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Potential for Zika virus introduction and transmission in resource limited countries in Africa and Asia-Pacific: A modeling study

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Summary

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IIB, OJB, MUGK, and KK contributed to the idea for the study. IIB, OJB, MUGK, MG, MIC, and KK contributed to the design of the study. IIB, OJB, MUGK, MG, MIC, SB, AGW, SIH, MAK, JSB, and KK contributed to the data analysis and IIB, OJB, MUGK, MG, MIC, SIH, MAK, JSB, and KK contributed to the data interpretation. IIB, OJB, MUGK, MG, MIC, and KK contributed to the writing of this manuscript.

Declaration of interests
KK is the founder of BlueDot, a social benefit corporation that models global infectious disease threats. MIC, MG, SB, and AGW have received employment income from BlueDot, and IIB has consulted to BlueDot. All other authors declare no competing interests.

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Background—As the epidemic of Zika virus expands in the Americas, countries across Africa and the Asia-Pacific region are becoming increasingly susceptible to the importation and possible local spread of the virus. To support public health readiness, we aim to identify regions and times where the potential health, economic, and social effects from Zika virus are greatest, focusing on resource-limited countries in Africa and the Asia-Pacific region.

Methods—Our model combined transportation network analysis, ecological modelling of mosquito occurrences, and vector competence for flavivirus transmission, using data from the International Air Transport Association, entomological observations from Zika's primary vector species, and climate conditions using WorldClim. We overlaid monthly flows of airline travellers arriving to Africa and the Asia-Pacific region from areas of the Americas suitable for year-round transmission of Zika virus with monthly maps of climatic suitability for mosquito-borne transmission of Zika virus within Africa and the Asia-Pacific region.

Findings—An estimated 2·6 billion people live in areas of Africa and the Asia-Pacific region where the presence of competent mosquito vectors and suitable climatic conditions could support local transmission of Zika virus. Countries with large volumes of travellers arriving from Zika affected areas of the Americas and large populations at risk of mosquito-borne Zika virus infection include, India (67 422 travellers arriving per year; 1·2 billion residents in potential Zika transmission areas), China (238 415 travellers; 242 million residents), Indonesia (13 865 travellers; 197 million residents), Philippines (35 635 travellers; 70 million residents), and Thailand (29 241 travellers; 59 million residents).

Interpretation—Many countries across Africa and the Asia-Pacific region are vulnerable to Zika virus. Strategic use of available health and human resources is essential to prevent or mitigate the health, economic and social consequences of Zika virus, especially in resource-limited countries.

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Keywords

Zika virus; air travel; globalization; mosquito; vector; Aedes; Africa; Asia-Pacific; Brazil

Introduction

Zika virus is a flavivirus that was first isolated in 1947 from a sentinel rhesus monkey in a Ugandan forest,1 with the first human cases identified 5 years later in Nigeria.2 Humans become infected with Zika virus mainly through the bites of several species of aedes mosquitoes, including *Ae. aegypti* and presumably *Ae. albopictus*.3 Eradication of Zika virus poses substantial challenges because of its sylvatic transmission cycle between aedes mosquitoes and non-human primates.4–8 While Zika virus is known to have circulated in parts of Africa and the Asia-Pacific region 1,9,10 a series of epidemics during the past decade have transported this virus eastward across islands in the Pacific ocean.11,12 On May 15, 2015, the Program for Monitoring Emerging Diseases (ProMED-mail) published a report confirming locally acquired cases of Zika virus in several northeastern Brazilian states, marking the first time this virus is known to have spread within the Americas. 13,14,15 On Feb 1, 2016 the World Health Organization declared this epidemic to be a

global Public Health Emergency of International Concern, mainly because of its rapid spread between countries, and its vertical transmission of human infection resulting in birth defects, including but not limited to microcephaly16–19 and an association with Guillain-Barré syndrome.20 As of June 27, 2016, autochthonous transmission of Zika virus has been confirmed in 40 countries and territories within the Americas.21

As the epidemic expands its range, increasing numbers of travellers are transporting Zika virus to distant geographies across the world.22 If competent mosquito vectors become infected from these travelers in areas where environmental conditions are conducive to the virus's spread, new epidemics could occur, subject to the presence of an immunologically susceptible human population.23 During warmer months across the northern hemisphere when mosquito vectors are most abundant, active, and capable of transmitting arboviruses to humans, the risk of new epidemics appearing outside of the Americas is expected to peak. To support public health readiness, we aim to identify regions and times where the potential for health, economic, and social effects of Zika virus are greatest, focusing on resource-limited countries in Africa and the Asia-Pacific region.

