Trends in Dengue Cases Imported into the United States from Pan America 2001–2012

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ABSTRACT: The objective of this study was to improve risk assessments of travel on dengue (DEN) virus (DENV) distribution. We investigated the exposure risk of US citizens traveling to DEN-endemic Pan American countries. The number of DEN cases reported in 51 Pan American countries from 2001 to 2012 was compared to the population of the same countries. The number of US travelers visiting the Pan American countries was categorized by region, and travel-related DEN infections were analyzed. US residents visiting the Dominican Republic exhibited the highest traveler-related DEN incidence. Brazil showed the most DEN cases in its residents (>1 million reported cases in 2010). The number of DEN cases continues to rise as does international travel and the geographic range of potential DENV vectors. DENV risk assessments may be improved by analyzing the possible routes of entry. Underreporting remains an issue for calculating DENV transmission risk by country and region.

KEYWORDS: dengue incidence, international travel, Pan America

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Introduction

Dengue (DEN) fever is the most diagnosed traveler-related illness, with 390–400 million cases/year worldwide[1,2] and an incidence rate of ~2.5%–5% of >2 billion people at risk.[3] However, only an estimated 3%–8% of symptomatic travelers are DEN virus (DENV)-positive via serological tests.[4] Infection with one DENV serotype may cause a range of symptoms (eg, asymptomatic, flu-like). Simultaneous and/or sequential infection with different serotypes increases the risk of serious illnesses such as DEN hemorrhagic fever (DHF) and DEN shock syndrome, which could lead to death.[5] Often, patients are unaware of initial infection and experience severe symptoms when secondary infection with another serotype occurs.[5]

A greater understanding of human travel patterns between DEN-endemic countries and the United States may improve risk assessments and identify potential routes of entry for DENV. The geographic ranges of the four DENV serotypes are expected to expand with international travel as humans are the primary reservoirs.[6] This increases the likelihood of multi-serotype epidemics that could impact public health. Risk assessments showing the impact of travel on DENV importation are essential to understand the role of human travel in pathogen spread.

Pan America can be categorized into four regions, that is, North America, Central America, South America, and Caribbean. Most DEN cases among US citizens occur as a result of endemic transmission in Puerto Rico, a US territory.[7] In 2010, 162,058,000 visitors entered the United States.[8] Of those, 1,197,866 were Brazilian.[9] DEN is endemic in Brazil where all four serotypes of DENV circulate.[10] Travelers returning to the United States from Brazil accounted for 70% of imported DEN cases between 1998 and 2008.[11,12]

Globally, >2 billion people/year are at risk for DEN infection and >21,000 DEN-related deaths/year occur; yet, the range of possible symptoms makes it difficult for medical diagnoses without a serological test.[13] Studies have identified young age, high body mass index, female sex, virus serotypes, and virus genotype as risk factors for severe DEN.[13] Patients recovering from DHF may experience symptoms such as fatigue for up to six months.[13]

These increased risks are important due to the economic burden of lost work time and associated medical costs.[14,15] A study of 2012 healthcare costs in the Philippines reported $345 million ($3.26 per capita) spent in direct medical costs for patients with DEN.[16] Pan American residents spend ~$2.1 billion/year for DEN-related medical costs.[17] In the United States, each person hospitalized with DEN pays ~$17,803 and less severe cases cost ~$1,610.[17] The median cost of medical treatment throughout Pan America is $1,227.[17] Costs vary substantially between countries due to the value of currency and variation in expenses, that is, difference in costs between hospitals.[18] Adequate healthcare facilities are not accessible to all patients with DEN, hence underreporting likely occurs.[19]

