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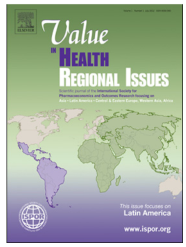

CLINICAL OUTCOMES STUDIES

Dengue Epidemiology and Burden of Disease in Latin America and the Caribbean: A Systematic Review of the Literature and Meta-Analysis

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A B S T R A C T

Introduction: Dengue virus infection is the most common arthropod-borne disease worldwide with approximately 50 to 100 million cases of dengue infection occurring annually. Globally, dengue incidence has increased in the last 40 years, especially in Latin American and Caribbean (LAC) countries where the highest incidence is found. This systematic review aimed to present information on dengue disease burden and use of health resources in the LAC region in the last 15 years. **Methods:** We searched the main international and regional databases and generic and academic Internet search engines. Gray literature was retrieved mainly from regional health ministries and Pan American Health Organization. A set of inclusion criteria was defined. **Results:** We identified 2,041 articles of which 25 met these criteria, 13 for incidence and 12 for the use of resources and related costs. The pooled incidence of classic dengue fever was 72.1 cases per 100,000 persons-years in the 44 LAC countries analyzed (95% confidence interval 71.5–72.7), with an upward trend from 1995 up to 2010. Case-fatality ratio was highest in 1997 (0.12 [0.05–0.22]) and lowest in 2009, and the overall mortality was 0.02 per 100,000 people. More than 60% of the cases in the LAC region came from Brazil. The length of hospital stay ranged from 5 to 13 days. **Conclusions:** Activities to control dengue transmission in the region have been important but insufficient. The surveillance of dengue burden of disease and circulating strains help shape and evaluate the present and future health policies.

Keywords: dengue, disease burden, disease costs, epidemiology, Latin America, resource use.

Introduction

Dengue virus infection is transmitted primarily by *Aedes aegypti* and is the most common arthropod-borne disease worldwide. There are approximately 50 to 100 million cases of dengue infection annually. Roughly 2.5 billion people live in endemic areas that receive around 120 million travelers each year. The worldwide incidence of dengue and dengue hemorrhagic fever (DHF) has increased over the last 40 years with an expanding geographic distribution [1], especially in Latin America [2] The most important macro determinants responsible for this rise include increasing population density, poor sanitary conditions in urban areas, deterioration of public health systems, and lack of effective vector control programs in many countries. Globalization of the economy, international travel, and climatic changes might also play a role in the spread of the disease [3]. Four types of dengue virus have been identified up to date: DENV-1, DENV-2, DENV-3, and DENV-4 [4,5]. During the 1960s and early 1970s, dengue transmission was partially interrupted in the Americas because of an *Aedes aegypti* mosquito eradication campaign designed to prevent yellow fever [6]. Vector surveillance and vector control measures, however, were not continued and mosquito reinfestations occurred, causing outbreaks by DEN-2 and DEN-3 in the Caribbean, Central America, and South America [7]. In the late 70s and early 80s, DEN-1 and DEN-4 were introduced in some Latin American and Caribbean (LAC) countries, causing devastating epidemics [8]. Since then, the region has reported the highest incidence of cases worldwide (68% of all cases worldwide from 2000 to 2006), with periodic outbreaks every 3 to 5 years. The largest occurred in 2002, with more than 1 million reported cases [9–11]. The average incidence rate of dengue cases reported in these countries for the period 2000 to 2007 was 71.5 per 100,000 people annually, and increased in relation to the period 1990 to 1999. The average incidence rate of DHF was 1.7 per 100,000 for the period

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2000 to 2007, with 1391 deaths occurring in this period [9]. The direct and indirect costs of dengue illness and vector control programs represent a substantial economic burden on both the health sector and the overall economy of the region [10]. The high morbidity and mortality associated with this disease leads to a serious drain on the economies and the health systems of the affected countries; for example, a recent study reported a US $2.1 billion average cost due to the dengue epidemic in the Americas per year [11].

There are two approaches to the prevention and control of dengue and DHF: vaccines and vector control programs. Unfortunately, vaccines for these viruses are still under development, and vector control programs are costly and difficult to sustain. Also, there is little information regarding economic evaluations of dengue control programs in Latin America and the Caribbean.

To evaluate the cost-effectiveness of new treatment alternatives and the introduction of a vaccine in the region, it is crucial to count with estimates of the epidemiologic burden of the disease in LAC countries, taking into consideration incidence, morbidity and mortality, serotype circulation, and health resource impact. We conducted a systematic review on dengue disease burden and use of health resources in the LAC region for the period 1995 to 2010.

Methods

Search Strategy and Selection Criteria

We conducted a systematic literature review based on scientific literature from international and regional databases, generic and academic Internet search, and meta-search engines. Databases containing regional proceedings or congresses' annals and doctoral theses were searched. Web sites from main regional medical societies, experts, and related associations were consulted. An annotated search strategy for gray literature was included to retrieve information from relevant sources such as regional Ministries of Health, Pan American Health Organization (PAHO), and reports from hospitals.

