Dengue

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Dengue, caused by four closely related viruses, is a growing global public health concern, with outbreaks capable of overwhelming health-care systems and disrupting economies. Dengue is endemic in more than 100 countries across tropical and subtropical regions worldwide, and the expanding range of the mosquito vector, affected in part by climate change, increases risk in new areas such as Spain, Portugal, and the southern USA, while emerging evidence points to silent epidemics in Africa. Substantial advances in our understanding of the virus, immune responses, and disease progression have been made within the past decade. Novel interventions have emerged, including partially effective vaccines and innovative mosquito control strategies, although a reliable immune correlate of protection remains a challenge for the assessment of vaccines. These developments mark the beginning of a new era in dengue prevention and control, offering promise in addressing this pressing global health issue.

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Introduction

Dengue is a systemic viral infection of increasing global importance. Epidemics of an illness compatible with dengue were first reported[1] in 1779 and the virus was first isolated in 1943.[2] Currently, dengue is endemic in more than 100 countries in tropical and subtropical regions of southeast Asia, Africa, the west Pacific, and the Americas.[3] Dengue is also seen in some regions of Europe, including France, Croatia, Portugal, and Germany, and some parts of the USA. Climate change, population growth, human mobility, and urbanisation are anticipated to exacerbate the dengue burden, primarily by increasing risk in endemic areas, as well as secondarily by expanding the range of the primary vector, *Aedes aegypti* mosquitoes, into new areas.[4] Studies predict that the global population at risk will increase from 53% in 2015, to 63% in 2080, with high environmental suitability for dengue in tropical and subtropical areas worldwide (figure 1).[5]

Dengue has an important economic impact, resulting in estimated global health-care costs of more than US$8·9 billion (95% CI 3·7 billion–19·7 billion) annually.[6,7] High costs are associated with loss of productivity, and direct medical costs are incurred from hospitalisation.[8,9] Dengue outbreaks can overwhelm health-care systems, disrupt economies, and reduce public confidence in government responses. Many commonly used vector control strategies, such as insecticide spraying, have failed to curb disease incidence but continue to be employed in the absence of robust evidence for their effectiveness or optimal implementation.[10] However, increased understanding of dengue epidemiology and immune mediators of symptomatic and severe disease, as well as the availability of effective clinical management, partially effective vaccines, candidate vaccines in the pipeline, and novel approaches to mosquito control, have the potential to inform and substantially improve the effectiveness of dengue control programmes.

Dengue viruses

DENV-1, 2, 3, and 4 are single-stranded RNA viruses in the genus *Flavivirus*, family Flaviviridae. *Flavivirus* includes other viruses transmitted by mosquitoes and ticks, such as Zika, West Nile, Japanese encephalitis, and tick-borne encephalitis viruses. The four dengue viruses are called serotypes because each has different interactions with the antibodies in human blood.[2] They share approximately two-thirds of their genomes,[2] with different genotypes existing within each serotype, which can vary in disease severity. DENV is primarily transmitted through the bite of an infected mosquito vector, with *Aedes aegypti* as the most common vector, although other species (eg, *Aedes albopictus*) can also sustain transmission. Other rare transmission routes include perinatal transmission, blood transfusion, and organ transplantation; two cases of sexual transmission have also been documented.[11–15] The incubation period from exposure to symptom development is typically 4–10 days.[16]

Epidemiology

The global burden of dengue illness has continued to rise throughout the past decade, with large outbreaks in endemic areas and more cases of dengue in travellers. During 2007–17, deaths from dengue increased by 65·5% to more than 40 500 (95% CI 17 600–49 800) annually.[17] Expansion of *Aedes* mosquito vectors and increasing dengue incidence in non-endemic areas is also a growing concern. New detections of local dengue transmission in areas without previous transmission and increased cases in areas with sporadic transmission have been documented in southern Europe and the USA, as well as unprecedented outbreaks at high altitudes as seen in Nepal.[18–20] Additionally, more DENV serotypes are cocirculating in endemic areas, producing

Search strategy and selection criteria

We searched PubMed for papers published between Sept 30, 2012, and Oct 10, 2022. We used the search terms "dengue" or "dengue virus". We also included references cited in these publications and relevant older references from our personal files. We consulted international dengue control, prevention, and treatment guidelines and WHO policy documents.

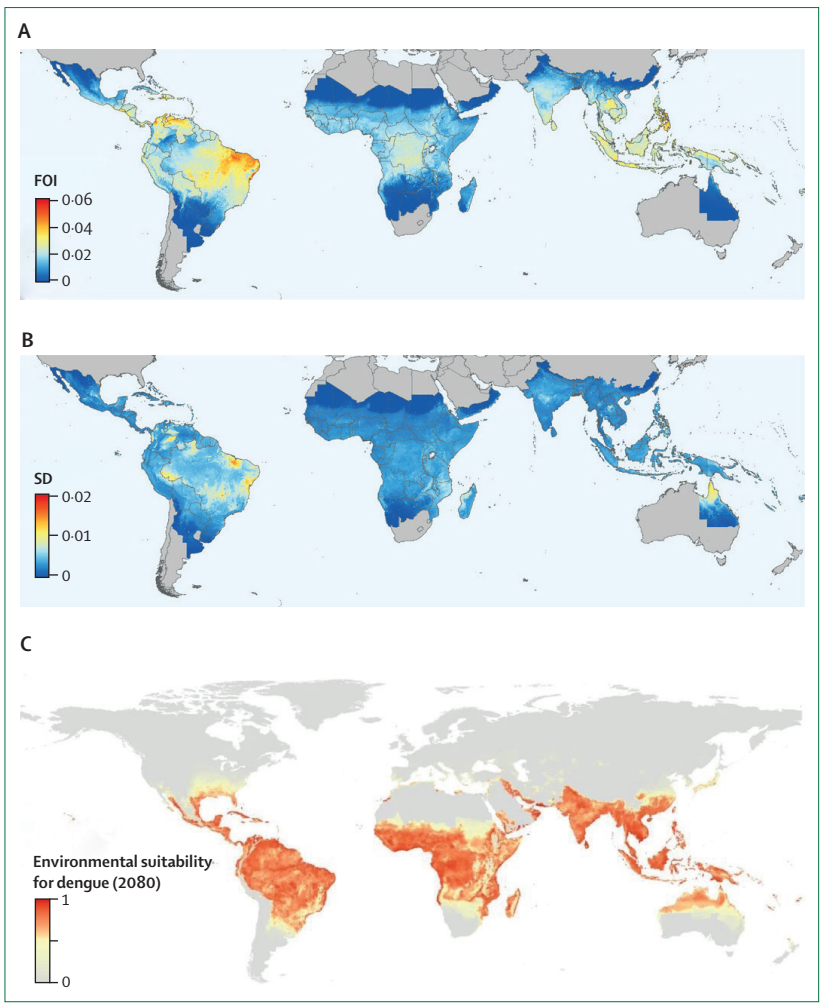

Figure 1: **Predicted global dengue risk**
Means (A) and standard deviations (B) of FOI estimates in dengue-endemic countries across 200 geographically stratified bootstrap samples. Average FOI was estimated from age-stratified seroprevalence or case notification date by use of environmental explanatory variables. Modified from Cattarino et al,[3] by permission of the American Association for the Advancement of Science. (C) Environmental suitability for dengue occurrence in 2080. Adapted from Messina et al.[5] FOI=force of infection.