DENV was first isolated in 1943, and serological tests were subsequently made available.[19] Currently, DEN cases are diagnosed based on symptoms rather than serological tests that are used simply to confirm infection for research.[19] Before 1970, DEN had only been detected in nine countries; however, by 1996, 102 countries had experienced epidemics.[20] In 1962, a comprehensive mosquito control effort was developed and implemented by the Brazilian government, Pan American Health Organization (PAHO), and the Rockefeller Foundation.[19] Although this effort attempted to eradicate the primary DENV vector, *Aedes aegypti* L., reinfestation occurred when plans deteriorated due to the loss of political interest.[12,19] Insufficient community participation and lack of support from the health sector added to the deterioration of the eradication program.[19] By 1980, DEN outbreaks increased globally, and in 1981, Cuba experienced an outbreak with 344,203 cases, including >10,000 DHF cases and >150 deaths.[19] From 2000 to 2012, all four DENV serotypes were found in Pan America, causing the highest number of cases to date.[19]

A. aegypti and *Aedes albopictus* Skuse are the two primary vectors of DENV and are distributed through Pan America.[13] *A. albopictus*, a day-biting species originally found in Asia, began geographic expansion in the 1980s and is still expanding today.[21] This anthropophilic mosquito species was introduced into the United States in 1985 from Asia in a shipment of tires.[14,22–24] *A. aegypti* takes multiple blood meals; hence, this species may infect multiple humans during a single gonotrophic cycle.[25] This mosquito species will stop blood feeding when disturbed and either return to the same host or a different host to complete a blood meal.[14,15] Rapid expansion of international and domestic human travel, urban sprawl, and insufficient vector control may facilitate the geographic expansion of DENV.[19]

Here, we conduct a risk assessment for 2001–2012 based on (1) residents and DEN cases in 51 Pan American countries, (2) visitors from 51 Pan American countries traveling to the United States, and (3) US residents traveling to DEN-endemic Pan American countries.

Materials and Methods

Travel statistics for 51 Pan American countries were tabulated from the Compendium of Tourism Statistics and the Office of Travel and Tourism Industries for 2001–2012 (Table 1).[9] Countries were categorized by region (ie, North America, Central America, South America, and Caribbean), and populations for 51 countries were tabulated.[26] For the purposes of this study, North America includes Canada and the United States, while Mexico is included in Central America. The number of clinically reported DEN cases was collected from the PAHO[10] and the Centers for Disease Control and Prevention (CDC) (J. Lehman, personal communication). The number of DEN cases was compared to the annual travel statistics and populations for each region. Regions with the most visitors to the United States were ranked, and further analyses were conducted for 18 countries whose residents visited the United States most frequently. The incidence rate per 100,000 people was determined ([the number of DEN cases reported in the country/the population of the country] × 100,000). Due to unreported data, Canada was excluded from North America for the purposes of calculating incidence rate. To determine the potential risk of traveling to an endemic country and becoming infected, the number of United States citizens traveling to each region was multiplied by the incidence rate for that region. This method was repeated for each consecutive year studied. The CDC provided information on DEN cases imported into the United States by citizen travelers from 2003 to 2011 (J. Lehman, personal communication). The number of imported DEN cases from each of the same 18 Pan American countries (residents visited the United States most frequently) was divided by the total number of cases for each year in each country to determine the country where the highest rate of incidence occurred in United States travelers.

Maps were created using Environmental Systems Research Institute ArcMap 10.1 (ESRI). Incidence rates[10] were input into attribute tables for specific countries. Graduated colors were used to display incidence rate per 100,000 people for each country. Maps were created for 2004, 2008, and 2012 to show spatiotemporal trends for the countries relevant to our study.

Results

We generally observed yearly increases in international travel to the United States from all regions of Pan America from 2001 to 2012 (Fig. 1). For the time period studied, most Pan American DEN cases occurred in Brazil (South American region), with >1 million cases reported in 2010 alone (Table 1). For US citizens, the highest number of imported DEN cases were observed in continental US travelers visiting the Dominican Republic, closely followed by Puerto Rico (Caribbean Region).

