain, there are some regions with slight probability of presence of the vector (Figure 4c).

Modelling of potential transmission risk for the population due to contact with the vector

Asia concentrates the highest risk levels of vector transmission worldwide, specifically in India and Pakistan, with extremely high risk levels (Figures 5d and 6d). Brazil, Venezuela and Colombia have the highest risk levels in South America, mainly in coastal areas; however, this risk decreases in Amazonia, related to lower human densities in these areas. In Central America, the risk level is generally very high, reaching extremely high values in Haiti and Cuba. In North America, Mexico and the USA have considerable risk, decreasing within the continent, by the reduction of the climatic influence of the Caribbean Sea (Figure 5b).

In Africa, the risk concentrates in the Atlantic coast, with highly populated countries. Near the Indian Ocean, the risk

level is lower, but is still quite high (Figure 5c). In Oceania, greater risk levels are largely concentrated in island countries, principally in the Philippines and Indonesia. Australia has lower levels of vector transmission risk because the zones with higher suitability for the vector coincide with low or very low population densities (Figure 5d and 6d). The most affected country in Europe would be Spain. Italy shows areas potentially affected, mainly in the south-west (Figures 4 and 5).

Estimation of the exposed human population

The human population in zones of high and very high transmission risk represents approximately 30.4% of the global human population (2 261 184 280). Roughly 3 billion people may be potentially exposed to some level of ZIKV transmission risk, from low to very high (Table 1).

Asia is the continent with the highest number of people potentially infected (including all risk levels). India is the country with most people potentially affected worldwide, followed by China and Indonesia (Figure 6d). America follows in the number of people potentially infected; the country with most affected people is Brazil. Only Canada does not show