Methods

Overview

To identify the areas most susceptible to Zika virus in Africa and the Asia-Pacific region (ie, all of Asia and all Pacific Islands), we performed and integrated a series of analyses. These included monthly flows of airline travellers departing from regions of the Americas in which conditions are suitable for year-round local transmission of Zika virus (as a proxy for where departing travellers are most likely to become infected with Zika virus during the current outbreak); monthly climatic suitability models for autochthonous transmission of Zika virus in Africa and the Asia-Pacific region, conditional on the predicted occurrence of competent aedes mosquito vectors; estimates of the number of people living in countries in Africa and the Asia-Pacific region where the potential for mosquito-borne transmission of Zika virus exists; and health expenditure per capita as a proxy of countries' capacity to detect and effectively respond to Zika virus importation and domestic epidemic transmission.

Geographic Range of Zika virus in the Americas

Given the high proportion of asymptomatic or subclinical Zika virus infections, combined with limited capacity for diagnostics in some parts of the Americas, substantial under-reporting or delayed reporting of Zika virus infections is widely presumed. Hence, we assumed that by July, 2016, more than 1 year after the first cases of Zika virus were confirmed in Brazil, the virus was active across all geographical areas in the Americas conducive to year-round transmission. To delineate this geographic range, we combined continuous distribution maps of *Ae. aegypti* and *Ae. albopictus*,24 regarding both as competent vectors, and converted the combined data into binary presence-absence maps. The combined geographical range was defined by the minimal extent that incorporated 90% of all known independently observed mosquito occurrences. We applied a model of dengue virus intra-mosquito dynamics25 to this combined map to assess whether the temperature profile for a given geographical range would enable adult female aedes mosquitoes to

survive long enough for dengue virus to complete its extrinsic incubation period (ie, to enable a newly infected mosquito to survive for long enough to become infectious).25 We used the dengue virus model to represent competence of Zika virus transmission because of the paucity of data on the extrinsic incubation period for Zika virus and how it varies in response to temperature or across aedes mosquito species. Evidence from previous studies shows similar extrinsic incubation periods across related flaviviruses.26 We judged this approach to be reasonable, because evidence suggests that dengue virus and Zika virus share many common epidemiological features, including the same vector species, rate of epidemic progression, and general latitudinal and seasonal limits in South America (appendix pp 1-11). We then paired this seasonal model was then paired with high-resolution empirical global temperature data27 to predict the number of days throughout a typical year (average year profile 1950-2000) in which local transmission of Zika virus would be possible.28 These data were then used to map areas where climatic conditions are conducive to year-round transmission of Zika virus via *A aegypti* or *A albopictus*. We subsequently refined this geographical range by excluding the USA, since at the time of analysis, there were no locally acquired mosquito-borne cases of disease and because the transmission of another emerging arbovirus transmitted by aedes mosquitoes – chikungunya – was absent or limited in 2014-15 (ie, the USA reported only 12 confirmed cases in Florida in 2014). We refer to this geographical extent as the ecological niche for Zika virus in the Americas.

Translocation of Zika virus out of the Americas

We established a 50 km buffer zone around the ecological niche for Zika virus in the Americas, to accommodate the potential movement of individuals travelling from areas of Zika virus activity to nearby commercial airports. For the 689 cities with one or more commercial airports falling within this zone, we analysed worldwide airline ticket sales and flight itinerary data from the International Air Transport Association (IATA) between Dec 1, 2014 and Nov 30, 2015. These itineraries included data on the initial airport of embarkation, final airport destination, and where applicable, connecting airports, representing an estimated 90% of all passenger trips on commercial flights worldwide (the remaining 10% of passenger data are estimates modelled by IATA). We then mapped the monthly final destinations of all travellers departing from airports within these buffered zones for airports in Africa and the Asia-Pacific region.

