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Review

Epidemiology (2012-2019) and costs (2009-2019) of dengue in Malaysia: a systematic literature review

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A B S T R A C T

Objectives: A systematic literature review was conducted to assess the epidemiology and economic burden of dengue in Malaysia.
Methods: Embase, MEDLINE, Evidence-Based Reviews databases, and gray literature sources were searched for English and Malay studies and surveillance reports on the epidemiology (between 2012 and 2019) and costs (between 2009 and 2019) of dengue in Malaysia. Independent screening of titles/abstracts, followed by full texts was performed using prespecified criteria.
Results: A total of 198 publications were included (55 peer-reviewed and 143 gray literature). Dengue incidence has been increasing in recent years, with 130,101 cases (dengue fever 129,578 cases; dengue hemorrhagic fever 523 cases) reported in 2019, which is the highest since 2012. All dengue virus serotypes co-circulated between 2004 and 2017, and major outbreaks occurred in a cyclical pattern, often associated with a change in the predominant circulating serotype. Economic impacts are substantial, including the societal impact of lost work (7.2-8.8 days) and school days (3.2-4.1 days) due to dengue.
Conclusion: The rising incidence and high cost of dengue, coupled with overlapping diseases, will likely result in further pressures on the healthcare system. To appropriately mitigate and control dengue, it is critical to implement integrated strategies, including vaccination, to reduce the burden of dengue.

Introduction

Dengue is a mosquito-borne viral disease caused by four distinct but closely related dengue virus (DENV) serotypes (World Health Organisation, 2022). Dengue is endemic in Malaysia and continues to be a serious public health threat since its first reported major outbreak in 1902 (Abubakar and Shafee, 2002).

The clinical manifestations of dengue vary from mild illnesses to severe complications, with a higher risk of severe disease in those who contract a secondary infection caused by a different DENV serotype (St John and Rathore, 2019; World Health Organisation, 2022). Initial symptoms of dengue resemble those of other febrile illnesses, often resulting in misdiagnosis and underestimation of its incidence (Capeding *et al.*, 2013; Fernández *et al.*, 2016; Tsheten *et al.*, 2021). The 2009 World Health Organization (WHO) classification subdivides dengue into three groups - dengue with or without warning signs and severe dengue (WHO, 2009). However, the 1997 WHO criteria, which classify dengue as dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome are still widely used in dengue reporting in Malaysia (Malaysia MoH, 2017-2020; Nealon *et al.*, 2016; Woon *et al.*, 2019).

Dengue is associated with substantial societal and economic burdens. Packierisamy *et al.* (2015) estimated that the total annual cost of dengue prevention and illness in Malaysia in 2009/2010 is at $175.7 million. However, the true cost of the disease in the

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country is unknown because surveillance is mostly passive, with sentinel surveillance restricted to urban areas (Chew *et al.*, 2016; Shepard *et al.*, 2012).

This systematic literature review aimed to describe publicly available epidemiological and cost data for dengue in Malaysia to better understand the burden and trends of the disease in the country.

Methods

The review was conducted in line with the Cochrane Handbook for Systematic Reviews of Interventions (Deeks *et al.*, 2011), and the results are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher *et al.*, 2009).

Search strategy and selection criteria

Embase, MEDLINE®, and the Evidence-Based Medicine Reviews databases were searched on November 6, 2019. Separate searches were conducted for epidemiology and cost studies (Supplementary Table 1). The publication year was restricted to 2012-2019 for epidemiology studies because a literature review had already been conducted from 2000 to 2012 (Mohd-Zaki *et al.*, 2014). The year 2012 was included in this review because the previous review did not cover the entire year. The cost studies were reviewed from 2009 to 2019. The date restrictions were not applied to the data collection period of the studies to allow the inclusion of data not captured by Mohd-Zaki *et al.* (2014). The search strategies included medical subject heading and free-text terms, and results were limited to studies published in English and Malay languages (Supplementary Table 3). Additional publications were captured from reference lists and gray literature sources, including international, national, and university databases (Supplementary Table 2).

The studies identified from the literature searches were screened in a two-stage screening process: first, by title and abstract and then, by full text. Both stages were conducted by two independent reviewers, and discrepancies were resolved by a third reviewer. Study design criteria were not applied to gray literature because methods and sources for data collection/analysis are often not clearly reported for this publication type. For studies with multiple publications, the source with the most recent or complete dataset was included.

