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Knowledge gaps in the epidemiology of severe dengue impede vaccine evaluation

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TMS produced the figure. All authors collaborated in the conceptualisation and writing of this Personal View.

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Abstract

The most severe consequences of dengue virus infection include shock, haemorrhage, and major organ failure; however, the frequency of these manifestations varies, and the relative contribution of pre-existing anti-dengue virus antibodies, virus characteristics, and host factors (including age and comorbidities) are not well understood. Reliable characterisation of the epidemiology of severe dengue first depends on the use of consistent definitions of disease severity. As vaccine trials have shown, severe dengue is a crucial interventional endpoint, yet the infrequency of its occurrence necessitates the inclusion of thousands of study participants to appropriately compare its frequency among participants who have and have not been vaccinated. Hospital admission is frequently used as a proxy for severe dengue; however, lack of specificity and variability in clinical practices limit the reliability of this approach. Although previous infection with a dengue virus is the best characterised risk factor for developing severe dengue, the influence of the timing between dengue virus infections and the sequence of dengue virus infections on disease severity is only beginning to be elucidated. To improve our understanding of the diverse factors that shape the clinical spectrum of disease resulting from dengue virus infection, prospective, community-based and clinic-based immunological, virological, genetic, and clinical studies across a range of ages and geographical regions are needed.

Introduction

The global incidence of dengue has doubled each decade for the past 30 years, with recent estimates of over 100 million infections and 50 million cases per year.[1-3] Although clinically severe disease is an uncommon outcome of dengue virus (DENV) infection, more than 50% of the estimated US $8·9 billion global financial burden of dengue results from patients who are admitted to hospital or die.[1,2] The epidemiological characteristics of dengue are variable and complex, and many facets are incompletely understood.[4] Studies that have used crosssectional surveillance data frequently report the proportion of patients with clinically severe disease, generally considering patients who have been admitted to hospital to have severe disease; however, because many patients with dengue either do not seek care or are not admitted for care,[5] there is little clarity about the actual frequency of severe disease among all ill individuals infected with any of the four dengue viruses (DENV-1–4). Such data have been reported from few prospective, mostly paediatric, cohort studies,[6] as well as from multi-site evaluations of paediatric dengue vaccine candidates;[7,8] however, the factors affecting the occurrence of clinically severe dengue (a term which, as used in this Personal View, includes both severe dengue[9] and dengue haemorrhagic fever and dengue shock syndrome[10]), and particularly the interplay between these factors, are not well understood. An improved understanding of the risk factors associated with developing clinically severe dengue is needed to optimise the design and evaluation of effective and safe clinical interventions and vaccine interventions, to reduce the morbidity and mortality of dengue.[11,12]

Status of past infection with a DENV (ie, serostatus) is perhaps the most well known risk factor for developing clinically severe dengue, considering that individuals with secondary DENV infection are typically over-represented among patients with clinically severe dengue;[12] however, clinically severe dengue can also occur after primary DENV infection in children and adults.[13] Studies with prospective data and mathematical models further show the importance of previous DENV infection as a risk factor for clinically severe dengue.[14,15]

Multiple mechanisms probably contribute to increased disease severity during secondary DENV infection. Nonneutralising antibody binding to the virus, followed by uptake in Fc receptor-bearing monocytes, might result in higher and longer magnitude of viraemia (ie, antibody-dependent enhancement). An accompanying exacerbated immune response might also occur, in which activated natural killer cells and memory T cells trigger inflammatory mediators that contribute to intravascular leakage.[16] The viral protein nonstructural protein 1 is secreted from infected cells and is independently associated with vascular leakage by damaging the endothelial glycocalyx and disrupting endothelial cell junctions. This process might be exacerbated during secondary infection due to heightened viraemia.[17]