Transmission of Zika virus within Africa and Asia-Pacific

Overview—Current evidence suggests that *A aegypti* and *A albopictus* are both potentially capable of transmitting Zika virus.29 However, the relative competence for each mosquito vector is not well understood. To address this uncertainty, we created three scenarios to reflect suitability for autochthonous Zika virus transmission in Africa and the Asia-Pacific region. We assumed that Zika virus suitability would either be the same as the global geographical range for dengue30 (scenario 1; most specific assumption); include the global geographical range for dengue, but also include areas where *A aegypti* occurrences are predicted and where conducive climatic conditions exist for autochthonous Zika virus transmission (scenario 2; intermediate assumption); or include the global geographic range of dengue, but also include areas where *A aegypti* and *A albopictus* occurrences are

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predicted and where conducive climatic conditions exist for Zika virus autochthonous transmission (scenario 3; most sensitive assumption).

Zika seasonal suitability maps

To account for seasonal variation in the geographical range of Zika virus suitability, we produced maps for each month of the year to delineate our three suitability extents described above (figures 1 and 2; appendix pp 1-11). We used mosquito species distribution models for *A aegypti* and *A albopictus*24 (originally fitted to annual data and covariates) to make monthly predictions by use of new monthly covariates for temperature-persistence suitability,25 relative humidity, and precipitation. Non-dynamic model covariates (e.g. urbanization) were assumed to be constant (appendix pp 1–11). We refined these seasonal maps by scaling their values so that the sum of all monthly maps equaled the annual mean map.23 This approach allowed us to account for relative changes in suitability throughout the year and between regions. The continuous seasonal maps were converted into binary range maps for each species. Final monthly vector maps show predictions of areas with high likelihood for observation or detection of mosquito populations, which were assumed to be sufficiently abundant to enable transmission of disease to humans.

To add spatiotemporal resolution to our predicted Zika virus transmission zones, we used an arbovirus incubation period model25,31 to identify regions and times where temperature would permit Zika virus transmission to humans (ie, mosquito survival exceeds the extrinsic incubation period). Pixels (areas of 5 km^2) for which temperature did not meet extrinsic incubation period criteria for at least 21 days of the month (ie, assuming that Zika virus could be sustained in human populations during days of absence in mosquitoes) were masked out of the final predicted transmission zones.

Populations at risk in Africa and the Asia-Pacific region

After defining our three suitability zones for autochthonous Zika virus transmission for each month of the year, we calculated the number of people living in each zone by extracting population data from LandScan (Oak Ridge, TN, USA), a satellite-based sensor dataset that estimates ambient population density worldwide in 1-km^2 grids. To link these datasets, we resampled our Zika virus suitability zone maps (originally at 5 km^2 resolution) 1 km^2 pixels by use of a nearest-neighbor sampling algorithm and aligned them with national boundaries to extract population values. For each country, we estimated the number of people at risk of mosquito-borne Zika virus exposure during the month in which the geographical range for Zika virus suitability was greatest. We did not make any assumptions about the degree of existing Zika virus immunity in populations in Africa and the Asia-Pacific region, despite sporadic and historical reports of Zika virus cases from the continent.23 As a proxy for healthcare and public health capacity, we ranked countries by health expenditures per capita (in 2014 US $) as reported by the World Bank.31

Results

70% of travellers departing from the ecological niche of Zika virus in the Americas for destinations in Africa and the Asia-Pacific region arrived in ten countries: China (238 415

travellers per year), Japan (179 926 travellers per year), Israel (106 365 travellers per year), Australia (96 430 travellers per year), Turkey (90 632 travellers per year), Angola (88 048 travellers per year), South Korea (87 768 travellers per year), United Arab Emirates (70 848 travellers per year), India (67 422 travellers per year) and South Africa (59 318 travellers per year [appendix pp 94-122]).

Worldwide, an estimated 2·6 billion people live in areas of Africa and the Asia-Pacific region where the presence of competent mosquito vectors and suitable climatic conditions could support local transmission of Zika virus. According to our most conservative scenario (scenario 1), populations living within the geographical range for Zika virus (during the month where the geographical range was broadest) were highest in India (1·2 billion people), China (242 million), Indonesia (197 million), Nigeria (179 million), Pakistan (168 million), and Bangladesh (163 million [appendix pp 94-22]). Geographical variability in the three suitability zones for autochthonous Zika virus transmission on a quarterly and monthly basis is shown for Africa (figure 1; appendix pp 12-24); and the Asia-Pacific region (figure 2; appendix pp 25-37).

