International Journal of Infectious Diseases 122 (2022) 521–528

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Epidemiology and costs of dengue in Brazil: a systematic literature review

João Bosco Siqueira Junior[1], Eduardo Massad[2], Abner Lobao-Neto[3], Randee Kastner[4], Louisa Oliver[5], Elaine Gallagher[6,*]

[1] Universidade Federal de Goias, Instituto de Patologia Tropical e Saude Publica, Goiania, Brazil
[2] School of Applied Mathematics, Fundacao Getulio Vargas, Rio de Janeiro, Brazil
[3] Takeda Brazil, Sao Paulo, Brazil
[4] Takeda Vaccines Inc., Cambridge, Massachusetts, United States
[5] Adelphi Values, Bollington, United Kingdom
[6] Takeda Pharmaceuticals International AG, Zurich, Switzerland

A R T I C L E I N F O

Article history:
Received 2 February 2022
Revised 2 June 2022
Accepted 29 June 2022

Keywords:
Dengue
Brazil
Epidemiology
Incidence
Serotype
Economic impact

A B S T R A C T

Objectives: Dengue infection is a growing public health problem, with the number of reported cases increasing in the Americas and worldwide. This review characterized the epidemiological and economic burden of dengue in Brazil.

Methods: Embase, MEDLINE, evidence-based review databases, and gray literature sources were searched for published literature and surveillance reports on epidemiology (between 2000 and 2019) and costs (between 2009 and 2019) of dengue in Brazil. Studies were included if they reported data on incidence, seroprevalence, serotype distribution, expansion factors, hospitalization, mortality, or costs. Data were summarized descriptively and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results: A total of 344 publications were included (167 peer-reviewed and 177 gray literature). Dengue outbreaks increased in incidence and frequency, with the highest incidence observed in 2015 at 807 cases per 100,000 population. Outbreaks were related to alternating predominant serotypes. Dengue was more frequent in young adults (aged 20-39 years) and in the Midwest. Cost and societal impacts are substantial and varied across regions, age, and public/private delivery of healthcare services.

Conclusion: The burden of dengue in Brazil is increasing and likely underestimated. Therefore, developing and implementing new strategies, including vaccination, is essential to reduce the disease burden.

Introduction

Dengue, a mosquito-borne infection, is a rapidly growing public health problem, and Brazil represents one of the countries with the highest burdens, with over 1.5 million cases reported in 2019 (DATASUS, 2019). Dengue was estimated to have caused over 92,000 disability-adjusted life years (DALYs) in Brazil in 2016, yielding a rate of 44.87 DALYs per 100,000 population (age-standardized). This represents a 4015-fold increase from the burden estimated in 1990, placing dengue as the neglected tropical disease for which burden increased the most in recent decades in Brazil (Martins-Melo *et al.*, 2018).

Dengue can present with common symptoms, including fever, muscle and joint pain, headache, and rash (Castro *et al.*, 2017; Guzman and Harris, 2015). As these symptoms are nonspecific, they may resemble other infections, including SARS-CoV-2, chikungunya, and Zika. Thus, accurate clinical diagnosis of dengue is challenging, which can result in misdiagnosis and under-reporting of the disease (Muller *et al.*, 2017). Furthermore, due to a high prevalence of asymptomatic infection, self-management of symptoms and under-reporting of hospitalized cases, the true burden of dengue is likely underestimated (Martelli *et al.*, 2015; WHO, 2021). Dengue epidemics in Brazil have shown a cyclical pattern, with shifting of the predominant serotypes. Intense epidemic peaks are interspersed with interepidemic periods of 3-4 years, which have decreased in length in recent years (Andrioli *et al.*, 2020).

Cases of dengue are mandatorily notifiable in Brazil through SINAN (Sistema de Informacao de Agravos de Notificacao), the

* Corresponding author: Elaine Gallagher, Takeda Pharmaceuticals International AG, Zurich, Switzerland.
E-mail address: elaine.gallagher@takeda.com (E. Gallagher).

https://doi.org/10.1016/j.ijid.2022.06.050

national surveillance information system. Until 2014, cases were classified into classic dengue, dengue with complications, dengue hemorrhagic fever, or dengue shock syndrome. In 2014, Brazil adapted the 2009 World Health Organization (WHO) dengue case classification (Nunes *et al.*, 2019; WHO, 2009).

Dengue is associated with a substantial economic burden (Selck *et al.*, 2014; Shepard *et al.*, 2016). Previous reviews show that although data lack standardization, financial impact is particularly relevant in Latin America and Brazil (Laserna *et al.*, 2018; Stahl *et al.*, 2013). During the dengue epidemic season of 2012-2013, the estimated societal cost of dengue in Brazil was $1212 million US dollars (USD) (when adjusted for under-reporting) (Martelli *et al.*, 2015).

To better characterize the trends and burden of dengue in Brazil, a systematic literature review for the period 2000-2019 (epidemiology) and 2009-2019 (costs) was conducted.

Methods

The review was conducted according to the Cochrane Handbook for Systematic Reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Deeks *et al.*, 2011, Moher *et al.*, 2009)

Information sources and search strategy

Embase, MEDLINE®, and the evidence-based medicine review databases were searched on 6 November 2019. Separate searches were conducted for epidemiologic and cost data in the OVID® search engine. The searches were limited to studies published in English or Portuguese since January 1, 2000 for epidemiology and January 1, 2009 for cost. Search criteria are listed in Supplementary Table 1. Regional scientific databases, such as Latin American and Caribbean Health Sciences Literature and Scientific Electronic Library Online, were also searched. Reference lists, gray literature sources, and major academic websites were searched for additional literature (Supplementary Table 2).

Eligibility criteria and study selection

Studies were included in the review if they reported incidence, seroprevalence, serotype distribution, expansion factor (EF), hospitalization, mortality, or direct and indirect costs of dengue in Brazil (Supplementary Table 3). The publication with the most recent or complete dataset was included for studies with multiple publications.

The study selection process involved two stages: (i) titles/abstracts were screened and (ii) full texts were screened. Two reviewers independently screened the studies at both stages, and a third reviewer resolved discrepancies. Duplicates and articles not satisfying the inclusion criteria were excluded after a review of the studies.

Data extraction and synthesis of results

Key data from each included study were collated into a data extraction form. Data were extracted by one reviewer and double-checked by a second reviewer. A third reviewer resolved discrepancies. Overall, data from surveillance sources were prioritized and complemented by peer-reviewed studies where needed. Meta-analyses were not planned in the original protocol. EFs were defined as the multiplication or adjustment factors used to correct under-reporting of dengue cases (Toan *et al.*, 2015; Undurraga *et al.*, 2013). Costs were converted to 2019 USD using the Brazilian consumer price index (IBGE, 2021).

Risk of bias and quality assessment

Two independent reviewers assessed study risk of bias and quality using the National Institutes of Health (NIH)'s tool for epidemiological studies and the National Health Service Wales' tool for cost studies (National Institutes of Health, 2019). Quality assessment was not performed for gray literature studies or reports that were not peer-reviewed.