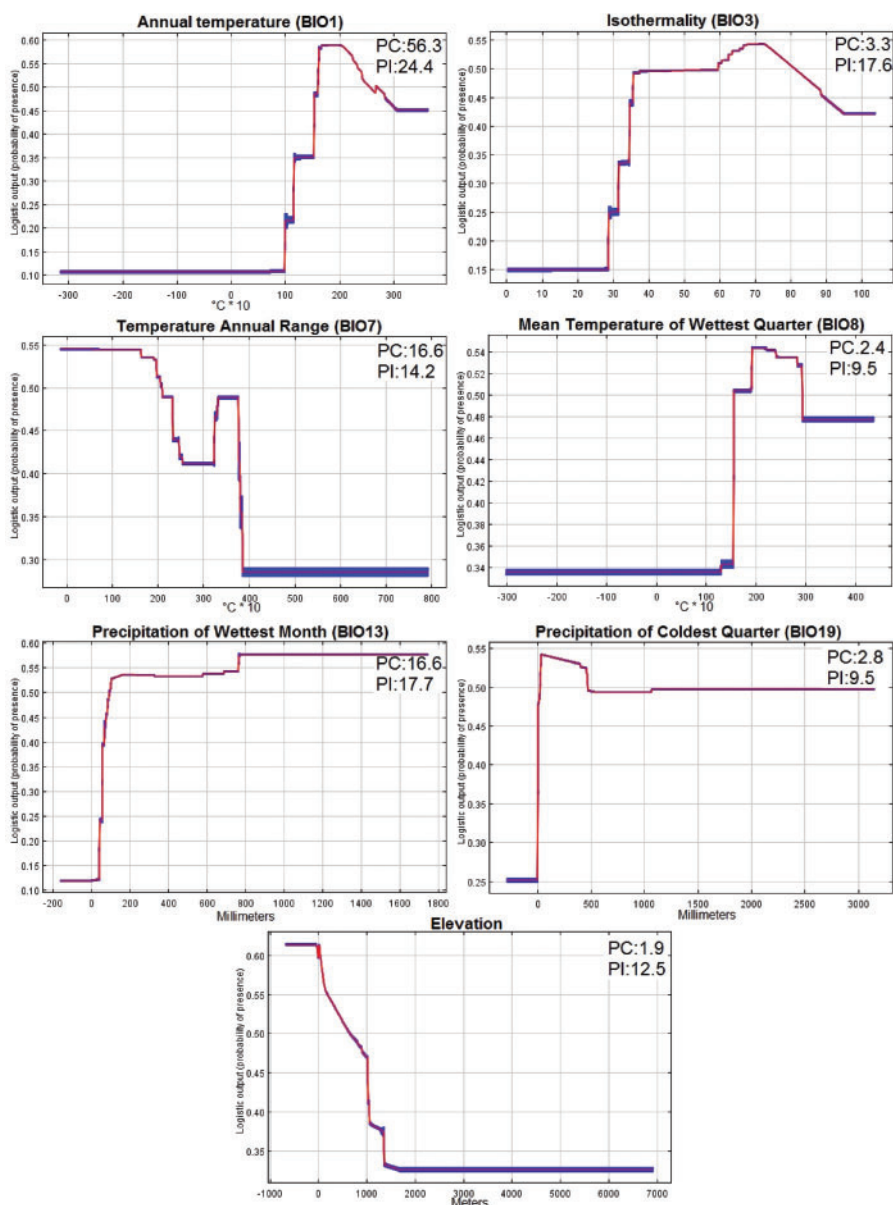


Figure 3. Response curves and contribution of the variables in the model of *Aedes aegypti*. These response curves show how the logistic prediction of the distribution of *A. aegypti* changes as each environmental variable is varied, keeping all other environmental variables at their average sample value. The Y axis shows the probability of presence expressed in logistic values (0 to 1). Two important metrics appear in the right corner: Percentage of contribution (PC) and Permutation Importance (PI); these are estimates of the relative contribution of the variables to the model.

population potentially affected in our prediction (Figure 6a). Africa has also a considerable number of inhabitants exposed to very high risk levels, and 56 countries could be affected (Figure 6c). Most of the people potentially affected by ZIKV in Oceania are in Australia and Thailand; only some islands will not be affected, mainly located in the north-western Pacific Ocean. In comparison, Europe has lower numbers of people exposed (Figure 6 and Table 1).

Our model indicates that 43.9% of the world population can be potentially affected by ZIKV, distributed in 178 countries (Supplementary Material 1, available as Supplementary Data at *IJE* online).

Discussion

About the model

Niche modelling has become one of the most widely used methods worldwide for ecologists to study the spatial distribution of organisms.^{33–37} Recently, the potential of this methodology to assess the distribution of vectors of infectious diseases worldwide was demonstrated.^{20,21} Our study used the MaxEnt 3.3.3k software as the method of species distribution modelling, which has been evaluated over other methodologies, showing better performance for modelling disease vectors.^{38–46}