On the basis of the volume of travellers arriving from airports within the ecological niche of Zika virus in the Americas, the resident population at risk for Zika virus exposure during the month of its broadest activity, and health expenditures per capita, we found that India, the Philippines, Indonesia, Nigeria, Vietnam, Pakistan and Bangladesh have some of the highest expected risks for Zika virus importation and population health impact (figure 3). Although China receives the greatest number of travellers of all countries in Africa or the Asia-Pacific region and has a large population predicted to be living within the geographical range of dengue virus, it spends significantly more on health than do many of the highest risk countries. Whereas countries such as Tanzania, Ethiopia, Mozambique and the Democratic Republic of Congo have smaller populations at risk of Zika virus exposure, each has a moderately high volume of travellers arriving from the Americas and low health expenditures (table).

Discussion

By integrating time-dependent analyses on the potential for international dispersion of Zika virus and environmental suitability for autochthonous transmission, we aimed to identify where and when populations would be most susceptible to the health, economic and social effects of Zika virus. In India alone, an estimated 1·2 billion people are susceptible to Zika virus exposure at the time of peak seasonal risk. In China, an estimated 242 million people live in southern regions of the country where large dengue virus epidemics have occurred previously, 33,34 and hence where Zika virus has the potential to circulate locally. However, the predicted suitability range for autochthonous transmission by aedes mosquitoes extends into northern China, where collectively, more than one billion people reside.24,28 In Africa, Angola receives the largest number of travellers from Zika virus-affected countries in the Americas, probably because of Angola's cultural and historic ties to Brazil. In Angola there is an historical and ongoing epidemic of yellow fever,34 an arbovirus also transmitted by *A aegypti*, that is already straining the public health system. The epidemiological significance of these ties has already been shown in the context of the exportation of chikungunya from

Angola to Feira de Santana, Brazil, which has since affected many countries across the Americas.34

Although our analysis emphasises the potential for autochthonous transmission of Zika virus via aedes mosquitoes, sexual transmission via travellers returning from Zika virus-affected areas is now well documented.37 Given the current geographical range of Zika virus within the Americas, many travellers returning from affected areas would benefit from health education to prevent sexual transmission. For example, since Zika virus RNA has been detected in semen 93 days after symptom onset,37 the US Centers for Disease Control and Prevention have issued recommendations to help to guide individuals in the prevention of sexual transmission of Zika virus.21 Although these recommendations could change as new evidence becomes available, our analysis of traveller flows from the Americas emphasises how populations in specific destinations in Africa and the Asia-Pacific region could benefit from intensified public health education.

Our findings must be considered in the context of a number of assumptions and data limitations. First, we regarded *A albopictus* as a competent vector for Zika virus, including it in one of our three analytical scenarios, even though our understanding of its capacity to transmit Zika virus is evolving.3 Furthermore, we did not account for other *Aedes* species such as *Aedes africanus* and *Aedes hensilli*1,8 which might be competent vectors for Zika virus in particular geographical areas. We also assumed that the extrinsic incubation period for Zika virus in aedes mosquitoes was similar to that of dengue virus, since the extrinsic incubation periods for other related arboviruses have been similar.26 In our estimates of the public health and health-care capacity of countries, we assumed that health expenditures per capita would be a reasonable proxy, recognizing that it will not address variability in resources within countries and might not adequately capture the many dimensions that comprise a country's ability to respond to imported or locally transmitted Zika virus.

As an emerging epidemic currently concentrated in the Americas, we were unable to validate the outputs of our analysis for the Africa and Asia-Pacific regions. Given that an estimated 80% of all Zika virus infections are asymptomatic, and because resource-limited countries in Africa and the Asia-Pacific region might have suboptimal surveillance capacity to readily detect Zika virus infections, our validation efforts were retrospective and focused on the Americas. For example, the predicted arrival of Zika virus into Brazil in 2013 coincided with a surge in the volume of airline travellers arriving into Brazil from countries with reported Zika virus activity.15 Although not formally assessed, the observed spread of Zika virus across the Americas has to a largely aligned with the findings of a modelling study that used a similar methodological approach to the one used in this analysis.38 At the time of writing, the only country in Africa to have confirmed locally acquired infections with the Asian strain of Zika virus (identical to the strain circulating in the Americas) is Cape Verde. In our analysis, we noted that Cape Verde received more than 7000 travellers from Zika virus affected countries in 2015 (ranked 27th of 118 countries), including direct flights from northeastern Brazil. Further validation efforts will become possible as more data on the observed spread of Zika virus becomes available.