Multiple studies have also shown important roles for various viral and host factors in disease severity (figure). Accumulating evidence for all four DENVs suggests that genotype-specific viral factors can result in phenotypic changes in viraemia, disease severity, and epidemic potential.[18-22] Additionally, host genetics has long been thought to have a role in disease severity, which has been evidenced by case-control studies.[23,24] Vascular leakage and shock tend to occur more frequently in children than in adults.[25] Several other risk factors for developing clinically severe dengue have been identified, including sex, underlying comorbidities (eg, asthma, obesity, diabetes, and cardiac disorders), pregnancy, virus serotype, and sequence of and interval between DENV infections (panel 1). Because multiple epidemiological factors are associated with disease severity, much effort has focused on the discovery of simple, generalisable biomarkers that reliably identify patients who will progress to clinically severe dengue, which has been elusive.[43]

Identification of pathophysiological risk factors that affect the development of clinically severe dengue is complicated by the unclear relative contribution of previous DENV infection, spatial and temporal heterogeneities in historic and current levels of population-level DENV transmission, and both host and viral characteristics. Although longitudinal cohort studies have proven to be instrumental in identifying and describing factors associated with disease severity,[6] these studies are resource-intensive and, by design, focus on individuals at high risk for infection (ie, children in highly endemic areas). This focus limits the generalisability of findings to other age groups, epidemiological contexts, and populations with variable frequencies of genetic predisposition to disease and prevalence of comorbid conditions, all of which might also influence disease severity. For example, the epidemiology of clinically severe dengue in Africa and in Afro Latino individuals has not been sufficiently investigated.[44] Resolving the factors that contribute to both the pathophysiology and the observed epidemiology of clinically severe dengue has gained attention after the results of the first licensed vaccine against dengue.

CYD-TDV (Dengvaxia), developed by Sanofi Pasteur, is a three-dose, live-attenuated, tetravalent vaccine.[45] Phase 3 clinical trials were completed among more than 30 000 paediatric participants from Asia and Latin America.[46,47] Under advice from the Strategic Advisory Group of Experts in April, 2016,[48,49] because of a safety signal in children aged 2–5 years in year 3 of the Asian trial, WHO initially recommended that the vaccine only be used in populations with DENV seroprevalence of 70% or greater by age 9.[49] In November, 2017, Sanofi Pasteur released new analyses of 60 months of follow-up data indicating that, despite substantial benefit among seropositive individuals, vaccination of seronegative individuals increased the risk of developing more severe disease (defined using definitions of either severe dengue or dengue haemorrhagic fever and dengue shock syndrome) on subsequent natural infection.[47,50] Consequently, WHO revised its recommendation for Dengvaxia such that only individuals who have been tested and shown to have evidence of previous DENV infection should be vaccinated.[51,52] In 2019, the US Food and Drug Administration approved the use of Dengvaxia in children aged 9–16 years who have evidence of previous DENV infection and live in areas of the USA where dengue is endemic.[53] The requirement for prevaccination screening and the current absence of a fully evaluated and available screening test with high specificity complicates the implementation of Dengvaxia in national vaccine programmes.

The outcomes of the trials of Dengvaxia and subsequent follow-up studies show the complexity and importance of elucidating the factors that contribute to dengue severity.[54] Such findings will be of continued importance during evaluation of Dengvaxia and additional dengue vaccine candidates, including Takeda's vaccine, TAK-003, for which the initial results are promising but not without concern regarding unequal protection by serotype and serostatus of potential vaccinees.[8] Other vaccine candidates have raised the concern of intraserotype antigenic variability potentially affecting vaccine effectiveness and either protection from or progression to clinically severe dengue.[55,56] The role of genotype variation on vaccine efficacy has also been reported for Dengvaxia.[57,58] In this Personal View, we describe current limitations that affect our understanding of the epidemiology of clinically severe dengue and make recommendations regarding how such challenges might be resolved.