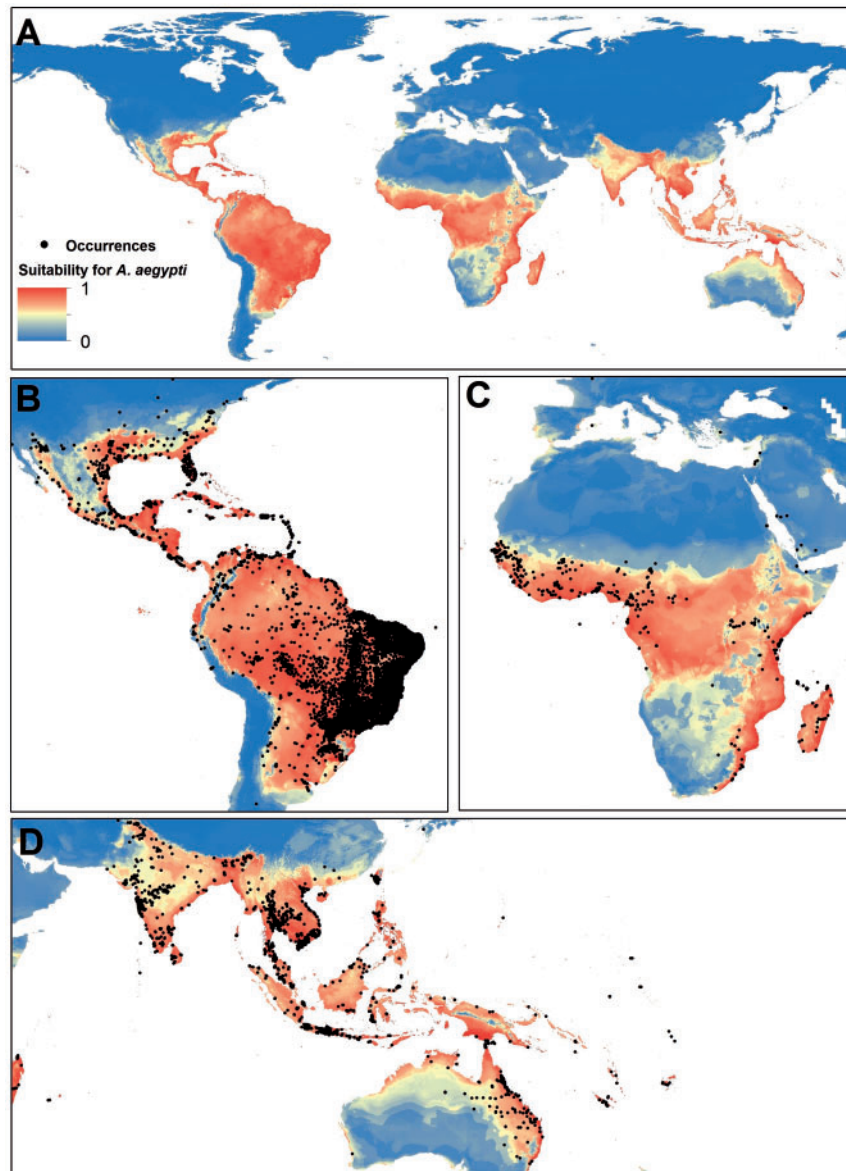


Figure 4. Suitability model of *Aedes aegypti*. (A) Map of the potential distribution of *A. aegypti* worldwide. (B) Zoom to areas with higher suitability for the vector in America. (C) Map of the potential distribution in Africa. (D) Zoom to areas with higher suitability for the vector Oceania and Asia.

Our model used a database of 20 203 occurrences, representing the largest database used for modelling of *A. aegypti* distribution worldwide. The relevance of the variables used was similar to that of Kraemer's model, with the annual mean temperature as an important factor in the distribution of *A. aegypti*; in our model, this variable had 56.3% of the weight. Our resulting spatial distribution of the vector is similar to that of Kraemer *et al.*²⁰; the main differences reside in the selected variables and in the spatial configuration and magnitude of probabilities of the vector's presence: in South Africa and Brazil, it showed slightly higher probabilities than the model of Kraemer *et al.*²⁰ We avoid using land-cover or vegetation indices as

variables, given that the presence database has records from 1960 to 2016, and those variables' values change very quickly, so, if current values are attributed to a presence point that had a very different value when it occurred, it could generate bias. However, our model is similar in distribution of that of Kraemer *et al.*²⁰, which probably relates to the lower degree of importance that land-cover and vegetation variables had in their model, hence the bioclimatic variables used in both models account for their similarity.

The scale of analysis represents an important factor in the choice of variables. Pearson and Dawson⁴⁷ argue that, on a large scale (over 2000 km study area), the distribution