Results

A total of 3585 records were identified; 3425 were from the epidemiology search and 160 from the cost search. After applying limits and deduplication and conducting title and abstract screening on 2858 records, a total of 263 publications were selected for full-text screening. Of these, 164 were selected for data extraction and inclusion in the review. Three additional publications captured from the review of reference lists were included, resulting in 163 publications in epidemiology and four in costs. However, eight publications identified in the epidemiology search also contained cost data and one publication in the cost search contained epidemiology data, yielding a total of 12 publications for the cost analysis and 164 publications for epidemiology analysis (Figure 1, Supplementary Figures 4 and 5). Furthermore, 177 gray literature articles were included in the review (Figure 1).

Consensus results of the risk of bias assessment for epidemiology and cost studies are detailed in Supplementary Tables 24 and 25.

National and regional epidemiology

National incidence data in Brazil are collated by the Ministry of Health (MoH) and reported to the WHO and the Pan American Health Organization (PAHO) Health Information Platform for the Americas Database (PLISA) (Supplementary Tables 6.1 and 6.2). Dengue incidence in Brazil was high during the study period (DATASUS, 2019, PAHO). Major epidemics with over 1,000,000 cases were registered in 2013, 2015, 2016, and 2019. Since 2000, the highest incidence was recorded in 2015 with 806.5 cases per 100,000 population, followed by 2019 with 735.2 cases per 100,000 population (Figure 2). A total of 10 publications generally agreed, with an increasing incidence trend throughout the study period (Supplementary Table 7). However, the studies varied in methodology and the magnitude of the incidence values. One study from the Global Burden of Disease reported a 184.3% increase in incidence from 446.6 per 100,000 population in 2000 to 1269.1 per 100,000 population in 2015. However, this study was is based on modelling (Araújo *et al.*, 2017).

Regional incidence of dengue was mostly retrieved from the DATASUS website and the MoH bulletins. The number of probable cases was reported since 2007, but incidence rates were only available from 2013 onwards (Brazil MoH, 2012–2019, DATASUS, 2019). The Southeast had the highest number of reported cases from 2007-2019. Values for this region were more than double those in the second most affected region (Midwest or Northeast) in 2010, 2013, 2015, 2016, and 2019 and reached over 1 million cases in 2015 and 2019. Notwithstanding, the highest incidence rates reported by the MoH between 2013 and 2019 were consistently observed in the Midwest region, ranging between 490.9 (2017) to 1744.2 (2013) cases per 100,000 population. The lowest rates were reported in the South region, with values between 8.5 (2017) and 238.1 (2016) cases per 100,000 population (Figure 2, Supplementary Table 8).

Most publications identified in the review (n = 71, Supplementary Table 9) reported local incidence by city or Federal District and two key publications reported regional incidence. Böhm *et al*

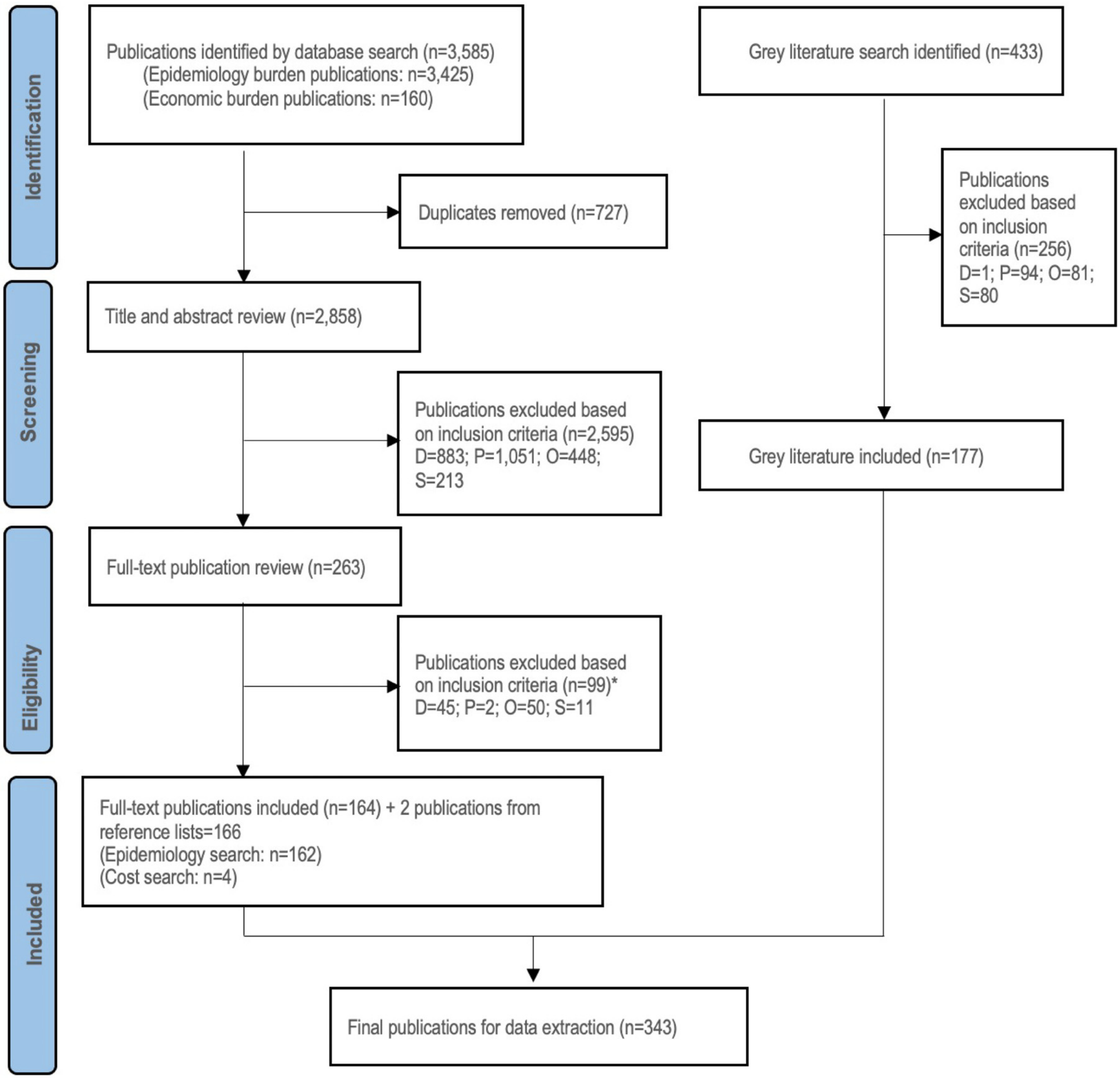

Figure 1. PRISMA flowchart for epidemiology and cost studies. D: duplicate; O: outcome; P: population; S: study design [a]One full text was not available (Santos *et al.*, 2003)

reported high incidence rates for the Midwest in the periods 2005-2007, 2009-2010, and 2012 (Böhm *et al.*, 2016). Burattini *et al* reported that the total number of cases between 2000 and 2014 was highest in the Southeast region (2,239,451 cases), followed by the Northeast (999,774 cases), Midwest (547,436 cases), North (446,450 cases), and finally, South (90,775 cases) (Burattini *et al.*, 2016). These publications are consistent with the data reported by DATASUS and the MoH.

