



Economic impact of dengue fever in Latin America and the Caribbean: a systematic review

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ABSTRACT

Objectives. To assess the economic impact of dengue in Latin America and the Caribbean using a systematic review that includes studies not previously considered by other reviews.

Methods. Cochrane methodology was used to conduct a systematic review of the cost of dengue in Latin America. PubMed Central, EMBASE, and the Biblioteca Virtual en Salud—which includes scientific, peer-reviewed journals not indexed by other databases—were searched from inception through August 2016. All articles that reported cost of illness data for countries in Latin America were included. Included studies underwent a methodological appraisal using a seven-question instrument designed for cost of illness studies. Extracted data were direct and indirect costs for outpatient and hospitalized cases and total cost of the disease. Values were adjusted to 2015 US dollars using the consumer price index.

Results. From a total of 848 initial references, 17 studies were included, mainly from Brazil, Colombia, Cuba, Mexico, and Puerto Rico; costs were available for 39 countries. The methodological appraisal showed that 70% of the studies met more than 70% of the evaluated items. The main economic impact of dengue was due to productivity costs. Average annual cost was more than US\$ 3 billion. Direct costs represented over 70% of the total share for hospitalized cases. For outpatients, direct medical costs were low, but social costs were significant since indirect costs may account for up to 80% of the total cost.

Conclusions. Dengue fever has a significant economic impact in Latin America. It is essential to develop new public health interventions, such as dengue vaccination, to decrease the propagation of the disease and its total cost.

Keywords

Dengue; cost of illness; health care costs; Latin America; Caribbean region.

Dengue virus, an arbovirus transmitted by mosquitoes of the genus *Aedes* (i.e., *A. aegypti* and *A. albopictus*) has

four serotypes: DEN-1, DEN-2, DEN-3, and DEN-4 (1). Dengue is present in tropical and subtropical areas, often where poor infrastructure and scarce human and technical resources make it hard to control (1, 2). The typical clinical presentation of fever, headache, retroocular pain, myalgia, and arthralgia is known as dengue fever without warning

signs; the presence of gastrointestinal symptoms and neurological and mucosal bleeding is known as dengue fever with warning signs; and the development of severe hemorrhage, signs of excessive capillary permeability, or organ compromise constitutes severe dengue (3). The rather high mortality of severe dengue (up to 40%) can be reduced

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to close to 1% with adequate medical treatment (1, 2).

According to the World Health Organization (WHO), from 50 million – 100 million dengue infections and about 20 000 dengue-related deaths occur worldwide every year (2). Bhatt and colleagues have estimated an annual average of 390 million infections (4). The incidence in the Region of the Americas increased from 16 per 100 000 people in 1980 to 71 per 100 000 in 2000 – 2007 (5). The cost of the disease is substantial and varies from year to year (6). Two recent studies calculated an annual global cost of US\$ 9 billion (7) – US\$ 39 billion (8).

There have been several efforts to estimate the economic impact of dengue in Latin America. In 2011, Shepard and colleagues (9) published an elegant estimation of the burden of disease for the Americas. It included studies through 2009, but due to the scarcity of data, most of the estimates relied on only two of those studies. Since 2009, a number of relevant studies in different countries have been published. In addition, previous systematic reviews of the topic did not include literature indexed by Latin American databases (9), thus missing important local data in a region where socioeconomic and geographic conditions vary greatly. This new data may allow a more current estimation of the cost of illness for dengue in Latin America.

Furthermore, primary prevention has partially controlled the course of the disease (1). The implementation of preventive measures, such as vaccination, are part of the control agenda; estimates of the burden of disease are required to determine potential impact (10). The objective of this paper was to assess the economic impact of dengue in Latin America and the Caribbean using a systematic review of the literature that includes studies not previously considered.

MATERIALS AND METHODS

Cochrane methodology was used to conduct a systematic review on the cost of dengue in Latin America and the Caribbean. PubMed Central (U.S. National Library of Medicine, Bethesda, Maryland, United States), EMBASE (Excerpta Medica Database, Elsevier, Amsterdam, the Netherlands), and BVS (Biblioteca Virtual en Salud, Latin American and Caribbean Center on Health Sciences Information, São Paulo, Brazil) were searched, from

inception – August 2016. BVS includes scientific literature from Latin America published in peer-reviewed journals not indexed in other databases. The terms used and adapted to each database were (“dengue”) AND (“cost* OR economics”) AND (each of the countries of Latin America and Caribbean, individually separated by “OR”). Supplemental material on the search strategy is available from the corresponding author upon request.

All cost studies that reported direct or indirect costs associated with dengue fever in Latin America or the Caribbean were included. Studies excluded were those regarding vector control costs, economic evaluations on disease control interventions, and reviews of the literature. No filters were applied.

An electronic form was developed to standardize the data extracted, including the variables of primary interest to the study: direct and indirect costs for outpatient and hospitalized cases and total cost of the disease. Direct costs were defined as expenses related to diagnosis, whether direct medical costs (e.g., hospital admission, diagnostic and treatment costs) or direct non-medical costs (e.g., transportation to the health care facility). Indirect medical costs consisted of productivity losses related to morbidity (11).

