OPEN LETTER

Considerations for the 2030 Sustainable Development Goals for dengue [version 1; peer review: 2 approved with reservations]

Collaborating Group on Dengue Disease Modelling

Abstract
Dengue circulates endemically in many tropical and subtropical regions. In 2012, the World Health Organization (WHO) set out goals to reduce dengue mortality and morbidity by 50% and 25%, respectively, between 2010 and 2020. These goals will not be met. This is, in part, due to existing interventions being insufficiently effective to prevent spread. Further, complex and variable patterns of disease presentation coupled with imperfect surveillance systems mean that even tracking changes in burden is rarely possible. As part of the Sustainable Development Goals, WHO will propose new dengue-specific goals for 2030. The 2030 goals provide an opportunity for focused action on tackling dengue burden but should be carefully developed to be ambitious but also technically feasible. Here we discuss the potential for clearly defined case fatality rates and the rollout of new and effective intervention technologies to form the foundation of these future goals. Further, we highlight how the complexity of dengue epidemiology limits the feasibility of goals that instead target dengue outbreaks.

Keywords
Dengue, WHO guidelines

This article is included in the 2030 goals for neglected tropical diseases collection.
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Competing interests: No competing interests were disclosed.

Grant information: This work was supported by the Bill and Melinda Gates Foundation [OPP1184344]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Collaborating Group on Dengue Disease Modelling. Considerations for the 2030 Sustainable Development Goals for dengue [version 1; peer review: 2 approved with reservations] Gates Open Research 2019, 3:1656 https://doi.org/10.12688/gatesopenres.13084.1

First published: 07 Nov 2019, 3:1656 https://doi.org/10.12688/gatesopenres.13084.1
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Background

Dengue virus (DENV) is a flavivirus transmitted by Aedes mosquitoes. There are an estimated 50 million symptomatic DENV infections each year through global tropical and subtropical regions. As part of the Sustainable Development Goals for neglected tropical diseases, the World Health Organization (WHO) is developing goals to be reached by 2030 for dengue control. These goals are an update to the previous 2012 WHO goals of reducing mortality and morbidity by 50% and 25%, respectively, between 2010 and 2020, which will not be achieved. Levels of dengue morbidity and mortality have instead continued to increase in many settings. Here we discuss how considering different aspects of DENV disease, transmission and control can help inform as to why the previous goals failed and the feasibility of any future goals.

Part of the complications in attempts to control dengue morbidity and morbidity is that infection by DENV can result in a wide spectrum of disease, ranging from no symptoms to severe haemorrhage. Fewer than 1% of infections result in death. However, the true proportion of infections that are fatal is rarely known as the underlying number of infections cannot be captured, with most infections being asymptomatic or too mild to be detected by surveillance systems. Even in settings with good surveillance, translating observed cases to underlying infection risk is rarely possible due to high levels of population immunity, variability in the proportion of infections that result in symptoms and high rates of asymptomatic transmission.

The number of cases can also vary by orders of magnitude across years for reasons often unknown but may be due to changes in population immunity, climate or changes in the serotype or virus. This underlying variability means it is difficult to define a baseline level of morbidity. There are also substantial differences in the risk of dengue within and across countries, however, this has been difficult to quantify. For example, India is believed to have the highest burden from dengue worldwide but very few cases are detected by surveillance systems. Risk mapping modelling exercises based on occurrence data can identify environmental suitability and endemic boundaries of transmission but is less successful at accurately capturing geographic variation in transmission and incidence.

Age-specific case data can help reconstruct infection risk (as it reflects underlying population immunity) but case age data is collected as part of routine surveillance activities. Age-stratified seroprevalence data can also be used to reconstruct infection risk but is rarely collected. There are also longer term trends that affect disease patterns. In particular, age-specific incidence is shifting in many settings due to transitions in the age structure of populations (which results in the mean age getting older) or from transitions from epidemic to endemic circulation (which results in younger ages). These shifts can lead to changes in morbidity and case fatality rates as both depend on age.

