
References with abstracts cited in the position paper in the order of appearance.


Dengue vaccines are currently in development and policymakers need appropriate economic studies to determine their potential financial and public health impact. We searched five databases (PubMed, EMBASE, LILAC, EconLit, and WHOLIS) to identify health economics studies of dengue. Forty-three manuscripts were identified that provided primary data: 32 report economic burden of dengue and nine are comparative economic analyses assessing various interventions. The remaining two were a willingness-to-pay study and a policymaker survey. An expert panel reviewed the existing dengue economic literature and recommended future research to fill information gaps. Although dengue is an important vector-borne disease, the economic literature is relatively sparse and results have often been conflicting because of use of inconsistent assumptions. Health economic research specific to dengue is urgently needed to ensure informed decision making on the various options for controlling and preventing this disease.

BACKGROUND: Dengue is the most common arbovirus infection globally, but its burden is poorly quantified. We estimated dengue mortality, incidence, and burden for the Global Burden of Disease Study 2013.
METHODS: We modelled mortality from vital registration, verbal autopsy, and surveillance data using the Cause of Death Ensemble Modelling tool. We modelled incidence from officially reported cases, and adjusted our raw estimates for under-reporting based on published estimates of
expansion factors. In total, we had 1780 country-years of mortality data from 130 countries, 1636 country-years of dengue case reports from 76 countries, and expansion factor estimates for 14 countries.

FINDINGS: We estimated an average of 9221 dengue deaths per year between 1990 and 2013, increasing from a low of 8277 (95% uncertainty estimate 5353-10 649) in 1992, to a peak of 11 302 (6790-13 722) in 2010. This yielded a total of 576 900 (330 000-701 200) years of life lost to premature mortality attributable to dengue in 2013. The incidence of dengue increased greatly between 1990 and 2013, with the number of cases more than doubling every decade, from 8·3 million (3·3 million-17·2 million) apparent cases in 1990, to 58·4 million (23·6 million-121·9 million) apparent cases in 2013. When accounting for disability from moderate and severe acute dengue, and post-dengue chronic fatigue, 566 000 (186 000-1 415 000) years lived with disability were attributable to dengue in 2013. Considering fatal and non-fatal outcomes together, dengue was responsible for 1·14 million (0·73 million-1·98 million) disability-adjusted life-years in 2013.

INTERPRETATION: Although lower than other estimates, our results offer more evidence that the true symptomatic incidence of dengue probably falls within the commonly cited range of 50 million to 100 million cases per year. Our mortality estimates are lower than those presented elsewhere and should be considered in light of the totality of evidence suggesting that dengue mortality might, in fact, be substantially higher.


Dengue is a systemic viral infection transmitted between humans by Aedes mosquitoes. For some patients, dengue is a life-threatening illness. There are currently no licensed vaccines or specific therapeutics, and substantial vector control efforts have not stopped its rapid emergence and global spread. The contemporary worldwide distribution of the risk of dengue virus infection and its public health burden are poorly known. Here we undertake an exhaustive assembly of known records of dengue occurrence worldwide, and use a formal modelling framework to map the global distribution of dengue risk. We then pair the resulting risk map with detailed longitudinal information from dengue cohort studies and population surfaces to infer the public health burden of dengue in 2010. We predict dengue to be ubiquitous throughout the tropics, with local spatial variations in risk influenced strongly by rainfall, temperature and the degree of urbanization. Using cartographic approaches, we estimate there to be 390 million (95% credible interval 284-528) dengue infections per year, of which 96 million (67-136) manifest apparently (any level of disease severity). This infection total is more than three times the dengue burden estimate of the World Health Organization. Stratification of our estimates by country allows comparison with national dengue
reporting, after taking into account the probability of an apparent infection being formally reported. The most notable differences are discussed. These new risk maps and infection estimates provide novel insights into the global, regional and national public health burden imposed by dengue. We anticipate that they will provide a starting point for a wider discussion about the global impact of this disease and will help to guide improvements in disease control strategies using vaccine, drug and vector control methods, and in their economic evaluation.