Study screening was performed independently by three of the researchers (AL, JBC, LB). Any disagreements on inclusion were discussed until a consensus was reached. To identify any additional, potentially-eligible article, the references of each relevant citation and review were manually examined. After reading the articles in full text, studies on the cost of dengue fever in any Latin American or Caribbean country were analyzed.

Although the best practice for systematic reviews is to perform a risk of bias assessment on all included articles, to the best of our knowledge, no specific tool exists for partial economic evaluations, such as cost of illness studies. Therefore, the study was limited to only examining the methodological quality of the reviewed articles. Methodological quality was assessed based on previously proposed relevant items in cost of illness studies (11). This was determined to be the best option since official, international guidelines for quality analysis of such studies are lacking (12, 13), and current, quality assessments of economic studies are not intended to evaluate cost of illness studies (14). The following

elements were evaluated: perspective, population, direct cost, indirect cost, discounting, incremental/attribution cost, and sensitivity analysis; for further details, refer to reference (11). These items were appraised by three of the researchers (AL, JBC, LB).

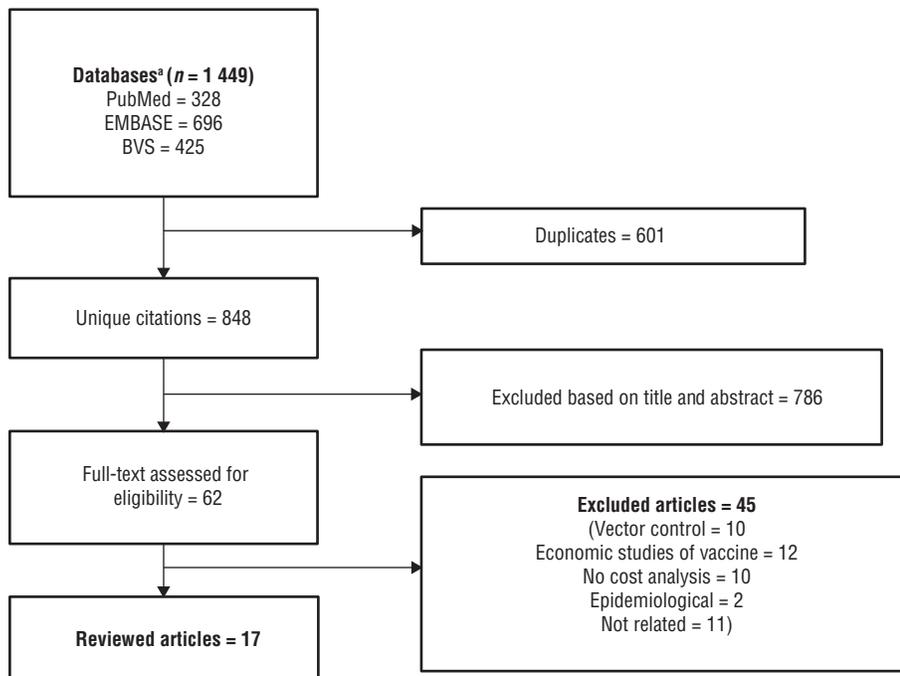
Since the results were presented in local currency or United States dollars of different years, the values were adjusted to 2015 US\$ using the consumer price index. Moreover, to standardize the costs described in the various studies (Table 1) and to summarize them (Table 2), in some cases it was necessary to perform additional calculations based on the original data (9, 17 – 22). Thus, simple averages between the private and public health systems, regions, years, and institutions were calculated. The explanation for each calculation is described in the results section. The results are presented as a narrative synthesis, by country, to allow for a better understanding of the challenges in each and its contribution to the total burden of dengue in Latin America. Countries with at least two articles reporting cost data were described in an extensive manner; those with only one article are presented in Table 2.

RESULTS

The initial search resulted in 848 unique citations of which 62 were reviewed in full text. Of these, 17 (9, 15 – 30) provided relevant, useful information (Figure 1) and were included in the analysis (Table 1). Most of these 17 were from Brazil, Colombia, Cuba, Mexico, and Puerto Rico. Altogether, costs were available for 39 countries (Table 2). All of the studies were partial economic evaluations (cost of illness studies). Overall, 70% of the studies (12 of the 17) met more than 70% of the evaluated criteria; direct costs and study perspective were reported by all authors; as expected, incremental/attribution costs were not evaluated by any article. A summary of the evaluation is presented in Table 3.

Argentina

Two studies were included for Argentina. Shepard and colleagues (9) estimated that direct medical costs represented the largest proportion of cost for both outpatient (59%; US\$ 316 / 536) and hospitalized (58%; US\$ 820 / 1 413) cases. Tarragona and colleagues (20) evaluated

FIGURE 1. Flow diagram of study selection for a systematic review of the economic impact of dengue fever in Latin America and the Caribbean

*PubMed Central (U.S. National Library of Medicine, Bethesda, Maryland, United States), EMBASE (Excerpta Medica Database, Elsevier, Amsterdam, the Netherlands), and BVS (Biblioteca Virtual en Salud, Latin American and Caribbean Center on Health Sciences Information, São Paulo, Brazil)

Source: Prepared by the authors from study data.

three geographic areas in Argentina and divided the cases into three scenarios: general ward management, specialty care, and intensive care (ICU). In an effort to standardize and to draw comparisons with other studies, the general ward cases were considered to be outpatient; specialty care was considered to be hospitalization; and the ICU cases were considered separately. It was reported that medical costs generated 47% (US\$ 119 / 253) of total costs for outpatient cases (90% of the total). For the hospitalized cases, medical cost represented the 56% (US\$ 174 / 308), and for ICU cases, 67% (US\$ 269 / 403). The costs shown in Table 2 correspond to averages obtained from the three geographic areas. Total costs are shown in Table 2.