Efforts to reduce morbidity are essentially reliant on interventions that reduce transmission. Existing interventions largely focus on vector control (mainly integrated vector management and insecticide use), which have been shown to temporarily reduce vector densities. However, despite their wide deployment, there is little/no evidence that these strategies have any impact on dengue incidence. The one licensed dengue vaccine provides imperfect protection. It has also been shown to increase the risk of severe disease/hospitalisation in individuals that have no antibodies against dengue at the time of vaccination. This has led to a WHO recommendation of pre-vaccination antibody screening. The expected impact of the currently licensed vaccine, if rolled out with an antibody screening test, is expected to be limited (≤20%) on incidence and only cost-effective in a few settings. This is compared to 20–30% if rolled out at the population level without screening. Large-scale implementation of imperfect vaccines with differential protection by serotype has the potential to lead to future rebounds in incidence.

New tools are in development, but their efficacies are currently unknown. There are two vaccine candidates (Takeda and NIH/Butantan), which are currently in phase III trials and results are expected within the next two years. Long-term follow up will be required to ascertain its long-term efficacy and risk profile. The increased risk among vaccinated sero naïves with the Dengvaxia vaccine only became evident after the third year of follow-up. In addition, novel vector control strategies such as the release of genetically modified or Wolbachia-infected Aedes aegypti mosquitoes to suppress mosquito populations or reduce vector competence are also in advanced stages of development.

Considerations for future goals

Focus on interventions that controls onwards spread

The combination of complex dengue epidemiology and the lack of effective interventions meant that the feasibility of the 2012 WHO goals were always in doubt. The development of new technologies focused on reducing transmission will be central to tackling future morbidity from dengue. The results from modelling suggest that intervention with efficacy 70% will be required to achieve negligible annual cases (i.e., reduce the reproductive number to under one). Current available interventions have an estimated efficacy far short of this value. We currently do not know whether an intervention (or combination of interventions) with those characteristics will become available in the next decade. Given that current interventions are insufficient to eliminate transmission, even settings that are able to reduce transmission will continue to experience regular instances of ongoing transmission and outbreaks. A goal of developing...
and rolling out of interventions of a sufficient efficacy to prevent transmission can help motivate efforts on technologies that have the ability to control onwards spread.

Case fatality rate (CFR) definitions need to be clear
A goal focused on reducing mortality should be central to future efforts to reduce the overall burden from dengue. Improvements in case management can lead to substantial reductions in the number of deaths from dengue. Some countries have been able to reduce mortality to very low levels. For example, Singapore has some of the best clinical care globally and has achieved a CFR of under 0.05%. Understanding reductions in mortality relies on a clear definition of the CFR. Reported CFRs are usually calculated as the proportion of detected hospitalised severe cases that are fatal, however, there is no consistent definition. Radically different estimates of CFR are possible depending on whether the denominator used is number of hospitalised/severe dengue cases or incidence of milder dengue fever (Figure 1). In addition, CFR may vary significantly if confirmed cases or all suspected cases are used. Dengue infection results in a wide spectrum of disease, with severe symptoms only occurring in a minority of infections. The cases that are detected by a surveillance system will depend on healthcare seeking patterns, local clinical management protocols, healthcare resources and surveillance reporting processes. These factors mean that the number of reported cases can vary considerably across settings and over time. Even in well-resourced settings, most dengue cases are based on imperfect clinical diagnoses without confirmatory testing, especially with milder cases.

Avoid goals based on reducing dengue ‘outbreaks’
For some pathogens, reducing the frequency and size of epidemics may form the basis for a simple and easy to understand goal to reduce disease burden. For example, the size and duration of outbreaks has been useful in measuring the pathway to measles and rubella elimination. However, the complexities of the dengue disease system severely reduce the potential for this approach here. Firstly, progress to outbreak-related goals cannot be causally associated with interventions. The underlying epidemiology of dengue is complex. In the absence of interventions, there can be orders of magnitude difference in the observed number of cases across years. For example, in Bangkok, Thailand, there are large fluctuations in the number of cases reported each year and continual year-round circulation despite largely consistent behaviour in intervention deployment (Figure 2). This poses challenges to monitoring the progress of reducing transmission risk from interventions.