Data extraction and synthesis

Data were extracted by one reviewer and cross-checked by a second reviewer. Any discrepancies were resolved by a third reviewer. Data from the national and regional surveillance sources were prioritized and supplemented with those from peer-reviewed publications as needed and available. We chose this approach because it minimized data overlap between the sources. Although national surveillance systems are limited by under-reporting, we considered epidemiological data from these sources as the more reliable source. Because most of the included publications were from surveillance sources, quality assessment was not performed because it would not influence data synthesis or certainty of evidence. No meta-analyses were carried out due to heterogeneity in the reported data. Costs were normalized to 2019 values based on average Malaysian consumer price index inflation rates (The World Bank, 2021).

Results

A total of 394 records were identified from the electronic database searches, of which 53 were selected for data extraction and inclusion in the review (48 in epidemiology and five in costs). Two additional publications identified from the screening of reference lists were included in the review, resulting in 49 publications included in the epidemiology review and six publications in the cost review. A total of 143 articles from the gray literature search were also included in the review (Figure 1).

National epidemiology

Overall dengue cases and incidence

Dengue (DF and DHF) incidence data for the period 2012-2019 were reported in Malaysian Ministry of Health (MoH) reports (Malaysia MoH, 2012-2018; Malaysia MoH, 2017-2020). In 2012 and 2013, incidence rates of 76 and 146 per 100,000 population were recorded. The rates increased substantially between 2014 and 2017, peaking in 2015 (396 per 100,000 population) and then decreased to 245 per 100,000 population in 2018 (Figure 2a) (Malaysia MoH, 2012-2018). The highest number of dengue cases was recorded in 2019, with 130,101 reported cases, corresponding to an incidence rate of 399 cases per 100,000 population (Malaysia MoH, 2017-2020; WHO, 2014–2019). Data from eight earlier studies were generally consistent with those reported by the MoH and WHO (Supplementary Table 4). A retrospective study reported that the number of dengue cases increased by 1561.3% from 1995 to 2014. In the same study, the incidence rate in 2010 was reported as 161.5 per 100,000 population and was predicted to increase to 940.0 per 100,000 population by the year 2040 (Bujang *et al.*, 2017).

Incidence by age

The national incidence of dengue stratified by age was reported in only one study (Woon *et al.*, 2018). According to 2013 data from the National Dengue Surveillance System, children aged 0-4 years were the most affected by dengue, followed by those aged 10-15 years. The incidence rate in children aged 0-4 years was 176.6 per 1000 population, with a total of approximately 450,000 cases. An estimated half a million dengue cases were also reported among children aged 5-15 years. Incidence decreased with increasing age, with no reported cases among those aged >75 years (Woon *et al.*, 2018). In the absence of recent or MoH data corroborating these findings, the data should be cautiously interpreted because they may not reflect the current age distribution of dengue in Malaysia.

Disease severity: case definitions, hospitalizations, and deaths

Malaysia MoH data on the incidence of dengue by case definition, particularly DF and DHF, were available between 2016 and 2019 (Supplementary Table 5). During this period, the incidence rates per 100,000 population ranged from 244.1 to 397.7 for DF and from 1.23 to 2.01 for DHF (Malaysia MoH, 2017-2020).

Between 2012 and 2018, the number of dengue deaths increased from 35 in 2012 to 147 in 2018, peaking in 2015 at 336 deaths (Figure 2b) (Malaysia MoH, 2012-2018). Within this period, case fatality rate (CFR) rose from 0.16% in 2012 to 0.28% in 2015 and thereafter, declined to 0.18% in 2018. These trends were supported by publications that report CFRs for overall dengue cases of between 0.18 and 1.36 in the period 1980-2013 (Supplementary Table 6). Only two studies stratified dengue deaths by age and showed that death rates increased with age (Shepard *et al.*, 2016; Woon *et al.*, 2016). The MoH did not publicly report CFRs for different severities of dengue; however, for the period 2016-2019, the MoH reported mortality rates for DHF as 0.75 in 2016, 0.55 in 2017, 0.45 in 2018, and 0.56 in 2019 (per 100,000 population) (Malaysia MoH, 2017-2020). Mia *et al.* (2013) reported the mortality rates of DHF and DF in the period 2000-2010 as 0.30 and 0.06 per 100,000 population, respectively.