The search was limited to CENTRAL (The Cochrane Library Issue 2010), MEDLINE, EMBASE, and LILACS (Latin American and Caribbean Health Science Literature) between January 1995 and November 2010. No language restriction was applied. The search strategy is detailed in Annex 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2013.10.002. The reference lists of articles finally included were manually searched for additional information. If data or data subsets of the same population were published in more than one source, the one with the largest sample size was chosen. Authors of relevant articles were contacted to obtain missing or extra information. Epidemiologic outcome measures included incidence, mortality, case-fatality ratio, hospitalizations, and patterns of circulation over time and serotype distribution over time. Economic outcomes included resource usage, indirect costs, and total costs of epidemics. Studies of any epidemiological design, economic evaluations, and costing studies published were included, when at least 50 cases were evaluated with data collection from 1995 onwards. Dengue being a disease with mandatory notification, all studies providing information at country level/province level supplemented the official countries' Ministries of Health databases (see Annex 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2013.10.002) and were thus included for meta-analyses, as long as no evidence of double counting of cases was detected.

Recently, the traditional World Health Organization dengue classification scheme (classic dengue fever, DHF, and dengue shock syndrome) was replaced with dengue without warning signs, dengue with warning signs, and severe dengue. We decided, however, to stick to the case definition and classification proposed by PAHO in its epidemiological bulletin because most PAHO data for the period of interest were reported in that way [12].

Review Methodology

Pairs of reviewers independently selected the articles on the basis of title and abstract according to prespecified criteria. During a second screening process, different pairs of reviewers independently categorized articles on the basis of retrieved full texts. Authors of articles were contacted when necessary to obtain missing or supplementary information. The risk of bias for observational studies was assessed through the Strengthening

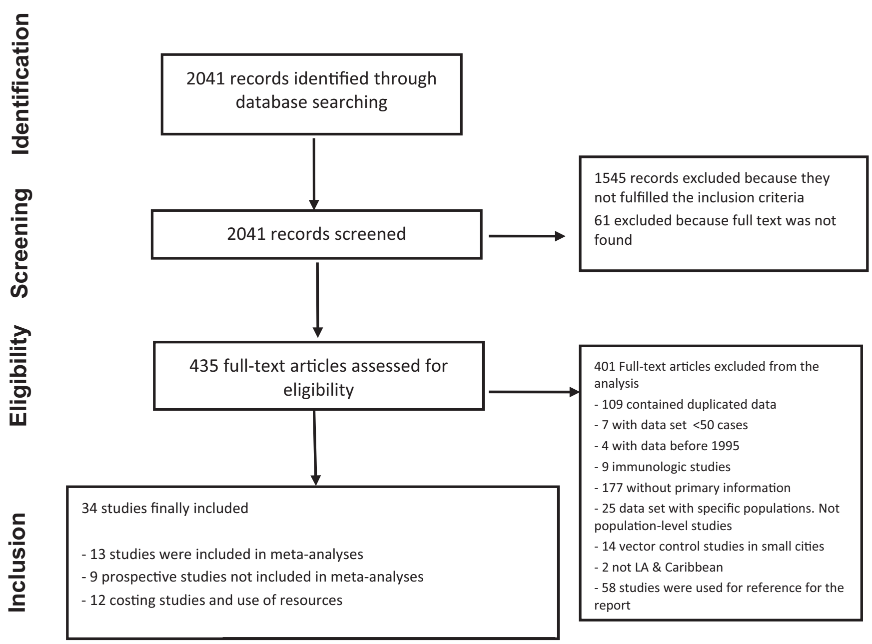

Fig. 1 – Study flowchart. LA, Latin American.

Table 1 – Characteristics of studies selected to supplement official countries' MoH databases for meta-analyses.

Author and reference	Design	Population	Outcome measures	Summary risk of bias
Salgado et al. [16]	*Design:* cross-sectional hospital-based study *Setting:* Neiva Huila, Colombia	Hospitalized children 0–13 y	Number of cases of hemorrhagic dengue Number of deaths	Low
Rigau-Perez [17,18]	*Design:* surveillance study *Setting:* Puerto Rico	Hospitalized and ambulatory population	Number of persons with dengue (classic and hemorrhagic) Serotypes Incidence of dengue/100,000 persons	Low
Ocazionez [19]	*Design:* surveillance study *Setting:* Santander, Colombia	General population	Number of persons with dengue	Low
Lyerla [20]	*Design:* surveillance study *Setting:* British Virgin Islands	Outpatient population	Number of persons with dengue	Very high
Harris et al. [21]	*Design:* surveillance study *Setting:* Nicaragua	Hospitalized and ambulatory population	Number of persons with clinical classic dengue Number of persons with hemorrhagic dengue	Low
Guzman [22]	*Design:* surveillance study *Setting:* Cuba	Hospitalized population	Number of persons with clinical classic dengue Number of persons with hemorrhagic dengue Incidence of classic dengue/ 1,000 person-years Incidence of hemorrhagic dengue/1,000 person-years	NA
Escobar-Mesa [23]	*Design:* ecologic study *Setting:* Veracruz, Mexico	Ambulatory patients	Number of persons with clinical classic dengue	Low
Chuit [24]	*Design:* ecologic study *Setting:* Argentina	General population	Number of persons with dengue (classic and hemorrhagic)	Low
Añez et al. [25]	*Design:* surveillance study *Setting:* Zulia, Venezuela	Hospitalized population	Number of persons with clinical classic dengue Number of persons with hemorrhagic dengue Incidence of classic dengue/ 1,000 person-years Case-fatality rate	Moderate
Chadee [26]	*Design:* surveillance study *Setting:* Trinidad & Tobago	General population	Number of persons with dengue (classic and hemorrhagic) Incidence of hemorrhagic dengue/100,000	Moderate
Anonymous [27]	*Design:* surveillance study *Setting:* Nicaragua	Children 1–9 y	Number of children with dengue (classic and hemorrhagic)	Low
Anonymous [28]	*Design:* cross-sectional descriptive *Setting:* Costa Rica, Panama	General population	Number of persons with dengue	NA
Avila Montes [29]	*Design:* surveillance study *Setting:* Honduras	General population	Number of persons with dengue per region	Low