Secondly, historic incidence in many locations is poorly characterized, limiting ability to define ‘putative epidemics’ - goals based on outbreaks necessitate a robust definition of what constitutes an ‘outbreak’. Most approaches rely on using background levels of incidence in a location to create epidemic thresholds. The type of cases captured by surveillance systems will differ substantially across locations (by level of severity, confirmation status) meaning there will be inconsistent definitions of epidemics in different countries. Changes in surveillance over time will also complicate the use of historical observed incidence. For example, using models fit to age data (which is more robust than changes in surveillance), it has been shown that over the period 1980 to 2000 there was a 50% decrease in the force of infection in Bangkok, Thailand. However, changes in surveillance, healthcare seeking and population growth have contributed to a large increase in detected cases over this period (Figure 2).

![Figure 1. Case fatality rate (CFR) estimates with different reporting scenarios. Assumes 40% of infections are symptomatic, 5% are hospitalised, 1% are very severe and 0.001% are fatal. For misclassification bias, assumes 5% of fatal cases and 20% of hospitalised cases are misclassified.](image1)

![Figure 2. Observed case counts in a tertiary care hospital in Bangkok, Thailand between 1973 and 2015. While the number of observed cases has risen steadily over this period, the underlying force of infection has fallen by over 50%.](image2)
Finally, surveillance efficiency scales probability of detecting outbreaks. There is a complex interaction between surveillance and the detection of putative outbreaks. Improved surveillance can accompany improvements in control but can also lead to detection of larger number of putative outbreaks simply because of improved detection. This may create situations where settings with the most effective control may detect larger numbers of outbreaks.

Proposed 2030 goals

Given these fundamental challenges, we propose two goals focused on the targeted deployment of interventions with efficacies that can limit onwards spread and on reducing CFR.

Goal 1: Reduce CFR among individuals with symptomatic dengue disease to below 0.05%. WHO needs to offer specific guidelines on CFR numerators and denominators and whether the calculation should be based on lab-confirmed or clinical case definitions.

Goal 2: By 2030, have initiated rollout of interventions with proven (via randomised trials ideally) potential to achieve long-term reductions of 70% or greater in dengue transmission or symptomatic case incidence (e.g. an effective vaccine, vector control strategy or other intervention or combination of above) in all dengue endemic countries (defined as sustained transmission dengue over multiple years).

Practical implications

Measurement and tracking progress

Specific definitions will be key to reliably achieving the goals. For the first goal, the numerator and the denominator need to be well defined. Most cases are diagnosed only clinically without systematic confirmatory laboratory testing. The true cause of death (numerator) or whether the patient was actually a dengue case is often unclear. Consistent denominator(s) to define what constitutes a ‘case’ need to be agreed. As the CFR varies by age, countries need to capture the age distribution of cases and deaths. Precise definition is also needed to reduce the risk of perverse incentives. The absence of specific guidance on case definitions could generate perverse incentives to lower measured CFR. For example, including non-specific febrile syndromes in the denominator or, in the absence of systematic confirmatory testing, classifying deaths as not dengue attributable to lower the numerator.

Spatially and temporally resolved estimates of dengue transmission (number of infections) and burden (number of symptomatic cases, severe cases, hospitalised cases, deaths) are lacking. Identifying subnational locations that experience the highest transmission and burden is critical to underpinning the targeted training of healthcare staff, allocation of and any future targeted deployment of new tools that can reduce transmission. Age-specific case data can be used to estimate infection intensity and can be paired with nationally representative seroprevalence studies in random subsets of the population to produce robust estimates of infection risk.