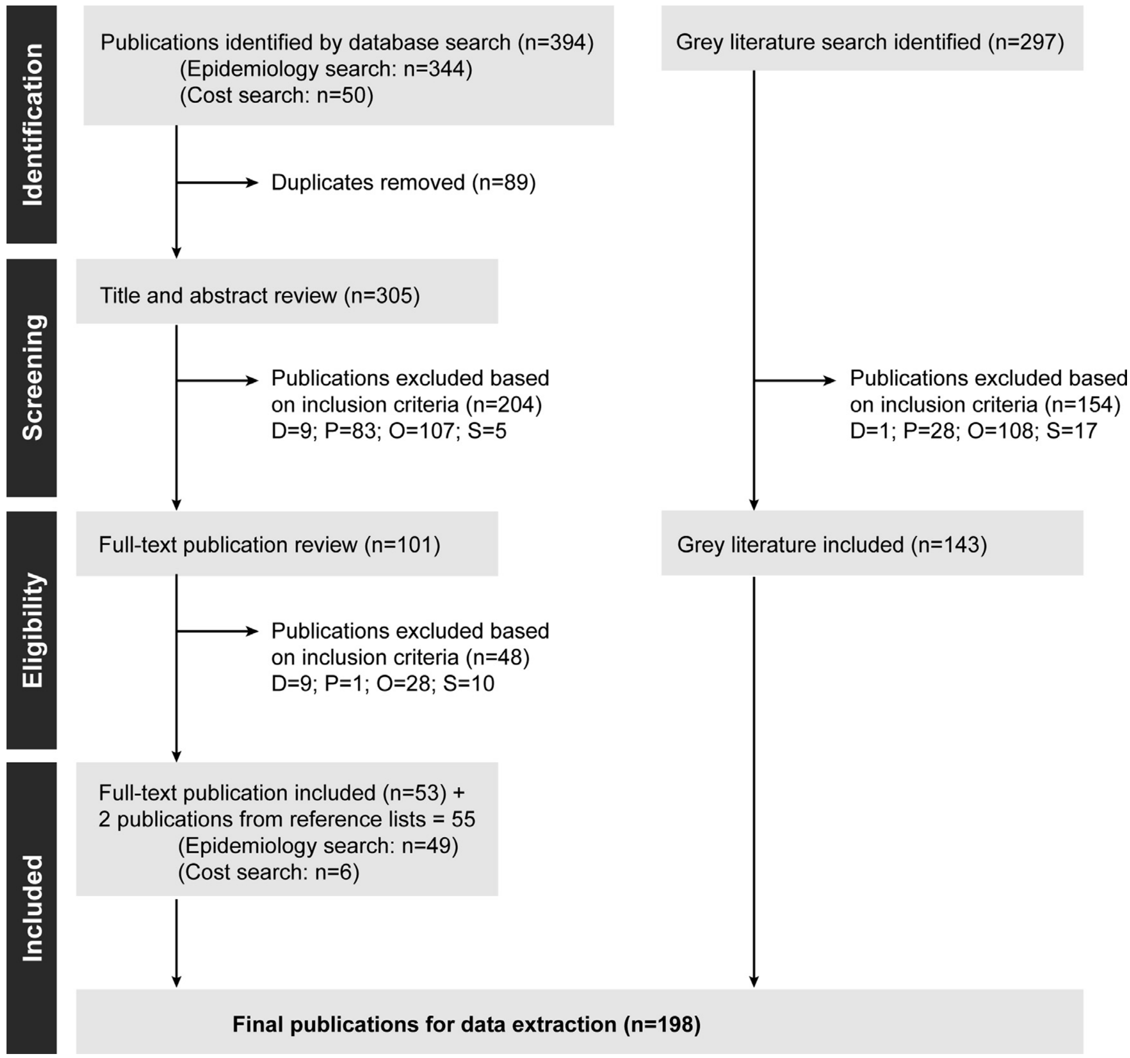

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flowchart for epidemiology and cost studies.
Abbreviations: D: duplicate; O: outcome; P: population; S: study design.

For dengue hospitalizations, nationwide data were obtained from three studies covering the period 2009-2013 (Supplementary Table 7) (Mallhi *et al.*, 2016; Shepard *et al.*, 2016; Woon *et al.*, 2018). In this period, the highest hospitalization rates were recorded in 2010 (3.96 per 1000 population) and 2013 (3.57 per 1000 population) (Woon *et al.*, 2018). In a study of 468 hospitalized cases, the mean duration of hospital stay was 4.2 ± 2.1 days, with 22.9% admitted for more than 3 days (Mallhi *et al.*, 2016).

Regional epidemiology

Overall incidence

The Malaysian MoH reported the regional incidence of dengue between 2015 and 2019. The data showed that the central Peninsular region, comprising mainly the Klang Valley (Selangor and Kuala Lumpur), was the most impacted by dengue. Variability was observed between the southern Peninsular region and the northern region, were throughout the period, the number of cases or incidence rates was higher in some states in the northern region than in the southern Peninsular region and *vice versa* (Supplementary Table 8) (Malaysia MoH, 2012-2018; Malaysia MoH, 2017-2020). Ng *et al.* (2015) further showed that the incidence of dengue in 2013 was higher in Peninsular than in East Malaysia. A total of 55% of the cases in the Peninsular region were from Selangor (central Peninsular) and 11% were from Johor (southern Peninsular). Data from the other studies found during this review focused on specific states and periods, making comparisons challenging (Supplementary Table 9).

