The elusive global burden of dengue

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The elusive global burden of dengue

Dengue has emerged in the past two decades as a rapidly growing and widespread public health problem, with over half of the world's countries and people now at risk.¹ In new estimates from the Global Burden of Disease study, Jeffrey Stanaway and colleagues² suggest that dengue incidence has increased six-fold from 1990 to 2013, accompanied by much flatter mortality trends. Dengue is still regarded as a neglected disease,³ yet its incidence is increasing at an alarming rate, by contrast with declines in other neglected diseases.⁴ WHO estimates that 50–100 million cases occur annually.⁵ In 2012, however, cartographic approaches[A: a cartographic approach suggests making a map to me. Can you clarify what cartographic approaches are in this sense?] put the number of dengue infections as high as 390 million (95% credible interval 284 million–528 million), but included both unapparent and apparent cases.¹ Their estimated number of apparent cases (96 million, 95% credible interval 67 million–136 million) lies at the high end of the WHO estimates.

Against this background, these new estimates from the Global Burden of Disease Study suggest a much lower number of cases for 2013: 58.4 million (95% uncertainty interval 23.6 million–121.9 million).² Why is it so difficult to arrive at consistent estimates?

Poor disease surveillance, low levels of reporting, lack of inexpensive point-of-care diagnostic tests, and inconsistent comparative analyses are the main reasons, in common with other diseases in low-income and middle-income countries. As good as modelling methods may be, outputs are inevitably compromised by scanty and poor quality data inputs, and they have no means of external validation.⁶ In the case of dengue, difficulties are further compounded by cyclical epidemics with major troughs and peaks that might be hard to model. It is of concern that despite applying large expansion factors, the authors' estimates of dengue incidence in the ten countries where recent dengue vaccine trials have been done were consistently lower than the carefully obtained prospective incidence data,⁷ highlighting the potential for underestimates throughout their modelling efforts.

While all estimates concur on rapid increases in dengue cases in recent decades, there is less evidence for the trends in deaths. Stanaway and colleagues' estimate of around 9000 deaths per year is far smaller than WHO's estimates published a decade ago (10 000–20 000 deaths per year) despite the well-documented increase in dengue cases. In the absence of any specific antiviral therapy for dengue, survival in severe cases depends largely on the effectiveness of

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Figure: Dengue case fatality rates for 39 countries estimated to have at least ten dengue deaths and autochthonous transmission
 Data from Stanaway and colleagues.² CFR=case fatality rate.

health services. Dengue is an acute systemic viral illness with many clinical manifestations, from mild fever to potentially fatal dengue shock syndrome. The hallmark of severe disease is vascular leakage. Early diagnosis of dengue and prompt treatment of plasma leakage with appropriate intravenous fluid replacement can reduce disease severity and mortality. Hence, in countries with good clinical case management, case fatality rates have dropped substantially, which could partly explain the lower estimates of deaths despite increasing incidence of dengue infections. Another explanation might be that dengue is increasingly common in adults, who have a ten-times lower case fatality rate than children.⁸

However, a population-based case fatality rate of 0.018% (9921 of roughly 50 million symptomatic cases of dengue) seems unbelievably low and stands in contrast to clinical studies that suggest a case fatality rate of 0.1–4%. Such stark discrepancies need to be better elucidated. Stanaway's estimates mainly relied on vital registration and surveillance data, with a few verbal autopsies—all likely to under-report dengue deaths. It was only in 2014 that revisions to the WHO verbal autopsy instrument specifically made provision for capturing dengue deaths.⁹

Stanaway and colleagues seems to have used relatively independent processes for modelling numbers of cases and deaths,² which could be both a strength and a weakness. The strength would be that the estimates of cases and deaths are not linked by any unsubstantiated modelling assumptions. The weakness would be that if either set of estimates are fragile, then inconsistent inter-relationships might arise. Based on the incident cases and deaths reported by Stanaway and colleagues, we calculated the case fatality rate for the 39 countries with at least ten dengue deaths, and having autochthonous transmission (figure). It is surprising that the new estimates suggest that the case fatality rate is ten-times lower in some African countries than in the USA. Better clinical care of patients with dengue in the USA might be expected to result in lower case fatality rates than in Africa; but deaths from dengue in the USA might be better documented. Nevertheless, a population-based case fatality rate of seven deaths per 100 000 cases for the African countries seems unlikely. For India, which has the largest national number of cases (18.6 million), a rate of nine

deaths per 100 000 cases also seems low, although there is a general lack of evidence about dengue mortality attached to realistic population-based denominators for comparison. Conversely, if Stanaway and colleagues' estimated case fatality rate for the USA (60.4 deaths per 100 000 cases) was applied universally to their global estimate of 58.4 million cases, then global deaths would exceed 35 000.

The Global Burden of Disease Study 2013 comprehensively and systematically attempts to estimate death and disability from 306 causes, producing estimates by year, age, sex and country for 1990–2013. In this context, we commend Stanaway and colleagues for their tremendous efforts in obtaining and modelling data to better document the global burden of dengue. Such data are important in light of another emerging flavivirus infection—Zika virus. Such data are also important because the first dengue vaccine has been licenced in some countries: policy decisions about when and how to introduce dengue vaccine on a national basis will draw on such estimates of the burden of disease. Because this first dengue vaccine, manufactured by Sanofi Pasteur, will be licensed only for children aged 9 years and older,¹⁰ the age-specific data (although crude) that Stanaway and colleagues collated are particularly useful.

Given the uncertainties around the estimated death rates, we agree with the authors that their "mortality estimates are lower than those presented elsewhere and should be considered in light of the totality of evidence suggesting that dengue mortality might, in fact, be substantially higher".

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We declare no competing interests.

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