Table 1 shows that reported clinical cases of DEN have increased where surveillance systems have become a priority, such as Brazil (mandatory reporting started in 2007). The South American Region had the highest number of DEN cases over the 12 years studied (Fig. 2). Incidence rates in all regions have increased since 2001 with the worst epidemics occurring in 2010 (Fig. 3). Of the 18 countries studied, Brazil (third highest number of travelers to United States) showed the highest number of DEN cases. The DEN incidence rate was highest in the South American region (341 cases/100,000 people in 2010), primarily attributed to Brazil. The Caribbean and South American regions both experienced DEN epidemics in 2010, while Central America had an epidemic in 2009 (Fig. 2). However, there is a large population difference between the South American Region and other regions such as the Caribbean, and Figure 3 accounts for these differences, that is, regional incidence with the population taken into account.

Figures 4–6 show DEN incidence in 2004, 2008, and 2012, respectively. In 2004, several countries had incomplete data available due, in part, to underreporting. Countries with higher incidence rates have at least three DENV serotypes

Table 1. Serologically confirmed DEN cases in 51 Pan American countries from 2001 to 2012.

COUNTRY	YEAR											
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
North America												
Canada	–	–	–	–	–	–	–	–	–	–	–	–
United States	96	29	40	10	98	143	488	199	178	648	283	545
Central America												
Belize	3	41	–	2	380	9	40	23	1,457	2,178	469	1,948
Costa Rica	9,237	12,251	19,669	9,408	37,798	12,124	26,440	7,160	6,946	31,773	13,854	22,243
El Salvador	1,093	18,307	7,436	13,344	15,290	22,088	12,476	5,774	15,040	22,406	20,836	41,793
Guatemala	4,516	7,599	6,750	6,352	6,341	2,428	5,886	3,230	10,438	17,045	2,565	9,547
Honduras	9,077	32,269	16,559	19,971	18,843	8,436	33,508	18,941	15,291	66,814	8,297	15,554
Mexico	6,210	9,844	5,018	8,202	16,862	27,287	48,436	31,154	249,763	57,971	67,918	164,947
Nicaragua	2,104	2,157	2,799	1,035	1,735	1,350	1,415	1,424	17,140	6,261	11,888	30,499
Panama	1,545	711	293	373	4,000	4,300	3,402	2,287	6,811	1,243	3,882	1,329
South America												
Argentina	11	214	135	3,284	34	181	173	40	26,612	1,185	213	2,043
Bolivia	176	892	6,548	7,390	4,443	2,040	7,332	3,181	84,047	5,191	26,681	42,704
Brazil	416,067	780,644	341,902	112,928	203,789	346,550	559,954	734,384	528,883	1,004,392	764,032	565,510
Chile (Only Easter Island)	–	636	–	–	–	3	28	25	27	–	1	34
Colombia	55,437	76,996	52,588	27,523	30,475	36,471	43,227	26,732	51,543	157,152	33,207	49,361
French Guiana	2,830	280	2,178	3,147	4,365	15,930	661	460	11,330	4,350	667	1,372
Guyana	60	202	33	47	178	118	201	324	994	1,468	1,093	2,189
Ecuador	10,919	5,833	10,319	6,165	12,131	6,044	10,587	1,894	4,489	1,042	7,659	18,995
Paraguay	38	1,871	137	164	405	4,271	28,182	1,953	6,143	13,553	42,945	33,063
Peru	23,329	8,875	3,637	9,774	6,358	5,531	6,907	10,278	8,813	18,392	29,810	29,994
Suriname	760	1,104	285	375	2,853	285	41	24	120	113	409	781
Uruguay	–	–	–	–	–	–	–	–	–	–	–	–
Venezuela	83,180	37,676	26,996	30,693	42,198	39,860	80,646	48,048	65,869	123,967	31,551	49,044
Caribbean												
Cuba	11,432	3,011	–	–	75	–	28	–	70	–	–	–
Dominican Republic	3,592	3,194	6,163	2,476	2,860	6,143	9,628	4,333	8,292	11,519	2,339	9,665
Puerto Rico	5,233	2,906	3,735	3,288	5,701	3,043	11,012	3,384	6,651	21,298	5,654	12,877
American Virgin Islands	–	–	–	–	–	–	73	–	–	–	–	–
Anguilla	25	5	2	–	–	–	–	9	–	1	9	9
Antigua and Barbuda	20	5	–	–	–	–	–	17	–	3	7	10
Aruba	–	25	–	173	–	5	–	–	845	1,415	3,027	667
Bahamas	–	–	180	1	–	–	–	1	–	8	7,000	5
Barbados	1,043	740	557	349	320	1	–	1	55	2,917	745	1,445
Bermuda	–	–	–	–	2	2	–	–	–	2	1	–
British Virgin Islands	23	–	–	–	1	–	6	15	65	9	939	214
Cayman Islands	–	1	1	–	1	–	9	1	–	8	2	53
Curacao	–	–	–	–	265	–	–	–	–	1,723	1,555	721
Dominica	5	–	–	4	11	19	111	80	2	635	40	29
Grenada	12	84	17	7	–	22	–	6	23	125	87	75