Brazil

Four studies were included for Brazil. Shepard and colleagues (9) reported that outpatient cases represented 78% of total costs. Direct costs for outpatient cases accounted for 17% (US\$ 72 / 416), the lowest in the Americas. For hospitalized cases, 43% (US\$ 413 / 966) were direct and 52% (US\$ 500 / 966) indirect costs. Suaya and colleagues (15) evaluated the

cost of dengue in five countries (Brazil, El Salvador, Guatemala, Panama, and Venezuela). From the perspective of that study, these countries represent 94% of the total cost in the region. For outpatient cases, indirect costs accounted for 83% (US\$ 292 / 353) of the total cost, and for hospitalized patients, 52% (US\$ 425 / 820). Vieira-Machado and colleagues (22) reported that in the city of Dourados (Mato Grosso do Sul, Brazil), direct medical costs equaled 2.5% (about US\$ 230 000 by 2015) of its per-capita gross domestic product (GDP). Costs in the private sector were 280% higher than in the public sector. Lastly, Martelli and colleagues (19) reported that 99.5% of cases corresponded to outpatient cases, where direct costs represented the lowest percentage of the total cost. On the other hand, hospitalized cases accounted for the largest proportion. To standardize the results in Table 2, the averages between the private and public health system or between geographic areas were calculated.

Colombia

Four studies were included for Colombia. Shepard and colleagues (9)

determined that dengue costs increased to US\$ 540 million in the Andean area (Bolivia, Colombia, Ecuador, Peru, and Venezuela). Castro-Rodríguez and colleagues (23) established direct and indirect costs for three periods, including an epidemic period in 2012; all these, from the social perspective. Total costs for 2012 represented 108% of the immunization program budget, 0.14% of the national budget, and 0.04% of the GDP, indicating a substantial economic impact. In a subsequent study, Castro-Rodríguez and colleagues (30) assessed total cost of the disease from a societal perspective, including prevention and monitoring activities that were corrected for underreporting. Costs were as high as US\$ 341 for 2010; burden of disease expressed in disability-adjusted life years (DALYs) was reported. Lastly, Castañeda-Orjuela and colleagues (21) estimated that the cost per case and the total cost for dengue (Table 2), including control activities and medical management, exceeded US\$ 60 MM annually; while control strategies surpassed the total costs, representing more than 70% of the total. Regarding the cost per case, an average was calculated based on the data reported by the authors.

Cuba

Three studies were included for Cuba. Shepard and colleagues (9) reported indirect costs to be 54% (US\$ 42 / 78) of the total cost in outpatient cases, whereas in hospitalized cases, most costs were direct (66%; US\$ 229 / 345). Baly and colleagues (24) estimated the cost of dengue in Guantánamo, and identified lost productivity as the largest proportion of the total cost. The costs of the vector control program were, according to these authors, the highest among dengue fever control programs worldwide (US\$ 1.96 person/month in the non-epidemic period and US\$ 2.21 person/month in the epidemic period). Finally, Valdés and colleagues (17) estimated the costs of the disease during the 1997 epidemic in Santiago de Cuba, reporting that 76% (US\$ 11 500 124 / 15 138 874) went toward vector control and only 19% (US\$ 2 833 301 / 15 138 874) to hospital costs. Because the data on cost of dengue fever treatment came from various health centers in Santiago de Cuba, the values in Table 2 are averages.