Seasonality

A total of 38 publications were reported on dengue seasonality (Supplementary Table 10). Overall, dengue incidence was highest during the rainy season, from October to May. However, the peak incidence months varied across studies, possibly due to regional climatic and environmental differences. An ecologic study in the Northeast (2003-2010) reported highest incidence between April and September, and the peak month varying from year to year (Silva *et al.*, 2016). In the North, the monthly average incidence of dengue between 2001 and 2012 was highest from December to March, with the peak incidence in February (Duarte *et al.*, 2019). Similarly, a cohort study in the Northeast (2007-2013) reported an increase in dengue cases between January and May (Costa and Calado, 2016). A retrospective study in the Southeast (2008-2015) reported March-May as the period of highest incidence. However, in 2015, dengue cases increased in January (Ferreira *et al.*, 2018). The authors concluded that the seasonal trend in incidence was due to increased rainfall, which led to high mosquito levels (Ferreira *et al.*, 2018). In most publications, increased rainfall and higher temperature were associated with an upsurge in dengue intensity. However, some level of dengue transmission continues throughout the year.

Age distribution

The number of dengue cases stratified by age was reported in the period 2007-2013 (DATASUS). Between 2007 and 2013, the most probable dengue cases were identified in the 20-39 age group, followed by the 40-59 age group (Supplementary Table 11). Six publications reported data stratified by age but only three of these reported incidence rates (Supplementary Table 12). These studies identified the age groups 20-39 and 21-35 as the groups with highest number of cases and incidence (Böhm *et al.*, 2016; Burattini *et al.*, 2016; Nascimento *et al.*, 2017). Böhm *et al* reported

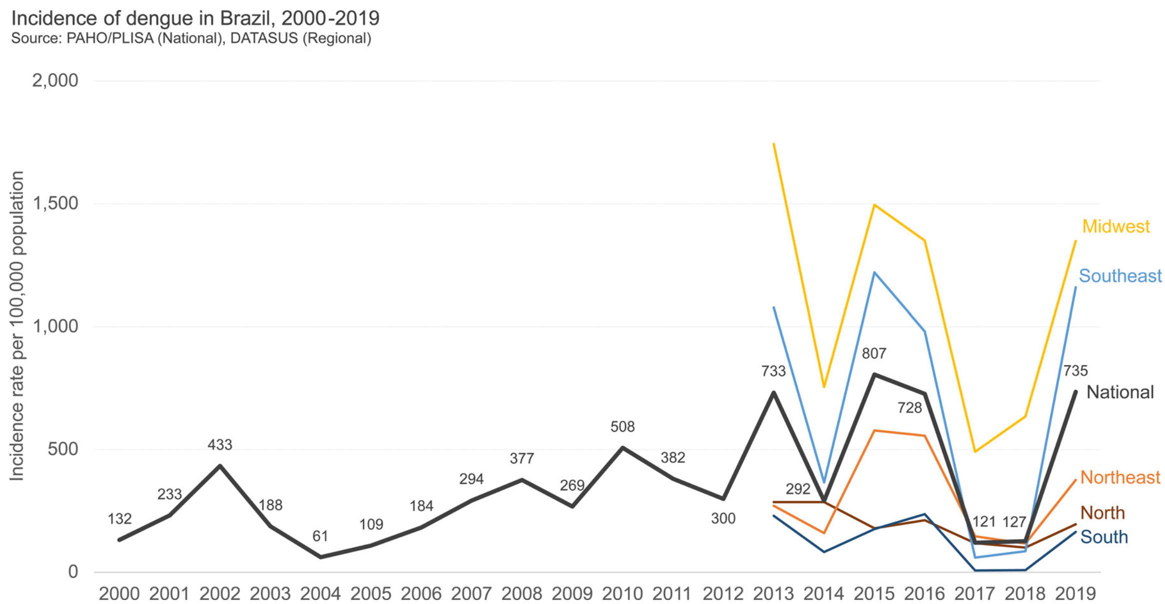

Figure 2. National incidence rates of dengue per 100,000 in Brazil, 2000-2019. National data from 2000-2018 were from PAHO/PLISA database. Since PAHO data for 2019 were discrepant from the MoH bulletin, the latter was used for 2019 because MoH is the primary data source. Regional incidence data were retrieved for the period 2013-2019 from DATASUS. PAHO, Pan American Health Organization; PLISA, Platform for the Americas Database

yearly incidences by age from 2002-2012. The highest incidence of dengue during this period was reported among those aged 20-39 years (53.0 [2004] to 598.6 [2010] cases per 100,000 population); although, the 10-19 age group had the highest incidence in 2008 (347.0 per 100,000) and in 2011 (418.1 per 100,000). The age groups with the lowest incidence were those aged <5, 5-9, and >60 years (Böhm *et al.*, 2016) (Supplementary Table 11). Burattini *et al* reported overall number of cases by age in the period 2000-2014. The highest number of cases were observed among those aged 21-35 years (1,270,950 cases) and the lowest number of cases were among those aged 1-5 years (158,616 cases) (Burattini *et al.*, 2016).

A total of 38 studies reported regional incidence by age group. However, the difference in age groups and stratification period makes data summarization challenging (Supplementary Table 13). Most studies reported highest incidences across ages 10-69 years. However, a descriptive study on the basis of surveillance data (2001-2012) from the Northeast showed an increase in incidence over time among children aged <9 years. Dengue incidence was highest in this age group in 2008 (2,331.3 cases per 100,000 population, rising from 406.9 per 100,000 population in 2001) (Oliveira *et al.*, 2018). This trend was supported by Barbosa *et al* (Barbosa *et al.*, 2012), which showed an increase in the incidence per 100,000 population, from 166.5 in 2000 to 1530.5 in 2008 in the 0-4 age group and from 264.77 in 2000 to 1580.8 in 2008 in the 5-14 age group.

Hospitalizations and deaths

The overall nationwide number of hospitalizations for dengue was obtained from the Brazilian Hospitalization Information System (SIH-SUS). In the period 2008-2019, the highest number of hospitalizations was registered in 2010 (95,008), followed by 2008, 2011 and 2015 (>70,000). The lowest number was reported in 2018 (17,858) (Figure 3) (DATASUS, 2019). Hospitalization rates from the identified studies ranged from <1-25.52%, with the latter associated with DENV2 serotype (Supplementary Table 14). Burattini *et al* reported the number and hospitalization rates of dengue by age group from 2000-2014. In this period, the number of hospitalizations was highest in age groups 21-35 (25,142) and 11-20 (23,897) and lowest in age groups 1-5 (7,485) and >65 (7,782). However, the percentage of hospitalizations among dengue cases was highest in the 6-10 age group (17.47%). From a regional perspective (Supplementary Table 15), the Southeast region registered the highest number of hospitalizations (55,275) but had the lowest hospitalization rate (4.91%). The highest hospitalization rates were observed in the Northeast (13.47%, 30,000 hospitalizations), followed by the South (9.7%, 2,483 hospitalizations) and North (9.2%, 10,506 hospitalizations) (Burattini *et al.*, 2016). It should be noted that this study used data from SINAN, which was previously shown to underreport dengue hospitalizations (Coelho *et al.*, 2016).