In order to help track the progress towards these goals, countries should implement WHO recommended guidance (to be generated) on measuring cases and deaths to document their progress in reducing CFR. Countries should also report subnational age distribution of cases (number of cases by single age class at admin level 1 or higher) as this allows infection risk estimation that is robust to surveillance bias. Countries should also implement WHO recommended guidance (to be generated) on measuring infection and morbidity (both overall and age-specific) to document progress in targeting interventions to 20% of their populations at risk. The guidance would include recommendations on using clinical cases and serological studies among other methods to measure risk and burden.

Technical feasibility

Reducing CFR to <0.05% with modern standards of care is technically feasible, however, it will depend on the clinical care available. While Singapore has a comprehensive surveillance system and some of the best clinical care and has achieved a very low CFR, other countries have poorer surveillance and absence of notified dengue-related deaths cannot be interpreted as absence of undetected mortality. The feasibility of rolling out an intervention with demonstrated potential to reduce dengue transmission or symptomatic infections by over 70% in all endemic countries will depend on such intervention (or combination of interventions) becoming available.

Operational feasibility

For the first goal, the targeted case management training of healthcare workers will be essential. In countries with limited existing surveillance, it will be particularly necessary to identify areas at risk where healthcare staff should be targeted for training and where resources should be allocated to guarantee adequate diagnosis and management of cases. It will also be necessary to monitor changing patterns of age groups at risk (e.g., whether resources should be concentrated in paediatric vs adult clinics) and the populations at risk (e.g., expanding geographic zones) to identify which locations and which health care workers (e.g., adult vs. paediatric physicians) are in need of training.

To meet the second goal, intervention(s) that reduce disease by 70% will need to be developed and identified. It will also be necessary to monitor uptake of an intervention and its effectiveness by maintaining surveillance for disease. For interventions that reduce burden by reducing transmission, it will be necessary to assess whether intervention effectiveness declines over time because of the reduction of immunity due to natural exposure that will occur with the reduction of infection.
It is likely that the optimal deployment of intervention tools will differ across settings, depending on the level of endemicity, population structure, existing surveillance capabilities and available interventions. This will require customized deployments for each setting.

**Considerations of cost**

Reducing the case fatality and dengue transmission will likely result in savings over the long term due to reduced healthcare expenditure. However, the precise impact will depend on the characteristics of the tools and their efficacy. The rollout of large-scale interventions in all dengue endemic countries will require major funding commitments.

**Conclusions**

The WHO goals represent an opportunity for targeted action on tackling a highly endemic pathogen with a substantial public health burden. Careful consideration of the specifics of dengue epidemiology and the current status of the available technologies are required for the ambitious, but ultimately feasible, goals to be reached.

**Data availability**

No data are associated with this article.

**Acknowledgements**

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**References**

5. PAHO: PAHO Dengue. Reference Source


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This article offers several useful and insightful comments. First, current WHO targets will not be met, so revised guidelines would be useful. Second, the global public health community does not yet have tools available for effective dengue control. Third, measuring progress, even if it occurred, would be extremely difficult due to challenges in diagnosing and reporting dengue, and the great variability in dengue incidence by time and place. Fourth, surveillance data that report dengue cases by age would add substantial information in estimating the force of infection. Fifth, a new goal of dengue control could be the reduction of the disease's case-fatality rate. Sixth, definitions matter, as the authors illustrate with the order-of-magnitude variation in the case-fatality rate of dengue, depending on how a “case” is defined.

As a generally favorable reviewer, I would nevertheless offer several suggested refinements for the authors' consideration. Where the authors wrote that “Fewer than 1% of infections result in death,” they may wish to make a more precise statement, “Far fewer than 1% of infections result in death.” The true rate is likely on the order of magnitude of 0.01%. The authors' statement that the reason for variability is often unknown seems to be counter to the rest of the sentence, as the authors suggest several plausible explanations. The authors may wish to reword the sentence to indicate that “Reasons for variability, incompletely understood, include ....”

Another detail relates to dengue in India, where the authors wrote “...very few cases are detected by surveillance systems.” As dengue's surveillance system collects data only from a limited number of sentinel facilities, the authors may wish to change “detected” to “reported.”