A literature survey and analysis was conducted to describe the epidemiology of dengue disease in Thailand reported between 2000 and 2011. The literature search identified 610 relevant sources, 40 of which fulfilled the inclusion criteria defined in the review protocol. Peaks in the number of cases occurred during the review period in 2001, 2002, 2008 and 2010. A shift in age group predominance towards older ages continued through the review period. Disease incidence and deaths remained highest in children aged ≤ 15 years and case fatality rates were highest in young children. Heterogeneous geographical patterns were observed with higher incidence rates reported in the Southern region and serotype distribution varied in time and place. Gaps identified in epidemiological knowledge regarding dengue disease in Thailand provide several avenues for future research, in particular studies of seroprevalence.


OBJECTIVES: To explore the variation in the spatial distribution of notified dengue cases in Colombia from January 2007 to December 2010 and examine associations between the disease and selected environmental risk factors.

METHODS: Data on the number of notified dengue cases in Colombia were obtained from the National Institute of Health (Instituto Nacional de Salud - INS) for the period 1 January 2007 through 31 December 2010. Data on environmental factors were collected from the Worldclim website. A Bayesian spatio-temporal conditional autoregressive model was used to quantify the relationship between monthly dengue cases and temperature, precipitation and elevation.

RESULTS: Monthly dengue counts decreased by 18% (95% credible interval (CrI): 17-19%) in 2008 and increased by 30% (95% CrI: 28-31%) and 326% (95% CrI: 322-331%) in 2009 and 2010, respectively, compared to 2007. Additionally, there was a significant, nonlinear effect of monthly average precipitation.
CONCLUSIONS: The results highlight the role of environmental risk factors in determining the spatial of dengue and show how these factors can be used to develop and refine preventive approaches for dengue in Colombia.

Since the first isolation of dengue virus (DENV) in 1943, four types have been identified. Global phenomena such as urbanization and international travel are key factors in facilitating the spread of dengue. Documenting the type-specific record of DENV spread has important implications for understanding patterns in dengue hyperendemicity and disease severity as well as vaccine design and deployment strategies. Existing studies have examined the spread of DENV types at regional or local scales, or described phylogeographic relationships within a single type. Here we summarize the global distribution of confirmed instances of each DENV type from 1943 to 2013 in a series of global maps. These show the worldwide expansion of the types, the expansion of disease hyperendemicity, and the establishment of an increasingly important infectious disease of global public health significance.

Dengue viruses have spread rapidly within countries and across regions in the past few decades, resulting in an increased frequency of epidemics and severe dengue disease, hyperendemicity of multiple dengue virus serotypes in many tropical countries, and autochthonous transmission in Europe and the USA. Today, dengue is regarded as the most prevalent and rapidly spreading mosquito-borne viral disease of human beings. Importantly, the past decade has also seen an upsurge in research on dengue virology, pathogenesis, and immunology and in development of antivirals, vaccines, and new vector-control strategies that can positively impact dengue control and prevention.


BACKGROUND: Anti-dengue virus (DENV) immunoglobulin M (IgM) seroconversion has been the reference standard for dengue diagnosis. However, paired specimens are rarely obtained, and the interval for this testing negates its usefulness in guiding clinical case management. The presence of DENV viremia and appearance of IgM during the febrile phase of dengue provides the framework for dengue laboratory diagnosis by using a single serum specimen.

METHODS: Archived paired serum specimens (n = 1234) from patients with laboratory-confirmed dengue from 2005 through 2011 were used to determine the diagnostic performance of real-time reverse transcription polymerase chain reaction (RT-PCR), for detection of DENV serotypes 1-4, and enzyme-linked immunosorbent assays (ELISAs), for detection of DENV nonstructural protein 1 (NS1) antigen and anti-DENV IgM.

RESULTS: During 1-3 days after illness onset, real-time RT-PCR and NS1 antigen testing detected 82%-69% and 90%-84% of cases, respectively, as viremia levels declined, while anti-DENV IgM ELISA detected 5%-41% of cases as antibody appeared. Over the 10-day period of the febrile phase of dengue, the cumulative effect of using these 3 types of tests in a diagnostic algorithm confirmed ≥ 90% of dengue cases.