increased case numbers and greater probability of severe disease from serotype re-introduction or replacement.[21]

DENV seroprevalence estimates vary widely across countries and regions, shaped by differences in underlying DENV transmission intensity and differences in methods and assays applied. High IgG antibody seroprevalence (>60%) has been reported in highly endemic areas in southeast Asia and the Americas; mid-range (10–60%) seroprevalence in areas with frequent or sporadic transmission, such as many countries in Africa and the Middle East; and low seroprevalence in non-endemic areas, such as the USA and Europe.[22] Vaccine trials have revealed high variability in DENV incidence across study sites in Latin America and Asia, ranging from 1·5 to 6·6 episodes of symptomatic dengue per 100 person-years among children aged 2–16 years.[23] The estimated force of infection (FOI), which is the per capita rate at which susceptible individuals become infected, similarly varies by region, with the highest FOI observed in areas near the tropics (figure 1). However, FOI estimates are restricted by surveillance data availability and temporal and interannual variability in dengue incidence.[3]

Risk of infection is driven by susceptibility to the four DENV serotypes; therefore, DENV incidence in hyperendemic locales is concentrated in children and young adults.[24] The average age of infection in these areas has been increasing in the past 3·5 decades, for reasons such as a decrease in the FOI due to changes in the population age structure,[25] effective vector control,[26] or possibly increased awareness and diagnosis of dengue in adults. In areas hyperendemic for DENV transmission, the risk for enhanced disease has been suggested to be concentrated within two age-related peaks: the first in infants, with possible contributions from waning maternal antibodies[27–29] and the second in individuals experiencing a second DENV infection. Dengue haemorrhagic fever has not yet been described in an infant born to a dengue-naive mother, strongly suggesting that maternal anti-DENV antibodies contribute to dengue haemorrhagic fever pathogenesis in infants. However, further studies of infants with severe dengue are needed to unequivocally show that maternally derived anti-DENV antibodies are an important risk factor for severe disease in infants.[30] Delayed diagnosis or detection of shock can lead to an increased risk of severe disease and death; this risk has also been shown to be higher for people with comorbidities, such as diabetes or pulmonary, heart, or renal disease, than for healthy individuals. A meta-analysis suggests that the relative risks of severe dengue associated with underlying chronic diseases and comorbidities could be much higher than that of secondary infection alone.[31]

Disparities in dengue risk have been identified, with increased risk occurring in areas with high population density and poor housing conditions.[32,33] Increasing population mobility and tourism have also been linked to increased dengue transmission, and imported DENV cases have led to outbreaks in non-endemic areas.[34] DENV transmission occurs commonly within and around households, with a potential increased risk among people in endemic areas who stayed near the home compared with people with greater mobility.[35,36] However, COVID-19-related disruptions and lockdowns in 2020 were found to result in a decrease in dengue incidence across endemic regions, with the strongest associations related to school closures and reduced time in non-residential areas, although changes in health-care access could have also contributed to the reduced case numbers reported.[37]

Dengue is the most frequent arboviral disease encountered among travellers, with an increasing global

pattern during 1995–2020.[38] Among travellers to southeast Asia in this period, incidence ranged from 50 dengue cases per 1000 ill travellers who sought care in the Geosentinel network of travel medicine providers during non-epidemic years, to 159 cases per 1000 ill travellers in epidemic years.[38] Although severe dengue often occurs during second infections in dengue-endemic regions, primary dengue infections can also be severe and result in fatal outcomes, which has been documented among travellers without previous dengue infection.[39] Additionally, asymptomatic infections have been reported to occur among travellers to dengue-endemic areas in a ratio of approximately 4:1, creating risks for the introduction of dengue viruses or novel serotypes from asymptomatic people into areas with competent mosquito vectors.[40]

Classification and clinical course

Dengue is a self-limiting acute febrile illness with non-specific manifestations. Among people infected with DENV, approximately 60–80% are asymptomatic or have subclinical infections, with increased risk of disease in secondary infection particularly among those with longer intervals since the previous DENV infection.[41,42] WHO guidelines previously classified symptomatic dengue virus infections as dengue fever, dengue haemorrhagic fever (DHF), or dengue shock syndrome (DSS). However, revised WHO guidelines in 2009 (panel 1) classified symptomatic dengue as dengue without warning signs, dengue with warning signs, or severe dengue (figure 2).[16,41,42]

Symptomatic dengue generally follows the clinical course of febrile, critical, and recovery phases (figure 3).[16,61] During the febrile phase, which lasts from 2 days to 7 days, an acute onset of high-grade fever (≥38·5°C) will typically occur; this fever can be accompanied by nausea, vomiting, a transient macular rash, aches, pains, and other constitutional symptoms.[16] The mucocutaneous manifestations of dengue are varied and can include transient facial erythema, petechial rash, conjunctival and scleral injection, and a maculopapular or morbilliform eruption 3–6 days after the onset of fever that can coalesce but with areas of sparing.[65] The tourniquet test[66] can be positive and minor bleeding, such as skin petechiae or bruises, can occur.[67] Most commonly, fever resolves and is followed by the recovery phase; in these cases, the illness would be categorised as uncomplicated dengue.

Some patients with dengue experience the critical phase, which generally occurs around days 4–6 of illness and often coincides with defervescence.[16,68] The hallmark of severe dengue is plasma leakage, when the blood's protein-rich fluid component flows from blood vessels into surrounding tissue, which can lead to shock and is sometimes associated with haemorrhage.[69,70] Some evidence shows that less severe capillary leakage might be more common in clinically diagnosed uncomplicated dengue than previously recognised.[71] Plasma leakage becomes clinically apparent near the time of defervescence and spontaneously improves after about 48–72 h.[72] Warning signs of possible clinical deterioration can precede the critical phase of dengue and can be used to detect disease progression, including abdominal pain or tenderness, persistent vomiting, clinically detectable extravasal fluid accumulation, mucosal bleed, lethargy or restlessness, liver enlargement, and an increase in haematocrit usually concurrent with a rapid decrease in platelet count (figure 3).[16,46] If the patient improves and recovers, the illness is classified as dengue with warning signs. However, the disease could continue to advance towards severe dengue, which occurs in approximately