Case definitions to identify and study clinically severe dengue

Case definitions are the metric by which clinical and epidemiological studies assess and compare outcomes; however, the use of consistent and comparable definitions has been an impediment to dengue research since the 19th century.[59] Of paramount importance is accurately diagnosing dengue by reliably identifying and differentiating acute, recent, and historic DENV infection through the detection of several factors: viral nucleic acid by RT-PCR; nonstructural protein 1 by ELISA; anti-DENV IgM or IgG antibody by ELISA, in some cases followed by confirmation with a neutralising antibody test; and viral antigen or antibodies by rapid diagnostic test.[60] Doing so is not trivial, given that much variation exists in assays used to define DENV infection and serostatus. Furthermore, many studies also seek to identify which individuals develop symptomatic DENV infection (ie, dengue), the definition of which also varies between studies. Some studies consider dengue to be any illness that meets a specified clinical case definition regardless of whether the individual

sought medical care or had laboratory diagnostic evidence of dengue, whereas other studies consider symptomatic dengue to be a clinically apparent disease, and other studies refer to subclinical infection as any infection for which the infected individual did not seek clinical care regardless of the presence or absence of disease. Similarly, various studies use different denominators for the calculation of dengue case fatality rates, including all DENV infections, all symptomatic DENV infections, all clinically apparent cases, or all people admitted to the hospital.[1,2,61-64] Hence, a need remains for the common use of terminology and case definitions to enable comparison across studies, to obtain a more holistic understanding of the pathophysiology and global burden of dengue.

These ambiguities are exacerbated when considering clinically severe manifestations of DENV infection. Nearly all epidemiological studies define disease severity according to either the WHO 1997 case definition for dengue haemorrhagic fever and dengue shock syndrome[10] or the 2009 revised case classification that reframed all patients with clinically severe disease into a single category of severe dengue[9] (panel 2). Notably, the WHO 1997 case definition of dengue haemorrhagic fever and dengue shock syndrome focuses on thrombocytopenia, haemorrhagic manifestations, plasma leakage, and shock as the metrics of severe disease in patients with dengue, and although the 2009 classification of severe dengue similarly includes bleeding and plasma leakage, this 2009 classification also includes other life-threatening manifestations of DENV infection (eg, meningoencephalitis and myocarditis) not captured by the definition of dengue haemorrhagic fever and dengue shock syndrome that might occur from pathophysiological processes distinct from those resulting in plasma leakage. Although systematic review of dengue case classification studies suggested that the 2009 classification is more sensitive,[66] evaluations in multiple jurisdictions have shown that both definitions have clinical merit as well as additional use for research studies.[66-68] In particular, while vaccine trials and other clinical studies need to monitor the impact of vaccine and other interventions on reducing the risk and costs of all disease and especially severe dengue, immunopathogenesis studies might be better served by use of the dengue haemorrhagic fever and dengue shock syndrome definition. Consequently, clinical research studies, and specifically vaccine trials, should ideally evaluate results using outcomes of both severe dengue and dengue haemorrhagic fever and dengue shock syndrome. In all cases, assessing factors associated with disease severity to identify generalisable epidemiological trends will be greatly assisted by use of consistent measures of clinical outcomes.

Incidence of clinically severe dengue

The large cohorts from the Dengvaxia vaccine trials in five Asian and five Latin American countries provide the best available estimates of the frequency of dengue, dengue haemorrhagic fever and dengue shock syndrome, and severe dengue across regions.[5,7] Among children aged 2–16 years, approximately 10% of febrile episodes were attributed to virologically-confirmed dengue (VCD), with 4·6 and 2·9 episodes of VCD per 100 person-years occurring in Asian and Latin American cohorts, respectively. The incidence of dengue haemorrhagic fever was less than 0·3 episodes per 100 person-years in each cohort; 61 (19·1%) of 319 VCD episodes in the Asian cohort and 43 (11·1%) 389 of VCD episodes

in the Latin American cohort required hospital admission. Among comparable age groups (9–12 years and 13–16 years), the burden of dengue was higher in Asia than Latin America.