Incidence by age

The age-related regional incidence of dengue is scarce and reported in only three studies. These studies were conducted in Kuala Lumpur, Putrajaya, and Penang and focused on children aged 0-16 years, thus limiting the comparison to older age groups and other regions in Malaysia (Supplementary Table 10). Overall, the incidence rate of virologically confirmed dengue (VCD) between 2011 and 2013 in Kuala Lumpur and Penang in children aged 2-16 years was 2241.2 per 100,000 person-years, and the most affected age group were those aged 9-12 years (3067.5 per 100,000 person-years). Among the VCD population, the incidence of DHF was 347.2 per 100,000 person-years in those aged 5-8 years, and no cases were reported in the other age groups (ages 2-4, 9-12, and 13-16 years) for the period 2011-2013 (L'Azou *et al.*, 2016).

Disease severity: reported cases, hospitalizations, and deaths

Between 2016 and 2019, the regional incidence of DF was higher than DHF, ranging from 13.29-1107.94 versus 0-8.99 per 100,000 population, respectively. This is expected because most

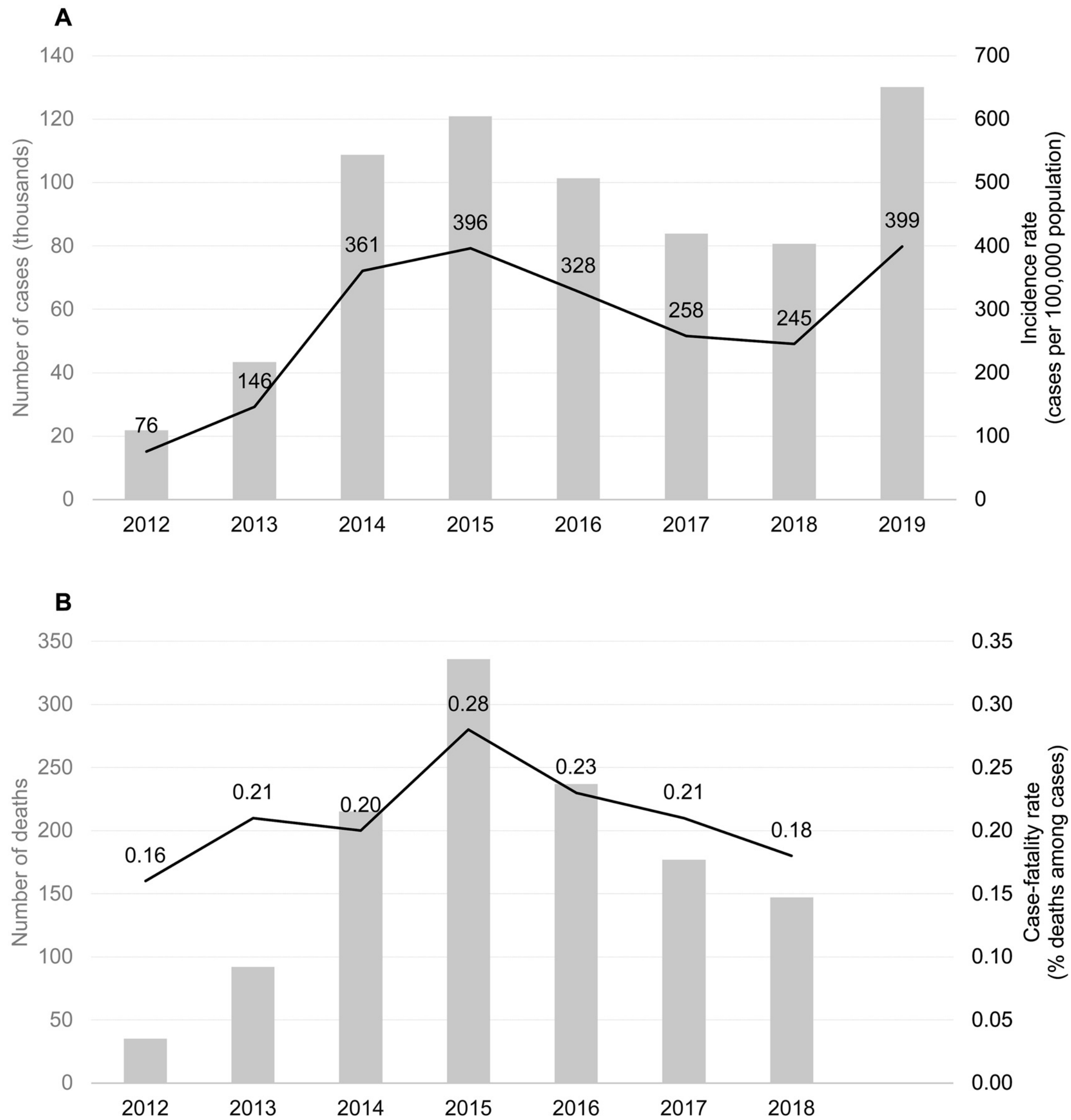

Figure 2. Dengue (dengue fever and dengue haemorrhagic fever) incidence and death in Malaysia. (a): Number of reported cases and incidence rate, 2012-2019. (b): Number of reported deaths attributed to dengue and case fatality rates, 2012-2018. Source MoH Malaysia.