NA, not applicable/available.

the Reporting of Observational studies in Epidemiology [13] checklist of essential items, modified according to Sanderson et al. [14] and Fowkes and Fulton [15]. Briefly, we used an algorithm (see Annex 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2013.10.002) programmed in a spreadsheet to estimate a summary risk of bias considering five

Table 2 – Meta-analysis of classic dengue incidence: lethality and mortality and hemorrhagic dengue incidence by country (1995–2009)*.

Study name	Number of years	Classic dengue incidence per 100,000 (CI)	Number of years	Hemorrhagic dengue incidence per 100,000 (CI)	Number of years	Classic dengue lethality % (CI)	Number of years	Classic dengue mortality per 100,000 (CI)
All countries all years		72.1 (71.5–72.7)		1.59 (1.56–1.62)		0.05 (0.05–0.06)		0.02 (0.02–0.02)
By country								
American Virgin Islands			2	4.17 (0.00–12.33)			2	4.17 (−4.00 to 12.33)
Anguilla	12	22.0 (9.8–34.1)	7	4.49 (0.09–8.89)	5	2.01 (0.01–7.29)	7	3.94 (−0.20 to 8.09)
Antigua & Barbuda	14	6.3 (3.6–8.9)	6	0.62 (0.00–1.33)	4	1.82 (0.00–7.25)	6	0.63 (−0.08 to 1.34)
Argentina	11	1.6 (1.2–2.0)	8	0.00 (0.00–0.00)	9	0.02 (0.01–0.04)	9	0.00 (0.00–0.00)
Aruba	9	28.7 (21.3–36.0)	2	0.50 (0.00–1.49)	3	0.28 (0.02–1.44)	4	0.53 (−0.20 to 1.26)
Bahamas	11	2.8 (1.4–4.2)	7	0.17 (0.00–0.35)	3	0.20 (0.07–1.36)	6	0.17 (−0.02 to0.36)
Barbados	13	162.5 (151.9–173.0)	10	0.17 (0.00–0.35)	8	0.10 (0.03–0.20)	10	0.23 (0.05–0.41)
Belize	13	15.5 (11.7–19.2)	7	0.19 (0.00–0.39)	5	0.14 (0.01–0.73)	5	0.18 (−0.04 to 0.41)
Bermuda	10	1.0 (0.2–1.8)	9	0.77 (0.06–1.47)	3	8.14 (0.04–31.81)	8	0.77 (0.02–1.52)
Bolivia	12	107.9 (95.7–120.0)	11	0.30 (0.22–0.38)	10	0.02 (0.01–0.05)	10	0.01 (0.00–0.02)
Brazil	14	196.7 (147.8–245.6)	14	0.62 (0.50–0.74)	14	0.01 (0.00–0.01)	15	0.03 (0.02–0.03)
British Virgin Islands	11	10.8 (4.0–17.6)	8	2.23 (0.04–4.41)	4	3.19 (0.00–12.52)	7	2.23 (−0.11 to 4.56)
Cayman Islands	12	2.0 (0.7–3.2)	8	1.16 (0.02–2.31)	4	14.64 (0.21–45.38)	7	1.18 (−0.06 to 2.42)
Chile	9	0.2 (0.1–0.3)	6	0.00 (0.00–0.01)	4	0.07 (0.01–0.41)	6	0.00 (0.00–0.01)
Colombia	14	101.9 (82.1–121.6)	14	9.23 (6.98–11.49)	14	0.07 (0.05–0.09)	14	0.07 (0.05–0.08)
Costa Rica	14	297.5 (214.5–380.6)	11	1.52 (1.07–1.98)	11	0.01 (0.00–0.01)	11	0.02 (0.00–0.03)
Cuba	8	12.4 (11.8–13.0)	6	0.19 (0.12–0.25)	4	0.11 (0.00–0.37)	7	0.01 (0.00–0.02)
Curaçao	4	21.9 (12.9–30.9)	2	0.37 (0.00–1.09)			2	0.37 (−0.35 to 1.09)
Dominica	13	28.4 (20.3–36.4)	9	1.08 (0.08–2.08)	6	0.46 (0.00–1.73)	7	0.70 (−0.03 to 1.43)
Dominican Republic	12	49.7 (36.6–62.8)	15	1.27 (0.88–1.66)			14	0.20 (0.14–0.27)
Ecuador	14	61.4 (45.4–77.4)	9	1.26 (0.85–1.66)	10	0.03 (0.01–0.06)	10	0.01 (0.00–0.02)
El Salvador	14	144.7 (105.9–183.5)	13	2.25 (1.95–2.55)	10	0.09 (0.03–0.18)	10	0.07 (0.04–0.11)
French Guiana	11	1444.1 (1020.2–1867.9)	13	0.64 (0.15–1.13)	7	0.02 (0.01–0.04)	9	0.30 (0.04–0.56)
Grenada	14	24.2 (17.8–30.5)	9	0.57 (0.08–1.05)	4	1.21 (0.00–4.70)	6	0.48 (−0.06 to 1.03)
Guadaloupe	11	161.6 (151.5–171.8)	8	1.19 (0.42–1.96)	6	0.05 (0.02–0.11)	7	0.16 (0.02–0.30)
Guatemala	14	46.0 (37.6–54.4)	14	0.13 (0.09–0.17)	10	0.06 (0.04–0.08)	10	0.02 (0.01–0.03)
Guyana	10	15.6 (10.2–21.0)	7	0.08 (0.00–0.15)	4	0.17 (0.00–0.71)	4	0.06 (−0.02 to 0.15)
Honduras	14	276.7 (214.4–338.9)	13	14.29 (11.77–16.80)	13	0.03 (0.03–0.04)	13	0.08 (0.05–0.11)
Jamaica	14	14.6 (12.0–17.1)	9	0.14 (0.03–0.24)	8	0.12 (0.04–0.26)	8	0.02 (0.00–0.04)
Martinique	13	435.5 (363.7–507.3)	10	1.74 (0.80–2.68)	7	0.08 (0.04–0.12)	8	0.34 (0.11–0.57)
Mexico	14	24.1 (17.6–30.7)	14	2.11 (1.59–2.63)	11	0.05 (0.02–0.08)	11	0.01 (0.01–0.02)
Montserrat	11	53.0 (16.4–89.6)	9	10.86 (0.80–20.93)	4	5.71 (0.00–21.24)	7	11.08 (−0.56 to 22.71)
Nicaragua	14	107.1 (79.7–134.5)	14	5.95 (4.38–7.52)	11	0.16 (0.12–0.20)	11	0.14 (0.08–0.19)