Other manifestations of severe dengue include myocarditis, liver failure, and neurological complications, including meningoencephalitis and Guillain-Barré syndrome. Such manifestations appear to be uncommon compared with shock and hemorrhage,[65,69,70,71] although reliable estimation of their prevalence requires enrolment of a large number of patients with dengue. Hence, only the Dengvaxia vaccine trial has yielded potentially generalisable estimates of the prevalence of uncommon but severe manifestations of dengue among non-vaccinated children aged 2–16 years (ie, among 1094 cases of VCD, 13 [1·2%] included visceral manifestations).[50]

Although clinical case definitions of non-shock severe manifestations of disease have historically been variable, which has further complicated estimation of their prevalence, suggested case definitions have been developed by a panel of clinical experts in 2018.[65] With the use of these definitions developed by the panel, the frequency of the various alternative manifestations of severe dengue should be assessed in both adult and paediatric populations, considering that the underlying prevalence of comorbidities that contribute to development of severe and fatal dengue (eg, chronic liver, kidney, or heart disease) differs in children and adults. Notably, accurate evaluations of such definitions are expected to be complicated in patients coinfected with DENV and other pathogens. For example, coinfection with DENV and chikungunya virus, *Leptospira* spp bacteria, or parasites of the genus *Plasmodium* might modulate clinical presentation.[72-76] Similarly, patients who are admitted to hospital are at increased risk for poor outcome due to nosocomial infections.[77] Although it would be ideal to systematically test patients with severe dengue for a wide array of other pathogens representing potential nosocomial infections or coinfections, geographical and temporal heterogeneity in the possibilities make this approach infeasible. An alternative approach would be banking of blood at different times during illness for targeted retrospective investigations.

Patient-specific risk factors for clinically severe dengue

Changes in clinical suspicion of dengue in adults and changing demographics in some countries have led to a renewed recognition of the burden of clinically severe dengue in adults.[4,78] Such observations have shown that the clinical features of dengue, and possibly its pathophysiology, might differ between children and adults, including the likelihood of progressing to symptomatic infection and developing the most common manifestations of severe dengue (eg, plasma leakage and shock are more common in children, whereas adults more frequently experience haemorrhage).[25,68,79-81] A variety of intrinsic and modifiable risk factors might predispose adults for severe dengue. For example, adults might be more likely to develop bleeding due to underlying peptic ulcer disease or anticoagulant medications,[82] and might also be more likely to have comorbidities, such as renal failure or heart failure, that complicate fluid management.[64]

Similarly, risk of developing uncommon but severe manifestations of DENV infection, such as myocarditis and meningoencephalitis, might increase with age or underlying

comorbidities. However, few data are available that have identified risk factors for developing such manifestations or estimated their relative frequency compared with shock and haemorrhage. Identification of these risk fators is complicated by the dearth of reports that reliably quantify and differentiate the proportion of patients with severe dengue that meet case definitions for severe organ involvement, as well as infrequent occurrence of such cases in cohort studies with well defined data on comorbidities, demographics, and infection history.

Consequently, studies that enrol both children and adults are needed to elucidate the mechanisms of progression to clinically severe dengue, including age-specific effects of serostatus.[26]

Interplay between disease severity and transmission intensity

Recent models have shown the global variability in DENV transmission intensity (ie, force of infection) and its strong effect on the observed epidemiology of both dengue and severe dengue.[3,83] The duration of protective immunity might be extended through boosting of antibody titres after re-exposure either to a DENV serotype with which the individual was previously infected or to a new DENV serotype.[29,84] Moreover, an individual's titre of cross-reactive neutralising antibodies affects their likelihood of progression to symptomatic infection,[15,29,85,86] possibly as a function of the interval between infections.[30,87,88] Accordingly, cross-protection from progression to dengue following heterotypic infection occurs for a short period of time (6 months to 2 years);[30,88] however, when infections occur more than 2 years apart, and specifically when mid-range antibody titres are present, the risk of developing severe dengue increases.[14,15,54,88] One model suggested that a sustained high force of infection might result in an overall lower incidence of symptomatic infection and severe dengue, whereas a mid-level force of infection could result in a higher proportion of both symptomatic infection and severe dengue.[89] If true, the potential effect of a dengue vaccine on these trends is unclear. If a high level of protective immunity against all four DENVs is not achieved, a dengue vaccine or other interventions that effectively reduce the overall force of infection could, in theory, increase the proportion of patients with dengue who develop severe dengue.[90,91]