TABLE 1. Characteristics of included studies

Author	Country	Year	Type	Perspective	Outcome	Discounting (US\$)	Funding
Shepard, 2011 (9)	All Americas	2000–2007	Partial economic analysis	Societal	Reported dengue cases, underreporting degree, indirect and direct cost per case of dengue, DALY	2010	Sanofi Pasteur
Tarragona, 2012 (20)	Argentina	2009	Partial economic analysis	Societal	Average individual cost, regional cost, national cost	2009	Not reported
Martelli, 2014 (19)	Brazil	2009–2013	Partial economic analysis	Societal and third party	Cost per case and overall cost of dengue	2012	Sanofi Pasteur
Suaya, 2009 (15)	Brazil, El Salvador, Guatemala, Panama, Venezuela, Mexico	2005	Partial economic analysis	Societal	Direct medical cost, non-direct medical cost, indirect cost	2005 [§]	Pediatric Dengue Vaccine initiative
Vieira Machado, 2014 (22)	Brazil	2010	Partial economic analysis	Third-party	Direct medical cost of the hospitalization of dengue cases, hospital admissions, mandatory reported dengue cases	2010	Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)
Castañeda-Orijuela, 2012 (21)	Colombia	2011	Partial economic analysis	Third-party	Annual number of dengue and severe dengue cases, average cost of care per patient, additional costs for activities of vector control and other community interventions	2011	Expanded Program on Immunization, Colombian Ministry of Health and Social Protection
Castro Rodríguez, 2015 (23)	Colombia	2010–2012	Partial economic analysis	Third-party	Cost per dengue case (direct medical costs incurred by health system, direct medical costs incurred by households, direct non-medical costs incurred by households and indirect costs incurred by households)	2012	Sanofi Pasteur
Castro Rodríguez, 2016 (30)	Colombia	2010–2012	Partial economic analysis	Societal	Burden of dengue (DALYs) in endemic years and epidemic year, economic cost of the disease (direct and indirect, prevention and monitoring activities costs)	2012	Sanofi Pasteur
Baly, 2012 (33)	Cuba	2006	Partial economic analysis	Societal	Economic cost of routine <i>A. aegypti</i> control in an at-risk environment without dengue endemicity, incremental costs incurred during a sporadic outbreak, mean hospitalization cost per case, economic productivity losses	2006	Partially funded through the framework agreement between the Institute of Tropical Medicine, Antwerp, and the Belgium Directorate
Valdés, 2002 (17)	Cuba	1997	Partial economic analysis	Societal	Costs for hospitalization and clinical-therapeutic control of patients, antivectorial control and laboratory surveillance	1997 ^a	Not reported
Durán-Arenas, 2014 (18)	Mexico	2012	Partial economic analysis	Third-party	Direct medical costs and productivity loss-related indirect costs	2012	Sanofi Pasteur
Undurraga E, 2015 (25)	Mexico	2010–2011	Partial economic analysis	Third-party	Economic burden of dengue (episode costs, dengue prevention and surveillance activities and other economic impacts), disease burden of dengue (DALYs)	2012	Sanofi Pasteur, partially supported by UBS Optimus Foundation
Wettstein, 2012 (26)	Nicaragua	1996–2010	Partial economic analysis	Societal	Total cost of dengue cases (direct, indirect and prevention activities), annual disease burden (DALYs)	2004–2010 ^b	Grant from the Doris Duke Foundation to AYC, National Institute of General Medical Sciences Models of Infectious Disease Agent Study (MIDAS)
Armien, 2008 (27)	Panama	2005	Partial economic analysis	Societal	Cost of dengue cases, cost of control efforts, loss in quality of life	2005	Pediatric Dengue Vaccine Initiative (PDVI), Schneider Institutes for Health Policy
Halasa, 2012 (29)	Puerto Rico	2002–2010	Partial economic analysis	Societal	Direct and indirect cost per dengue case, projection of annual cost of dengue and annual number of dengue cases, aggregate economic cost of dengue	2010	Sanofi Pasteur
Von Allmen, 1979 (28)	Puerto Rico	1977	Partial economic analysis	Societal	Cost of epidemic: indirect an direct costs	1977	Not reported
Añez, 2008 (16)	Venezuela	1997–2003	Partial economic analysis	Societal	Direct and indirect cost per dengue case	1997–2003	Not reported

Notes: ^aAs the study did not report discounting year, we made the calculation with 1997 Consumer price index, given that it was the year of the epidemics

^bAs the study did not report discounting year, we made the calculation with the lowest value with the CPI of 2004 and the highest value with the CPI of 2010, as mentioned in the original study.

Abbreviation: §= international dollars

Source: Prepared by the authors from study data.

TABLE 2. Cost per ambulatory case, cost per hospitalized case and cost per year reported in each study and country, adjusted to US dollars of 2015