The national case fatality rates (CFRs) and deaths due to dengue for the period 2000-2019 were retrieved from the PAHO database (PAHO, 2020). The CFR was highest in 2014 (0.069%) and in 2010 (0.066%), but the highest numbers of deaths due to dengue were registered in 2015 (863) and in 2019 (789) (Figure 3). Seven publications reporting nationwide data (Supplementary Table 16) found that the CFR for DF ranged from 0.01-5.8%. However, the highest value was registered for people with comorbid renal failure.

According to the 2019 MoH bulletin (up to epidemiologic week 47), the highest CFR for dengue by age group was registered in the group aged >80 years (0.92%), followed by the 60-79 years (0.16%) (Brazil MoH, 2012-2019). The age group with the lowest CFR was the group aged 1-4 years (0.01%) (Supplementary Table 17). In the same bulletin, the regional CFRs of probable dengue cases were 0.04% in the North and Northeast, 0.05% in the Southeast, 0.06% in the South, and 0.07% in the Midwest. No publications reported regional CFR; although, 21 studies identified CFR within specific cities or federal districts (Supplementary Table 18).

Seroprevalence

Seroprevalence was not reported at a national level. From 20 publications reporting data at a regional level, seroprevalence varied depending on age, sex, region, and testing method (Supplementary Table 19). Overall, seroprevalence increased with age (Chiaravalloti-Neto *et al.*, 2019; Sacramento *et al.*, 2018). High rates were observed in those aged 5-14 years (69.9-84%) in three set-

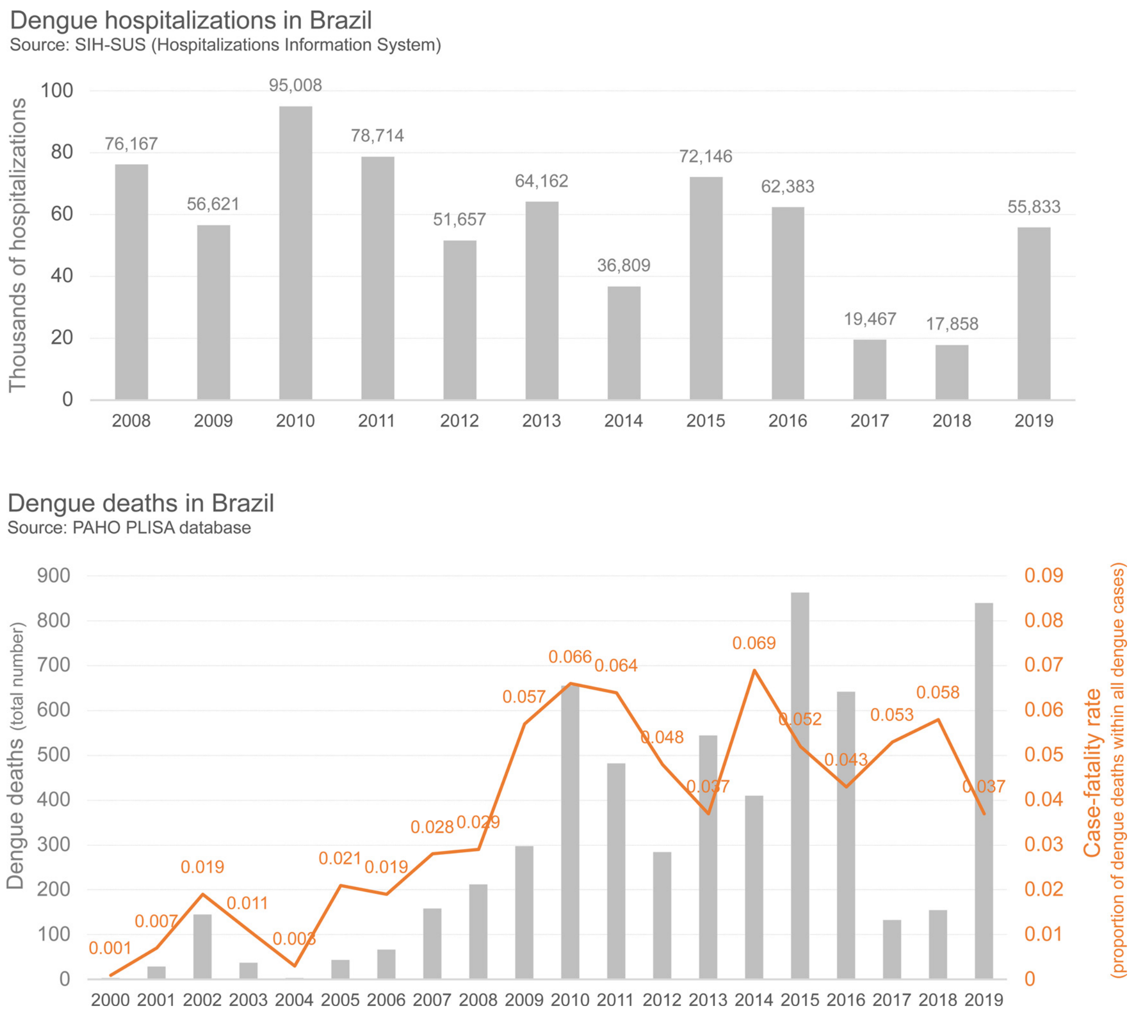

Figure 3. Dengue severity in Brazil. Top: Dengue-related hospitalizations, 2008-2019. Source SIH-SUS. Bottom: Deaths due to dengue and case-fatality rate in Brazil, 2000-2019. Source: PAHO/PLISA database. PAHO, Pan American Health Organization; PLISA, Platform for the Americas Database

tings in Northeast Brazil (2005-2006) but still lower than those aged ≥15 years (77.7-96.8%) (Braga *et al.*, 2010).

Serotype distribution

According to data from the PAHO database, DENV1-3 have co-circulated in Brazil between 2000 and 2009 and all serotypes have been cocirculated in Brazil since 2010 (PAHO, 2020). The Brazilian MoH reported serotype distribution in weekly bulletins. However, the reports are inconsistent throughout time and challenging to interpret because yearly distributions do not add up to 100%. Nonetheless, the data suggest an overall predominance of DENV4 in 2012, DENV1 from 2014-2016, and DENV2 in 2018 but with regional variation (Supplementary Table 20) (Brazil MoH, 2012–2019).

A total of 56 publications reported serotype distributions within different regions and states of Brazil and are generally consistent with MoH reports (Supplementary Table 21). Three key studies report results from >100,000 notified dengue cases; although, not all cases were serotyped. In the Northeast, one study showed that DENV1 predominated and cocirculated with DENV2 between 1995 and 2001, with DENV3 becoming predominant between 2002 and 2006 (Cordeiro *et al.*, 2007). Another study showed that the predominant serotypes were DENV1 in 2001, DENV3 in 2003 and 2007, and DENV2 in 2008 (Barbosa *et al.*, 2012). A study in the Southeast reported DENV1 (52.2%) and DENV4 (47.8%) as the most frequent serotypes between November 2012 and July 2013 (Amâncio *et al.*, 2014).