Although post-secondary DENV infections are less likely to result in symptomatic infection,[92,93] the effect of previous infection with other flaviviruses on the severity of dengue is only beginning to be understood.[94] In Thailand, pre-existing antibodies against Japanese encephalitis virus were associated with an increased risk of developing symptomatic DENV infection,[95] whereas early studies from Sabin showed that Japanese encephalitis virus antibodies protected against symptomatic DENV infection.[87] The original Japanese encephalitis virus vaccine efficacy study observed a nonsignificant decrease in dengue haemorrhagic fever among vaccinees, and disease severity among individuals with dengue was reduced.[96] Interestingly, dengue haemorrhagic fever-like illness was reported in a patient with West Nile virus infection and historic DENV infection.[97] Conversely, although data from Colombia and Puerto Rico showed no apparent effect of pre-existing anti-DENV antibodies on the magnitude of viraemia during Zika virus infection in vivo,[98,99] recent reports from Brazil and Nicaragua showed that DENV crossreactive

immunity protects against symptomatic Zika virus infection.[28,100,101] By contrast, recent findings have shown that previous Zika virus infection increases the risk of subsequent symptomatic infection with DENV-2 and worsens disease severity.[28] Overall, potential immune interactions and asymmetries between DENV and other flaviviruses are of interest for both better epidemiological understanding and vaccine development, and require further investigation.[94]

Accuracy of hospital admission as a proxy for disease severity

Clinically severe dengue is a crucial clinical endpoint, but this endpoint is not readily targeted in either clinical or community-based cohort studies because it requires very large numbers of study participants. Instead, multiple vaccine trials have used hospital admission as the most readily available clinical endpoint to evaluate potential increases in disease severity. Although reasonable with respect to study design and cost effectiveness, in practice many factors affect rates of hospital admission among patients with dengue, including age and sex of the patient,[102,103] comorbidities,[9] status of hydration,[104] occurrence of an epidemic,[105,106] presence of dengue warning signs,[9] clinical acuity,[102,103] and socioeconomic status.[107] When trials are done in multiple jurisdictions in which both patient characteristics and hospital admission practices differ, hospital admission as an outcome is not a precise or reliable indicator of disease severity. Consequently, differences in disease severity based on the observed frequency of hospital admission should be interpreted with caution, particularly when comparing between regions. The use of dengue warning signs is also limited as a measure of disease severity, given that some warning signs are variably defined (eg, abdominal pain or lethargy), and the presence of warning signs does not clearly represent a true increase in disease severity.

Because appropriate clinical management can result in substantial decreases in both morbidity and mortality among patients with dengue,[41,108,109] patient outcomes can also be worsened by attitudes regarding seeking care for dengue-like illness, access to care, and biases in hospital admission of patients with dengue by age, sex, and other characteristics.[4,107] Patients' risk of developing clinically severe dengue is also affected by a variety of factors beyond their control, including the experience of medical personnel managing the patient and the availability of clinical and diagnostic resources, including intensive care facilities. In areas with poor health-care infrastructure or other societal disruptions that limit the patients' ability to receive appropriate medical care, dengue patient outcomes suffer and case fatality rates increase.[110] These variables, as well as infrastructure for case reporting,[13,44] hamper the comparison of the burden and epidemiology of clinically severe dengue between regions and over time and affect estimates of the global burden of dengue, disability-adjusted life years lost to dengue, and ultimately the effectiveness of vaccines and other interventions.