CONCLUSION: The use of molecular or NS1 antigen tests to detect DENV and one to detect anti-DENV IgM in a single serum specimen collected during the first 10 days of illness accurately identified ≥90% of dengue primary and secondary cases.

Monath TP. Dengue: the risk to developed and developing countries. Proc Natl Acad Sci U S A. 1994;91(7):2395-400.

Dengue viruses are members of the Flaviviridae, transmitted principally in a cycle involving humans and mosquito vectors. In the last 20 years the incidence of dengue fever epidemics has increased and hyperendemic transmission has been established over a geographically expanding area. A severe form, dengue hemorrhagic fever (DHF), is an immunopathologic disease occurring in persons who experience sequential dengue infections. The risk of sequential infections, and consequently the incidence of DHF, has risen dramatically, first in Asia and now in the Americas. At the root of the emergence of dengue as a major health problem are changes in human demography and behavior, leading to unchecked populations of and increased exposure to the principal domestic mosquito vector, Aedes aegypti. Virus-specified factors also influence the epidemiology of dengue. Speculations on future events in the epidemiology, evolution, and biological expression of dengue are presented.

This review describes and commentates on recent advances in the understanding of dengue pathogenesis and immunity, plus clinical research on vaccines and therapeutics. We expand specifically on the role of the dermis in dengue virus infection, the contribution of cellular and humoral immune responses to pathogenesis and immunity, NS1 and mechanisms of virus immune evasion. Additionally we review a series of therapeutic intervention trials for dengue, as well as recent clinical research aimed at improving clinical diagnosis, risk prediction and disease classification.


Recently, the Vaccines to Vaccinate (v2V) initiative was reconfigured into the Partnership for Dengue Control (PDC), a multi-sponsored and independent initiative. This redirection is consistent with the growing consensus among the dengue-prevention community that no single intervention will be sufficient to control dengue disease. The PDC’s expectation is that when an effective dengue virus (DENV) vaccine is commercially available, the public health community will continue to rely on vector control because the two strategies complement and enhance one another. Although the concept of integrated intervention for dengue prevention is gaining increasingly broader acceptance, to date, no consensus has been reached regarding the details of how and what combination of approaches can be most effectively implemented to manage disease. To fill that gap, the PDC proposed a three step process: (1) a critical assessment of current vector control tools and those under development, (2) outlining a research agenda for determining, in a definitive way, what existing tools work best, and (3) determining how to combine the best vector control options, which have systematically been defined in this process, with DENV vaccines. To address the first step, the PDC convened a meeting of international experts during November 2013 in Washington, DC, to critically assess existing vector control interventions and tools under development. This report summarizes those deliberations.


Severe dengue virus (DENV) infection is epidemiologically linked to pre-existing anti-DENV antibodies acquired by maternal transfer or primary infection. A possible explanation is that DENV immune complexes evade neutralization by engaging Fcgamma receptors (FcgammaR) on
monocytes, natural targets for DENV in humans. Using epitope-matched humanized monoclonal antibodies (mAbs) and stable FcgammaRII-transfected CV-1 cells, we found that DENV neutralization by IgG1, IgG3, and IgG4 mAbs was enhanced in high-affinity FcgammaRII transfectants and diminished in low-affinity FcgammaRII transfectants, whereas neutralization by IgG2 mAbs (low-affinity ligands for both FcgammaRs) was diminished equally. In FcgammaR-negative Vero cells, IgG3 mAbs exhibited the strongest neutralizing activity and IgG2, the weakest. Our results demonstrate that DENV neutralization is modulated by the Fc region in an IgG subclass manner, likely through effects on virion and FcgammaR binding. Thus, the IgG antibody subclass profile generated by DENV infection or vaccination may independently influence the magnitude of the neutralizing response.


