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Forum

The Uncertainty Surrounding the Burden of Post-acute Consequences of Dengue Infection

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Post-acute consequences currently form a significant component of the dengue disability-adjusted life year (DALY) burden estimates. However, there is considerable uncertainty regarding the incidence, duration,

and severity of these symptoms. Further research is needed to more accurately estimate the health and economic burden of these dengue manifestations.

The Burden of Dengue

Dengue is the most prevalent mosquito-borne viral disease affecting humans in the world today, occurring mainly in the tropics and subtropics. Symptomatic infection commonly presents as a mild to moderate acute febrile illness lasting 2–7 daysⁱ [1]. Headache, nausea, vomiting, muscle and joint pains, and rash, are prominent features. Although most infected individuals recover from the acute episode without complications, a small proportion of patients can develop potentially life-threatening disease during the critical phase known as severe dengueⁱ. A key metric to measure and compare the burden of different diseases is the disability-adjusted life year (DALY): one DALY is equivalent to one healthy life year lost. A key reason why DALYs are used to quantify disease burden is that this metric incorporates the burden of nonfatal health outcomes, as focusing only on mortality gives an incomplete picture of the actual burden of a diseaseⁱⁱ. An overview of the approach used to estimate DALYs for dengue is presented in Box 1.

The Global Burden of Disease (GBD) 2013 and 2017 study estimates for dengue are summarized in Figure 1ⁱⁱⁱ [2]. When breaking down the DALY burden by its different components, it is apparent that, despite only applying to 8.5% of symptomatic cases, the estimated healthy life lost due to post-acute chronic symptoms (Box 1) contributed notably to the burden estimate (Figure 1). This demonstrates that the post-acute consequences/sequelae of dengue are a key driver of the overall DALY burden estimates. This article aims to explore the variation

in the definitions and incidence of these post-acute consequences, and how these may influence the uncertainty around estimates of dengue's health and economic burden.

The Post-acute Consequences of Dengue Infection

A range of post-acute consequences of dengue have been reported across different studies [3]. The most consistently reported included myalgia, weakness, headache, fever, and fatigue [3–7]. However, some of these symptoms, such as fever or headache, are quite common and are prevalent during an acute dengue episode. Defining the end of an acute dengue episode can be difficult, and it is unclear if any of these symptoms were truly carried on into the post-acute period or misclassified as post-acute. Other symptoms also reported include vomiting, diarrhoea, nausea, chills, and poor appetite [4]. Both hospitalized patients and outpatients can experience these post-acute consequences and they have not been shown to associate with the severity of the acute episode [4,8]. Furthermore, post-acute consequences were usually associated with female gender and older age [3,4,9].

The estimated proportion of patients experiencing post-acute consequences varies significantly across studies and tends to decrease over time after the acute illness [3,6]. Figure 2 illustrates the percentage of patients reporting dengue symptoms that may result in productivity losses (fatigue, asthenia, or trouble working) by elapsed follow-up time. However, there were differences in how the various studies defined and quantified these symptoms. For instance, Seet *et al.* [4] used a validated fatigue questionnaire to assess particular symptoms relating to the physical and mental status of their patients. In contrast, other studies have only quantified the number

Box 1. The Health Burden Measurement of Dengue: The Disability-Adjusted Life Year (DALY)

The potential years of healthy life lost due to disability are calculated as the product of the incidence of the different types of dengue-related morbidity, the average duration of illness, and the corresponding disability weight. The disability weight factor ranges between 0 and 1, which reflects the severity of the disease sequelae (0 represents perfect health, and 1 represents death). Since the GBD 2010 [16] study, the disability weights used for dengue are no longer disease-specific but are instead general weights for an acute episode of an infectious disease, stratified by severity. Specifically, since the GBD 2013 study, the healthy life years lost due to disability have been estimated as follows [10]:

- (i) 94.5% of symptomatic patients were assigned the disability weight of 'infectious disease, acute episode moderate' with a mean duration of 6 days (disability weight: 0.051). The description of the disability weight was: 'has a fever and aches, and feels weak, which causes some difficulty with daily activities' [10].
- (ii) 5.5% of symptomatic patients were assigned the disability weight 'infectious disease, acute episode severe' with a mean duration of 14 days (disability weight: 0.133) [10]. The description of the disability weight was 'has a high fever and pain, and feels very weak, which causes great difficulty with daily activities'.
- (iii) 8.5% of symptomatic patients were assumed to have post-acute chronic fatigue and assigned the disability weight 'infectious disease, post-acute consequences' with a mean duration of 6 months (disability weight of 0.219). The description of the disability weight was 'is always tired and easily upset. The person feels pain all over the body and is depressed' [10]. These assumptions were based on [5].

of patients experiencing any fatigue or trouble working after recovery from dengue [6,8]. It was noteworthy that the time that the majority of studies followed up patients was short.