Expansion factors

Five studies reported EFs to account for dengue under-reporting in Brazil (Supplementary Table 22). Two of these studies, on the basis of the same data, reported higher EF for ambulatory (EF 3.2) than for hospitalized cases (EF 1.6) (Boiron *et al.*, 2018; Martelli *et al.*, 2015). On the basis of these EFs, an estimated 18.2 million ambulatory cases and 366,934 hospital cases were likely underreported from 2008-2017 (Boiron *et al.*, 2018). Duarte *et al* estimated that 37% of suspected dengue cases identified in the SIH-SUS (from 1996-2002, Southeast) were not reported to SINAN (Duarte and França, 2006). Similarly, Coelho *et al* reported a 33% increase in the number of hospitalizations recorded in SIH-SUS (48,174 cases) compared with SINAN (36,145 cases) between 2008 and 2013 in 10 municipalities in Brazil. Notwithstanding, the hospitalizations registered in SINAN are underreported because the database is limited to cases from public health systems only (Coelho *et al.*, 2016). Coudeville *et al* compared the incidence data from a dengue vaccine phase III trial with a national surveillance system and reported an EF of 1.8 (Coudeville *et al.*, 2016). In comparison, Sarti *et al* reported higher EFs at the national (26.7), state (16.9), and local (19.4) levels. However, the authors analyzed limited study locations and age ranges (9-19 years) (Sarti *et al.*, 2016).

Dengue costs: direct medical and nonmedical

A total of 12 publications reported the costs of dengue in Brazil between 2005 and 2017. All costs were adjusted to 2019 USD, except for three studies because they did not report the year's valuation.

From a societal perspective, the estimated costs of dengue, including ambulatory, hospital, and fatal cases, varied from $516.79 million (2009) to $1688.3 million (2013) USD after adjusting for under-reporting (Martelli *et al.*, 2015). Other studies reported 2010 as the year of higher total cost of dengue hospitalizations or direct medical costs (Amaral *et al.*, 2014; Camasmie Abe and Miraglia, 2018; Godói *et al.*, 2018). Shepard *et al* reported an overall annual aggregated cost of $1014.3 million USD, with more than half of the cost related to ambulatory cases ($678.56 million USD) and indirect costs ($859.77 million USD) (Shepard *et al.*, 2016).

Overall, hospitalized cases had higher total costs per case (mean ± standard deviation: $3416.27 ± 2,188.35 USD) than ambulatory cases ($1472.24 ± 1,695.50 USD). When stratified, all cost categories were also higher for hospitalized than for ambulatory cases: direct medical ($1465.92 ± 775.08 vs $187.45 ± 128.48 USD), direct nonmedical ($183.24 ± 136.90 vs $67.40 ± 82.14 USD) and indirect ($1769.21 ± 2,036.70 vs $1213.18 ± 1663.90 USD) (Suaya *et al.*, 2009). This was supported by Shepard *et al*, who reported an overall average cost per case of $531.63 USD (Shepard *et al.*, 2016).

The total direct medical cost per case was generally higher in private than in the public healthcare sector ($1671.16 ± 3,786.79 vs. $713.93 ± 1,590.22 USD, respectively) and among those aged >60 years ($1882.49 ± 4,431.11 USD) than those aged <15 years ($1011.69 ± 748.40 USD). However, in the public sector, the cost was highest among aged <15 years ($1189.05 ± 2492.67 USD) and lowest among those aged 15-60 years ($452.80 ± 890.45 USD) (Vieira Machado *et al.*, 2014). Additionally, the average cost of dengue deaths in children ($449,924.12 USD) was higher than in adults ($293,913.28 USD) (Shepard *et al.*, 2016).

Over a 16-year period (2000-2015), costs for dengue treatment were highest in the Southeast (21% of the total national costs, $34.16 million USD) and Northeast regions (48% of the total national costs, $81.12 million USD) (Godói *et al.*, 2018). The higher rates/number of cases and hospitalizations in the regions may be partly responsible (Godói *et al.*, 2018). The total cost per case also varied by region, public versus private sector, and healthcare setting (Martelli *et al.*, 2015).

Societal impact

Six studies reported on the societal impact of dengue between 2010 and 2017, but data were limited (Supplementary Table 23). Most studies reported the number of hospital days as the proxy for societal impact because they imply school/work absenteeism. Overall, patients showing dengue with warning signs, severe dengue, or requiring a platelet transfusion had the highest number of hospital days (Machado *et al.*, 2019; Vieira Machado *et al.*, 2014). As expected, hospitalized patients also had a higher number of workdays lost (10.7 ± 5.2 vs 7.1 ± 5.1) or school days (6.8 ± 5.4 vs 5.2 ± 3.9), a higher number of days of illness (17.4 ± 8.4 vs 15.0 ± 8,.4), and higher number of ambulatory visits (4.0 ± 2.7 vs 3.6 ± 2.7) than a patient who was not hospitalized.

For patients of economically active age, the average number of hospital days was estimated at 3.89 days per patient (Pereira *et al.*, 2014). However, in Vieira Machado *et al*, the longest hospital stay (15 ± 2.8 days) was reported for laboratory-confirmed dengue in the public healthcare system for patients who did not meet the WHO dengue platelet transfusion criteria (Vieira Machado *et al.*, 2014). As expected, the average number of hospital days was lower for classical dengue (3.2 days) than dengue hemorrhagic fever (5 days) (Silva *et al.*, 2013).

Discussion

This review summarizes the trends and burden of dengue in Brazil in the past 10-20 years. Information retrieved from surveillance data and publications shows that the burden of dengue has been increasing in recent years, with incidence reaching over 500 cases per 100,000 population in 2010, 2013, 2015, and 2019 (DATASUS, 2019; PAHO, 2020). Except for 2015, these peak years coincided with outbreak years in neighboring countries, such as Colombia (Gutierrez-Barbosa *et al.*, 2020).

Although the highest number of cases were reported in more populous regions (Southeast), the highest incidence rates in the past decade were consistently recorded in the Midwest (Andrioli *et al.*, 2020, Brazil MoH, 2012–2019, DATASUS, 2019). Evident in this review and corroborated by previous analyses, dengue incidence and hospitalizations are underreported in surveillance databases due to the high rate of asymptomatic infections, self-management of symptoms, or misdiagnosis of cases. In addition, public databases fail to report episodes from private health institutions (Bhatt *et al.*, 2013; Boiron *et al.*, 2018; Coelho *et al.*, 2016; Undurraga *et al.*, 2013; WHO, 2021; Wichmann *et al.*, 2011). For public health officials to understand the disease burden and appropriately assess the cost-benefit of interventions, accurate reporting of dengue is essential (Undurraga *et al.*, 2013).

Dengue cases were primarily concentrated in the rainy season, with varied peak incidence months each year (Silva *et al.*, 2016). The seasonal surges could overwhelm healthcare systems and negatively impact the management and outcomes of other diseases during crucial periods (Clark *et al.*, 2005; García *et al.*, 2011). This could be further exacerbated when seasonal peak of dengue coincides with other diseases, as observed in 2020 with COVID-19 (Lorenz *et al.*, 2020). Brazil is one of the countries most affected by the COVID-19 pandemic, with about 21 million cases reported by September 7, 2021 (Pan American Health Organization 2021). Because the occurrence of COVID-19 overlapped with a higher incidence of dengue in Brazil in 2020, the burden of dengue on the national healthcare system is expected to increase as the infection curve of COVID-19 grows and dengue serotypes are reintroduced (Nacher *et al.*, 2020; Rabiu *et al.*, 2021). Furthermore, cocirculation and coinfection of COVID-19 with dengue could affect disease management; the quality of patient care; and increase the risk of morbidity, mortality, and socioeconomic impacts (Ridwan, 2020; Tsheten *et al.*, 2021). COVID-19 outbreaks coinciding with dengue outbreaks may profoundly impact Brazil's already strained healthcare system (Nacher *et al.*, 2020; Rabiu *et al.*, 2021). These impacts may affect specific regions differently, as reported for Valle del Cauca in Colombia (Cardona-Ospina *et al.*, 2021). Early-stage clinical manifestations of dengue are similar to those of COVID-19 and other viral infections, complicating diagnosis and confounding surveillance.