Finally, the population health consequences of imported Zika virus from the Americas will depend heavily on underlying levels of immunity to Zika virus in Africa and the Asia-Pacific region. Although sporadic cases of Zika virus have been reported in both continents,23 the breadth and extent of previous infection to Zika virus remains unknown. To fill this gap in knowledge, serological surveys in Africa and Asia-Pacific are needed. Furthermore, the degree and duration of protective immunity stemming from infection with Zika virus is also unknown. This point is especially relevant when considering whether previous infection with the African strain of Zika virus confers any protective benefit against infections with the Asian strain of the virus.

As the Zika virus epidemic in the Americas intensifies and expands, hundreds and possibly thousands, of infected travellers are now transporting the virus to distant regions of the world. Given the broad global range of aedes mosquitoes and the arrival of summer in the northern hemisphere, these translocation events could catalyse new Zika virus epidemics, in much the same manner that the epidemic in Brazil began. The potential for epidemics to occur in parts of Africa and the Asia-Pacific region is particularly worrying given the vast numbers of people who are potentially susceptible to Zika virus and are living in environments where health and human resources to prevent, detect, and respond to epidemics are limited. Our findings could offer valuable information to support time-sensitive public health decision-making at local, national and international levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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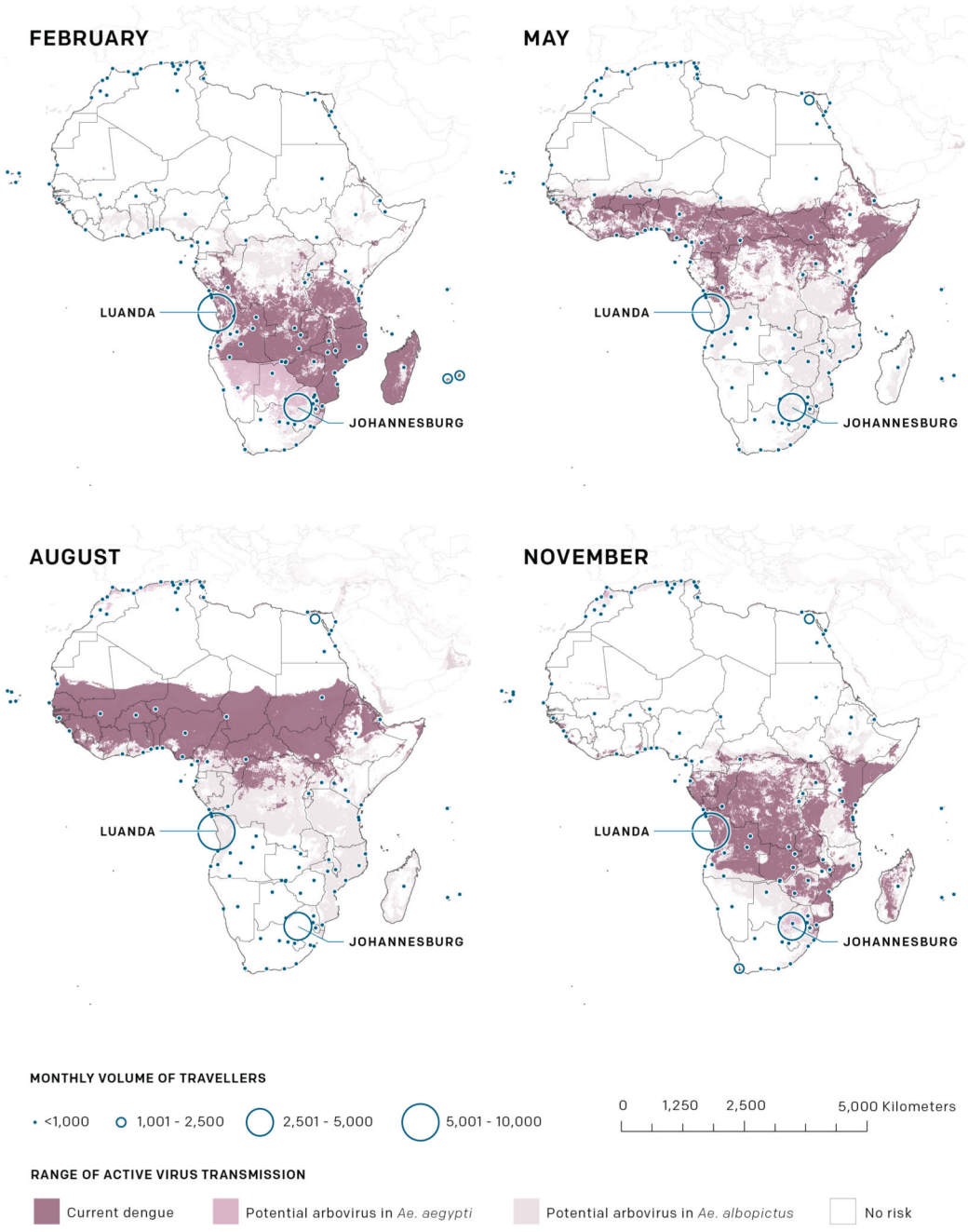