Author – Year	Country	Ambulatory case			Hospitalized case			Cost per year (\$, millions)		
		n	Direct (\$)	Indirect (\$)	Total (\$)	n	Direct (\$)		Indirect (\$)	Total (\$)
Shepard, 2011 (9)	Antigua and Barbuda	-	317	424	741	-	1 045	1 142	2 187	NA
Shepard, 2011 (9)	Argentina	-	316	220	536	-	818	595	1 413	NA
Tarragona, 2012 (20)	Argentina	183	119	134	253	183	174–269	134	308–403	6.6–9.9
Shepard, 2011 (9)	Bahamas	-	385	601	986	-	1 528	1 621	3 149	NA
Shepard, 2011 (9)	Barbados	-	342	413	755	-	1 237	1 115	2 352	NA
Shepard, 2011 (9)	Belize	-	274	125	399	-	577	338	915	NA
Shepard, 2011 (9)	Bolivia	-	113	55	168	-	264	162	426	NA
Martelli, 2014 (19)	Brazil	1 657	88	117	205	378	424	184	608	410–1 249
Shepard, 2011 (9)	Brazil	-	72	345	416	-	466	500	966	1 466
Suaya, 2009 (15)	Brazil	413	61	292	353	137	396	425	820	164
Vieira Machado, 2014 (22)	Brazil	-	-	-	-	507	-	-	282	NA
Shepard, 2011 (9)	Chile	-	295	225	520	-	717	605	1 322	NA
Castañeda-Orjuela, 2012 (21)	Colombia	-	-	-	85*	-	-	-	789–1 248*	55–64
Castro Rodriguez, 2015 (23)	Colombia ^a	462	44	115	159	627	89	206	294	2010: 173 2011: 134 2012: 136
Castro Rodriguez, 2016 (30)	Colombia ^b	-	-	-	-	-	-	-	-	2010: 341 2011: 175 2012: 189
Shepard, 2011 (9)	Colombia	-	84	117	201	-	523	316	839	NA
Shepard, 2011 (9)	Costa Rica	-	318	189	508	-	717	510	1 227	NA
Baly, 2012 (33)	Cuba	-	-	-	-	-	248	101	349	NA
Shepard, 2011 (9)	Cuba	-	36	42	78	-	229	115	345	NA
Valdés, 2002 (17)	Cuba	-	-	-	-	13 461	210	57	267	NA
Shepard, 2011 (9)	Dominica	-	245	158	402	-	499	424	923	NA
Shepard, 2011 (9)	Dominican Republic	-	102	157	260	-	601	425	1 026	NA
Shepard, 2011 (9)	Ecuador	-	150	105	255	-	409	285	693	NA
Shepard, 2011 (9)	El Salvador	-	33	84	116	-	500	108	608	NA
Suaya, 2009 (15)	El Salvador	100	30	77	107	89	456	98	555	2
Shepard, 2011 (9)	Grenada	-	287	185	472	-	608	499	1 106	NA
Shepard, 2011 (9)	Guadeloupe	-	487	314	801	-	2 881	847	3 728	NA
Shepard, 2011 (9)	Guatemala	-	36	85	121	-	499	78	577	NA
Suaya, 2009 (15)	Guatemala	64	33	74	107	21	438	69	507	1.50
Shepard, 2011 (9)	Guyana	-	55	48	103	-	295	128	423	NA
Shepard, 2011 (9)	French Guiana	-	488	326	814	-	2 880	880	3 761	NA
Shepard, 2011 (9)	Haiti	-	151	23	174	-	276	62	338	NA
Shepard, 2011 (9)	Honduras	-	70	65	135	-	341	175	516	NA
Shepard, 2011 (9)	Jamaica	-	92	138	230	-	463	351	814	NA
Shepard, 2011 (9)	Martinique	-	487	565	1 052	-	3 002	1 400	4 404	NA
Durán- Arenas, 2014 (18)	Mexico	-	64	29	93	-	1 102	1 209	2 311	NA
Shepard, 2011 (9)	Mexico	-	301	227	528	-	702	612	1 314	NA
Undurraga, 2015 (25)	Mexico	43 130	356	109	466	18 752	1 216	148	1 370	175
Shepard, 2011 (9)	Nicaragua	-	127	29	156	-	252	80	333	NA
Wettstein, (26)	Nicaragua	-	-	-	-	-	-	-	-	6–29
Armien, 2008 (27)	Panama	5 413	101	302	403	76	902	391	1 292	20
Shepard, 2011 (9)	Panama	-	112	340	452	-	1 016	436	1 452	NA
Suaya, 2009 (15)	Panama	130	100	303	403	6	902	391	1 292	1.10
Shepard, 2011 (9)	Paraguay	-	72	67	139	-	375	181	556	NA
Shepard, 2011 (9)	Peru	-	126	155	281	-	447	339	786	NA
Halasa, 2012 (29)	Puerto Rico	591	434	956	1 279	1 831	4 164	1 811	5 975	42
Shepard, 2011 (9)	Puerto Rico	-	571	33	603	-	2 053	3 194	5 247	NA
Von Allmen, (28)	Puerto Rico	-	-	-	-	-	-	-	-	23–61
Shepard, 2011 (9)	Saint Kitts and Nevis	-	401	295	696	-	793	930	1 724	NA

(Continued)

TABLE 2. (Continued)

Author – Year	Country	Ambulatory case			Hospitalized case			Cost per year (\$, millions)		
		n	Direct (\$)	Indirect (\$)	Total (\$)	n	Direct (\$)		Indirect (\$)	Total (\$)
Shepard, 2011 (9)	Saint Lucia	-	272	176	448	-	554	475	1 029	NA
Shepard, 2011 (9)	Saint Vincent and Grenadines	-	95	171	265	-	570	461	1 030	NA
Shepard, 2011 (9)	Suriname	-	118	187	305	-	683	503	1 186	NA
Shepard, 2011 (9)	Trinidad and Tobago	-	573	576	1 149	-	1 546	1 555	3 101	NA
Shepard, 2011 (9)	Uruguay	-	359	265	624	-	838	716	1 554	NA
Añez, 2006 (16)	Venezuela	26 645	5	16	21	3 606	112	32	137	229
Shepard, 2011 (9)	Venezuela	-	148	211	360	-	1 009	337	1 346	NA
Suaya, 2009 (15)	Venezuela	130	84	120	204	70	570	190	761	NA
Shepard, 2011 (9)	Virgin Islands- American	--	152	466	618	-	4 849	1 258	6 106	NA
Shepard, 2011 (9)	Virgin Islands-British	-	387	1 143	1 530	-	2 354	3 090	5 439	NA

Notes: ^aFrom a health system perspective; ^bFrom a societal perspective;

To standardize the results, the averages between the private and public health system, or between regions studied depending on the case, were calculated.