All four DENV serotypes fluctuated in frequency throughout the study period. DENV1 re-emerged in 2009 and became predominant in 2010 in most states in the Midwest, Southeast, and South (Brazil MoH, 2010). DENV1 cocirculated with DENV4 between 2011 and 2013 (Colombo *et al.*, 2016; Rocha *et al.*, 2017) and predominated between 2014 and 2016, whereas in 2018, predominance shifted to DENV2 (Brazil MoH, 2012–2019). Major dengue outbreaks appear to be related to shifting of predominant serotypes. The exchange in serotypes between regions of Brazil and other neighboring countries, such as Colombia or Panama, may play a role in the occurrence of local outbreaks (Díaz *et al.*, 2019; Gutierrez-Barbosa *et al.*, 2020). This highlights the need to monitor serotype distributions at the regional and national levels because this may help predict the occurrence of an upcoming outbreak.

Mortality due to dengue has also increased; tens of thousands of hospitalizations have been registered yearly since 2008, reflecting an increase in severity (DATASUS, 2019; PAHO, 2020). This may be partly due to the predominance of DENV2, which has been associated with the highest risk of mortality and hospitalization due to dengue (Vicente *et al.*, 2016). Furthermore, this serotype was identified as a cause of the high incidence and increased disease severity observed in children in 2008 (Barbosa *et al.*, 2012; Böhm *et al.*, 2016; Oliveira *et al.*, 2018). Though young adults (20-39 years) have the highest incidences (Böhm *et al.*, 2016; Burattini *et al.*, 2016; DATASUS, 2019; Nascimento *et al.*, 2017), some studies suggest that dengue incidence has increased in children (Barbosa *et al.*, 2012; Oliveira *et al.*, 2018) and that severe dengue cases and hospitalizations due to dengue were higher among children (6-10 years) (Burattini *et al.*, 2016), suggesting that broad age groups should be targeted to reduce both disease burden and those at risk of more severe outcomes.

Summarizing seroprevalence data was challenging due to the varying testing methods, regions, and populations analyzed. Overall, studies agreed that seroprevalence increases with age, with specific adult populations of hyperendemic areas in the Northwest and Southwest reaching >85% seropositivity (Braga *et al.*, 2010; Chiaravalloti-Neto *et al.*, 2019).

Dengue was shown to cause a significant and increasing economic burden; although, its true burden is likely underestimated. Hence, using EFs to adjust for under-reporting is necessary (Coelho *et al.*, 2016; Martelli *et al.*, 2015; Sarti *et al.*, 2016). After adjusting for under-reporting, total national costs of dengue were estimated to be over $2,586.42 million USD in 2013. Although the costs for treating a hospitalized case were higher, overall outpatient treatment and indirect costs contributed the largest portion of the cost (Martelli *et al.*, 2015; Shepard *et al.*, 2016), and it is expected to increase after an increase in dengue cases and changing serotypes likely to result in future outbreaks.

This review has several important strengths, which lie in the methodology and broad study period: 2000-2019 for epidemiology and 2009-2019 for cost/burden. To the best of our knowledge, this is the first systematic review analyzing dengue costs in Brazil. However, there are several limitations, some of which have been reported in an earlier analysis (Teixeira *et al.*, 2013). Incidence and hospitalization of dengue cases are underreported. Classification and reporting of disease severity are inconsistent through the years; data quality is inconsistent across the country and age group data for overall incidence has been limited since 2014. National seroprevalence data were rarely reported. This information is required to understand the overall exposure to dengue. Furthermore this review did not focus on the coevolution of dengue with other arboviral diseases, such as chikungunya and Zika, which have been shown to influence dengue epidemiology (Perez *et al.*, 2019). In the economic burden analysis, studies identified were heterogeneous in definitions, source data, and methodology and did not allow comparison of the data across the studies. Costs associated with long-term persistent effects of dengue were not identified, which, if reported, could significantly increase the economic burden of dengue. In Mexico, these effects were estimated to increase the total economic burden of dengue by 13% (Tiga *et al.*, 2016). Although this study did not capture the costs of vector control methods, different studies have reported that these account for 40-72% of the overall economic burden and have questionable efficacy (Castañeda-Orjuela *et al.*, 2012; Castro *et al.*, 2017). On the other hand, a pilot vaccination program has uncovered potential challenges in achieving high vaccination coverage (Preto *et al.*, 2021). As such, the success of dengue vaccination depends on using different approaches.

Conclusion

Dengue incidence has been increasing in magnitude and frequency in recent years, causing a significant economic and societal burden in Brazil. However, due to under-reporting, the true burden of dengue may be substantially underestimated. It is, therefore, crucial to implement public health interventions, such as vaccination and improved vector control, that will prevent the multiplication of dengue cases.

Conflicts of interest

JBSJ is a speaker and part of the board for Takeda Brazil. EM has no competing interests to declare. EG, RK, and AL are employees of Takeda. RK owns stocks in Takeda. LO is an employee of Adelphi Values and has served as a paid consultant for Takeda Pharmaceuticals.

Acknowledgments

The authors acknowledge Egbe Ubamadu and Ana Goios (P95 Epidemiology and Pharmacovigilance, Leuven, Belgium) for their assistance in data extraction and critical review of the systematic literature review, writing, and preparing figures, which was funded by Takeda Pharmaceuticals.

Funding

This study was funded by Takeda Pharmaceuticals.

Ethical approval

Not required

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.06.050.