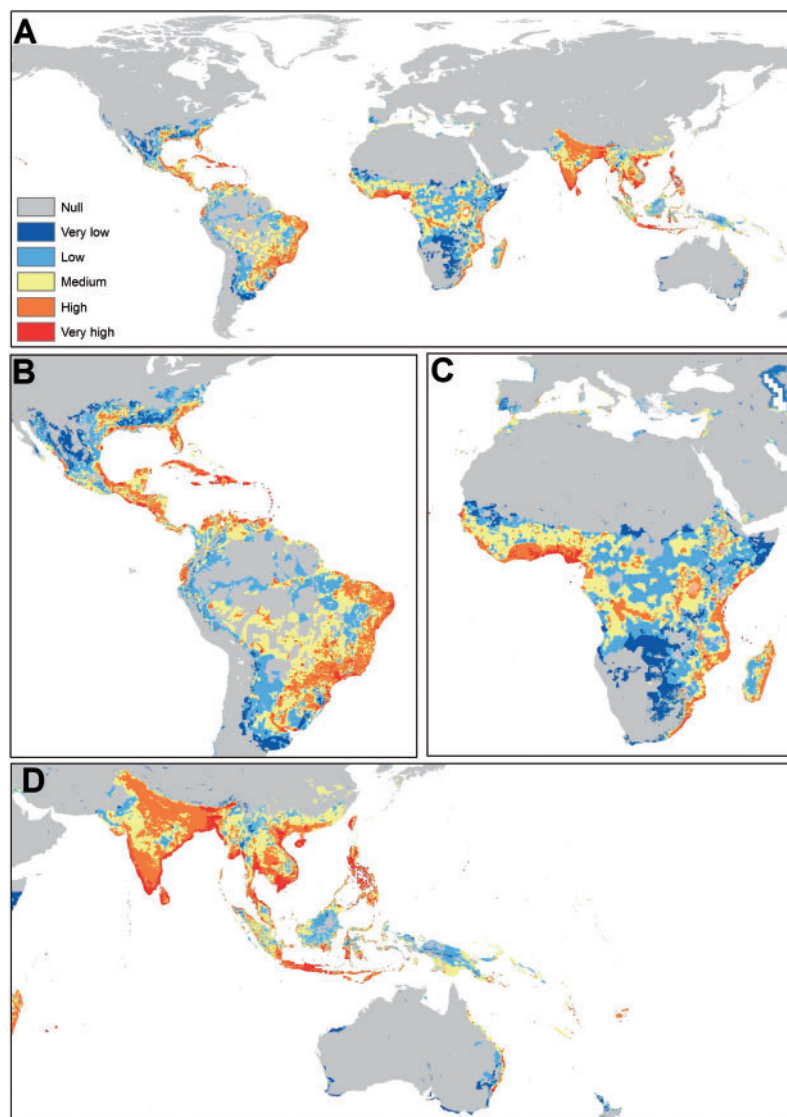


Figure 5. Transmission risk model of ZIKV due to *Aedes aegypti* vector. (A) Map of the global transmission risk of ZIKV by *A. aegypti*. (B) Zoom to areas with higher transmission risk in America. (C) Map of the transmission risk in Africa. (D) Zoom to areas with higher transmission risk in Oceania and Asia.

is mainly explained by climate; so we chose to work mainly with bioclimatic layers. In addition to these, other variables could influence the spatial distribution of the vector, such as availability of reproduction sites for the vector that could be related to the availability of sanitation or sewage systems⁴⁸; unfortunately, they were not available in a spatially explicit manner on a global scale.

In the studies of Kraemer *et al.*²⁰ and Messina *et al.*²¹, the probability of occurrence of the vector was assessed, but the human population exposed to this threat was not evaluated. Vries⁴⁹ developed a spatially explicit risk model of malaria in Kenya without using niche modelling, using a classification of a number of coverages based on the suitability of the insect in each; then he compared this level of suitability with the population exposed to the vector. The

present study used the MaxEnt technique to evaluate the level of the vector's habitat suitability, and combined the interaction with the spatial distribution of human population, measured as human density.

Our estimation of the population at risk could be considered conservative because the database of CIESIN-IFPRI-World Bank-CIAT²⁷ was built with an estimate of the world population of the year 2000. Considering that the population has increased about 20%,⁵⁰ we expect the number of potentially affected people to be higher. Our model did not consider other ZIKV vector species or person-to-person transmission pathways, which could also increase the population at risk. We assumed that all *A. aegypti* mosquitoes are potential vectors of the disease, in the same way as Messina *et al.*²¹ Since only the females can