Uncertainty Surrounding the Health Burden of the Post-acute Consequences of Dengue

The assumption within the DALY burden estimates that, on average, 8.5% of

symptomatic dengue cases experience 6 months of chronic fatigue, is supported by some literature, but there is clearly notable variation in both the types of post-acute consequences experienced and their duration. The disability weight (infectious disease, post-acute consequences) used for dengue chronic fatigue is described as: 'Is always tired and easily upset. The person feels pain all over the body and is depressed'. However, many studies seem to report just the number experiencing some fatigue, trouble working, or mild difficulty in daily activities. Therefore, the severity of the post-acute consequences being experienced by dengue patients may not be accurately represented by the disability weight as currently used. Teixeira *et al.* also found that the severity of these post-acute consequences decreased over time [5]. In comparison, the 'infectious disease, post-acute consequences' disability weight is 65% higher than the weight applied during a severe (most likely hospitalized) dengue episode (Box 1) and is similar to the weight used for blindness (0.187) [10]. It is also interesting that the same post-acute consequences disability weight is assigned for Ebola in the GBD 2015 study^{iv}. The definition used for this disability weight is similar to the general definition of chronic fatigue syndrome utilized by the Centers for Disease Control and Prevention in the USA [11,12].

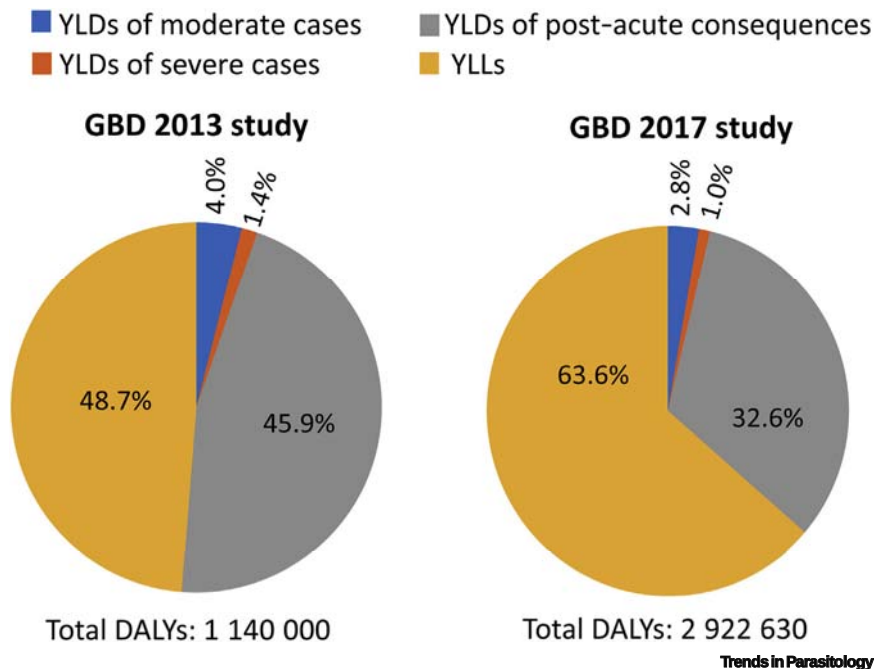


Figure 1. Breakdown of the Disability-Adjusted Life Year (DALY) Burden Estimates for Dengue from the Global Burden of Disease (GBD) Studies 2013 and 2017. Data were adapted from Stanaway *et al.* [2] for the GBD 2013 study (relating to 2013) and Kyu *et al.* [15] for the GBD 2017 study (relating to 2017). DALYs were calculated based on the following information. In the GBD 2013 study, in 2013 there were an estimated 58.4 million symptomatic cases and 9221 deaths [2]. In the GBD 2017 study, in 2017 there were an estimated 104.7 million symptomatic cases and 40468 deathsⁱⁱⁱ. Abbreviations: YLDs: years of healthy life lost due to disability, YLLs: years of life lost due to premature death.