Table 2 – continued

Study name	Number of years	Classic dengue incidence per 100,000 (CI)	Number of years	Hemorrhagic dengue incidence per 100,000 (CI)	Number of years	Classic dengue lethality % (CI)	Number of years	Classic dengue mortality per 100,000 (CI)
Panama	14	70.0 (50.2–89.8)	12	0.08 (0.04–0.11)	11	0.03 (0.01–0.06)	11	0.02 (0.01–0.04)
Paraguay	10	107.2 (90.9–123.5)	9	0.02 (0.00–0.04)	9	0.02 (0.01–0.03)	9	0.01 (0.00–0.02)
Peru	15	25.7 (18.6–32.9)	9	0.13 (0.08–0.18)	10	0.01 (0.01–0.02)	10	0.00 (0.00–0.00)
Puerto Rico	14	151.3 (115.8–186.8)	14	1.00 (0.69–1.30)	14	0.08 (0.06–0.10)	14	0.09 (0.05–0.12)
St. Kitts & Nevis	11	23.3 (14.7–31.9)	6	1.22 (0.00–2.51)	4	0.49 (0.01–2.25)	5	1.05 (−0.25 to 2.35)
St. Lucia	14	21.3 (16.5–26.2)	11	0.35 (0.07–0.63)	7	0.23 (0.00–0.85)	8	0.32 (0.01–0.63)
St. Vincent & Grenadines	14	32.0 (23.7–40.3)	9	0.51 (0.06–0.97)	8	4.24 (0.43–11.68)	8	0.47 (0.01–0.93)
Suriname	14	157.6 (118.9–196.4)	10	3.65 (2.25–5.06)	6	0.21 (0.01–0.69)	6	0.14 (−0.04 to 0.32)
Trinidad & Tobago	14	146.6 (115.1–178.1)	12	4.10 (3.36–4.84)	9	0.13 (0.03–0.31)	9	0.09 (0.01–0.17)
Turks & Caicos Islands	9	3.1 (0.5–5.7)	7	2.50 (0.00–5.13)			6	2.47 (−0.34 to 5.28)
Uruguay	6	0.0 (0.0–0.0)	5	0.01 (0.00–0.03)			5	0.01 (0.00–0.03)
Venezuela	14	161.8 (124.9–198.7)	14	15.90 (12.46–19.34)	14	0.03 (0.01–0.06)	14	0.04 (0.02–0.05)

PAHO, Pan American Health Organization.
* Information from PAHO and relevant country-level studies. The availability of the data explains the different number of years considered for each country.

criteria (methods for selecting participants, methods for measuring exposure and outcome variables, methods to control confounding, design-specific bias, and statistical methods). Disagreements were solved by consensus. We followed the general guide lines of the Meta-analysis of Observational Studies in Epidemiology [30].

Statistical Analysis

To analyze our data, we conducted proportion meta-analyses. Arcsine transformations were applied to stabilize the variance of proportions (Freeman-Tukey variant of the arcsine square-root of transformed proportions method) [31]. The pooled proportion was calculated as the back-transformation of the weighted mean of transformed proportions, using inverse arcsine variance weights. We applied DerSimonian-Laird weights for the random effects model [32] when heterogeneity between studies was found [33]. We calculated the I^2 statistics as a measure of the proportion of the overall variation in the proportion that was attributable to between-study heterogeneity [34].

The person-time incidence rate, or incidence density rate, is an appropriate measure of incidence when follow-up times are unequal [35]. To calculate pooled incidence rate ratios, we used the Comprehensive Meta-Analysis software package (Biostat, Englewood, NJ). Specific type distribution was assessed by age, country, admission status, and, where possible, patterns of circulation of strains over different years.