The authors' laudable suggestion of a goal of reducing the case-fatality rate might be made more practical by basing it on statistics reported by most national surveillance systems. This could be the fatality rate of hospitalized lab confirmed dengue cases. As national surveillance systems vary about their inclusion of cases from outpatient settings and testing, this definition would be practical and improve comparability.

In the discussion of misclassification of possible dengue fatalities, the authors may also wish to
note that misclassification could not only increase apparent deaths, as the authors hypothesize, but could also lower them. Follow up of autopsies from Puerto Rico of patients with post-mortem confirmations of dengue found that a substantial portion had not been diagnosed during their lifetime. Thus, routine dengue surveillance did not count these fatalities.

As innovations in dengue control are rapidly involving, the authors may wish to incorporate the latest data. A new modeling study of the latest dengue vaccine (Coudeville, Baurin and Shepard, Vaccine 1) showed that it would be cost-effective in a much broader range of settings, including median values from vaccine trial sites where the sero-prevalence of dengue was at least 30%. Global observational data on Wolbachia show consistent benefits, with the first randomized trial (in Yogyakarta, Indonesia) expected to be completed by the end of 2020 (Katie Anders, presented at annual meeting of Am Soc Trop Med & Hygiene, 2019).

Finally, the authors may wish to add some nuances to their goal for vector control being implemented in all countries with transmission. They may wish to limit their goal geographically for large countries such as China and the United States, where dengue affects only the warmest parts, note that some vector control technologies are most applicable to densely populated areas, and replace “all” by a quantitative goal, such as 80%.

References

Is the rationale for the Open Letter provided in sufficient detail?
Yes

Does the article adequately reference differing views and opinions?
Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Partly

Is the Open Letter written in accessible language?
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?
Yes

**Competing Interests:** Research grants and other support from Sanofi Pasteur and Takeda Vaccines

**Reviewer Expertise:** Health economics, particularly cost of illness, cost-effectiveness analysis, and health financing, particularly for vector-borne illnesses and vulnerable populations

I confirm that I have read this submission and believe that I have an appropriate level of
expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 18 November 2019

https://doi.org/10.21956/gatesopenres.14226.r28209

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PROGRAMS TO REDUCE DENGUE MORTALITY.
Scott B. Halstead, M.D.

The reviewer agrees a 2030 WHO goal should be to reduce dengue mortality and morbidity. The methods described here cannot achieve the specific reduction goals listed. These are comments by a disease modeling group who have suggested sustainable WHO 2030 targets for dengue morbidity and mortality rates. A note must be made at the outset. A case fatality rate of less than 0.05% already has been achieved by some large countries, Brazil and Mexico, in the American region. PAHO calculates CFR to the base of all reported cases of dengue. By contrast, in Southeast Asia, Thailand and Vietnam, countries that are widely lauded, have maintained a case fatality rate around 0.1% for a period of 10 years. By contrast, for a recent 5 year period, average CFRs in other countries were: Indonesia - 0.985%, India – 0.26%, Sri Lanka – 0.195%, Philippines – 0.49%, Cambodia – 0.27% and Malaysia – 0.22%.3 CFRs are more meaningful if calculated among clinically congruent patients. When the first country reports were listed, CFRs in Southeast Asia were calculated among hospitalized cases. In the Americas, if the denominator used is severe cases, the average CFR for 2019 in the region was 4.9%.1 Standardizing the denominator will be the first problem to be solved. “Severe” dengue is the right idea. Sanofi defined “severe” as hospitalized dengue cases with a platelet count of <100,000/ mm3 and evidence of vascular permeability4. But, here is the problem: the 2009 WHO case definition says that “severe dengue” is any of the following: plasma leakage, circulatory compromise, significant bleeding, altered level of consciousness, severe gastrointestinal involvement, or severe impairment of liver, kidney or heart5. My suggestion: use the 1997 WHO case definition without any requirement for hemorrhage. The reason for this suggestion is reviewed in a recent history6.