Figure 1. Seasonal geographical suitability for Zika virus transmission in Africa and seasonal volume of airline travellers arriving from the Americas

Monthly maps are shown for Africa. Travellers arriving from the Americas refers to travellers originating from regions of Latin America and the Caribbean that are suitable for year-round transmission of Zika virus.

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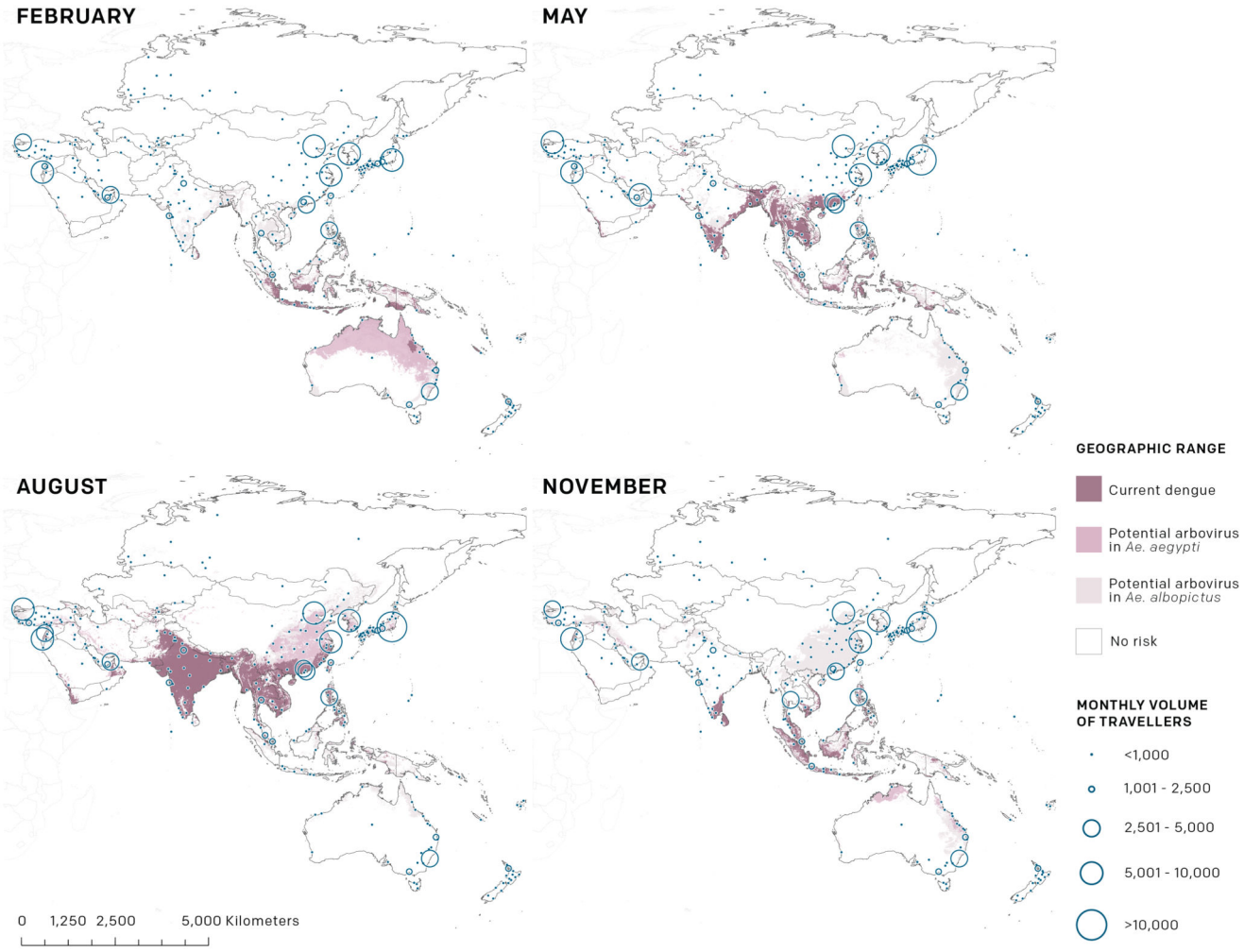