Results

We identified 2041 articles through the search strategy after removing duplicates. Following the screening by title and abstract, 1545 articles were excluded because they did not meet the inclusion criteria and 61 because the full text was not available. A total of 435 studies were classified as potentially eligible (Fig. 1). After full-text analysis, 34 studies were deemed to be relevant and 25 were included. Thirteen studies were selected for the meta-analysis (see Table 1), and 12 studies were included for the use of resources and related costs analysis [16,21,25,36–43]. Nine prospective studies with active case detection were excluded from the meta-analyses because they did not provide country-level information; the results of these studies are summarized in the text, and their characteristics in Annex 4 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2013.10.002.

After the methodological quality assessment, 12 included studies were classified as low risk of bias and 10 as moderate risk of bias. The assessment was not applicable in 3 studies (see Annex 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2013.10.002). The I^2 statistic showed heterogeneity of more than 70% in the main meta-analyses.

Incidence, Lethality, and Mortality of Classic and Hemorrhagic Dengue

Incidence of classic dengue was diverse in different parts of the region for the period studied; meta-analyses for country data are shown in Table 2. For the period studied, the incidence of classic dengue per 100,000 was higher in French Guiana (1444.1 [95% confidence interval (CI) 1020.2–1867.9]), Martinique (435.5 [95% CI 363.7–507.3]), Honduras (2767 [95% CI 214.4–338.9]), Costa Rica (297.5 [95% CI 214.5–380.6]), and Brazil (196.7 [95% CI 147.8–245.6]) than in the rest of the region, with peaks observed in 1995, 1998, 2000, 2001, and 2009. Regarding the incidence of hemorrhagic dengue per 100,000, it was found to be higher for the period considered in Venezuela (15.90 [95% CI 12.46–19.34]), Honduras (14.29 [95% CI 11.77–16.80]), Montserrat (10.86 [95% CI 0.80–20.93]), and Colombia (9.23 [95% CI 6.98–11.49]), with peaks in 1997, 1998,