Although several vaccine candidates are presently in various phases of clinical trials, the field still lacks an effective tool to determine protective immunity. The presence of cross-neutralizing antibodies limits a serological approach to identify the etiology and distinguish lifelong from short-lived humoral protection. A recent study indicated that cross-reactive but not serotype-specific antibodies require high antibody concentration to co-ligate FcyRIIB and inhibit infection. Here, we tested if these differences could allow us to distinguish serotype-specific from cross-neutralizing antibodies. Using 30 blinded early convalescent serum samples from patients with virologically confirmed dengue, we demonstrate that neutralization in the presence of FcyR-mediated phagocytosis in THP-1 correctly identifies the DENV serotype of the infection in 93.3% of the cases compared to 76.7% with plaque reduction neutralization test. Our findings could provide a new approach for evaluating DENV neutralization and suggest that in addition to blocking specific ligand-receptor interactions for viral entry, antibodies must prevent viral uncoating during FcyR-mediated phagocytosis for complete humoral protection.


Four dengue virus serotypes (DENV1-4) circulate globally, causing more human illness than any other arthropod-borne virus. Dengue can present as a range of clinical manifestations from undifferentiated fever to Dengue Fever to severe, life-threatening syndromes. However, most DENV infections are inapparent. Yet, little is known about determinants of inapparent versus symptomatic DENV infection outcome. Here, we analyzed over 2,000 DENV infections from 2004 to 2011 in a
prospective pediatric cohort study in Managua, Nicaragua. Symptomatic cases were captured at the study health center, and paired healthy annual samples were examined on a yearly basis using serological methods to identify inapparent DENV infections. Overall, inapparent and symptomatic DENV infections were equally distributed by sex. The mean age of infection was 1.2 years higher for symptomatic DENV infections as compared to inapparent infections. Although inapparent versus symptomatic outcome did not differ by infection number (first, second or third/post-second DENV infections), substantial variation in the proportion of symptomatic DENV infections among all DENV infections was observed across study years. In participants with repeat DENV infections, the time interval between a first inapparent DENV infection and a second inapparent infection was significantly shorter than the interval between a first inapparent and a second symptomatic infection. This difference was not observed in subsequent infections. This result was confirmed using two different serological techniques that measure total anti-DENV antibodies and serotype-specific neutralizing antibodies, respectively. Taken together, these findings show that, in this study, age, study year and time interval between consecutive DENV infections influence inapparent versus symptomatic infection outcome, while sex and infection number had no significant effect. Moreover, these results suggest that the window of cross-protection induced by a first infection with DENV against a second symptomatic infection is approximately 2 years. These findings are important for modeling dengue epidemics and development of vaccines.


Dengue, a mosquito-borne virus of humans, infects over 50 million people annually. Infection with any of the four dengue serotypes induces protective immunity to that serotype, but does not confer long-term protection against infection by other serotypes. The immunological interactions between serotypes are of central importance in understanding epidemiological dynamics and anticipating the impact of dengue vaccines. We analysed a 38-year time series with 12 197 serotyped dengue infections from a hospital in Bangkok, Thailand. Using novel mechanistic models to represent different hypothesized immune interactions between serotypes, we found strong evidence that infection with dengue provides substantial short-term cross-protection against other serotypes (approx. 1-3 years). This is the first quantitative evidence that short-term cross-protection exists since human experimental infection studies performed in the 1950s. These findings will impact strategies for designing dengue vaccine studies, future multi-strain modelling efforts, and our understanding of evolutionary pressures in multi-strain disease systems.

As the four serotypes of dengue virus (DENV) systematically spread throughout the tropical and subtropical regions globally, dengue is increasingly contributing to the overall morbidity and mortality sustained by populations and thereby challenging the health infrastructures of most endemic countries. DENV-human host-mosquito vector interactions are complex and cause in humans either asymptomatic or subclinical DENV infection, mild to severe dengue fever (DF), severe dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS). Over the past decade, we have seen an increase in research funding and public health efforts to offset the effects of this pandemic. Though multiple vaccine development efforts are underway, the need remains to further characterize the determinants of varying severities of clinical outcomes. Several long-term prospective studies on DENV transmission and dengue severity have sought to define the epidemiology and pathogenesis of this disease. Yet, more studies are required to quantify the disease burden on different populations, explore the impact of DENV serotype-specific transmission on host-responses and dengue severity and measure the economic impact of dengue on a population. In this section, we will review the critical past and recent findings of dengue prospective studies on our understanding of the disease and the potential role of future prospective cohort studies in advancing issues required for vaccine field evaluations.