The values were adjusted to 2015 US dollars using the consumer price index (CPI).

Abbreviation: NA, Not available

Source: Prepared by the authors from study data.

TABLE 3. Quality assessment of the included studies

	Perspective	Population	Direct cost	Indirect cost	Discounting	Incremental / attributable cost	Sensitivity analysis	Total
Shepard, 2011 (9)	+	(+)	+	+	+	NA	+	86%
Tarragona, 2012 (20)	+	(+)	+	+	+	NA	0	71%
Martelli, 2014 (19)	+	+	+	+	+	NA	+	86%
Suaya, 2009 (15)	+	+	+	+	+	NA	0	71%
Vieira Machado, 2014 (22)	(+)	+	+	0	+	NA	0	57%
Castañeda-Orjuela, 2012 (21)	(+)	0	+	0	+	NA	(+)	57%
Castro Rodríguez, 2015 (23)	+	0	+	+	+	NA	+	71%
Castro Rodríguez, 2016 (30)	+	0	+	+	+	NA	+	71%
Baly, 2012 (33)	+	0	+	+	+	NA	0	57%
Valdés, 2002 (17)	(+)	+	+	0	0	NA	0	43%
Durán- Arenas, 2014 (18)	+	(+)	+	+	+	NA	0	71%
Undurraga E, 2015 (25)	+	(+)	+	+	+	NA	+	86%
Wettstein, 2012 (26)	+	0	+	+	0	NA	+	57%
Armien, 2008 (27)	+	(+)	+	+	+	NA	+	86%
Halasa, 2012 (29)	+	+	+	+	+	NA	+	86%
Von Allmen, 1979 (28)	+	(+)	+	+	(+)	NA	(+)	86%
Añez, 2008 (16)	+	(+)	+	+	(+)	NA	0	71%

Nomenclature: + present; (+) partly fulfilled; 0 absent; NA, not applicable.

Source: Prepared by the authors from study data.

Mexico

Three studies were included for Mexico. Shepard and colleagues (9) estimated that Mexico incurred 7% of the total dengue fever cost in the Americas for 2007. Outpatient cases, given their greater frequency, generated the greatest economic impact. Durán-Arenas and colleagues (18) found out that the “real” management costs differed widely from

the costs calculated with an “ideal” treatment scheme, both in the public and private systems. They associated these with failures in the health system. Regarding the indirect costs, they highlighted higher out-of-pocket costs for patients in the public system. The costs per case are found in Table 2 and correspond to an average of the real values in both health systems. Lastly, Undurraga and colleagues (25) estimated that the

indirect cost per case of fatal dengue exceeded US\$ 60 000.

Nicaragua

Two studies were included for Nicaragua. Shepard and colleagues (9) estimated that direct medical costs for both outpatient and hospitalized cases represented most of the total costs (81% (US\$ 127 / 156) and 76% (US\$ 252 / 333),

respectively). Wettstein and colleagues (26) calculated that of the total cost of dengue in 1996 – 2010, including prevention activities, outpatient cases (81% – 99%) made up the majority. Indirect costs were as high as 50% of total costs, attributed mainly to years of premature death.

Panama

Two studies were included for Panama. Shepard and colleagues (9) identified indirect costs to be 75% (US\$ 340 / 452) in outpatient cases. By contrast, in hospitalized cases, indirect costs were only 30% (US\$ 436 / 1 452). Armien and colleagues (27) estimated similar proportions for outpatient and hospitalized cases in an epidemic year, with the cost of dengue control and surveillance at 30% of the total.

Puerto Rico

Three studies were included for Puerto Rico. Shepard and colleagues (9) reported direct medical costs to be 95% (US\$ 571 / 603) of the total cost per outpatient case. By contrast, indirect costs were the largest proportion of the total cost per hospitalized case (61%; US\$ 3 194 / 5 247). Von Allmen and colleagues (28) reported that direct costs exceeded US\$ 18 million, while indirect costs were as high as US\$ 42 million; hospital costs of complicated cases were not included. Halasa and colleagues (29) reported that the proportion of direct and indirect costs were similar, with 48% (US\$ 20 103 / 42 113) versus 50% (US\$ 21 167 / 42 113) of total costs, respectively. However, the indirect costs were higher in outpatient cases (75%; US\$ 956 / 1 279) than in inpatient cases (30%; US\$ 1 811 / 5 975), for which direct costs accounted for the highest burden. Hospitalized cases represented 63% (US\$ 26 380 / 42 113) of the total cost, and fatal cases represented 18% (US\$ 7 516 / 42 113), with a cost per case exceeding US\$ 460 000.