(*Continued*)

Table 1. (*Continued*)

COUNTRY	YEAR											
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Guadeloupe	–	93	495	–	3,364	2,948	3,266	2,234	2,234	41,100	824	1,032
Haiti	–	–	–	–	–	–	–	–	–	–	–	240
Jamaica	39	90	52	9	46	79	1,448	359	70	2,827	408	4,670
Martinique	4,471	392	791	–	6,083	4,086	5,082	586	1,378	37,100	275	1,269
Montserrat	1	1	1	–	–	–	–	2	–	–	3	1
Netherlands Antilles	–	–	–	–	–	–	–	–	–	852	939	121
St. Bartolome	–	–	–	–	–	–	–	–	805	–	23	32
St. Kitts and Nevis	89	20	2	4	–	1	–	49	2	19	47	1
St. Lucia	292	51	5	11	1	–	39	98	18	74	585	33
St. Martin	–	–	–	–	–	–	–	–	1,698	2,450	168	253
St. Vincent and the Grenadines	3	125	3	4	8	5	2	6	10	133	47	193
Trinidad and Tobago	2,244	6,246	2,289	546	411	37	47	2,366	24	2,497	1,243	2,473
Turks and Caicos Islands	–	–	2	1	1	–	–	–	–	–	24	16

Note: –, data not available.[9,10]

circulating (eg, Brazil, Venezuela, and Mexico), and its residents travel to the United States most frequently. Table 2 shows that the number of DENV serotypes in most countries increased between 2004 and 2012. Caution is advised in interpreting Figures 1 and 2 since most countries did not mandate DEN reporting until 2009.

Discussion

Most US citizens experiencing DEN acquired the illness while visiting the Dominican Republic, closely followed by Puerto Rico (Caribbean Region). Countries endemic for DEN pose a higher risk for travelers than nonendemic countries and thus create a higher risk for DENV incidence and spread. As travel and geographic range of potential DENV vectors continue to increase, incidence of DEN will likely increase.[14] There is also an increased risk of introducing new DENV serotypes into naïve populations. Regions that are visited frequently and where all four DENV serotypes are prevalent (eg, South America) pose the greatest risk to travelers.

A. albopictus and *A. aegypti* are both found in the United States; hence, traveler-imported cases are a concern for some