The authors note at the outset that epidemiological patterns and intensity of dengue disease have varied greatly over time and between geographic locales. Dengue now is global. At the end of WWII, all four dengue viruses (DENV) became endemic in Southeast Asia. High transmission rates there led over several decades to a stable pattern of seasonal outbreaks of moderate to severe hospitalized disease. Outbreaks varied in size from year to year and impacted mainly children. Economic and demographic changes then lowered dengue virus transmission rates resulting in an expansion of the age range of those affected. As new DENVs were inserted into the Indian subcontinent and then into the Western Hemisphere they produced introductory virgin soil epidemics of dengue fever and then as multiple viruses became established, disease patterns
moved toward the epidemiological and clinical features of Southeast Asia. The take home message: everywhere in its range, dengue viruses produce a wide age range of diseases that vary from mild to severe causing modest case fatal rates. Despite the best modeling efforts, dengue epidemiology remains essentially chaotic. This means that surveillance, per se, is not a useful tool for managing the control of transmission or anticipating and managing clinical burden.

The key dengue challenges during 2020 to 2030 are to reduce morbidity and mortality. But, how? This review does not discuss methods in any detail. There is the very real possibility that one or both new tetravalent dengue vaccines will provide significant levels of protection across a wide age range and without vaccine sensitization of seronegatives. Phase 3 reports summarizing 18 months post vaccination data for the Takeda TDV vaccine have been published\(^7\). These show the vaccine to be highly effective at reducing hospitalization of DENV 1 and 2 infections. The vaccine contains a real live-attenuated DENV 2. Is the protection observed attributable to vaccine or an example of the heterologous cross-protection that follows a primary dengue infection\(^8\)? If so, it might “wear off” resulting in vaccine related sensitizations. Phase 2 challenge studies of the NIH TV003 show a very high rate of protection against DENV 2 infection\(^9\). Should this protection be confirmed by phase 3 studies, the entire dengue control landscape may change. The authors are correct to surmise that the NIH vaccine, even if highly protective, is unlikely to be available at the quantity needed to immunize billions of people during the next decade. Exciting large field trials introducing Wolbachia into urban areas, in progress, may provide a method to achieve a major reduction in transmission of dengue viruses by Aedes aegypti\(^10,11,12\). In addition, there are several other technologies that promise to reduce the efficiency of dengue virus transmission by vector mosquitoes\(^10,13\).

I agree with the authors that the most important goal for 2020 – 2030 is to reduce dengue mortality. This cannot be accomplished through enhanced surveillance or improved predictions of disease intensity. Dengue incidence will be unpredictable at national and local levels. What is needed is an entire health system that is prepared and trained to provide optimal clinical care. Dengue illnesses are short and fast moving. Classical dengue shock syndrome occurs suddenly and rather late in illness, three to five days after onset of fever. Physiological status can change in a matter of minutes. WHO has issued comprehensive technical guides that carefully describe dengue illness, diagnosis and treatment regimens\(^5\). This important information may have helped reduce dengue fatality rates. Unfortunately, good information does not by itself change medical practice. Dengue is managed successfully at large scale by countries such as Thailand and Vietnam. They have trained all the components of a system that swiftly and accurately identifies patients with acute capillary permeability and then provides them the correct sustenance.

Reasons for many fatal outcomes in dengue are well understood: 1) the patient is delayed in presenting for health care, 2) misdiagnosis and 3) mismanagement. It is widely known, but seldom discussed, that a significant percent of all fatal outcomes in dengue are due to fluid overload. Countries that have successfully lowered case fatality rates have addressed all three risks. The general public must be informed again and again about the risk of fatal dengue, told to seek medical attention early in illness and be aware of key warning signs. In the clinic, diagnosis and management of dengue requires a mix of education and training. The pathophysiology of dengue disease should be taught at all levels in medical education. Training in diagnosis and treatment must be included in relevant post-graduate medical training. Hospital based clinicians in dengue endemic countries should receive special training in dengue diagnosis and resuscitation. As with any skill, repetition and practice are necessary to achieve and sustain competence. Some countries
with low case fatality rates have introduced obligatory short training courses for all hospitalists. An issue to be addressed is whether hospitalists should be credentialed in dengue treatment. A key component of a nation-wide system of sustained excellent critical care of dengue is that any health care provider who has a patient with management problems should have access 24/7 to expert consultant advice. Dengue care units must have the equipment, sonographic or x-ray, needed to identify and quantitate invisible fluid losses into serosal spaces. Hospitals in Southeast Asian countries place microhematocrit centrifuges directly on patient wards permitting ward personnel to measure hematocrit levels at frequent intervals. Hematocrit monitoring has proven to be very valuable for accurate regulation of fluid resuscitation and avoiding fluid overload.