A prospective study on dengue (DEN) viruses was initiated in October 1995 in Gondokusuman kecamatan, Yogyakarta, Indonesia. This report presents data from the first year of the study. The studied cohort included all children 4-9 years of age living in the kecamatan. Blood samples for serology were collected from 1,837 children in October 1995 and again in October 1996. Blood samples for virus isolation and serology were collected from cohort children who were seen in municipal health clinics with febrile syndromes or admitted to hospitals with a provisional diagnosis of dengue hemorrhagic fever. Dengue serotype antibody prevalence and 1995-1996 infection rates were calculated using a single dilution (1:60) 70% plaque reduction endpoint neutralization test. Prevalence of dengue antibody at the beginning of the study was DEN 1 = 12%, DEN 2 = 16%, DEN 3 = 2%, DEN 4 = 4%, and two or more dengue infections = 22%. Total dengue antibody prevalence increased from 38% in 4-year-old children to 69% in 9-year-old children. During the observation period, primary dengue infection rates were DEN 1 = 4.8%, DEN 2 = 7.7%, DEN 3 = 4.2%, and DEN 4 = 3.4%, while two or more dengue infections occurred in 6.7% of the study population. The secondary
The dengue infection rate was 19.0%. From febrile cases, all four dengue viruses were isolated with DEN 3 predominating. Seven children were hospitalized, including one fatal case with a hospital diagnosis of dengue shock syndrome. Based upon presence of antibody in the initial cohort bleeding and the serologic response both weeks and several months following illness, all had secondary dengue infections. Neutralizing antibody patterns in the initial cohort bleeding and in late convalescent serum samples permitted recognition of dengue infection sequence in five patients: DEN 2-DEN 1 (3), DEN 2-DEN 4 (1), DEN 1-DEN 3 (1), and none in the sequence DEN 1-DEN 2. In the total cohort 6.5% of the observed secondary infections were of the sequence DEN 2-DEN 1, while 4.9% were DEN 1-DEN 2, a highly pathogenic sequence in previous studies. Reduced pathogenic expression of secondary DEN 2 with enhanced pathogenic expression of secondary DEN 1 infections was an unexpected finding. Further studies will be required to understand the respective contributions to pathogenicity of antibody from initial dengue infections versus the biological attributes of the second infecting dengue viruses.

Thein S, et al. Risk factors in dengue shock syndrome. Ibid. 1997;56(5):566-72. Despite a growing body of evidence predominantly, but not exclusively, from Thailand suggesting that the risk of developing dengue shock syndrome (DSS) is greatest following an anamnestic dengue infection, particularly if the most recent infection was with dengue 2 virus, there continues to be debate about the justification for these claims. This report describes a five-year, prospective study in two townships (suburbs) in Yangon (Rangoon) Myanmar (Burma) in which attempts were made to confirm the data from an earlier prospective study in Thailand and to address some of the criticism of earlier studies. This investigation found the incidence of anamnestic dengue infections in DSS patients to be significantly higher than in the community from which they were drawn and a significantly higher risk of developing DSS following an anamnestic infection (particularly with dengue 2 virus) than following a primary infection with any serotype.

Balmaseda A, et al. High seroprevalence of antibodies against dengue virus in a prospective study of schoolchildren in Managua, Nicaragua. Trop Med Int Health. 2006;11(6):935-42. To investigate the incidence of dengue virus (DENV) infection in Nicaragua, a 2-year prospective study was conducted in schoolchildren 4-16 years old in the capital city of Managua. Blood samples were collected before the rainy season in 2001, 2002 and 2003, and were assayed for DENV-specific antibodies. Participants were monitored for dengue-like illness, and acute and convalescent blood samples were collected from suspected dengue cases. In 2001 and 2002, 602 and 397 students were recruited, respectively, and paired annual serum samples were available from 467 and 719
participants in 2001-2002 and 2002-2003, respectively. The overall seroprevalence of anti-DENV antibodies was 91%, increasing from 75% at age 4 to 100% at age 16. The incidence of DENV infection was 12% in Year 1 and 6% in Year 2 (P < 0.001). During Year 1, four laboratory-confirmed dengue cases were detected, with one DENV2 isolate; during Year 2, there were six confirmed dengue cases, with one DENV1 isolate. These and additional circulating serotypes were confirmed by plaque reduction neutralisation test. This study demonstrates surprisingly high transmission of DENV in urban Nicaragua.