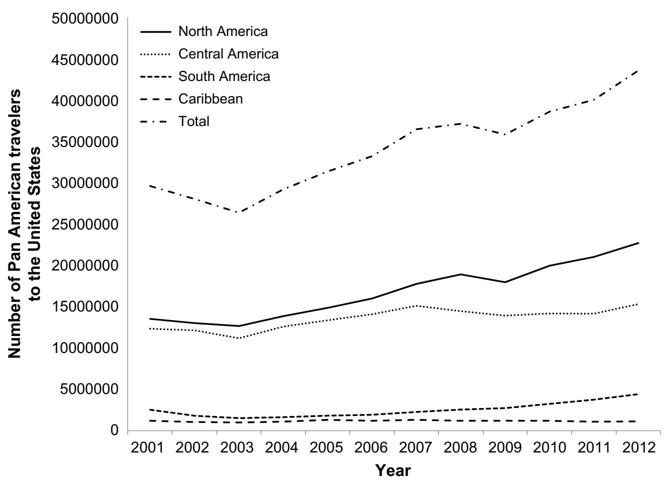

Figure 1. International travel to the United States from Pan American regions.

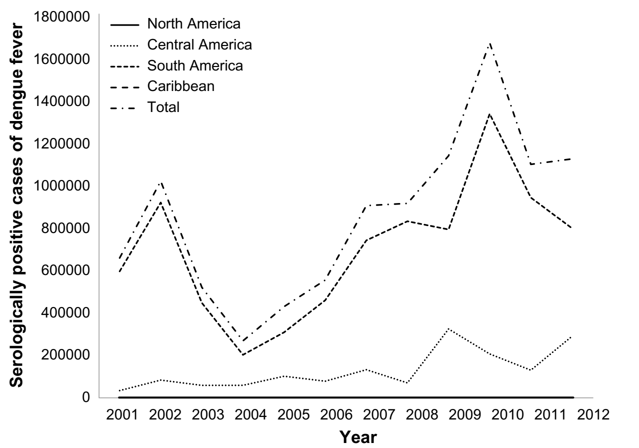

Figure 2. Serologically confirmed DEN cases in Pan American regions. **Note:** Data from Canada are not included since DEN is not a reportable infection.

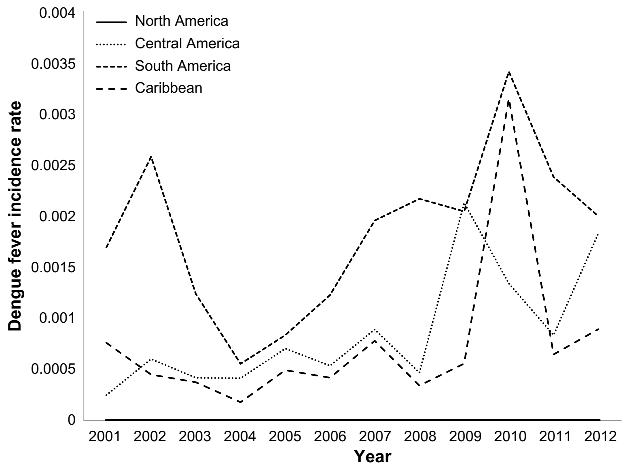

Figure 3. Incidence rate of DEN infection in Pan American regions. Regional incidence rate = ([the number of DEN cases reported in the region/the population of the region] × 100,000). Data from Canada are not included since DEN is not a reportable infection.

regions since local mosquito populations may contribute to subsequent transmission. Florida had 125 locally transmitted cases from 2009 to 2014, while Hawaii (four cases in 2011), Texas (24 cases from 2013), and New York (one case in 2013) also experienced locally transmitted cases.[15,27] In the United States, there were 177 imported human DEN cases reported from 22 different states in 2009, 642 imported cases from 39 states in 2010, 245 imported cases from 32 states in 2011, 544 imported cases from 34 states in 2012, 772 imported cases from 41 states in 2013, and 357 imported cases from 37 different states in 2014 (J. Lehman, personal communication[27]).

Until 2009, DEN was not a nationally reportable disease in many Pan American countries, including the United States; hence, cases prior to 2009 may be underreported. Some countries only report serologically positive cases; hence, physician-diagnosed cases (relying solely on symptoms) may be underreported.[10] Increases in DEN cases reported here after 2009 may be an indication of improved surveillance in addition to increasing incidence of cases.