dengue cases are not severe. Throughout the period, the incidence rates showed an increasing trend; however, the upper end of the range dropped from 814.33 in 2016 to 694.46 per 100,000 in 2018 for DF and from 5.70 in 2016 to 3.17 per 100,000 population in 2017 for DHF. For both DF and DHF, 2019 was the year with the highest incidence rates (1107.94 and 8.99, respectively). By locality, the incidence rates were highest in Selangor, followed by Kuala Lumpur-Putrajaya for DF; whereas for DHF, the highest incidence rates alternated between Selangor and Kuala Lumpur-Putrajaya (both in central Peninsular Malaysia). No cases of DF or DHF were recorded in Labuan (East Malaysia) for this period (Malaysia MoH, 2017-2020).

For regional hospitalizations and deaths related to dengue, the data are difficult to compare across studies due to the small sample size, differences in population, and the year studied (Supplementary Table 11 and 12). The most comprehensive data were reported by Mallhi *et al.*, in which 667 dengue cases were hospitalized between 2011 and 2013 in Kelantan, in the east coast of Peninsular Malaysia. The mean length of hospital stay was 4.88 $\pm$ 2.74 days, of which 49.2% of the cases were hospitalized for a prolonged period of >3 days. Among hospitalized patients, 11.1% were diagnosed with DHF and 0.8% met the criteria for dengue shock syndrome (Mallhi *et al.*, 2017). In Seremban, Negeri Sembilan in the central Peninsular region, a total of 94 (78.3%) of 120 patients with confirmed dengue were hospitalized between 2010 and 2011, with a mean duration of stay of 5.63 $\pm$ 1.23 days (Mia *et al.*, 2016).

During the period 2013-2014, of the 322 dengue deaths reported in the country, 90% occurred in the west coast and the remaining 10% occurred in the east coast of Malaysia. At the state level, Selangor contributed the highest death rate (34.5%), followed by Johor (15.2%), whereas Terengganu and Perlis contributed the lowest rates of 0.6% and 0.3%, respectively (Woon *et al.*, 2016).

Seasonal incidence

A total of eight studies reported on the seasonality of dengue in Malaysia. Overall, dengue incidence increased during the two monsoon seasons, from October to March in the northeast and from late May to September in the southwest (Arima *et al.*, 2013; Hassan and Mohd Hashim, 2017; Liew *et al.*, 2016; Ngah-Mohamed *et al.*, 2017). At the national level, data on the seasonality of dengue was reported for 2011, 2013, 2018, and 2019. In 2011, the highest number of dengue cases was recorded in January, during the second epidemiological week; whereas in 2013, dengue cases peaked in the latter part of the year (October-December) (Arima *et al.*, 2013; Liew *et al.*, 2016; Ng *et al.*, 2015). Similarly, in 2018, dengue cases peaked in December; whereas in 2019, the highest number of cases was reported in July (WHO, 2019). Colder weather, increased rainfall, and humid weather were significantly associated with increased dengue cases in Temerloh, Pahang (central Peninsular Malaysia) in 2016 (Hassan and Mohd Hashim, 2017) but not in Kuala Lumpur in 2009, where the period of increased rainfall (March) showed a dispersed distribution of dengue cases, and the period of lowest rainfall showed a clustered distribution pattern (Aziz *et al.*, 2012).

Seroprevalence

Seroprevalence of dengue across different regions and subdistricts of Malaysia was identified in 13 studies on diverse populations (Supplementary Table 13). The study with the highest seroprevalence rate of 86.6% in healthy adults aged at least 18 years was conducted in the rural Sungai Segamat subdistrict of Johor, south region of Peninsular Malaysia from April to May 2015.