BACKGROUND: Antibodies induced by infection with any 1 of 4 dengue virus (DENV) serotypes (DENV-1-4) may influence the clinical outcome of subsequent heterologous infections. To quantify potential cross-protective effects, we estimated disease risk as a function of DENV infection, using data from longitudinal studies performed from September 2006 through February 2011 in Iquitos, Peru, during periods of DENV-3 and DENV-4 transmission.

METHODS: DENV infections before and during the study period were determined by analysis of serial serum samples with virus neutralization tests. Third and fourth infections were classified as postsecondary infections. Dengue fever cases were detected by door-to-door surveillance for acute febrile illness.

RESULTS: Among susceptible participants, 39% (420/1077) and 53% (1595/2997) seroconverted to DENV-3 and DENV-4, respectively. Disease was detected in 7% of DENV-3 infections and 10% of DENV-4 infections. Disease during postsecondary infections was reduced by 93% for DENV-3 and 64% for DENV-4, compared with primary and secondary infections. Despite lower disease rates, postsecondary infections constituted a significant proportion of apparent infections (14% [for DENV-3 infections], 45% [for DENV-4 infections]).

CONCLUSIONS: Preexisting heterotypic antibodies markedly reduced but did not eliminate the risk of disease in this study population. These results improve understanding of how preinfection history can be associated with dengue outcomes and DENV transmission dynamics.

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BACKGROUND: An estimated 100 million people have symptomatic dengue infection every year. This is the first report of a phase 3 vaccine efficacy trial of a candidate dengue vaccine. We aimed to assess the efficacy of the CYD dengue vaccine against symptomatic, virologically confirmed dengue in children.

METHODS: We did an observer-masked, randomised controlled, multicentre, phase 3 trial in five countries in the Asia-Pacific region. Between June 3, and Dec 1, 2011, healthy children aged 2-14 years were randomly assigned (2:1), by computer-generated permuted blocks of six with an interactive voice or web response system, to receive three injections of a recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV), or placebo, at months 0, 6, and 12. Randomisation was stratified by age and site. Participants were followed up until month 25. Trial staff responsible for the preparation and administration of injections were unmasked to group allocation, but were not included in the follow-up of the participants; allocation was concealed from the study sponsor, investigators, and parents and guardians. Our primary objective was to assess protective efficacy against symptomatic, virologically confirmed dengue, irrespective of disease severity or serotype, that took place more than 28 days after the third injection. The primary endpoint was for the lower bound of the 95% CI of vaccine efficacy to be greater than 25%. Analysis was by intention to treat and per protocol. This trial is registered with ClinicalTrials.gov, number NCT01373281.

FINDINGS: We randomly assigned 10,275 children to receive either vaccine (n=6851) or placebo (n=3424), of whom 6710 (98%) and 3350 (98%), respectively, were included in the primary analysis. 250 cases of virologically confirmed dengue took place more than 28 days after the third injection (117 [47%] in the vaccine group and 133 [53%] in the control group). The primary endpoint was achieved with 56·5% (95% CI 43·8-66·4) efficacy. We recorded 647 serious adverse events (402 [62%] in the vaccine group and 245 [38%] in the control group). 54 (1%) children in the vaccine group and 33 (1%) of those in the control group had serious adverse events that happened within 28 days of
vaccination. Serious adverse events were consistent with medical disorders in this age group and were mainly infections and injuries.

INTERPRETATION: Our findings show that dengue vaccine is efficacious when given as three injections at months 0, 6, and 12 to children aged 2-14 years in endemic areas in Asia, and has a good safety profile. Vaccination could reduce the incidence of symptomatic infection and hospital admission and has the potential to provide an important public health benefit.