While underreporting and misdiagnosis remain an issue for calculating DENV transmission risk, we observed increases in case frequency for the period studied. Many patients infected with one serotype of DENV are asymptomatic or experience flu-like symptoms and do not seek medical treatment.[28] Others cannot afford to go to the doctor or do not have easy access for treatment and, therefore, go unreported.[14] There is a lack of uniform application of the case definition of DEN, and some countries have instituted their own case definitions.[29] In addition, complicated reporting systems and/or lengthy reporting requirements may reduce motivation of health care workers to submit positive test results.[3] Underreporting impacts public health because it is an enormous

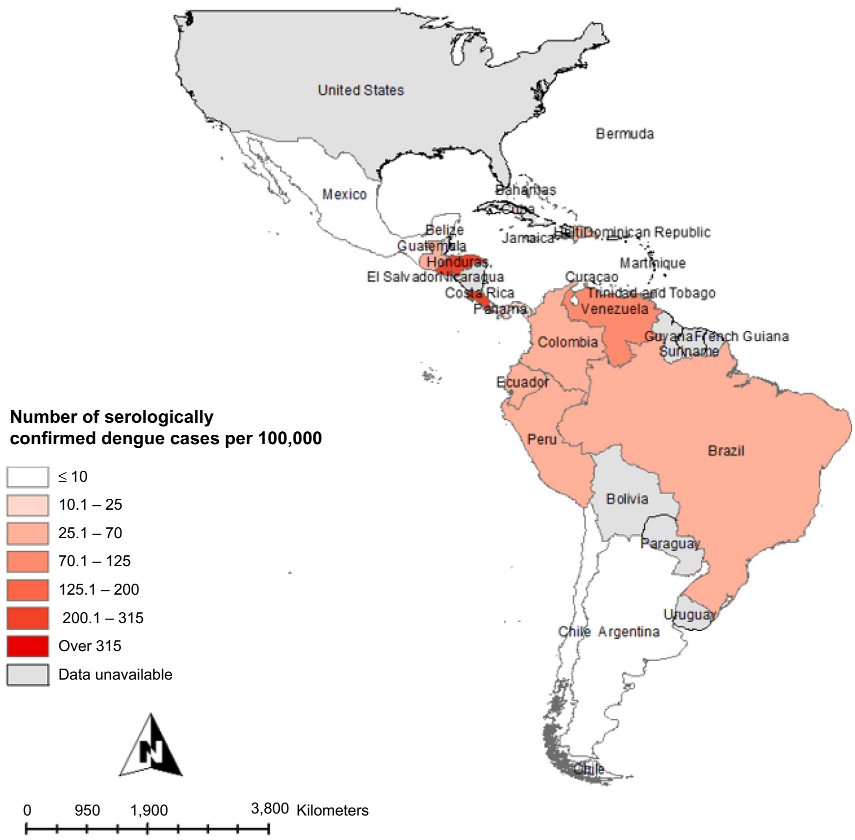

Figure 4. DEN incidence rates in Pan America in 2004.