The seroprevalence of dengue was found to increase with age, with the highest rate of 98.30% observed in those aged ≥55 years in Sungai Segamat subdistrict in 2015 (Dhanoa *et al.*, 2018; L'Azou *et al.*, 2018, 2016; Mohamed Ismail *et al.*, 2014; Wong *et al.*, 2014). However, a prospective cohort study of suspected dengue cases aged 0-79 years in Kuala Lumpur reported the highest seroprevalence rates in those aged 20-29 years, followed by those aged 10-19 years in 2011 (Chew *et al.*, 2012). In a secondary analysis of data from two clinical trials conducted in Kuala Lumpur and Penang between June 2011 and December 2013, the rates of dengue seropositivity in children aged 2-4 years, 5-8 years, 9-12 years, and 13-16 years were 32.4%, 34.1%, 57.8%, and 66.7%, respectively (L'Azou *et al.*, 2016). In a similar study of participants aged 0-17 years conducted between 2010 and 2012, the seroprevalence rates were 42.5% (based on CYD32 trial) and 33.6% (based on CYD14 trial) in those aged 2-8 years and 54.4% (CYD32) and 61.5% (CYD14) in those aged 9-17 years. However, primary dengue infection was higher in the younger age group than in the older age group (CYD32: 45.1% vs 12.9%; CYD14: 34.0% vs 18.7%, respectively) (L'Azou *et al.*, 2018).

Serotype distribution

Serotype distribution of DENV was identified from 12 studies covering different regions and showed all four DENV serotypes cocirculated annually in the country between 2004 and 2017 (Supplementary Table 14). DENV type 1 (DENV-1) was the most commonly reported serotype during the study period, with rates ranging from 25.5% to 64.8% (Ab-Fatah *et al.*, 2015; Arima *et al.*, 2013; Dhanoa *et al.*, 2017; Gintarong *et al.*, 2018; Suppiah *et al.*, 2018; Willeam Peter *et al.*, 2019; Zainol *et al.*, 2015). Shifts in the DENV serotype predominance were also reported during the study period, with some regional variations. For example, in a study conducted in Sabah, East Malaysia, predominance shifted from DENV type 4 (DENV-4; 84.5%) in 2013 to DENV-1 (89.6%) in 2014 and then DENV type 2 (DENV-2; 45%) in 2015 (Najri *et al.*, 2017). In Selangor and Kuala Lumpur combined, DENV-1 predominated between 2014 and 2016 and, in 2017, predominance shifted to DENV-2 (Suppiah *et al.*, 2018). Furthermore, Mia *et al.* (2013) reported a nationwide shift in dominance from DENV-1 in 2004 and 2005 to DENV-2 in 2006 and 2007. DENV-4 was the least reported circulating serotype between 2004 and 2007. The authors noted that DENV-1 and DENV-4 were not commonly isolated in 2009 up until 2010, when they re-emerged. Data for the year 2008 was not reported. Similarly, Ng *et al.* (2015) found that DENV-2 replaced DENV type 3 and DENV-4 dominance patterns in the 2013 dengue outbreak, and the rate of DENV-2 in the southernmost parts of Johor and Malacca increased to 70-90% after August 2013. This shift in the dominant circulating serotype was suggested to result in the high fatality rate of 0.5% reported in both states compared with the whole of Malaysia (0.18%).

Expansion factor

Expansion factors (EFs), numbers by which the reported cases are multiplied for more accurate assessments of incidence, can be derived by comparing cases identified by active surveillance to passive surveillance programs. Four studies reported highly varied EFs to account for the under-reporting of dengue in Malaysia (Supplementary Table 15). The highest EF was reported for private ambulatory cases (178.84) and the lowest for public hospitalized cases (1.3) (Shepard *et al.*, 2012). By case definitions, one study reported an EF of 31.7 for VCD and an EF of 10.4 for all VCD episodes that were also clinically diagnosed as dengue. VCD was defined as a dengue diagnosis based on virological laboratory confirmation, irrespective of the clinical diagnosis (Nealon *et al.*, 2016). Coudeville *et al.* (2016) compared the incidence data of a phase III trial with data from the national surveillance system and calculated an EF of 14.3. Woon *et al.* (2018) did not report an EF but showed that the number of dengue cases and hospitalizations reported to the Malaysian surveillance system are substantially underestimated, thus warranting the use of EFs to obtain a more accurate estimate. Between 2001 and 2013, the notification rates of dengue infections ranged from 0.68 to 1.81 per 1000 population; whereas for hospitalization, the rates varied from 2.08 to 3.57 per 1000 population between 2009 and 2013. These rates were a small proportion of the number of incidents and hospitalized cases notified to the surveillance system each year (0.7-2.3% and 3.0-5.6%, respectively).