***Panel 1*: The 1997 versus the 2009 WHO dengue classification and case definitions**

- The 1997 WHO classification and case definitions of dengue, dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS)[43] originated from a clinical study in the 1960s of 123 children in Thailand.[44] A case definition of DHF is met when all four criteria of fever, haemorrhagic manifestations, thrombocytopenia, and evidence of plasma leakage are present. DHF has four increasing grades of severity towards DSS (grades III and IV). A definition of DHF is required to classify cases as DSS (ie, DHF plus circulatory failure). The 1997 WHO classifications offer distinct advantages for research studies, as the clinical phenomena described relate to underlying mechanisms of immunopathogenesis (ie, antibody-dependent enhancement) and could guide treatment pathways (eg, the timing and degree of fluid replacement with plasma leakage). Disadvantages of the 1997 criteria include failure to capture severe disease beyond DHF (eg, cardiac or hepatic end-organ damage) and poor capacity to facilitate the triage of patients with dengue. The WHO regional office for southeast Asia proposed the term expanded dengue syndrome to describe cases with atypical yet serious manifestations.[45]
- The 2009 WHO classification system evolved to facilitate triage and management of patients with dengue,[46] and to capture a broader spectrum of dengue-related disease. Individuals are classified as having dengue, dengue with warning signs, and severe dengue.[16]
- The 2009 WHO criteria have been widely implemented to guide dengue clinical management decisions, but they have also been criticised due to the broad recommendations for hospitalisation of patients with dengue warning signs. Multiple studies indicate the general approach of hospitalising for dengue with warning signs, as per the 2009 WHO criteria, could increase the identification of individuals who will progress to severe disease (ie, through improved sensitivity of the criteria), at the expense of increasing hospitalisation of individuals who will not progress to severe disease.[47,48] The positive predictive value of individual warning signs for severe dengue has been reported to range from 12% to 58%, with some warning signs (eg, clinical fluid accumulation) having better values than others.[49] The availability and increasing use of dengue rapid diagnostic tests could facilitate the use of the 2009 simpler dengue classification scheme. However, rapid diagnostic tests are not available in most endemic countries. More precise definitions of the 2009 warning signs and severe dengue are needed, as are improved risk prediction tools for clinical and research use.[50–53]
- The 2009 classification of dengue without warning signs, dengue with warning signs, and severe dengue[16] has been adapted in several countries and international guidelines,[54–57] while the 1997 dengue, DHF, and DSS classification[43] continues to be used in others.[58–60]

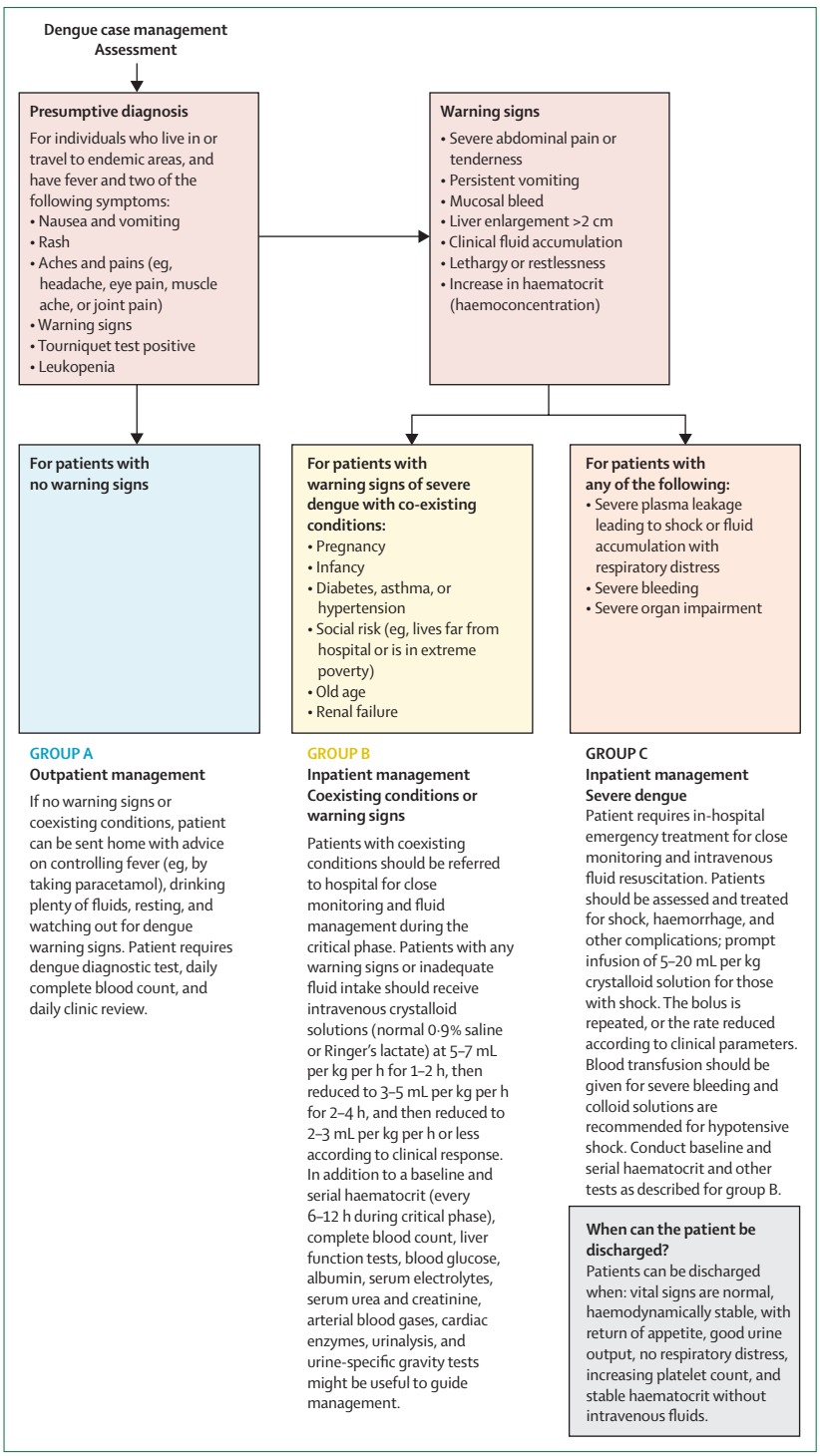

Figure 2: **Dengue clinical course, classification, laboratory abnormalities, and management**
Adapted from WHO's *Handbook for Clinical Management of Dengue*.[61]

2–5% of patients.[46,73] Rates of progression to severe disease are highly variable by age, underlying comorbidities, clinical resources, expertise in managing dengue, and possibly the infecting DENV serotype and genotype.[46]

The median case fatality rate for patients with dengue is 5% (range 0·01–39%).[74] The criteria for severe dengue include: severe plasma leakage leading to shock or to fluid accumulation with respiratory distress, severe bleeding as evaluated by a clinician, and severe organ involvement including the CNS, heart, or liver (indicated by an aspartate aminotransferase or alanine aminotransferase concentration of 1000 international units per litre or more).[16] Shock is signalled by a rising haemoconcentration followed by an increase in diastolic pressure with narrowing pulse pressure, rapid pulse, restlessness, hypotension, signs of poor peripheral perfusion (eg, cold extremities and slow capillary refill time), and reduced urinary output. Repeat shock episodes might occur during the critical phase.[75] Circulatory compromise is generally worse in the extremes of age; in children (age ≤18 years), this is probably due to increased vascular permeability and a reduced capacity to maintain cardiovascular homoeostasis, while factors in older people (age ≥60 years) include comorbidities and vascular ageing.[76] Epistaxis, gum bleeding, hypermenorrhoea, haemoglobinuria, and other haemorrhagic manifestations are most often seen during the critical phase.[67] The risk for severe bleeding (eg, from the gastrointestinal or vaginal tract) increases in profound or prolonged shock, in association with coagulation abnormalities combined with tissue hypoxia and acidosis.[77]