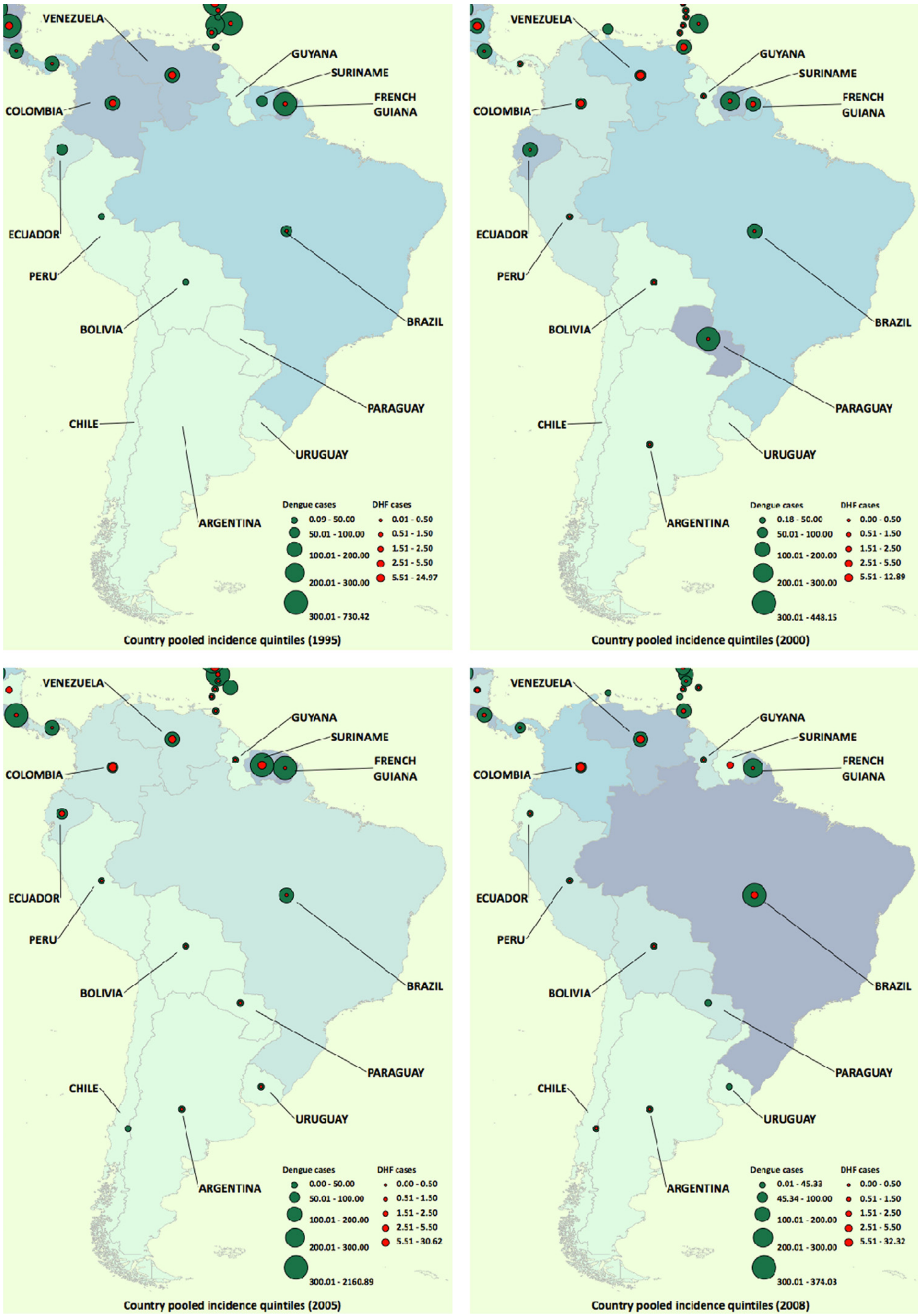

Fig. 2 – South America. Country pooled DF and DHF incidence quintiles (in gradient shading) and relative number of cases in different years (1995–2008). DF, dengue fever; DHF, dengue hemorrhagic fever.

and 2009. Chile and Uruguay registered the lowest incidences of both dengue and hemorrhagic dengue. The distributions of classic and hemorrhagic dengue pooled incidence by quintiles in Latin America and the Caribbean countries for the period 1995 to 2010 are depicted in Figs. 2 and 3.

Regarding the incidence of classic dengue from prospective studies, two studies carried out in Nicaragua reported data from a cohort of 3800 children aged 2 to 9 years during the years 2004 to 2008 [44,45]; the incidence rate ranged from 343 to 1,759 cases per 100,000 person-years. One study from the municipality of Sao Luis, Sao Paulo, Brazil [46], showed the occurrence of 12,008 notified cases of dengue disease during 1997 and 1998, with an incidence of 535.6 and 671.0 per 100,000 people, respectively. Data from Martinique, French Guyana, showed 560 laboratory-confirmed dengue cases in a population older than 14 years from 2005 to 2008 [47]. Five studies reported the incidence of dengue disease in the general population [48–52]. One study [51] reported 2424 cases (incidence rate of 52,67/100,000) in Uberlandia, Brazil, during 1999; the highest incidence rate was observed in people aged between 20 and 59 years. Ribeiro et al. [49] reported 3442

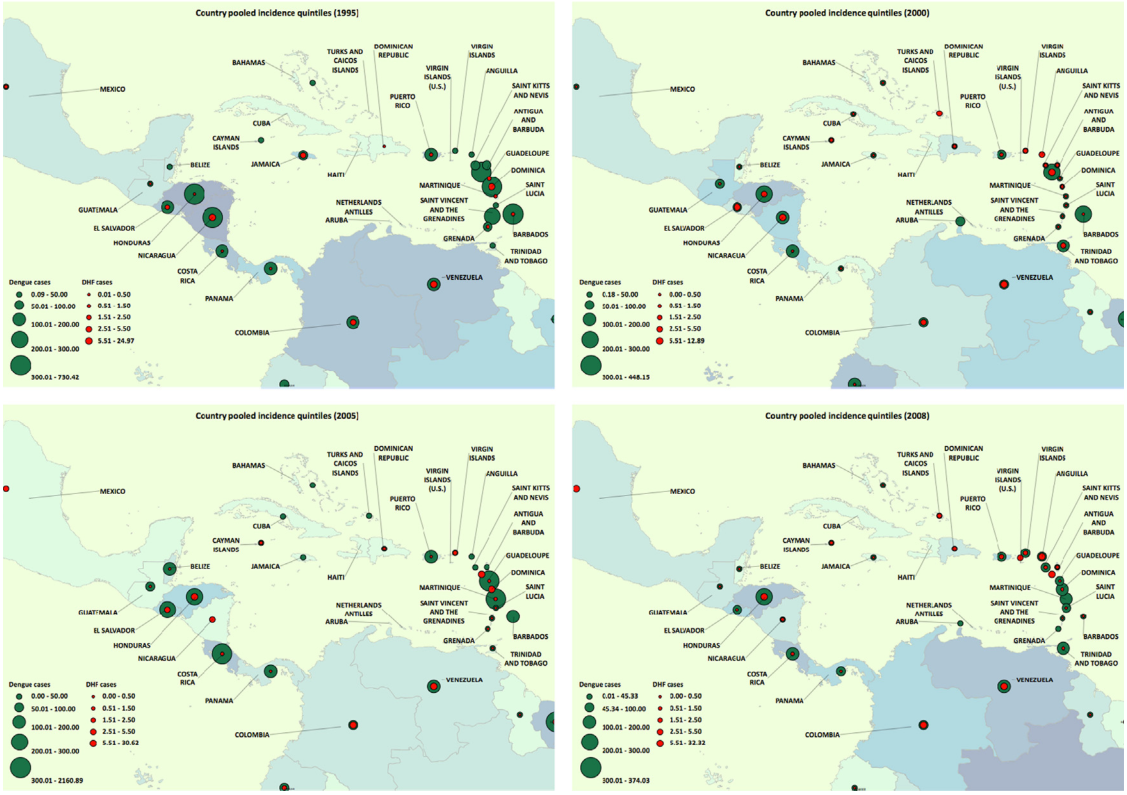

Fig. 3 – Pooled DF and DHF incidence quintiles (in gradient shading) and relative number of cases in different years (1995–2008) in the Caribbean countries. DF, dengue fever; DHF, dengue hemorrhagic fever.

notified cases of dengue, mainly the DEN-1 serotype, in the municipality of São Sebastião, Sao Paulo, Brazil, during the epidemic of 2001 and 2002. Another study from the State of Sao Paulo, Brazil [52], reported 14,554 notified cases (incidence of 381–432/100,000) mainly affecting the population aged older than 15 years. One study from the city of Iquitos, Peru [50], showed 11 cases (incidence of 9.7/1,000) in a cohort of 1,135 school children during 2000 and 56 cases (incidence of 11.5/1,000) in a cohort of 4,850 participants during 2004 and 2005. Another study from the city of Ibague, Colombia [48], reported 232 cases in 1995, 290 cases in 1996, and 1455 in 1997.