Any change in medical practice requires planning and leadership. While WHO clearly should play a role in design and support of national programs to reduce fatal dengue, this effort will depend upon extraordinary financial assistance and leadership. To begin the effort, the different successful country approaches must be studied and translated into the appropriate diversity of educational and training programs needed. If a program is created under WHO aegis, a monitoring and advisory entity such as the Task Force for Child Survival will be needed. It is understood that every country, and for that matter, many constituencies within countries, will pose challenges, their solutions requiring high competencies and diplomacy.

Some may say that all fatal cases of dengue are not caused by capillary leakage. That is true. But, how many? Dengue viruses infect a broad spectrum of populations that differ in many ways. This diversity is relevant both to the spectrum of dengue disease and to the possibilities of successful intervention. Clearly, dengue infections in the old and infirm are associated with increased incidence of fatal outcome. Thus far, little is known about the pathophysiology that contributes to death in these cases. In some instances, when looked for carefully, capillary leakage has contributed to disease severity. Resuscitation of fluid losses has reduced case fatality rates. But, not to zero. Individuals of any age who present with the dengue vascular permeability syndrome, seen early enough, with appropriate care, should survive. The program recommended here will be directed at improving management of each of the three steps needed to correctly identify and treat patients with dengue capillary leakage. Once fully implemented we may begin to identify the scale and nature of the other factors that contribute to fatal outcome in dengue.

References


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Partly

Does the article adequately reference differing views and opinions?
Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
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Is the Open Letter written in accessible language?
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** dengue pathogenesis, vaccine development

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
Theodore Tsai, Theodore F Tsai MD MPH FIDSA, Boston, MA USA, USA

The authors rightly draw attention to how the absence of an agreed denominator for dengue CFR impedes surveillance of dengue treatment and control but I believe they should have drawn more attention to the CFR numerator and how and when dengue-related deaths are ascertained. Various underlying conditions such as diabetes mellitus, SS and SC hemoglobinopathy, chronic renal and liver disease and perhaps increased BMI have been associated with increased severity of dengue or even fatal outcome but practitioners, particularly those caring for adult patients, may not associate an exacerbation of these underlying conditions with acute dengue. Many of these NCDs are more prevalent in older adults in whom the clinical features and presentation of acute dengue are less distinct than in younger patients. Dengue-related deaths in these patients may be missed because practitioners fail to consider dengue as having occurred and do not seek a specific diagnosis. Even if dengue is recognized as occurring concurrently with the NCD exacerbation, how and whether dengue is mentioned in the death certificate as a contributing cause may vary. For these reasons, the numerator of dengue deaths may be underestimated in populations where dengue occurs in adults and especially where older adults are at risk.

Recommendations and guidelines are needed to improve recognition of dengue in older adults and in persons with underlying NCDs that pose a risk for more severe dengue. Specific training should be provided on how dengue should be recorded on a death certificate when the acute infection has contributed to death from a preexisting condition and, finally, those responsible for surveillance need to agree what constitutes a dengue-related death.

Influenza-related cardio-respiratory deaths are estimated by measuring departures from a baseline of off-season rates; can modelers, who are among the authors, provide estimates of excess NCD deaths or hospitalizations attributable to dengue?

**Competing Interests:** I am a full time employee of Takeda Vaccines, a sponsor of a candidate dengue vaccine.