Involvement of other organ systems can also occur during the various phases of dengue. Hepatitis and elevated liver enzymes are common among patients with symptomatic dengue, but acute liver failure, encephalitis, myocarditis, and acute kidney injury are infrequent.[78–81] Sight-damaging ophthalmic inflammation during dengue has also been described.[82] Dengue during pregnancy has implications for the mother. A greater risk of DHF and DSS has been reported among pregnant women compared with non-pregnant women,[83] as well as an increased risk of maternal death.[84,85] Dengue also poses a risk to the fetus, with an increased risk of miscarriage,[86] stillbirth, and neonatal death.[85]

During the recovery phase of dengue, extravasated fluids are resorbed and wellbeing improves. The patient could develop an erythematous—sometimes pruritic—Herman's rash with white islands of normal skin.[87] In adults, postviral fatigue and depression for several weeks to months have been described.[88]

Most patients with dengue recover without difficulty, but promptly recognising people who will require medical intervention is essential. A systematic review showed that warning signs were associated with progression to severe dengue but identified potential additional markers, including low serum albumin and elevated aspartate aminotransferase and alanine aminotransferase concentrations.[31] Thrombocytopenia is also commonly seen in patients with dengue, and reduced platelet counts have been associated with progression to severe disease.[31] Ultrasonography can be used to detect plasma leakage in

dengue.[89] Ascites, pleural effusion, and gallbladder wall thickening are the most common findings, but standard protocols for sonographic procedures and improved information about the positive predictive value of early and low-volume plasma leakage for development of severe dengue are needed.[90,91] Investigations are ongoing to establish whether inflammatory and vascular markers in the febrile phase of dengue could be useful to predict severe outcomes.[92,93]

Dengue management

Currently, no effective prophylactic or therapeutic agent against dengue exists.[94] Chloroquine, balapiravir, celgosivir, lovastatin, corticosteroids, ivermectin, plasma infusion, recombinant activated factor VII, anti-D globulin, immunoglobulin, and IL-11 have not been shown to be beneficial.[95–97] However, clinical trials are restricted by small sample sizes, heterogeneous populations, and difficulties in assessing outcomes, and additional work is needed to thoroughly assess potential benefits of these agents. A randomised controlled trial of montelukast, a leukotriene receptor antagonist used to reduce asthma exacerbation, is ongoing among adult patients with dengue to evaluate its efficacy in preventing dengue with warning signs (NCT04673422). The small molecule, JNJ-A07, which blocks the intracellular replication of DENV, has shown promise in preclinical studies.[98] Preclinical studies of therapeutic monoclonal antibodies against dengue are also ongoing.[99]

In the absence of specific therapy, the management of dengue remains supportive. The 2012 WHO handbook,[61] since adapted to other guidelines,[54,100] focuses on a stepwise approach of assessment and treatment according to groups A, B, and C (figure 2). Group A patients (ie, people with no warning signs, comorbidities, or difficult social circumstances) are sent home with daily in-person monitoring. Groups B (patients with comorbidities or warning signs) and C (patients with severe dengue) require hospital management and intravenous fluids (figure 2).[55] Fluid replacement is lifesaving in severe dengue but must be administered cautiously and discontinued when plasma leakage subsides to avoid iatrogenic fluid overload.[101] Among patients with thrombocytopenia, prophylactic platelet transfusion does not prevent bleeding and could contribute to fluid overload.[102,103] Although these guidelines are based mainly on expert opinion and small randomised controlled trials,[104–107] case fatality rates have been considerably reduced with judicious fluid replacement. Some areas of uncertainty remain, such as in the choice of colloid solution and blood products, the use of fluid boluses, and the optimal treatment of recurrent shock episodes. Steroid use is not recommended as it has not shown clinical benefit.[76,95] Training in clinical management, including early recognition of plasma leakage, remains an essential strategy to reduce morbidity and mortality.

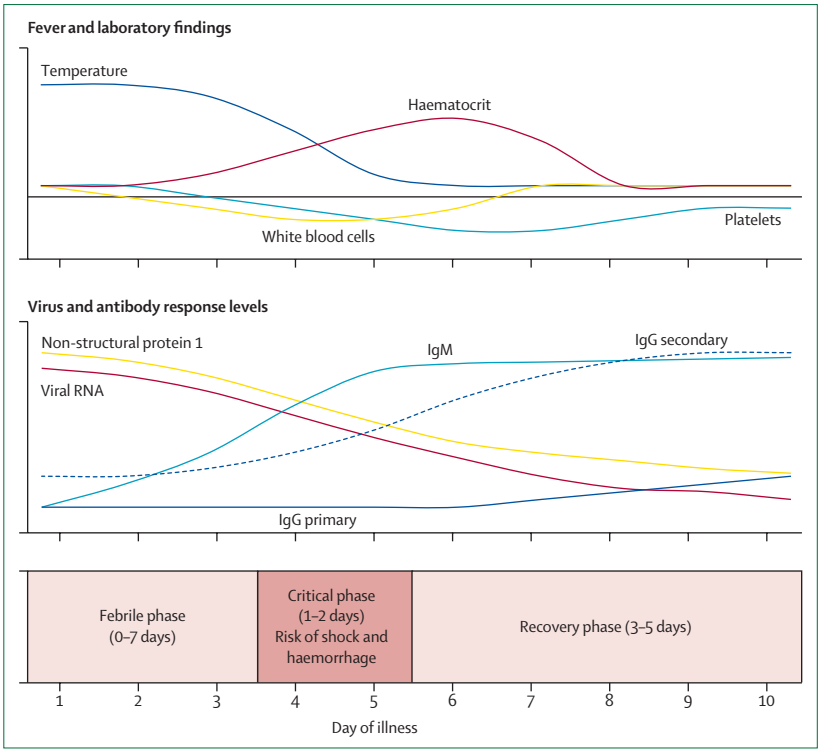

Figure 3: **Dengue laboratory findings, virus detection, and immune response**
Data from WHO's dengue guidelines for diagnosis, treatment, prevention, and control,[16] Hunsperger et al,[62] Chaloemwong et al,[63] and Dussart et al.[64]

Dengue diagnosis

The differential diagnosis of dengue is broad. During the febrile phase, it includes other viral infections (eg, measles, rubella, enterovirus, adenovirus, influenza, and other arboviruses), and bacterial (leptospirosis and typhoid fever) and parasitic (malaria) illnesses that might be present in dengue-endemic areas.[108] A diagnosis of dengue infection during the acute phase can be made with whole blood, plasma, or serum collected up to 7 days after symptom onset by detection of viral RNA through nucleic acid amplification tests (NAAT),[109] detection of viral antigens such as dengue non-structural protein 1 (NS1), enzyme-linked immunosorbent assay (ELISA), rapid diagnostic tests, and detection of IgM antibodies from day 4 to approximately 12 weeks post-onset through serological testing (figure 3).[110] NAAT assays are the preferred method of dengue diagnosis;[109] in addition to their diagnostic specificity, molecular methods can be used to identify the virus serotype.