Venezuela

Two studies were included for Venezuela. Shepard and colleagues (9) reported that Venezuela, with 15% of the total cost, was one of the main contributors to the economic burden of dengue in the Americas. Indirect costs were the largest proportion in outpatient cases

(59%; US\$ 211 / 360). In hospitalized cases, direct medical costs accounted for the largest proportion (75%; US\$ 1 009 / 1 346). Añez and colleagues (16) found that 65% were indirect costs. In order to analyze the results obtained by these authors, it was necessary to calculate the indirect costs according to the number of days of absenteeism, multiplied by the minimum wage in 1997 – 2003. The grand total was divided by 7 (years) to determine the average annual cost.

DISCUSSION

The incidence of dengue fever has increased substantially due to several factors including population growth, urbanization, tourism, global warming, forced displacement, barriers to preventive care, and geographic conditions that delay government interventions (31).

The economic cost of dengue in Latin America is high, exceeding US\$ 3 billion annually; in some countries, such as Brazil, it may be as high as US\$ 1.4 billion annually. Although most cases are managed in the outpatient setting, the indirect costs represent the largest proportion of the total share, and thus, a high burden for society. In contrast, the costs of a hospitalized case are mostly direct medical costs that generate a heavy burden on health systems. Despite uncertainty on the real incidence due to underreporting of dengue in the region, all of the studies highlight its high economic impact. Different methodologies have been used in the various studies, which make it tough to establish comparisons. Moreover, several authors have reported that surveillance and vector control programs represent a major economic share of dengue's cost of illness (17, 27, 32 – 39).

The estimation of a high cost for Latin America is consistent with the large number of annual cases. Bhatt and colleagues (4) estimated more than 13 million apparent cases (i.e., any level of clinical severity), comprising 14% of cases worldwide in 2010, far fewer than Asia (70%). However, this proportion could be 40% if unapparent cases were included (i.e., oligo or asymptomatic). Along these lines, Shepard and colleagues (7) estimated a total cost for Latin America of US\$ 1.7 billion for 2013; they argued that the reduction in the total cost from the US\$ 3 billion estimate of their previous study (9) was due to the fact that very few cases of unapparent dengue fever receive medical

attention. On the other hand, Selck and colleagues (8) estimated a cost for the Americas in 2011 of up to US\$ 10 billion, which would correspond to 25% of the world total.

The studies included in this review report that about 90% of the dengue cases are ambulatory, and that these account for the largest proportion of the total cost in Latin America. This estimation was confirmed by Shepard and colleagues using different data sources; however, this behavior has not been observed in Asia, where the costs of hospitalization are higher, nor in Africa, where the costs for fatal cases are dominant (7). The proportion of indirect costs tends to be higher for outpatient cases in all Latin American countries, which negatively impacts individual, family, and societal productivity. Nonetheless, these costs may be higher: some studies estimate that the total costs could increase by 13% due to persistent symptoms (40, 41).

Regarding hospitalized cases of dengue in Latin America, costs may vary from US\$ 130 – US\$ 5 000. This wide range appears to be related to differences in medical services costs that could explain why direct medical costs represent the largest proportion (50%) of the total share. These cases do not seem to exceed 5% of the total, but their cost is about 10% of the total cost in the region (7). This proportion is small compared to Asia, where hospitalized cases represent 60% of the total cost (7). In addition, indirect costs and fatal cases—which yield hospitalization costs before the fatal outcome—represent the remaining 50% of the grand total and generate an important burden for society. Shepard and colleagues determined a cost per fatal case of up to US\$ 80 000 (7), close to the figures reported by the studies included in this review.

A review of disease burden of dengue as measured by DALY and quality adjusted life years (QALY) was avoided given the heterogeneity in the applied methodologies. Stanaway and colleagues (42) have estimated 1.14 million DALY lost worldwide. According to the studies included in this review, in Nicaragua the lost DALY were from 99 – 805 per million inhabitants (26); in Colombia, from 83 – 199 (30); and in Mexico, 65 (25). Shepard and colleagues (9) estimated lost DALYs for all the regions along the continent. The impact evaluation was performed from both the societal and

health system perspectives. The burden of disease differed between countries according to: (a) the number of people infected; (b) the medical costs in each system; and (c) the economic potential of each citizen relative to the national GDP. About 60% of dengue fever costs for the region are the result of indirect costs, expressed in the loss of productivity due to non-fatal dengue cases (9).

Limitations. Certain shortcomings of this study should be considered. The lack of a specific risk of bias tool for partial economic evaluations limited the review to a methodological quality appraisal. In addition, variations in the methodology of cost estimation hindered stronger comparisons. These differences were probably due to the definition of cost categories, sources of information, the inherent difficulties in estimating the extent of underreporting, among others; for example, in most studies the treatment type was not described nor was the criteria for classifying a case as requiring hospitalization or ICU care. Constenla and colleagues (43) considered that much of the heterogeneity in

economic studies of dengue fever is due to an absence of methodological guidelines. Although specific guidelines exist for endemic countries in the Americas, socioeconomic and geopolitical specifics limit the ability to collect economic and clinical information and favor underreporting of cases (43).