Conclusions

Although large cohorts to evaluate dengue vaccine efficacy have provided valuable insight into the epidemiology of dengue in endemic areas, major gaps in study methods and knowledge persist and preclude a thorough understanding of the epidemiology of

clinically severe dengue. These gaps include several factors: inconsistent use of case definitions; unknown generalisability and relative contribution of demographic, virological, immunological, genetic, and clinical characteristics on the risk of developing clinically severe dengue; unclear comparability of hospital admission rates between and within regions; and absence of generalisable data on the frequency of severe dengue and death due to dengue, which are the major drivers of the human and economic burden of dengue (table). Moving forward, use of uniform measures of disease severity, including case definitions and clinical endpoints, will provide the most reasonable measure by which to make comparisons.[111] Multi-partner consortiums should be formed to better elucidate the generalisable aspects of clinically severe dengue and identify key determinants of disease severity by combining and comparing data from paediatric and adult prospective cohort studies in multiple jurisdictions and by integrating these data with findings from facility-based enhanced surveillance.[112] Mathematical models combined with data from both seroprevalence and cohort studies will aid in estimating the parameters governing clinically severe dengue by explicitly incorporating the similarities and differences between cohorts and by including the uncertainty from different types of data.[66,113] As vaccines and other interventions likely to affect the intensity of DENV transmission are introduced, a thorough understanding of the factors affecting the occurrence of clinically severe dengue will be of increasing importance to assess and implement interventions for, and define progress in, reducing the disease burden resulting from DENV infection.

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Key messages

- A holistic understanding of the myriad factors that affect progression to clinically severe dengue is needed to optimise the design and evaluation of safe and effective vaccines, to reduce the morbidity and mortality of dengue.
- Multiple, oftentimes disparate, case definitions have been used to define patients with clinically severe dengue, which complicates the comparison of findings from diverse studies. To overcome this impediment in the field, clinical research studies, and specifically vaccine trials, should evaluate results using outcomes of both severe dengue and dengue haemorrhagic fever and dengue shock syndrome.
- Multiple disease manifestations constitute clinically severe dengue (eg, shock, haemorrhage, encephalitis, and myocarditis) that might arise from diverse pathophysiological pathways resulting from dengue virus (DENV) infection, which in turn are affected by factors specific to the individual, virus, and population. Combined, these pathways and the diverse factors that contribute to them obscure both the incidence and causes of clinically severe dengue.
- Although previous infection with a heterologous DENV is the best characterised risk factor for developing severe dengue, currently, there is only a nascent understanding of the complex interplay between disease severity and transmission intensity, including both the timing between infections and sequence of infections.
- Hospital admission is a frequently used but unreliable indicator of patients with clinically severe disease. Prospective cohort studies of children and adults in geographically diverse settings are needed to better elucidate the diverse factors that contribute to clinically severe dengue, which in turn will improve both the design and the evaluation of dengue vaccines.

Panel 1:

Factors associated with clinical severity of disease resulting from dengue virus (DENV) infection

- Age (eg, infants, children, and older people)[13,25]
- Previous DENV infection[12,26]
- Sequence of DENV infections[19,27]
- Pre-existing intermediate titres of anti-DENV antibodies[14,15,28]
- Timing between DENV infections[14,29,30]
- Infecting DENV (both serotype and genotype)[18-22]
- Magnitude of viraemia[31-33]
- Comorbidities (eg, asthma, diabetes, obesity, and cardiac disorders)[34,35]
- Sex[13,36,37]
- Pregnancy[38,39]
- Nutritional status[36,40]
- Host genetics and race[23,24]
- Quality of clinical care[41]
- Immunocompromised[42]

Panel 2:

Dengue clinical* case definitions as established by WHO in 1997 and 2009

WHO 1997

Dengue fever:

- Fever, along with at least two of the following:
  - Headache
  - Retro-orbital pain
  - Myalgia
  - Arthralgia
  - Rash
  - Haemorrhagic manifestations
  - Leukopenia