NS1 can be detected in other bodily fluids such as urine, saliva, and cerebrospinal fluid.[111] NS1 tests can be as sensitive as molecular tests during the first 7 days of symptoms in primary infections, although sensitivity is lower in secondary infections; after seven days, although sensitivity is reduced, NS1 has been detected in serum up to 12 days post symptom onset.[111,112] Dengue IgM antibodies are detectable for a longer period, from day 4 to approximately 12 weeks post symptom onset.[113] Dengue

IgG is detectable around day 7 in primary infections; the antibody concentration increases slowly thereafter and is thought to persist for life. In patients with secondary infections, anti-dengue IgG titres rise rapidly within the first week of illness (figure 3). Although serological assays provide less certainty than NAAT or NS1 due to cross-reactivity with other flaviviruses and longer antibody duration, a positive anti-DENV IgM suggests recent infection (within the past 12 weeks). Additionally, seroconversion or a four-fold rise in titres on anti-DENV IgM or IgG assays in paired samples is strongly suggestive of recent infection.[113] Many rapid tests are available and are an important tool for the early diagnosis of dengue. Meta-analyses suggest that immunochromatographic tests that combine IgM, IgG, and NS1 detection have the best performance compared with tests detecting individual analytes, with pooled sensitivity of 90–91% and specificities of 89–96%.[114,115] Unfortunately, these tests are not widely available in dengue-endemic areas. In patients from areas in which transmission of other flaviviruses is common, plaque reduction neutralisation tests (PRNT) can help distinguish DENV from other flaviviruses. PRNTs, however, are rarely available in clinical laboratories and typically do not provide results within a meaningful timeframe for clinical management. PRNTs might be valuable in circumstances such as pregnancy, when differentiating between Zika virus (ZIKV) and dengue could have important clinical implications.[110] NS1 antibody ELISA tests for ZIKV have high specificity due to the substantial amino acid differences between DENV and ZIKV NS1, and can be useful for differential diagnosis.[111]

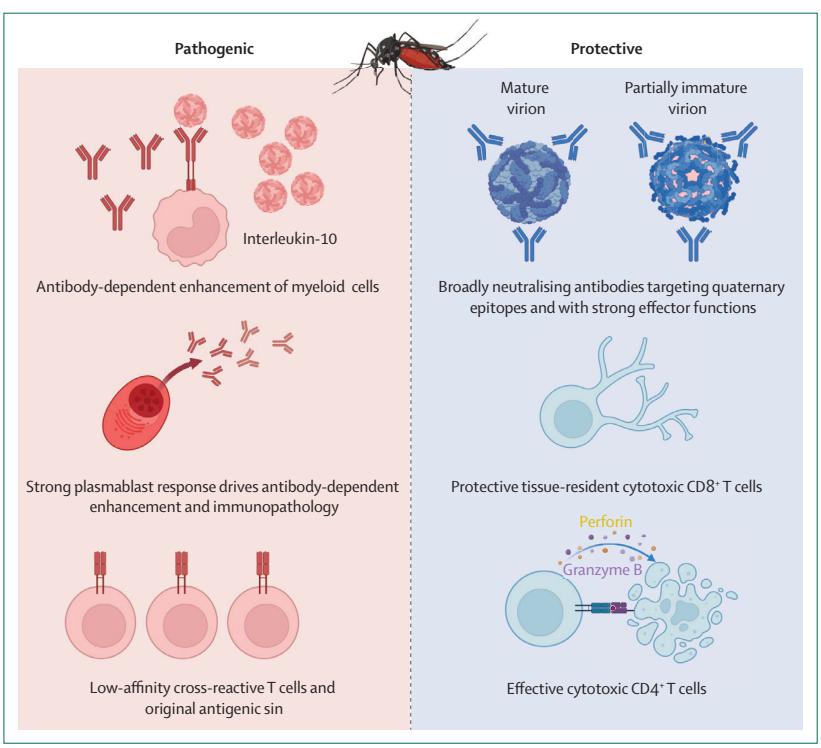

Figure 4: **Correlates of dengue pathogenesis and protection**
Types of immunological responses associated with increased dengue disease (a pathogenic response, generally during a secondary infection, is associated with antibody-dependent enhancement of myeloid cells,[117–119] strong plasmablast response,[122–124] and weak T-cell response[125]) or reduced disease (a protective response is associated with broadly neutralising antibodies[126,127] and effective, cytotoxic CD8+ and CD4+ T cells[128–131]). Figure created with BioRender.com.

Dengue immunology

DENV infection is initiated in the skin when an infected mosquito takes a bloodmeal, injecting the virus along with salivary proteins that increase recruitment of susceptible immune cells to the site of infection.[116] Myeloid cells are a key target of DENV infection, including monocytes, macrophages, and dendritic cells. A first DENV infection results in an early innate response characterised by stimulation of interferon gamma (IFNγ). By contrast, in subsequent DENV infections, binding (but not neutralising) antibodies induced by previous exposure to DENV (or a related flavivirus) facilitate infection of myeloid cells via the fragment crystallisable gamma receptor (FcγR), producing a larger population of viruses and further exacerbating disease severity in a process called extrinsic antibody-dependent enhancement (ADE).[117–121] Entry via the FcγR also mediates intrinsic ADE, which suppresses IFNγ stimulation and innate immunity and shifts towards a T-helper-2 response dominated by secretion of IL-10, minimising induction of other proinflammatory cytokines and hindering the early cellular and humoral immune response (figure 4).[117] ADE is thought to increase replication of the virus at this key early stage and elevate the risk of progression to severe dengue, DHF, and DSS.[132,133] However, although pre-infection binding antibody concentrations are associated with increased viremia and risk of DHF and DSS, the causal link from ADE to elevated viremia to DHF or DSS has not been shown.[120]

Mediators of severe disease

$CD14^+CD16^+$ monocytes increase in early DENV infection[122,134] and help to trigger a strong plasmablast response characterised by secretion of high concentrations of anti-DENV antibodies.[122,134] The role that excess antibody production has in acute dengue is not clear, but could contribute to disease pathogenesis by furthering ADE, increasing autoantibodies, and potentially changing glycosylation of antibodies, which is strongly associated with DHF and DSS.[123,124] DENV can also directly infect B cells, and although B-cell infection does not substantially contribute to viremia, it does drive proliferation of B cells and stimulation of cytokines.[135] Elevated viral load might also mediate severe disease by increasing secretion of NS1. In in-vitro and animal models, NS1 concentrations directly and indirectly trigger vascular leakage, disrupting the glycocalyx and tight junctures between endothelial cells lining blood vessels and further facilitating plasma leakage and dissemination of virus into tissue.[136] However, the association between NS1 concentrations and severe disease

has not been clearly shown in clinical studies.[69] Severe dengue is also associated with liver and spleen pathology, with autopsies revealing DENV tropism for liver macrophages (ie, Kupffer cells) and splenic macrophages, which secrete high amounts of cytokines and mediate damage due to deposition of complement, resulting in necrosis in liver and splenic endothelial cells.[137]