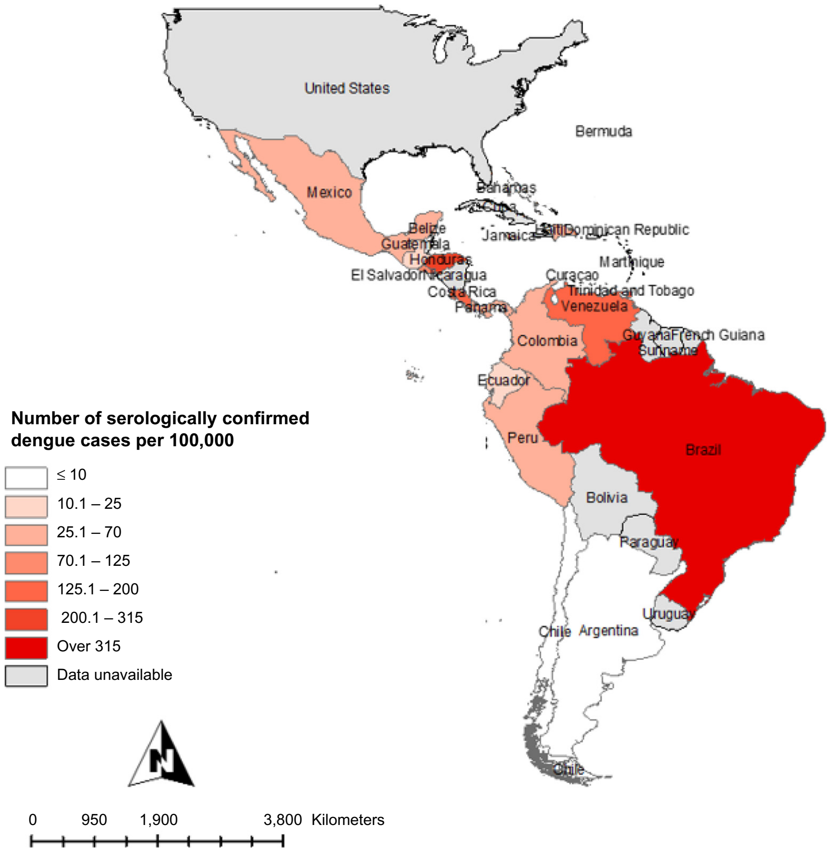

Figure 5. DEN incidence rates in Pan America in 2008.

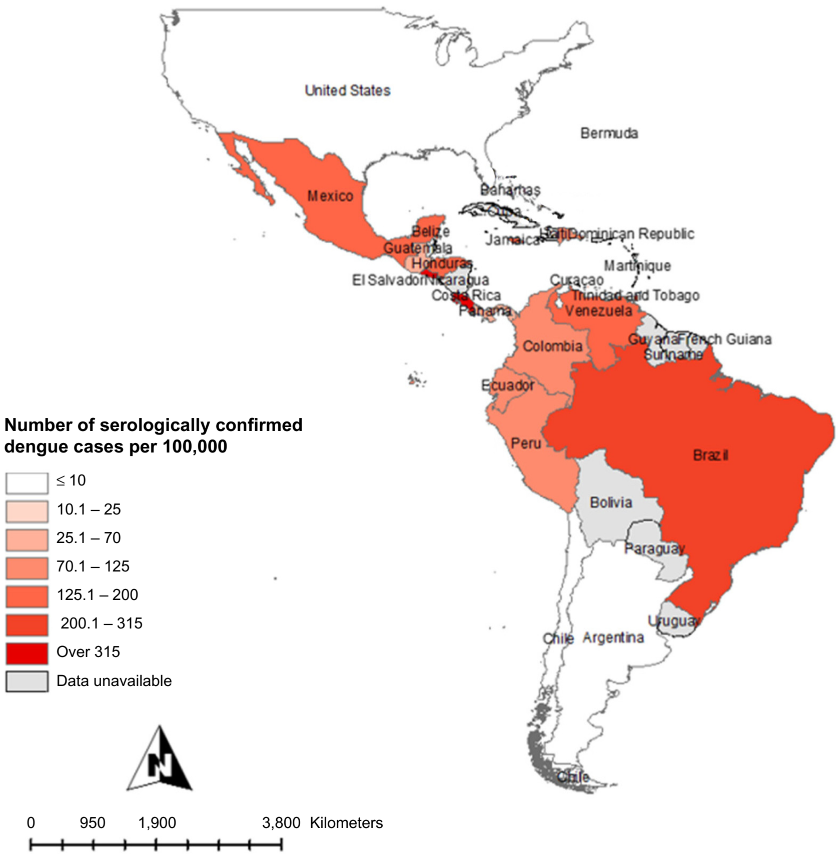

Figure 6. DEN incidence rates in Pan America in 2012.

Table 2. DEN serotypes detected in 18 Pan American countries that visited the United States most frequently in 2001–2012[10].