References

Amâncio FF, Ferraz ML, Almeida MC, Pessanha JE, Iani FC, Fraga GL, et al. Dengue virus serotype 4 in a highly susceptible population in Southeast Brazil. J Infect Public Health 2014;7:547–52.
Amaral LM, Fernandes RA, Takemoto MLS, Padula AC, Vasconcellos JF, Haas LC, et al. Brazilian program for research and development in neglected diseases: analyses of hospitalization patterns and costs. Value Health 2014;17:A271.
Andrioli DC, Busato MA, Lutinski JA. Spatial and temporal distribution of dengue in Brazil, 1990–2017. PLOS ONE 2020;15.
Araújo VEM, Bezerra JMT, Amâncio FF, Passos VMA, Carneiro M. Increase in the burden of dengue in Brazil and federated units, 2000 and 2015: analysis of the Global Burden of Disease Study 2015. Rev Bras Epidemiol 2017;20:205–16.
Barbosa IR, Araújo LdF, Carlota FC, Araújo RS, Maciel IJ. Epidemiologia do dengue no Estado do Rio Grande do Norte, Brasil, 2000 a 2009. Epidemiol Serv Saúde 2012;21:149–57.
Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature 2013;496:504–7.
Böhm AW, Costa CD, Neves RG, Flores TR, Nunes BP. Dengue incidence trend in Brazil, 2002–2012. Epidemiol Serv Saude 2016;25:725–33.
Boiron L, Durand L, Araujo RR. Economic impact of dengue in Brazil over 10 years (2008–2017). Value Health 2018;21:S151–2.
Braga C, Luna CF, Martelli CM, de Souza WV, Cordeiro MT, Alexander N, et al. Seroprevalence and risk factors for dengue infection in socio-economically distinct areas of Recife, Brazil. Acta Trop 2010;113:234–40.
Brazil M. Nota técnica: identificação de Áreas de maior Vulnerabilidade para Ocorrência de Dengue no período de Transmissão 2010/2011 com vistas a subsidiar a intensificação das ações de controle, 2010.
Brazil M. Epidemiological bulletins, 2012–2019.
Burattini MN, Lopez LF, Coutinho FA, Siqueira-Jr JB, Homsani S, Sarti E, et al. Age and regional differences in clinical presentation and risk of hospitalization for dengue in Brazil, 2000–2014. Clinics (Sao Paulo) 2016;71:455–63.
Camasmie Abe K, Miraglia SGEK. Dengue incidence and associated costs in the periods before (2000–2008) and after (2009–2013) the construction of the hydroelectric power plants in Rondonia. Brazil. Epidemiol Serv Saude 2018;27.

Cardona-Ospina JA, Arteaga-Livias K, Villamil-Gómez WE, Pérez-Díaz CE, Katterine Bonilla-Aldana D, Mondragon-Cardona Á, et al. Dengue and COVID-19, overlapping epidemics? An analysis from Colombia. J Med Virol 2021;93:522–7.

Castañeda-Orjuela C, Díaz H, Alvis-Guzman N, Olarte A, Rodriguez H, Camargo G, et al. Burden of disease and economic impact of dengue and severe dengue in Colombia, 2011. Value Health Reg Issues 2012;1:123–8.

Castro MC, Wilson ME, Bloom DE. Disease and economic burdens of dengue. Lancet Infect Dis 2017;17:e70–8.

Chiaravalloti-Neto F, da Silva RA, Zini N, da Silva GCD, da Silva NS, Parra MCP, et al. Seroprevalence for dengue virus in a hyperendemic area and associated socio-economic and demographic factors using a cross-sectional design and a geostatistical approach, state of Sao Paulo, Brazil. BMC Infect Dis 2019;19:441.

Clark DV, Mammen Jr MP, Nisalak A, Puthimethee V, Endy TP. Economic impact of dengue fever/dengue hemorrhagic fever in Thailand at the family and population levels. Am J Trop Med Hyg 2005;72:786–91.

Coelho GE, Leal PL, Cerroni Mde P, Simplicio AC, Siqueira Jr JB. Sensitivity of the dengue surveillance system in Brazil for detecting hospitalized cases. PLOS Negl Trop Dis 2016;10.

Colombo TE, Vedovello D, Pacca-Mazaro CC, Mondini A, Araújo JP, Jr Cabrera E, et al. Dengue virus surveillance: detection of DENV-4 in the city of Sao Jose do Rio Preto, SP, Brazil. Acta Trop 2016;164:84–9.

Cordeiro MT, Schatzmayr HG, Nogueira RM, Oliveira VF, Melo WT, Carvalho EF. Dengue and dengue hemorrhagic fever in the State of Pernambuco, 1995–2006. Rev Soc Bras Med Trop 2007;40:605–11.

Costa IM, Calado DC. Incidence of dengue cases (2007–2013) and seasonal distribution of mosquitoes (Diptera: Culicidae) (2012–2013) in Barreiras, Bahia, Brazil. Epidemiol Serv Saude 2016;25:735–44.

Coudeville L, Baurin N, L'Azou M, Guy B. Potential impact of dengue vaccination: insights from two large-scale phase III trials with a tetravalent dengue vaccine. Vaccine 2016;34:6426–35.

DATASUS. Casos Prováveis por Faixa Etária segundo Ano 1° Sintoma(s) Período: 2007–2013. http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinannet/cnv/denguebr.def, 2019 (accessed 28 November 2019).

Deeks JJ, Higgins J, Altman DG, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration; 2011 updated.

Díaz Y, Chen-Germán M, Quiroz E, Carrera JP, Cisneros J, Moreno B, et al. Molecular epidemiology of dengue in Panama: 25 years of circulation. Viruses 2019;11:764.

Duarte HH, França EB. [Data quality of dengue epidemiological surveillance in Belo Horizonte, Southeastern Brazil]. Rev Saude Publica 2006;40:134–42.

Duarte JL, Diaz-Quijano FA, Batista AC, Giatti LL. Climatic variables associated with dengue incidence in a city of the Western Brazilian Amazon region. Rev Soc Bras Med Trop 2019;52.

Ferreira AC, Chiaravalloti Neto F, Mondini A. Dengue in Araraquara, state of Sao Paulo: epidemiology, climate and Aedes aegypti infestation. Rev Saude Publica 2018;52:18.

García G, González N, Pérez AB, Sierra B, Aguirre E, Rizo D, et al. Long-term persistence of clinical symptoms in dengue-infected persons and its association with immunological disorders. Int J Infect Dis 2011;15:e38–43.

Godói IP, Da Silva LVD, Sarker AR, Megiddo I, Morton A, Godman B, et al. Economic and epidemiological impact of dengue illness over 16 years from a public health system perspective in Brazil to inform future health policies including the adoption of a dengue vaccine. Expert Rev Vaccines 2018;17:1123–33.

Gutierrez-Barbosa H, Medina-Moreno S, Zapata JC, Chua JV. Dengue infections in Colombia: epidemiological trends of a hyperendemic country. Trop Med Infect Dis 2020;5.

Guzman MG, Harris E. Dengue. Lancet 2015;385:453–65.

IBGE, INPC.Índice Nacional de Preços ao Consumidor. https://www.ibge.gov.br/estatisticas/economicas/precos-e-custos/9258-indice-nacional-de-precos-ao-consumidor.html?=&t=o-que-e, 2021 (accessed 4 October 2021).

Laserna A, Barahona-Correa J, Baquero L, Castañeda-Cardona C, Rosselli D. Economic impact of dengue fever in Latin America and the Caribbean: a systematic review. Rev Panam Salud Publica 2018;42:e111.

Lorenz C, Azevedo TS, Chiaravalloti-Neto F. COVID-19 and dengue fever: A dangerous combination for the health system in Brazil. Travel Med Infect Dis 2020;35.

Machado AAV, Negrão FJ, Croda J, de Medeiros ES, Pires MADS. Safety and costs of blood transfusion practices in dengue cases in Brazil. PLOS ONE 2019;14.

Martelli CM, Siqueira Jr JB, Parente MP, Zara AL, Oliveira CS, Braga C, et al. Economic impact of dengue: multicenter study across four Brazilian regions. PLoS Negl Trop Dis 2015;9.

Martins-Melo FR, Carneiro M, Ramos Jr AN, Heukelbach J, Ribeiro ALP, Werneck GL. The burden of Neglected Tropical Diseases in Brazil, 1990–2016: A subnational analysis from the Global Burden of Disease Study 2016. PLOS Negl Trop Dis 2018;12.