T-cell responses

The role of DENV-specific T cells has been debated, as they have been implicated in both pathogenic and protective immunity (figure 4). With regard to a pathogenic role, $CD8^+$ T cells induced by previous DENV infection have been shown to have low affinity for the new infecting serotype, proliferating but with little cytotoxic function, which results in delayed viral clearance and stimulation of proinflammatory cytokines that mediate leakage and disease.[125] However, other studies suggest a protective role, with increased magnitude and more multifunctional, cytokine-producing DENV-specific $CD8^+$ T-cell responses and specific human leukocyte antigen (HLA) alleles associated with reduced viremia, and lowering the probability of progression to symptomatic disease and severe dengue.[128–130]

DENV-specific $CD4^+$ cells promote $CD8^+$ T cells and stimulate B cells. Individuals with multiple previous DENV exposures have populations of clonally expanded cytotoxic $CD4^+$ cells that could be protective.[131] By contrast, although T follicular helper (Tfh) cells are crucial for facilitating maturation of the B-cell response, Tfh expansion in acute dengue has been associated with secondary and severe dengue and a strong plasmablast response, suggesting a possible role in immunopathology.[138,139]

DENV serotypes and post-secondary DENV antibodies

Although all DENV serotypes can result in symptomatic or severe disease, differences have been identified in risk by serotype and infection number (ie, primary or secondary). DENV-2-associated and DENV-4-associated dengue illnesses are more frequently identified as secondary DENV infections, whereas DENV-1 and DENV-3 can cause frequent primary disease.[140–142] DENV-4 has been associated with a reduced risk of disease compared with the other serotypes, as shown by observations of silent DENV-4 epidemics in Thailand.[143] All sequences of infecting serotypes can cause severe disease and no defined order in the sequence of DENV infections for worse outcomes exists, although different patterns have been described.[144,145] Antigenic differences between serotypes could be important in explaining the magnitude of dengue epidemics,[146–148] and viral sequence, genotype, and changes in non-structural proteins could also help establish epidemic severity.[149,150]

Sequential infection with distinct DENV serotypes induces antibodies capable of neutralising DENV-1–4 without triggering ADE, probably by activating cross-reactive memory B cells to undergo further affinity maturation and target quaternary epitopes conserved across serotypes, therefore providing broad protection. High concentrations of cross-reactive binding antibodies and multiple previous DENV infections are associated with reduced risk of symptomatic disease.[132,143,151] Consistent with this observation, the Dengvaxia and Qdenga dengue vaccines have high efficacy against symptomatic and severe disease in DENV-immune individuals but not naive individuals, further suggesting that sequential exposure to distinct DENV strains is important for inducing broad protection.[152,153] A few post-secondary broadly neutralising antibodies have been identified, such as envelope-dimer-dependent epitope (EDE) antibodies. These antibodies target conserved quaternary epitopes and neutralise by disrupting the conformational changes required for viral entry.[126,127] EDE-like broadly neutralising antibodies might be useful correlates of protection for the evaluation of new dengue vaccines.

Dengue vaccines

The need for a tetravalent formulation that induces simultaneous and balanced protection against all four serotypes has slowed the development of a dengue vaccine. Among people with a previous DENV infection, even a vaccine dominated by one serotype is likely to induce cross-protective immunity by activating memory B and T cells. However, in DENV-naive individuals with no immune memory, the protective immune response will strongly depend on the immunogenicity of each serotype-specific vaccine component.[154]

There are currently three leading dengue vaccines. Dengvaxia (CYD-TDV), developed by Sanofi Pasteur (Lyon, France), was the first licensed dengue vaccine.[155] Qdenga (TAK-003), developed by Takeda (Osaka, Japan), was approved by the European Commission in December, 2020, and is licensed in several countries, including Indonesia, Brazil, Argentina, the UK, and Germany.[156–158] The third, TV003, was developed by the National Institutes of Health (Bethesda, MD, USA) and is in phase 3 trials.[159] All three are live vaccines and contain four different attenuated vaccine viruses (ie, are tetravalent) targeting each of the DENV serotypes. However, they differ in the number of doses required (one to three) and time to complete the series (up to 1 year), which could affect feasibility and preferences for use in different settings. Additionally, the need for a dengue test to establish eligibility (ie, a prevaccination screening) poses a logistical barrier for vaccines recommended only for use among people with a previous DENV infection. Several other dengue vaccine candidates are undergoing clinical trials or preclinical evaluation, including other live-attenuated vaccines, inactivated vaccines, recombinant vaccines, and DNA vaccines.[160] The successful mRNA vaccine technology used for SARS-CoV-2 is also being evaluated for dengue and could provide dengue vaccine candidates in the future.[161]

Dengvaxia

Dengvaxia uses a three-dose schedule, with doses administered 6 months apart. The vaccine was first recommended by WHO in 2016 for people aged 9 years and older living in highly endemic areas.[162] Long-term follow-up data over 5 years from phase 3 trials and further analyses of the efficacy results[163] showed that seropositive children (with evidence of previous DENV infection) were protected from severe dengue if they were vaccinated with Dengvaxia. However, risk of hospitalisation for dengue and severe dengue was increased among children aged 2–16 years without previous DENV infection who were vaccinated with Dengvaxia and had a subsequent infection over a 5-year follow-up period in the trial (hazard ratio for hospitalisation 1·75, 95% CI 1·14–2·70; severe dengue 2·87; 95% CI 1·09–7·61). After these findings, WHO revised the recommendations for the vaccine to only be given to children with laboratory-confirmed evidence of a past DENV infection.[164]

For children aged 9–16 years with evidence of previous DENV infection, Dengvaxia had an efficacy of about 80% against the outcomes of symptomatic virologically confirmed dengue (VCD), hospitalisation for dengue, and severe dengue.[163,165] Among seropositive children the efficacy by serotype varied,[166] with highest protection against DENV-4 (89%), followed by DENV-3 (80%), and lowest against DENV-1 (67%) and DENV-2 (67%; table).[163]

The requirement for a laboratory test before vaccine administration creates a unique challenge for Dengvaxia implementation. Qualifying laboratory tests include a positive NAAT or NS1 test done during an episode of acute dengue, or a positive result on prevaccination screening tests for serological evidence of previous infection (ie, the presence of IgG antibodies) that meet specific performance characteristics. To reduce the risk of vaccinating someone without previous DENV infection, high specificity in a prevaccination screening test is a priority. International working groups and the US Centers for Disease Control and Prevention recommend using tests with a minimum sensitivity of 75–85% and minimum specificity of 95–98%.[155,169] Few commercially available tests currently meet these requirements.[170]

Qdenga

Qdenga, developed by Takeda, consists of two doses given 3 months apart. Among children aged 4–16 years, efficacy against VCD was 64% among seropositive children and 54% among seronegative children at 3 years after vaccination. Efficacy against hospitalisation for dengue was higher than for VCD, at 86% among seropositive children and 79% among seronegative children.[167] Differences in efficacy were observed by serotype. Among seronegative children, there was no efficacy against DENV-3 and DENV-4 (table). Notably, estimates indicated a potential increased risk for hospitalisation after infection with DENV-3, although numbers were small (three cases in the placebo group and 11 cases in the vaccine group) and were mainly observed at one site.[153] In December, 2022, the European Commission approved the use of Qdenga regardless of serostatus following a positive opinion from the European Medicines Agency.[156] The next step for its use in Europe is official recommendations from each EU country.[171] Qdenga has been approved in several countries and Germany has started vaccination among travellers.[158] In September, 2023, the vaccine received a recommendation from the Strategic Advisory Group of Experts (SAGE) on immunisation that encouraged the introduction of Qdenga in settings with high transmission intensity to maximise its effect on public health and minimise any potential risk in seronegative people. SAGE recommended that the vaccine be introduced to children aged 6–16 years, and that post-authorisation studies should be conducted to further study the vaccine's effectiveness and safety against serotypes 3 and 4.[172] Takeda also plans to submit filings to other regulatory agencies.[173]