Meta-analyses on lethality (or case-fatality rate) showed that pooled estimates ranged from 0.01% in Brazil and Peru to 14.6% in Cayman Islands. Pooled mortality rate ranged from less than 0.01 per 100,000 in Argentina and Peru to 11.08 in Montserrat. High rates were also found in American Virgin Islands, Anguilla, Turks & Caicos Islands, and British Virgin Islands (see Table 2).

Health Resources Use Associated With Dengue Disease

Twelve articles provided information about the use of resources or related costs [16,21,25,36–43]. Table 3 summarizes their characteristics and main outcomes assessed. The mean duration of the illness in inpatients ranged from 5 to 19 days. The mean duration range in outpatients was similar. The length of stay in general wards was 3.8 in Brazil, El Salvador, Guatemala, Panama, and Venezuela [36] and 4 days in Patillas Puerto Rico [43]. The length of stay in the intensive care unit was 5 days in a Cuban study from 2001 [41]. The length of stay for classic dengue in Nicaragua was 5.7 days and for DHF 6 days [21]; in Peru, it was 3.5 days [40]. One study provided information about the use of resources or related costs due to dengue disease in Santiago de Cuba during 1997 [41]. Direct and indirect costs per dengue case during 2005 in Brazil, Guatemala, El Salvador, Panama, and Venezuela for outpatients ranged from US $88 in Guatemala and El Salvador to US $291 in Brazil. For inpatients, it ranged between US $418 in Guatemala and US $1065 in Panama [36] (US $2005). The economic burden of disease during the 2009 epidemic in Argentina ranged from US $7.1 million to US $10.7 million [38].

Discussion

This study analyzes the burden of dengue disease in the LAC region in the last 15 years. Official sources consisted of ministry reports and PAHO information including the Dengue Net [53]. The overall pooled incidence of classic dengue fever was 72.1 cases per 100,000 person-years in the 44 countries included in the review considering all years with available data. An increase in the incidence observed in the region from 1995 up to 2010 has been highlighted [9].

Between 2001 and 2009, Venezuela, Brazil, Costa Rica, Colombia, Honduras, and Mexico reported more than 75% of all cases in the region, with Brazil showing the highest number of cases [54,55]. These data are similar to those of our study. Based on seroprevalence studies, however, the reported cases represent only a proportion of the true total number [56]. Some studies done in the US-Mexican border showed an antibody prevalence of 39% to 50% against dengue, especially in Nuevo Laredo and Matamorros cities, which represented more than 20 times the number of cases notified for the period 1980 to 2007 [57,58]. Dengue has been found to occur in regular cycles with intervals of 3 to 5 years [59]. Our study shows that the cycles for dengue in the LAC region in the period studied have been irregular with

Table 3 – Characteristics of costing studies identified (LAC 1995–2010).

Author	Location	Denominator	Results
Suaya et al. [36]	Brazil 2005	Inpatients/ outpatients	Length of stay in general bed: 4 d Mean duration of illness (inpatient): 11 d Mean duration of illness (outpatient): 12 d Cost per visit: US $291 Cost per admission: US $676
	El Salvador 2005	Inpatients/ outpatients	Length of stay in general bed: 3.8 d Mean duration of illness (inpatient): 11 d Mean duration of illness (outpatient): 12 d Cost per visit: US $88 Cost per admission: US $457
	Guatemala 2005	Inpatients/ outpatients	Length of stay in general bed: 3.8 d Mean duration of illness (inpatient): 11 d Mean duration of illness (outpatient): 12 d Cost per visit: US $88 Cost per admission: US $418
	Panama 2005	Inpatients/ outpatients	Length of stay in general bed: 3.8 d Mean duration of illness (inpatient): 11 d Mean duration of illness (outpatient): 12 d Cost per visit: US $332 Cost per admission: US $1065
	Venezuela 2005	Inpatients/ outpatients	Length of stay in general bed: 3.8 d Mean duration of illness (inpatient): 11 d Mean duration of illness (outpatient): 12 d Cost per visit: US $168 Cost per admission: US $627
Armien et al. [37]	Panama Province 2005	Children outpatients	Mean duration of illness: 18 d Household cost per visit: US $100 Cost per visit: US $66
		Adults outpatients Inpatients	Mean duration of illness (outpatients): 20 d Household cost per visit: US $306 Cost per visit: US $62 Household cost per admission: US $506 Government cost per admission: US $559 Mean duration of illness: 20 d Household cost per visit: US $269 Government cost per visit: US $63 Direct and indirect costs per case
		Inpatients/ outpatients	Outpatient: US $332 Inpatients: US $1065
Coudeville et al. [10]	Central America and Mexico 2000–2007	Inpatients/ outpatients	Direct costs per dengue case: US $323
	Andean Sub region 2000–2007	Inpatients/ outpatients	US $373
	Brazil 2000–2007	Inpatients/ outpatients	US $453
	Southem cone 2000–2007	Inpatients/ outpatients	US $197
	Caribbean 2000–2007	Inpatients/ outpatients	US $1244
Hammond et al. [39]	Nicaragua, Managua, and Leon	Inpatient	Mean duration of illness: 5 d
Leiva et al. [40]	Peru	Inpatient	Length of stay for dengue hemorrhagic fever: 3.5 d Mean duration of the illness: 5 d
Valdés et al. [41]	Santiago de Cuba	Inpatients	Length of stay in intensive care unit: 5 d
Navarro et al. [42]	Venezuela	Inpatient	Mean duration of the illness: 5 d
Salgado et al. [16]	Colombia	Inpatient	Mean duration of the illness: 6 d
Ramos et al. [43]	Puerto Rico Patillas	Inpatients	Length of stay in general bed: 4 d
Harris et al. [21]	Nicaragua	Inpatient	Length of stay for classic dengue: 5.7 d