When considering how generalizable the estimates regarding the proportion of cases that experience post-acute consequences are, it is vital to consider the local epidemiology. This is because post-acute consequences are often associated with older age [4,9] and may therefore be more common in low-transmission settings where exposures occur, on average, later in life than in high-transmission settings, resulting in more adult infections. This means that using estimates of the proportion of cases experiencing post-acute consequences from lower-transmission

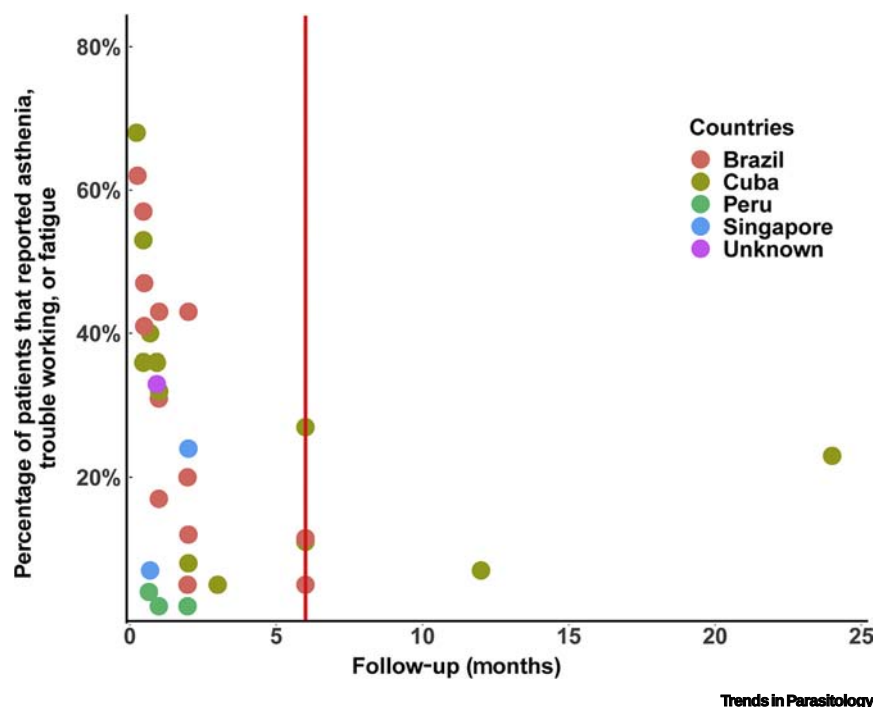


Figure 2. The Association between the Percentage of Patients Reporting Symptoms That May Result in Productivity Losses (Fatigue, Asthenia, or Trouble Working) and Follow-up. The red line shows a cut-off of 6 months. The values were taken from a review by Tiga *et al.* [3], with additional data from Teixeira *et al.* [6] and Zeng *et al.* [8].

settings (most of the studies reported results in Latin America – Figure 2) may not be representative of the global burden of these post-acute consequences.

The Economic Burden of the Post-acute Consequences of Dengue

Although the health burden of the post-acute consequences of dengue has been estimated to be substantial, there are almost no data related to their corresponding economic burden. A recent study estimated that accounting for the post-acute consequences would increase the economic burden of dengue in Mexico by an additional 13%. Specifically, the post-acute consequences were estimated to contribute an incremental economic cost of US\$1.95 million in direct costs and US\$20.68 million in productivity costs (indirect costs) (2012 prices) [3]. The productivity costs were calculated based on the assumption that adult patients experiencing post-acute consequences

had a 45% reduction in productivity. However, this was based on the productivity losses experienced by those diagnosed with chronic fatigue syndrome [13,14], which may not reflect the potentially lesser degrees of fatigue/lethargy experienced by those with the post-acute consequences of dengue.

Moving Forward

Although there is evidence that post-acute consequences of dengue are not rare, there is significant uncertainty regarding their severity, the types of symptoms experienced, and their duration. More research and better data are needed to more accurately estimate the health and economic burden of these post-acute consequences. Specifically, the following are needed:

- A more accurate estimate of the proportion of dengue cases that experience post-acute consequences and their

duration. It is vital that data are collected from a range of epidemiological settings, and capture different age ranges.

- A greater understanding and description of the severity of these post-acute consequences and of the types and severity of symptoms experienced.
- The disability weight ‘infectious disease, post-acute consequences’ should potentially be stratified by severity level (similar to the infectious disease, acute episode weights).
- More data on the economic burden of these post-acute consequences.

Concluding Remarks

Currently, post-acute consequences are assigned a relatively high disability weight and form a significant component of the dengue DALY estimates. However, there is considerable uncertainty regarding the incidence, duration, and severity of these symptoms. Further research is urgently needed to more accurately estimate the health and economic burden of these manifestations of dengue. Crucially, future cost-effectiveness analyses should explicitly state how the number of DALYs averted were estimated, and if post-acute consequences were included.

Acknowledgments

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Resources

ⁱhttp://apps.who.int/iris/bitstream/handle/10665/204161/Fact_Sheet_WHD_2014_EN_1629.pdf?sequence=1

ⁱⁱwww.who.int/healthinfo/global_burden_disease/metrics_daly/en/

ⁱⁱⁱ<http://ghdx.healthdata.org/gbd-results-tool>

^{iv}<http://ghdx.healthdata.org/record/global-burden-disease-study-2015-gbd-2015-disability-weights>

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