The included studies also did not address other factors, such as dengue's effect on tourism, as evidenced at the FIFA World Cup of Brazil (44). In what is a coincidence between studies, the magnitude of dengue's impact highlights the need to implement public health measures for its prevention. Cost studies will allow future economic analyses of possible interventions, such as vector control and vaccination of selected population groups. An example of such an analysis was carried out by the Mexican Group of Dengue Fever Experts, which analyzed the effects of a vaccination program in Mexico (10).

Conclusions

The share distribution of the cost of dengue differs among countries,

underscoring the socioeconomic and geographic differences among countries of Latin America. However, local data for most countries is unavailable and a call for action to address this gap is pivotal. Of note is that much of the information available for many countries was based on extrapolated data from other nations, which helps partially on decision making. To understand its impact, the implementation of any dengue prevention and control interventions, such as vaccination, requires current data on the cost of illness for each country. Additionally, vector control and education in at-risk communities are cornerstones of preventing not just dengue fever, but also emerging and reemerging diseases such as Chikungunya, Mayaro, and Zika that share a common vector.

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Repercusiones económicas del dengue en América Latina y el Caribe: una revisión sistemática

RESUMEN

Objetivos. Evaluar las repercusiones económicas del dengue en América Latina y el Caribe mediante una revisión sistemática que abarcó estudios no considerados en otras revisiones anteriores.

Métodos. Se usó la metodología de Cochrane para hacer una revisión sistemática del costo del dengue en América Latina. Se hizo una búsqueda en PubMed Central, EMBASE y la Biblioteca Virtual en Salud, que incluyen revistas científicas arbitradas no indizadas por otras bases de datos, desde su aparición hasta agosto del 2016. Se incluyeron todos los artículos que contenían datos sobre el costo de la enfermedad para los países de América Latina. Los estudios incluidos se sometieron a una evaluación metodológica para la cual se usó un instrumento de siete preguntas diseñado para los estudios sobre los costos de las enfermedades. Los datos extraídos fueron los costos directos e indirectos para los casos de pacientes ambulatorios y hospitalizados y el costo total de la enfermedad. Los valores se ajustaron a dólares de los Estados Unidos del 2015 con base en el índice de precios al consumidor.

Resultados. De un total de 848 referencias iniciales, se incluyeron 17 estudios, principalmente de Brasil, Colombia, Cuba, México y Puerto Rico; se encontraron datos sobre los costos en 39 países. La evaluación metodológica indicó que 70% de los estudios reunían más de 70% de los puntos evaluados. La principal repercusión económica del dengue se debió a los costos por pérdida en la productividad. El costo anual promedio fue de más de USD 3.000 millones. Los costos directos representaron más de 70% del total para los casos de pacientes hospitalizados. En cuanto a los pacientes ambulatorios, los costos médicos directos fueron bajos, pero los costos sociales fueron considerables, ya que los costos indirectos pueden representar hasta 80% del costo total.

Conclusiones. El dengue tiene importantes repercusiones económicas en América Latina. Es fundamental elaborar nuevas intervenciones en materia de salud pública, como la vacunación contra el dengue, para reducir la propagación de la enfermedad y su costo total.

Palabras clave

Dengue; costo de enfermedad; costos de la atención en salud; América Latina; Región del Caribe.

Impacto econômico da dengue na América Latina e Caribe: revisão sistemática

RESUMO

Objetivos. Avaliar o impacto econômico da dengue na América Latina e o Caribe por meio de uma revisão sistemática que incluiu estudos não considerados anteriormente por outras revisões.

Métodos. Utilizou-se a metodologia Cochrane para realizar uma revisão sistemática do custo da dengue na América Latina. Foi realizada uma busca dos bancos de dados PubMed Central, EMBASE e Biblioteca Virtual em Saúde— a qual inclui periódicos científicos com avaliação por pares não indexados por outros repositórios— desde sua criação até agosto de 2016. Todos os artigos que relataram dados de custo de doença para países da América Latina foram incluídos. Os estudos incluídos foram submetidos a uma avaliação metodológica usando um instrumento de sete perguntas desenvolvido para estudos de custo de doença. Os dados extraídos foram os custos diretos e indiretos para casos ambulatoriais e hospitalizados e o custo total da doença. Os valores foram ajustados para dólares de 2015, usando-se o índice de preços ao consumidor.

Resultados. De 848 referências inicialmente identificadas, 17 estudos foram incluídos, principalmente do Brasil, Colômbia, Cuba, México e Porto Rico; dados sobre custos estavam disponíveis para 39 países. A avaliação metodológica demonstrou que 70% dos estudos apresentavam mais de 70% dos itens avaliados. O principal impacto econômico da dengue foi devido aos custos de produtividade. O custo médio anual foi superior a US\$3 bilhões. Para casos que exigiram hospitalização, os custos diretos representaram mais de 70% do custo total. Para pacientes ambulatoriais, os custos médicos diretos foram baixos, mas os custos sociais foram significativos, pois os custos indiretos podem representar até 80% do custo total.

Conclusões. A dengue tem impacto econômico considerável na América Latina. É essencial desenvolver novas intervenções de saúde pública, como a vacinação contra a dengue, para diminuir a propagação da doença e seu custo total.

Palavras-chave

Dengue; efeitos psicossociais da doença; custos de cuidados de saúde; América Latina; Região do Caribe.