Figure 2. Seasonal geographical suitability for Zika virus transmission in Asia-Pacific and seasonal volume of airline travellers arriving from the Americas

Monthly maps are shown for Asia-Pacific region. Travellers arriving from the Americas refers to travellers originating from regions of Latin America and the Caribbean that are suitable for year-round transmission of Zika virus.

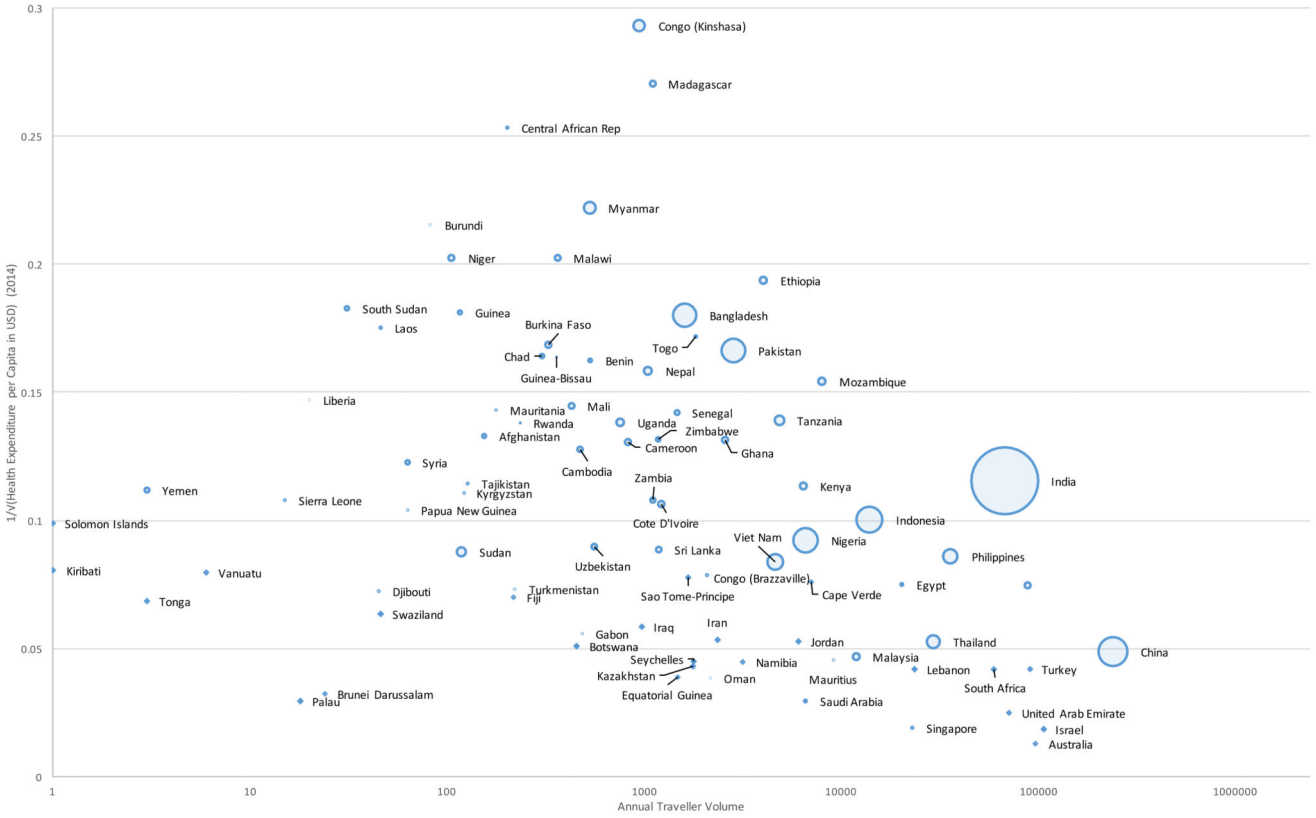

Figure 3. Volume of airline travellers arriving from the Americas by peak resident population at risk of Zika virus exposure and health expenditures per capita