TV003

TV003 was developed by the National Institutes of Health and was formulated by selecting serotype-specific components to provide a balanced safety and immunogenicity profile on the basis of an evaluation of multiple monovalent and tetravalent candidates (table).[174,175] TV003 consists of a single dose and has been licensed to several manufacturers globally, including Merck & Co in the USA and the Instituto Butantan in Brazil. Phase 3 trials in Brazil are underway.[176,177] Preliminary results from 2-year follow-up of the phase 3 trial were released in December, 2022. Through 2 years of follow-up, the efficacy against VCD was 89% among seropositive people and 74% among seronegative people. Results by serotype are available for DENV-1 and DENV-2, with higher efficacy among seropositive participants (DENV-1 97% efficacy and DENV-2 84% efficacy) compared with seronegative participants (DENV-1 86% efficacy and DENV-2 58% efficacy).[168] Efficacy for other serotypes is not available but is expected as part of the phase 3 trial.[178]

Vector control

People who live in or travel to dengue-endemic areas can prevent mosquito bites by using approved insect repellents and wearing clothing that covers their arms and legs. The use of screened windows and doors and air conditioning have also been shown to be protective.[179–181] Bednets can reduce mosquito populations and can have an effect on dengue transmission.[182] Chemical control of *Aedes* species mosquitoes is restricted by widespread insecticide resistance in endemic areas.[183] Novel vector control methods have been developed, including the use of genetically modified mosquitoes.[184] Genetically modified mosquitoes carry a gene that is passed to their offspring and kills females in the larval stage. Male

	Dengvaxia (CYD-TDV)[163]	Qdenga (TAK-003)[167]	TV003[168]
Manufacturer	Sanofi Pasteur	Takeda	US National Institutes of Health, Instituto Butantan, and Merck & Co
Status	Recommended by WHO for two patient groups: seropositive people aged 9–45 years, or all people regardless of serostatus in high seroprevalence areas (>80% seropositivity). Licensed in 20 countries. Recommended for seropositive children aged 9–16 years living in endemic areas in the USA[155]	Recommended by WHO to be considered for introduction in children aged 6–16 years in settings with high transmission intensity. Licensed in several countries, including Indonesia, Brazil, Argentina, the UK, and Germany	Ongoing phase 3 trial
Platform	Four chimeric viruses for each DENV serotype on a yellow fever virus backbone	Attenuated DENV-2 and three chimeric viruses for each of the four DENV serotypes	Attenuated DENV-1, DENV-3, and DENV-4, and a chimeric virus for DENV-2 on a DENV-4 backbone
Ages of trial participants	9–16 years	6–16 years	2–59 years
Doses	Three doses 6 months apart	Two doses 3 months apart	One dose
Prevaccination antibody screening recommended?	Yes	No	Unknown
Timeframe for efficacy endpoint	25 months for VCD and 60 months for hospitalisation	54 months for VCD and hospitalisation	24 months for VCD
Efficacy among seropositive people			
VCD: overall	76% (64% to 84%)	64% (58% to 69%)	89% (78% to 96%)
VCD: by serotype			
DENV-1	67% (46% to 80%)	56% (45% to 65%)	97% (81% to 100%)
DENV-2	67% (47 to 80%)	80% (73% to 86%)	84% (63% to 94%)
DENV-3	80% (67% to 88%)	52% (37% to 64%)	NR
DENV-4	89% (80% to 94%)	71% (40% to 86%)	NR
Hospitalisation: overall	79% (46% to 80%)	86% (79% to 91%)	NR
Hospitalisation: by serotype			
DENV-1	78% (55% to 90%)	67% (37% to 82%)	NR
DENV-2	82% (66% to 90%)	96% (90% to 98%)	NR
DENV-3	63% (18% to 83%)	74% (39% to 89%)	NR
DENV-4	89% (62% to 99%)	100% (NE)	NR
Efficacy among seronegative people			
VCD: overall	39% (–1% to 63%)	54% (42% to 63%)	74% (58% to 84%)
VCD: by serotype			
DENV-1	41% (–7% to 67%)	45% (26% to 60%)	86% (69% to 94%)
DENV-2	–21% (–136% to 38%)	88% (79% to 93%)	58% (21% to 78%)
DENV-3	52% (–6% to 78%)	–16% (–108% to 36%)	NR
DENV-4	65% (24% to 84%)	–106% (–629% to 42%)	NR
Hospitalisation overall	–41% (–168% to 93%)	79% (64% to 88%)	NR
Hospitalisation by serotype			
DENV-1	–37% (–219% to 41%)	78% (44% to 92%)	NR
DENV-2	–141% (–795% to 35%)	100% (NE)	NR
DENV-3	15% (–225% to 78%)	–88% (–573% to 48%)	NR
DENV-4	7% (–712% to 89%)	100% (NE)	NR

Ranges in parentheses are 95% CIs. The Dengvaxia trial included participants aged 2–16 years but the vaccine is licensed for seropositive individuals aged 9 years or older. Estimates of efficacy against hospitalisation by serotype in seronegative participants aged 2–8 years are: DENV-1:–42 (95% CI 34 to –205); DENV-2: –436 (–58 to –1723); DENV-3: –141 (9 to –540); and DENV-4: –16 (70 to –344). DENV=dengue virus. NE=not possible to estimate due to a zero cell in one of the groups. NR=not reported. VCD=virologically confirmed dengue.

Table: **Comparison of vaccine efficacy for the target use population for live attenuated tetravalent dengue vaccines that are licensed or in phase 3 trials**

offspring, however, survive and pass this gene to future generations. As a result, mosquito populations decrease over time.[184,185]

Strategies using *Wolbachia*, an intracellular bacterium found in about 60% of all insects[186] but not commonly found in wild *Aedes* mosquitoes,[187] have also been used for vector control. *Wolbachia*-mediated suppression refers to a reduction in wild populations of *Aedes* mosquitoes and is achieved by releasing *Wolbachia*-infected males into the environment to mate with uninfected wild females, as the

resulting eggs do not hatch.[188] In *Wolbachia* replacement, both *Wolbachia*-infected males and female mosquitoes are released, which pass the bacteria to their offspring and gradually replace the wild population.[189,190] In mosquitoes, *Wolbachia* infection reduces transmission of arboviruses, including dengue, chikungunya, and Zika viruses, when infected female mosquitoes take a bloodmeal. This method has shown reductions of nearly 80% in dengue cases and related hospitalisations in areas of implementation[191] and is currently being deployed in Brazil and Indonesia.[192]