wide variations and intervals, while the peaks have increased in frequency.

PAHO began recording serotype circulation in 1995 and since then all four serotypes have been reported in the LAC region. The number of countries with more than one circulating serotype has increased. As more countries are found to have numerous dengue serotypes, the probability of secondary infection increases, leading to a higher risk of both DHF and dengue shock syndrome [9]. By the end of 2011, PAHO reported more than 1 million cases of dengue fever in Latin American countries, with more than 18,000 severe cases and 716 deaths. All four dengue serotypes were circulating by then in the region [2].

The reinfestation of countries that were once free of vector and the entry of even more virulent viral genotypes have complicated the situation in the region [60]. DHF epidemics have become more frequent, reflecting a change in the pattern of dengue viral infections. The countries with the highest incidence rates of DHF during the study period were Venezuela, Honduras, Montserrat, Colombia, and Nicaragua; 15.9, 14.2, 10.9, 9.2, and 6.0 per 100,000 person/year, respectively. DHF cases in 2009 increased by more than 50% compared with 1995. While dengue serotypes in the Americas and Southeast Asia are similar and endemic in both regions, DHF rates in the Americas are lower compared with those reported in Southeast Asia [61].

The overall mortality observed in the study period was low compared with that reported in other regions (0.02 per 100,000 person-years), but the increases in mortality and DHF rates occurred at the same time within the region. Countries with the highest reported mortality rates were the Caribbean island countries, such as Montserrat, American Virgin Islands, Anguilla, and Turks & Caicos Islands. In the rest of America, Nicaragua, Honduras, El Salvador, Colombia, Venezuela, and Brazil have the highest reported mortality with rates of 0.14, 0.08, 0.07, 0.07, 0.04, and 0.03 per 100,000 person-years, respectively.

Dengue classic fever was analyzed by age group in only four countries of the region with available data (Bolivia, Brazil, Mexico, and Colombia). Adults aged 15 to 59 years were the most affected group. Since 2006, there has been an important increase in the groups aged 5 to9, 10 to 19, and 20 to 39 in Brazil, with a worrisome increase in children younger than 5 years. In that country during 2007 an epidemic change in the age-group profile of cases was observed; children were increasingly affected with severe dengue, more closely resembling the epidemiological profile seen in South-East Asia [62]. Other studies found similar data, while reports in Venezuela showed a higher incidence in children since 2005 with a peak in 2007 [25].

According to the 13 articles providing information on the use of resources or related costs, the mean duration of the illness for inpatients ranged from 5 days (in Nicaragua, Peru, and Venezuela) to 13 days (Brazil) and from 9 days (El Salvador) to 20 days (Panama) for outpatients. Suaya et al. [36] reported in 2009 that an average episode represented 14.8 lost days for ambulatory patients and 18.9 days for hospitalized patients. The averaged total cost per hospitalized case was three times that of an outpatient case. These data are consistent with those of another study conducted in the period 2005 to 2006 [36]. Variations in costs found in this study may reflect actual local differences in direct costs of treatment, health services, and wage rates. Dengue poses a heavy economic burden to the health system and society. A most recent report estimated an aggregate annual total cost of dengue during the period of 2000 to 2007 of US $2.1 billion for the region [11]. Currently, dengue is considered fifth in terms of disability-adjusted life-years in the list of neglected tropical diseases in the Americas [63].

To our knowledge, this is the first meta-analysis and systematic review with exhaustive information on the burden of disease and use of resources in the LAC region. As observed in other studies [11,36,64,65], our analysis has some limitations in estimating the real burden and resource use of dengue disease in the region. Underreporting of cases, for example, is known to threaten validity. The differences in illness duration possibly reflected variations in methodologies to assess this outcome. Few studies examined direct and indirect costs.

Conclusions

During the last 15 years, an increase in DHF and classic dengue has been observed in many countries. The pattern of intermittent epidemics with long intervals changed to annual outbreaks in multiple locations and persistent cocirculation of several serotypes, and situation of hyperendemicity. Young adults were the most affected in the region, with some countries showing increments in cases in the pediatric population. To date, activities to control dengue in the region have been only moderately effective. It is necessary to improve surveillance and make efforts to reduce the problem of underreporting. Dengue-endemic countries and the global public health community need a stronger voice to persuade society, funding agencies, and policymakers of the importance of dengue disease.

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Supplemental Materials

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