Dengue costs: direct and indirect costs

Six studies reporting on the economic burden and costs of dengue in Malaysia were identified. All costs were adjusted to 2019 US dollars, using the Malaysian consumer price index. Overall, the studies showed that the costs of hospital cases were higher than ambulatory cases. From a societal perspective, Shepard *et al.* (2012) found that the direct and indirect costs after adjusting for under-reporting were higher for hospitalized cases than for ambulatory cases. The total costs per case were estimated at $555.19 (hospitalized) versus $247.00 (ambulatory) in the private sector and $518.07 (hospitalized) versus $269.48 (ambulatory) in the public sector. The total aggregated annual national cost of dengue illness was estimated at $68.9 million, with the private sector accounting for 45.1% and the public sector 54.9%. Furthermore, direct costs represented 33% of the total cost, and indirect costs represented 67%. This is supported by other studies reporting national and local costs, except Shepard *et al.* (2016) who reported the highest total annual aggregated cost of dengue as $689.7 million and that direct costs ($408.8 million) were higher than indirect costs ($280.9 million). The aggregated annual indirect cost of death was reported as $41,163,405.5 and higher in children ($344,772.99 per case) than in adults ($224,556.09 per case) even though the number of deaths was lower in children than in adults (39 vs 124 cases).

Only two studies reported the regional costs of dengue. In the Seremban district (Negeri Sembilan state), the mean direct medical and nonmedical costs of dengue per case to the household in 2010 was $10.91 and $34.35, respectively, and the indirect cost, of which work days lost contributed the majority, was $398.28 (Mia *et al.*, 2016). From a societal perspective, Suaya *et al.* (2009) reported higher average dengue costs for Klang Valley, Kuala Lumpur in 2005: ambulatory cases (direct medical $561.84, direct nonmedical $56.74, indirect $303.06 per case) and hospitalized cases (direct medical $2183.7, direct nonmedical $222.8, indirect $344.58 per case).

Societal impact

Information on the societal impact of dengue in Malaysia was limited, with only two studies reporting local data for 2005 and 2010-2011 (Supplementary Table 16). Average household days lost due to dengue ranged from 11.2 to 18.7, and the overall household impact was higher for hospitalized than ambulatory cases (16.2 vs 11.2 days, respectively) (Mia *et al.*, 2016; Suaya *et al.*, 2009). In Suaya *et al.*'s report, students comprising 31% of the ambulatory and 51% of the hospitalized cohort lost an average of 3.2 and 4.1 days of school, respectively. Furthermore, working patients, representing 62% of ambulatory and 42% of hospitalized cases, lost an average of 7.2 and 8.8 days of work, respectively (Suaya *et al.*, 2009).

Discussion

In line with a previous literature review (Mohd-Zaki *et al.*, 2014), this review also found the incidence of dengue in Malaysia to be increasing, with the number of cases exceeding 80,000 annually between 2014 and 2019. The year 2019, a year of severe outbreaks in several countries in Southeast Asia (Cambodia, Indonesia, Lao PDR, Philippines, Thailand, and Vietnam), including Malaysia, recorded the highest dengue incidence (Wiyono *et al.*, 2021), followed by 2015. The rising incidence of dengue is likely due to a number of compounding factors, which include urbanization, shifts in the dominant DENV serotype, vector expansion, and climate change (temperature, humidity, and rainfall), which is favorable for the breeding of *Aedes* spp. mosquitoes, the main vector of DENV (Chrostek *et al.*, 2020; Hii *et al.*, 2016; Suppiah *et al.*, 2018). Considering the current dengue trends in Malaysia, the incidence rate is projected to reach 940.0 per 100,000 population (362,434 cases) in the year 2040 (Bujang *et al.*, 2017). Therefore, several alerts have been raised to highlight the need to contain dengue surges, particularly now that COVID-19 is a parallel threat with extensive health care, societal, and economic burdens (Malaysia Kini, 2020; Olive *et al.*, 2020). Furthermore, individuals stand the risk of co-infection by both viruses, and those with underlying medical conditions are especially prone to experience severe symptoms (Awani, 2020; Nacher *et al.*, 2020; Olive *et al.*, 2020). In addition, the coexistence of dengue and COVID-19 may result in an underestimation of cases, a decline in surveillance and control interventions, and an increase in social inequalities (Malaysia Kini, 2020; Olive *et al.*, 2020).

From a regional perspective, the Peninsular states of Malaysia are the most affected by dengue, which is in line with data previously reported by Mohd-Zaki *et al.* (2014) In this review, the central region, in particular Selangor, presented the highest total dengue incidence and the number of deaths (Malaysia MoH, 2017-2020; Ng *et al.*, 2015; Woon *et al.*, 2016). The impact of the disease is highest during the monsoon seasons, with the peak month varying each year among localities. Nonetheless, dengue cases are recorded throughout the year, and climate change may affect the seasonal and geographical distribution of the transmission (Naish *et al.*, 2014; WHO, 2019).