Moher D, Liberati A, Tetzlaff J, Altman DGPRISMA Group. referred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.

Muller DA, Depelsenaire AC, Young PR. Clinical and laboratory diagnosis of dengue virus infection. J Infect Dis 2017;215:S89–95.

Nacher M, Douine M, Gaillet M, Flamand C, Rousset D, Rousseau C, et al. Simultaneous dengue and COVID-19 epidemics: difficult days ahead? PLOS Negl Trop Dis 2020;14.

Nascimento LBD, Siqueira CM, Coelho GE, Siqueira JBJ. Dengue in pregnant women: characterization of cases in Brazil, 2007–2015. Epidemiol Serv Saude 2017;26:433–42.

National Institutes of Health. Quality assessment tools. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools, 2019 (accessed 11 September 2019).

Nunes PCG, Daumas RP, Sánchez-Arcila JC, Nogueira RMR, Horta MAP. Dos Santos FB. 30 years of fatal dengue cases in Brazil: a review. BMC Public Health 2019;19:329.

Oliveira RMAB, Araújo FMC, Cavalcanti LPG. Entomological and epidemiological aspects of dengue epidemics in Fortaleza, Ceara, Brazil, 2001–2012. Epidemiol Serv Saude 2018;27.

Pan American Health Organization. PAHO daily COVID-19 update, https://www.paho.org/en/documents/paho-daily-covid-19-update-7-september-2021, 2021 (accessed 8 September 2021).

Pereira CA, Barata MM, Hoelz Mde P, Medeiros VN, Marincola Fde C, Costa Neto C, Marinho DP, Oliveira TV, Trigo AG, Medeiros TK. [Economic evaluation of cases of dengue fever attributed to the disaster of 2011 in Nova Friburgo (State of Rio de Janeiro/Brazil)]. Cien Saude Colet 2014;19:3693–704.

Perez F, Llau A, Gutierrez G, Bezerra H, Coelho G, Ault S, et al. The decline of dengue in the Americas in 2017: discussion of multiple hypotheses. Trop Med Int Health 2019;24:442–53.

PLISA PAHO. Database. https://www.paho.org/data/index.php/en/mnu-topics/indicadores-dengue-en.html, 2020 (accessed 3 March 2020).

Preto C, Maron de Mello A, Cesário Pereira Maluf EM, Teixeira Krainski E, Graeff G, de Sousa GA, et al. Vaccination coverage and adherence to a dengue vaccination program in the state of Parana, Brazil. Vaccine 2021;39:711–19.

Rabiu AT, Mohan A, Çavdaroğlu S, Xenophontos E, Costa ACS, Tsagkaris C, et al. Dengue and COVID-19: A double burden to Brazil. J Med Virol 2021;93:4092–3.

Ridwan R. COVID-19 and dengue: a deadly duo. Trop Doct 2020;50:270–2.

Rocha BAM, Guilarde AO, Argolo AFLT, Tassara MP, da Silveira LA, Junqueira IC, et al. Dengue-specific serotype related to clinical severity during the 2012/2013 epidemic in centre of Brazil. Infect Dis Pover 2017;6:116.

Sacramento RHM, de Carvalho Araújo FM, Lima DM, Alencar CCH, Martins VEP, Araújo LV, et al. Dengue fever and Aedes aegypti in indigenous Brazilians: seroprevalence, risk factors, knowledge and practices. Trop Med Int Health 2018;23:596–604.

Sarti E, L'Azou M, Mercado M, Kuri P, Siqueira JB, Jr Solis E, et al. A comparative study on active and passive epidemiological surveillance for dengue in five countries of Latin America. Int J Infect Dis 2016;44:44–9.

Selck FW, Adalja AA, Boddie CR. An estimate of the global health care and lost productivity costs of dengue. Vector Borne Zoonotic Dis 2014;14:824–6.

Shepard DS, Undurraga EA, Halasa YA, Stanaway JD. The global economic burden of dengue: a systematic analysis. Lancet Infect Dis 2016;16:935–41.

Silva FD, dos Santos AM, Corrêa Rda G, Caldas Ade J. Temporal relationship between rainfall, temperature and occurrence of dengue cases in Sao Luis, Maranhao, Brazil. Cien Saude Colet 2016;21:641–6.

Silva MA, Fernandes RA, Takemoto M, Haas LC, Amaral LM, Vasconcellos JF, et al. How much dengue costs to Brazil? A retrospective administrative claims analysis from the public payer perspective. Value Health 2013;16:A347.

Stahl HC, Butenschoen VM, Tran HT, Gozzer E, Skewes R, Mahendradhata Y, et al. Cost of dengue outbreaks: literature review and country case studies. BMC Public Health 2013;13:1048.

Suaya JA, Shepard DS, Siqueira JB, Martelli CT, Lum LC, Tan LH, et al. Cost of dengue cases in eight countries in the Americas and Asia: a prospective study. Am J Trop Med Hyg 2009;80:846–55.

Teixeira MG, Siqueira JB, Jr Ferreira GL, Bricks L, Joint G. Epidemiological trends of dengue disease in Brazil (2000–2010): a systematic literature search and analysis. PLOS Negl Trop Dis 2013;7:e2520.

Tiga DC, Undurraga EA, Ramos-Castañeda J, Martínez-Vega RA, Tschampl CA, Shepard DS. Persistent symptoms of dengue: estimates of the incremental disease and economic burden in Mexico. Am J Trop Med Hyg 2016;94:1085–9.

Toan NT, Rossi S, Prisco G, Nante N, Viviani S. Dengue epidemiology in selected endemic countries: factors influencing expansion factors as estimates of underreporting. Trop Med Int Health 2015;20:840–63.

Tsheten T, Clements ACA, Gray DJ, Adhikary RK, Wangdi K. Clinical features and outcomes of COVID-19 and dengue co-infection: a systematic review. BMC Infect Dis 2021;21:729.

Undurraga EA, Halasa YA, Shepard DS. Use of expansion factors to estimate the burden of dengue in Southeast Asia: a systematic analysis. PLoS Negl Trop Dis 2013;7:e2056.

Vicente CR, Herbinger KH, Fröschl G, Malta Romano C, de Souza Areias Cabidelle A, Cerutti Junior C. Serotype influences on dengue severity: a cross-sectional study on 485 confirmed dengue cases in Vitoria, Brazil. BMC Infect Dis 2016;16:320.

Vieira Machado AA, Estevan AO, Sales A, Brabes KC, Croda J, Negrão FJ. Direct costs of dengue hospitalization in Brazil: public and private health care systems and use of WHO guidelines. PLoS Negl Trop Dis 2014;8:e3104.

Wichmann O, Yoon IK, Vong S, Limkittikul K, Gibbons RV, Mammen MP, et al. Dengue in Thailand and Cambodia: an assessment of the degree of underrecognized disease burden based on reported cases. PLoS Negl Trop Dis 2011;5:e996.

World Health Organization. Dengue: guidelines for diagnosis, treatment, prevention and control. New ed. Switzerland: World Health Organization; 2009.

World Health Organization, Dengue and severe dengue factsheet. https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue, 2021 (accessed 3 September 2021).