Dengue controversies, gaps, and opportunities

Many of the key questions in dengue research revolve around the role and behaviour of antibodies in protective immunity and ADE, and how these change at different timepoints after infection (panel 2). Previous work theorised that a first DENV infection induced antibodies that waned over 2 years to titres that could subsequently enhance severe dengue disease, and that secondary DENV infection with a different serotype induced stable, cross-serotype protective antibodies.[193] However, instead of waning over 2 years, cross-reactive binding antibodies associated with protection or enhancement are stable by around 8 months after primary infection and are maintained at that set point for many years after.[143,194] By contrast, anti-DENV antibodies induced after secondary DENV are less stable, wane rapidly for 8 months, and then gradually decay over longer periods. One study showed vaccine efficacy waned much faster than geometric mean antibody titres to DENV-1–4, suggesting a component of immunity other than waning antibodies that could explain the loss of protection.[195]

Although serotype-specific immunity (ie, homotypic immunity) has been thought to impart lifelong protection, some evidence suggests that reinfections with a given DENV serotype could occur.[196] This evidence bears further evaluation; if proven, the absence of lifelong homotypic immunity would have important implications for dengue vaccines and our understanding of DENV epidemiology.

Additionally, factors shaping the variability observed in the severity of dengue epidemics remain poorly understood. Investigators in Taiwan have reported increasing severity throughout the time course of a given epidemic, associated with increased viral diversity, which they hypothesise to be driven by cross-protective immunity.[197,198] Whether these same phenomena are replicated in other regions, with different levels of population immunity and transmission patterns, is unclear.

Identification of a satisfactory immune correlate of protection—a biomarker measuring immune response to vaccination that is associated with vaccine efficacy—remains an important challenge for DENV epidemiological studies and assessments of vaccine immunogenicity (panel 2). This challenge is mainly due to the dominance of immunity to cross-reactive epitopes that do not provide effective protection. In the Dengvaxia paediatric vaccine trial, the discordance between vaccine efficacy and neutralisation response rates indicated that PRNT neutralisation response is not a completely valid correlate of protection. However, increased PRNT titres after three doses of Dengvaxia were associated with a reduced rate of VCD and hospitalisation overall and for each infecting serotype.[199] After vaccination, geometric neutralising antibodies by PRNT to DENV-1–4 of a ratio of at least 1:100 were associated with around 50% protection against symptomatic dengue, while titres of at least 1:500 were associated with 80% vaccine efficacy; high titres were also associated with protection against dengue disease requiring hospitalisation.[199,200] In the Qdenga vaccine trials, neutralising antibody titres were lower in participants with VCD compared with healthy controls; these differences were most evident among seropositive

***Panel 2*: Priorities for future dengue virus (DENV) research**

DENV prevention and control

- Effectiveness of combined vaccine and vector control programmes in decreasing or eliminating DENV infection and illness
- Long-term data on the effectiveness of interventions, such as vaccines and Wolbachia-based vector control

Immune correlates of protection

- Immune signatures durably associated with immunopathogenesis and immunoprotection for DENV
- Clinical and immunological interactions between DENV and non-DENV flaviviruses
- Establishing whether the durability of homotypic protection is lifelong
- Importance of immune boosting in maintaining protective immunity for DENV
- Gaps in vaccine efficacy for specific subgroups (eg, in young children and DENV-naive children, and incomplete serotype-specific protection) that could lead to enhancement of severe disease

DENV epidemiology

- Identifying the conditions under which homotypic DENV reinfection might be possible, including frequency of occurrence and associated risk factors
- Identifying and understanding the features of settings where DENV severity increases during the course of an epidemic
- Harmonisation of surveillance and laboratory methods across regions experiencing DENV transmission; increased data sharing, and establishing a coordinated genomic surveillance strategy

Management and diagnosis

- Improved point-of-care diagnostics
- Clinical evaluation of the effect of antivirals
- Improved triage and risk assessment tools (eg, biomarkers and ultrasound)

participants.[153] Techniques such as antibody depletion of cross-reactive antibodies provide improved information about serotype-specific immunity and have shown associations with serotype-specific vaccine efficacy.[153,199–201] Depletion assays have shown that Dengvaxia is dominated by DENV-4 type-specific antibodies and the Takeda dengue vaccine by DENV-2 type-specific antibodies, with mostly cross-reactive antibodies against other serotypes.[154,202] Many of these serotype-specific antibodies bind quaternary epitopes (ie, two adjacent E proteins simultaneously). The role of neutralising antibodies binding quaternary epitopes is an area of research into correlates of protection.

The role of immunological boosting, defined here as qualitative or quantitative changes in immunity associated with re-exposure to DENV in an individual already exposed to that serotype, remains poorly understood. The effects of boosting are proposed to be evident in dynamic antibody patterns among individuals residing in hyperendemic locales over time.[203] If boosting were an important contributor to maintenance of DENV immunity and durability of protection, interventions that decrease the force of infection (eg, incompletely protective vaccination programmes or partially effective mosquito control programmes) could yield paradoxical effects by lowering levels of boosting and increasing the susceptible population. However, partially effective vaccines and mosquito control interventions complement each other, contributing effectiveness when the other is lacking. Mathematical modelling suggests that combining interventions could yield consistent high effectiveness.[204] Designing and implementing a dengue control programme that uses a combination of available interventions is a public health priority.

The immunological and clinical interactions between DENV and non-DENV flaviviruses remain poorly understood, but data suggest that the relationship could be highly context-dependent and not bidirectional. ZIKV infection has been suggested to predispose people to DHF with a subsequent infection with some, but not necessarily all, serotypes.[121] By contrast, increased levels of DENV immunity are associated with protection against Zika in adults and children,[205] while reduced levels could increase the risk of Zika microcephaly.[206,207] Japanese encephalitis virus immunity has been variably associated with risk of dengue illness[208] but also with possible protection.[209] Given the substantial immunological cross-reactivity observed between DENV and non-DENV flaviviruses, these interactions could have consequences for both the clinical outcomes of DENV infection and the immunological outcomes of DENV vaccination. Further research on these interactions is needed, across a range of flavivirus-endemic regions of the world, to inform DENV vaccine development and evaluation efforts, as well as diagnostics.

Dengue surveillance remains a key challenge in assessing global dengue burden and temporal and geospatial trends. The large proportion of asymptomatic and subclinical cases contributes substantially to transmission but complicates detection, and the non-specific presentation of acute febrile illness can easily be mistaken for other causes. The non-specific dengue symptoms are a particular challenge in malaria-endemic regions in which cases have similar presentations, in areas with restricted diagnostic test availability, and regions with infrequent or sporadic dengue transmission. National dengue surveillance systems also vary widely in surveillance and laboratory capacity, and in case definitions used; future efforts should work towards strengthening country-level surveillance and laboratory capacity, harmonising case definitions, establishing regional strategies (eg, for genomic surveillance), and encouraging public data sharing to better inform dengue preparedness and response efforts.

Contributors

GP-B coordinated the writing of the manuscript and wrote the first and final drafts. LEA was responsible for the section on epidemiology, LCK for the virus and the immune response, JD for dengue clinical presentation and management, and KBA for controversies, gaps, and opportunities. All authors contributed to and approved the final manuscript.

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