The x-axis shows log of the annual volume of travellers arriving from airports within the ecological niche of Zika virus in the Americas, y-axis shows the transformation of health expenditures per capita (square root of 1/health expenditures per capita), and the size of circles shows the populations residing within the geographical range of Zika virus during the month of its broadest activity. Travellers arriving from the Americas refers to travellers originating from regions of Latin America and the Caribbean that are suitable for year-round transmission of Zika virus. Due to highly skewed distribution of values, volume of airline travellers was plotted on a logarithmic scale.

Population at risk of Zika virus exposure refers to resident populations living in areas suitable for Zika virus transmission during the month when the geographical range of suitability is broadest. Health expenditures are measured in 2014 US$; because of highly skewed distribution of values, we transformed health expenditures per capita for visualisation purposes.

Table 1

Countries in Africa and Asia-Pacific ranked by monthly volume of airline travellers arriving from the Americas and peak resident population at risk of Zika virus exposure

Travellers arriving from the Americas refers to travellers originating from regions of Latin America and the Caribbean that are suitable for year-round transmission of Zika virus. Resident population at risk of Zika virus exposure refers to resident populations living in areas suitable for Zika virus transmission during the month when the geographical range of suitability is broadest. Scenario 1 is Zika virus extent equal to dengue extent; scenario 2 is Zika virus extent equal to dengue extent plus *Aedes aegypti* extent; and scenario 3 is Zika virus extent equal to dengue extent plus *A aegypti* plus *Aedes albopictus* extents.

Rank	Country	Month of Peak Exposure to Zika virus	Population at risk during peak exposure month [millions]			Traveller volume at peak exposure* (number of travellers)	Health expenditure per capita (US$), 2014	Health expenditure per capita rank (of 104 countries), 2014	Alignment of Peak travel and peak exposure†
			Scenario 1 (most conservative scenario)	Scenario 2	Scenario 3 (least conservative scenario)				
1	India	August	1181·6	1181·6	1208·3	5430	75	71	No
2	China	July	241·8	969·7	1134·9	19266	419·7	27	Yes
3	Indonesia	December	196·9	196·9	227·6	1012	99·4	62	No
4	Nigeria	July	178·5	178·5	181·5	359	117·5	59	No
5	Pakistan	August	168·0	168·0	172·5	236	36·2	90	No
6	Bangladesh	July	162·9	162·9	162·9	106	30·8	94	No
7	Vietnam	September	82·7	82·7	85·6	481	142·4	54	Yes
8	Philippines	July	70·2	70·2	80·9	3597	135·2	55	Yes
9	Thailand	September	59·3	59·3	60·5	1464	360·4	31	No
10	Myanmar	June	50·9	50·9	53·4	47	20·3	101	No
11	Democratic Republic of Congo	November	47·3	47·3	62·1	105	11·6	104	Yes
12	Tanzania	March	35·9	35·9	42·9	567	51·7	80	Yes
13	Sudan	August	32·9	32·9	33·0	1	129·8	56	No
14	Nepal	July	26·5	26·5	30·2	50	39·9	86	No
15	Uganda	April	24·6	24·6	30·4	39	52·3	79	No
16	Mozambique	February	23·4	23·4	23·7	568	42	85	No
17	Taiwan	July	22·0	22·0	22·3	1259	*No data*	*No data*	No
18	Kenya	April	21·7	21·7	28·1	457	77·7	69	No
19	Malaysia	November	21·7	21·7	26·9	927	455·8	26	No
20	Ethiopia	July	22·4	22·4	44·5	350	26·6	97	No

*Based on the month when the size of the population exposed to dengue virus was predicted to be greatest

†Based on alignment of month of peak E=exposure to Zika virus (based on dengue extent) and months with peak travel volumes (defined as top quartile)