COUNTRY	YEAR											
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
North America												
Canada	–	–	–	–	–	–	–	–	–	–	–	–
Central America												
Costa Rica	2	1,2	1,2	1,2	1	1,2	1	1,2	1,2	1,2,3	1,2,3	1,2,3
El Salvador	2	1,2,3,4	2,4	1,2,4	2,4	1,2,4	1,2	–	1,2,3,4	1,2	1,2,3,4	1,2,3
Guatemala	2,4	2,3,4	1,2,3,4	1,2,3,4	1,2,3,4	1,2,4	1,2,4	1,2	2,4	1,2,3,4	1,2	1,2,3
Honduras	2,3,4	2,4	1,2,4	1,2,4	1,2,4	–	1,2,4	2,4	1,2	1,2,3,4	1,2	1,2
Mexico	–	1,2,3	–	1,2,3,4	1,2,3	1	1,2,3,4	1,2,3	1,2,3,4	1,2,3	1,2,3,4	1,2,3,4
Panama	2	2	2	1,2,3	1,2	–	3	3	1,3	1,3	1,2,3	1,2,3
South America												
Argentina	–	1,3	1,2,3	3	2	2,3	2,3	1	1	1,2,3	–	2,3
Brazil	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3	1,2,3,4	1,2,3,4	1,2,3,4
Chile (Only Easter Island)	–	1	–	–	–	–	1	1	1,4	–	1	–
Colombia	1,2,4	1,3,4	1,2,3	1,2,3,4	1,2,3,4	1,2,3,4	1,2,3,4	1,2,3,4	1,2,3	1,2,3,4	–	–
Ecuador	1,2	1,2,3	3	3	2	3	3	–	1,3	1,2,3	1,2	2,4
Peru	1,2,3,4	1,3	1,2,3	1,2,3	1,2,3,4	3	1,2,3,4	1,3,4	1,2,3,4	1,2,3,4	1,2,3,4	1,2,3,4
Venezuela	1,2,3,4	2,3,4	1,2,3	1,2,3,4	1,2,3,4	1,2,3,4	1,2,3,4	1,2,3,4	1,2,3,4	1,2,3,4	1,2,3,4	1,2,3,4
Caribbean												
Dominican Republic	–	2	2	2,4	–	1,2	1,2,3,4	–	1,2,4	1,2,4	2	2
Bahamas	–	–	2,4	–	–	–	–	–	–	1,2	1	–
Jamaica	–	–	–	–	–	–	2,4	3	–	2	–	–
Trinidad and Tobago	2,3	2,3	3	–	2,3	2,3	3	2,3	2	2	1,4	–

Note: –, data not available.

barrier to obtaining an accurate risk assessment. In Belo Horizonte, Brazil, the level of reporting of hospitalized patients with DEN was ~63% between 1997 and 2002.[30]

Identification of DENV via cell culture or nucleic acid detection (polymerase chain reaction) requires sophisticated laboratories,[31] and there is limited accuracy in rapid tests.[3] As a result, the mobilization of resources from the local, national, and international communities for the elimination of the vector and better infection care[3] needs improvement.

There is no DEN vaccine,[32] and there is great concern for people already infected with one or more serotypes regarding their reaction to a vaccine.[33] With >43 million travelers entering the United States by air from Pan American countries, the risk for travel-related DEN exists. Continued surveillance, improved DEN-reporting systems, and risk assessment are needed to prevent further DEN expansion and reduce the risk of importation.

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Author Contributions

Conceived and designed the experiments: CAMV, SLR. Analyzed the data: CAMV. Wrote the first draft of the manuscript: CAMV. Contributed to the writing of the manuscript: CAMV, SLR. Agreed with manuscript results and conclusions: CAMV, SLR. Jointly developed the structure and arguments for the paper: CAMV, SLR. Made critical revisions and approved the final version: CAMV, SLR. Both authors reviewed and approved the final manuscript.

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