Dengue haemorrhagic fever:

- Fever or history of fever lasting 2–7 days
- Haemorrhagic tendencies, including at least one of the following:
  - Positive tourniquet test
  - Petechiae, ecchymoses, or purpura
  - Bleeding from the mucosa, gastrointestinal tract, injection sites, or other locations
  - Haematemesis or melena
- Thrombocytopenia (≤100 000 cells per μL)
- Evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following:
  - An increase in haematocrit equal to or greater than 20% above average for age, sex, and population
  - A decrease in haematocrit following volume replacement treatment equal to or greater than 20% of baseline
  - Signs of plasma leakage, such as pleural effusions, ascites, and hypoproteinaemia

Dengue shock syndrome:

- All four criteria for dengue haemorrhagic fever, plus evidence of circulatory failure manifested by:
  - Rapid and weak pulse and narrow pulse (<20 mmHg); OR

- Hypotension for age, cold, clammy skin, and restlessness

WHO 2009

Dengue:

- Fever, and two of the following:
  - Nausea, vomiting
  - Rash
  - Aches and pains
  - Tourniquet test positive
  - Leukopenia
  - Any warning sign

Dengue with warning signs:

- Meet criteria for dengue, plus any of the following:
  - Abdominal pain or tenderness
  - Persistent vomiting
  - Clinical fluid accumulation
  - Mucosal bleed
  - Lethargy, restlessness
  - Liver enlargement (>2 cm)
  - Increase in haematocrit concurrent with rapid decrease in platelet count

Severe dengue:†

- Meet criteria for dengue, plus any of the following:
  - Severe plasma leakage leading to:
    - Shock
    - Fluid accumulation with respiratory distress
  - Severe bleeding, as evaluated by clinician
  - Severe organ involvement:
    - Liver: aspartate transaminase or alanine aminotransferase more than or equal to 1000 units
    - CNS: impaired consciousness
    - Heart or other organ

* Completion of full case definitions also require completion of relevant epidemiological and laboratory criteria not specified here. †Refined by Tomashek and colleagues.[65]