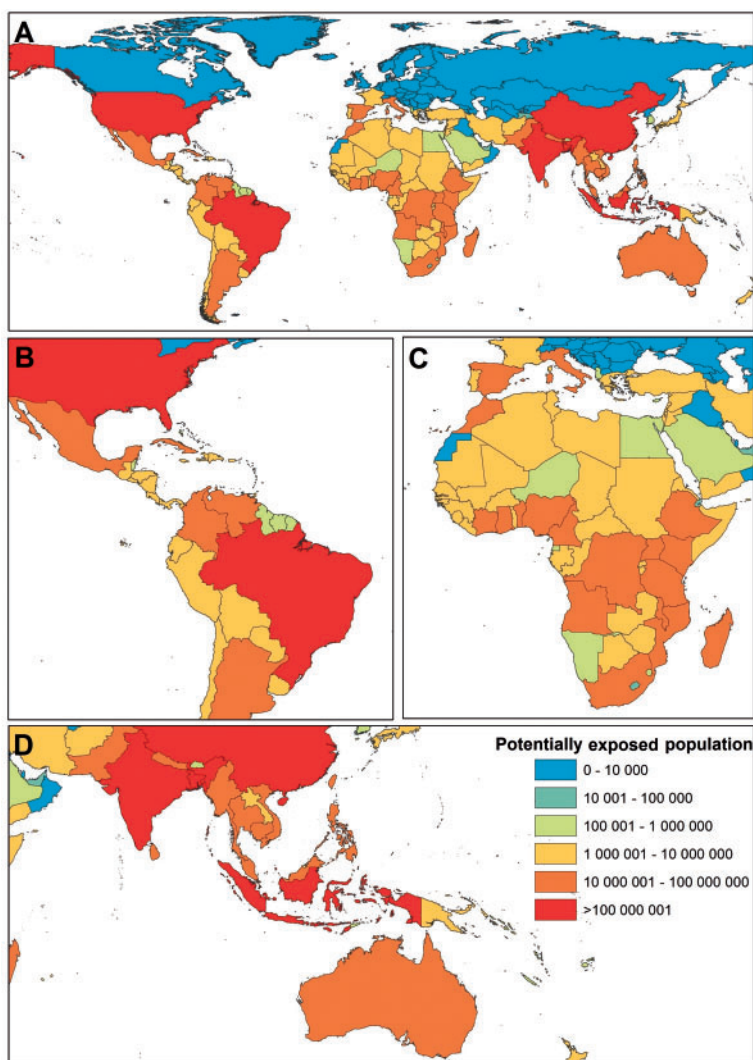


Figure 6. Estimate of the population potentially exposed to ZIKV. (A) Map of the exposed human population to ZIKV worldwide. (B) Zoom to areas with higher potentially exposed population in America. (C) Map of the exposed human population to ZIKV in Africa. (D) Zoom to areas with higher potentially exposed population to ZIKV in Oceania and Asia.

Table 1. Population exposed to ZIKV: quantification of the exposed human population in millions by continent, grouped by the modelled risk level of ZIKV exposure

Continent	Very high	High	Medium	Low	Very low	Total
Africa	95.37	187.43	231.04	63.10	7.31	584.25
America	205.26	145.17	140.45	34.33	3.03	528.24
Asia	529.92	1059.06	464.96	42.01	0.43	2096.38
Europe	0.85	8.05	25.30	4.29	0.13	38.62
Oceania	7.62	3.82	6.14	2.64	0.20	20.42
Total	839.02	1403.53	867.89	146.37	11.10	3267.91

actually transmit the virus by biting, we could be overestimating the risk; however, at this scale of analysis, there should be no difference in the environmental conditions preferred by females or males⁵¹ and there are suspicions of

rapid seasonal amplification of the virus, probably due to efficient vertical transmission to their progeny (including males) and/or maintenance in vertebrate reservoirs.^{1,7}

Public health repercussions

Our model predicted that over 2.261 billion people live in sites at high or very high risk of transmission of ZIKV—greater than the Messina *et al.*²¹ estimate. If we consider the overall risk of vector transmission, the population exposed could reach 3.267 billion people, representing around 43.9% of the world population in 2016. Recently, WHO¹⁷ released a global alert for the expansion of the virus worldwide, and recommended that affected countries perform a series of actions to reduce the risk of infection. In the present study, we show that the transmission risk by *A. aegypti* is not

homogeneous throughout the tropics, depending on the abundance of both the vector and the human population, although the number of people actually affected will be largely influenced by the control actions implemented by each government. The responses recommended by WHO are focused on preventing and managing medical complications by targeting pregnant women; by sexual and reproductive health education and care; and by integrated mosquito management.¹⁷ If there are short budgets for implementing these actions, it may create conditions that increase the risk and the probability of spread of the vector, along with unsanitary conditions, overcrowding and hospital deficits, particularly of populations in urban slums and other densely populated areas.¹⁷ There was no information available about the gender distribution worldwide in a spatially explicit way, so we could not stratify the risk by vulnerable group. We provide a worldwide map of risk in downloadable format at 5-km² pixel as a tool for management of the disease and public health (see [Supplementary Material 3](#), available as [Supplementary Data](#) at *IJE* online).

By the end of 2015, there were 49 countries/territories with active transmission of ZIKV.⁵² The data presented in our study suggest that 170 countries are at risk of vector transmission ([Supplementary Material 1](#) and [3](#), available as [Supplementary Data](#) at *IJE* online). Our prediction is partially consistent with the diagnosis made by WHO,¹⁷ differing in the countries without risk of infection; in our study, in America, only Canada will have null vector transmission risk by *A. aegypti*. We found that Chile would have suitable sites for the vector, which was shown to be true in April 2016, with *A. aegypti* findings in Arica, a city near Peru⁵³; these presence points were not available to be included in our model's database, which confirms the validity of our prediction.

The virus has spread worldwide, with a significant proportion of the global population exposed to risk. Various agencies and governments must join forces to control the virus, especially in zones with higher risk, in countries with less sanitation and poorer resources.

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