Seroprevalence varied widely across regions of Malaysia and revealed that a large proportion of individuals with asymptomatic DENV infection might be undetected by the national surveillance system (Dhanoa *et al.*, 2018; Mohamed Ismail *et al.*, 2014). Furthermore, the sentinel surveillance system does not represent all regions of Malaysia (Chew *et al.*, 2016), and it is conducted on a need and priority basis. Although a high dengue seropositivity rate was reported among those aged 20-29 years, followed by those aged 10-19 years, in general, the seroprevalence of dengue increased with age, in line with the findings of a previous review (Chew *et al.*, 2012; Dhanoa *et al.*, 2018; Mohd-Zaki *et al.*, 2014).

DENV serotypes have been co-circulated throughout Malaysia, with all four serotypes reported annually during 2004-2017. For the most part, dominance fluctuated between DENV-1 and DENV-2, and the latter has been associated with increasing disease severity (Mia *et al.*, 2013; Najri *et al.*, 2017; Ng *et al.*, 2015; Suppiah *et al.*, 2018). Although it is not clear which DENV serotype caused the highest deaths in 2015, owing to the paucity of information from the MoH and other sources, regional incidence data suggest that a shift from DENV-1 to DENV-2 may have been responsible (Suppiah *et al.*, 2018). This highlights the need to monitor the circulating serotypes to help predict the next major outbreaks, enable health officials to implement prompt preventive strategies, and improve the accuracy of the current forecasting models for dengue outbreaks in Malaysia (Salim *et al.*, 2021).

This is the first review to analyze the costs of dengue in Malaysia, and the data show that dengue is associated with a substantial and increasing economic and societal burden. However, due to under-reporting, the true burden of disease is likely greater than what is reported. On this topic, Woon *et al.* (2018) further observed that the number of dengue infections and hospitalizations reported to the surveillance system between 2001 and 2013 was an insignificant proportion of the actual incident cases. Therefore, the use of EFs specific to different treatment settings and contexts to account for the under-reporting of dengue cases is essential because underestimation of the cases can affect the overall economic impact of the disease (Shafie *et al.*, 2017). After adjusting for under-reporting, Shepard *et al.* (2016) reported a total annual national cost of dengue of $689.7 million, with direct costs ($408.8 million), of which hospital cases ($358.7 million) contributed the highest portion. It should be noted that other studies found the indirect cost to be higher than the direct cost, which can be explained by the significant impact on work and school days lost by patients and caregivers due to dengue illness.

The economic burden of dengue in Malaysia at a regional level was scarcely reported. Therefore, the cost variations among different Malaysian states could not be established. However, data from two studies suggest that the variances in dengue costs may be due to the period evaluated, severity of the cases, and evaluation of indirect cost (productivity loss) associated with illness or care.

Strengths and limitations of the review

The key strength of this review is the comprehensive search of multiple sources and capturing of studies not available at the time of conducting the study by Mohd-Zaki *et al.* (2014), allowing a broader period to be analyzed. Furthermore, to the best of our knowledge, this is the first systematic review to analyze the costs of dengue in Malaysia. Nevertheless, several limitations and data gaps were identified. First, incidence, hospitalizations, and deaths by age group and disease severity are understudied and would help to characterize the groups most affected by dengue. Although the MoH reported the nationwide mortality rate for DHF for the period 2016-2019, the age distribution of dengue incidence, CFRs, and hospitalization at both the national and regional levels were not publicly available for this review (the data may be available upon request). Also, journal articles did not report the number of deaths or CFRs for the year 2010. Furthermore, seroprevalence data were mainly from the state and district level and focused on a limited age group, which is needed to understand the overall exposure to dengue. Our assessment of the DENV serotype distribution did not include the frequency and distribution of the genotypes, which can further help improve dengue prevention and management. In the cost analysis, the studies were heterogeneous in methodology and did not stratify the results by region or age.

Conclusion

Dengue is endemic in Malaysia, with 130,101 cases reported in 2019. The rising incidence of dengue, coupled with overlapping diseases with similar clinical and laboratory features, is likely to further burden the health care system. It is therefore vital to implement integrated strategies, including early detection and vaccination, to prevent the transmission of dengue infection. Continuous monitoring of DENV serotypes is advised because large epidemics and increased death rates tend to follow shifts in DENV serotype dominance. Furthermore, because it is established that dengue cases are under-reported, surveillance systems should adjust for under-reporting using appropriate EFs for accurate assessment of the disease and evaluation of the impact of dengue prevention strategies, such as vaccination.

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Ethical approval

Not required.

Declaration of Competing Interest

EG, RK, and RH are employees of Takeda. SHL was an employee of Takeda at the time this research was performed. RK and RH own stocks in Takeda. LO is an employee of Adelphi Values and has served as a paid consultant for Takeda Pharmaceuticals. SEWP and SA have no conflict of interests to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.09.006.

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