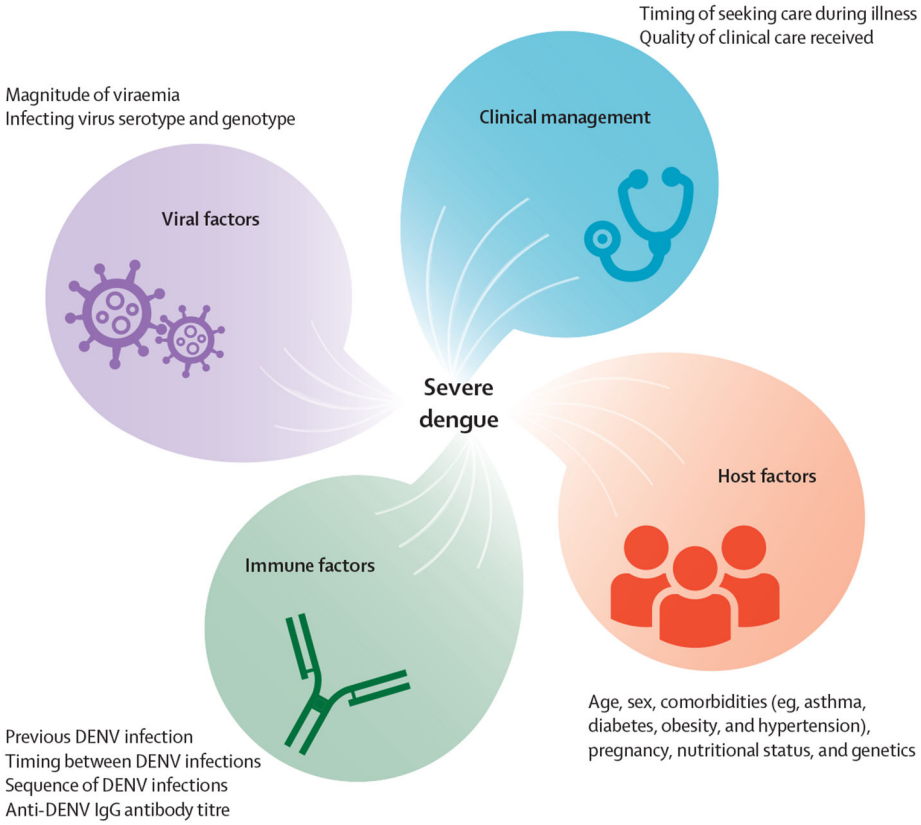

Figure: Factors for which epidemiological evidence has shown an association with the clinical severity of disease resulting from DENV infection

DENV=dengue virus.

Table:

Knowledge gaps in the epidemiology of clinically severe dengue

	Relevance	Challenges	Next steps
How best to implement use of uniform measures of disease severity?	Comparability of study findings and burden of dengue in different jurisdictions.	Disagreement in the field regarding if separate or unified definitions should exist for clinical management, case classification, and research studies.	Definitions for research studies should differentiate between complications of DENV infection and exacerbation of underlying illnesses to appropriately measure patient outcomes.
What is the frequency of the different manifestations of clinically severe dengue (eg, shock *vs* haemorrhage *vs* encephalitis *vs* myocarditis)?	Although shock and haemorrhage are the most common manifestations, the relative frequency of the other manifestations has not been defined. Evaluation of vaccine safety will necessitate an appropriate capture of clinically severe dengue in all populations.	Large sample sizes are needed to reliably capture and describe the frequency of uncommon events, such as clinically severe dengue. Less common manifestations might be more common in individuals with comorbidities.	Multi-year, multi-centre study from sites managing large numbers of patients with clinically severe dengue. Case-control study to compare patients with uncommon manifestations of clinically severe dengue to matched patients with non-severe dengue.
What demographic and epidemiological variables affect progression to clinically severe dengue?	Many factors have been identified, but few have been consistently identified across studies. Manifestations of clinically severe dengue might differ by age, sex, serostatus, genetic backgrounds, and infecting DENV serotype and genotype; comorbidities (eg, asthma, diabetes, and obesity) increase risk of severe dengue, but it is unclear how. Co-infection might increase disease severity, particularly in patients who are admitted to hospital. Unclear if or how factors interact. Mechanism of pathogenesis are not fully understood, complicating vaccine design and evaluation.	Severe dengue is an uncommon occurrence. Diagnostic testing for co-infection might not be feasible in or done on patients with dengue. Enrolling a sufficient number of individuals to evaluate outcomes while controlling for interactions is prohibitive.	Combine data from studies in various settings after ensuring equivalent collection and definition of relevant variables. Develop outbreak protocols to systematically address these issues.
How does disease severity affect care-seeking, hospital admission, and detection by surveillance?	Case surveillance is often biased by severity of disease. Surveillance in many jurisdictions is the sole indicator used to estimate burden of disease, disability-adjusted life years lost to dengue, and potential vaccine impact.	Modifying surveillance is both infeasible and will probably affect analysis of long-term trends. Collection of community-based data is resource-intensive.	Conduct enhanced surveillance to better define the frequency of clinically apparent dengue, which might be used as a jurisdictional multiplier. Conduct rapid community-based surveys during epidemics to estimate frequency with which individuals with dengue seek care, are admitted to hospital, and are identified by surveillance.
Can hospital admission be used as a proxy for clinically severe dengue?	Hospital admission is a more common outcome and easier to document than clinically severe dengue. Hospital admission is an important measure for vaccine evaluation.	Hospital admission practices can differ widely between and within jurisdictions.	Evaluate data from individual settings to determine if trends in clinically severe dengue are reflected by those of patients with dengue who have been hospital admission.

DENV=dengue virus.