BACKGROUND: In light of the increasing rate of dengue infections throughout the world despite vector-control measures, several dengue vaccine candidates are in development.

METHODS: In a phase 3 efficacy trial of a tetravalent dengue vaccine in five Latin American countries where dengue is endemic, we randomly assigned healthy children between the ages of 9 and 16 years in a 2:1 ratio to receive three injections of recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV) or placebo at months 0, 6, and 12 under blinded conditions. The children were then followed for 25 months. The primary outcome was vaccine efficacy against symptomatic, virologically confirmed dengue (VCD), regardless of disease severity or serotype, occurring more than 28 days after the third injection.

RESULTS: A total of 20,869 healthy children received either vaccine or placebo. At baseline, 79.4% of an immunogenicity subgroup of 1944 children had seropositive status for one or more dengue serotypes. In the per-protocol population, there were 176 VCD cases (with 11,793 person-years at risk) in the vaccine group and 221 VCD cases (with 5809 person-years at risk) in the control group, for a vaccine efficacy of 60.8% (95% confidence interval [CI], 52.0 to 68.0). In the intention-to-treat population (those who received at least one injection), vaccine efficacy was 64.7% (95% CI, 58.7 to 69.8). Serotype-specific vaccine efficacy was 50.3% for serotype 1, 42.3% for serotype 2, 74.0% for serotype 3, and 77.7% for serotype 4. Among the severe VCD cases, 1 of 12 was in the vaccine group, for an intention-to-treat vaccine efficacy of 95.5%. Vaccine efficacy against hospitalization for dengue was 80.3%. The safety profile for the CYD-TDV vaccine was similar to that for placebo, with no marked difference in rates of adverse events.

CONCLUSIONS: The CYD-TDV dengue vaccine was efficacious against VCD and severe VCD and led to fewer hospitalizations for VCD in five Latin American countries where dengue is endemic.
BACKGROUND: A candidate tetravalent dengue vaccine is being assessed in three clinical trials involving more than 35,000 children between the ages of 2 and 16 years in Asian-Pacific and Latin American countries. We report the results of long-term follow-up interim analyses and integrated efficacy analyses.

METHODS: We are assessing the incidence of hospitalization for virologically confirmed dengue as a surrogate safety end point during follow-up in years 3 to 6 of two phase 3 trials, CYD14 and CYD15, and a phase 2b trial, CYD23/57. We estimated vaccine efficacy using pooled data from the first 25 months of CYD14 and CYD15.

RESULTS: Follow-up data were available for 10,165 of 10,275 participants (99%) in CYD14 and 19,898 of 20,869 participants (95%) in CYD15. Data were available for 3203 of the 4002 participants (80%) in the CYD23 trial included in CYD57. During year 3 in the CYD14, CYD15, and CYD57 trials combined, hospitalization for virologically confirmed dengue occurred in 65 of 22,177 participants in the vaccine group and 39 of 11,089 participants in the control group. Pooled relative risks of hospitalization for dengue were 0.84 (95% confidence interval [CI], 0.56 to 1.24) among all participants, 1.58 (95% CI, 0.83 to 3.02) among those under the age of 9 years, and 0.50 (95% CI, 0.29 to 0.86) among those 9 years of age or older. During year 3, hospitalization for severe dengue,
as defined by the independent data monitoring committee criteria, occurred in 18 of 22,177 participants in the vaccine group and 6 of 11,089 participants in the control group. Pooled rates of efficacy for symptomatic dengue during the first 25 months were 60.3% (95% CI, 55.7 to 64.5) for all participants, 65.6% (95% CI, 60.7 to 69.9) for those 9 years of age or older, and 44.6% (95% CI, 31.6 to 55.0) for those younger than 9 years of age.

CONCLUSIONS: Although the unexplained higher incidence of hospitalization for dengue in year 3 among children younger than 9 years of age needs to be carefully monitored during long-term follow-up, the risk among children 2 to 16 years of age was lower in the vaccine group than in the control group.


http://www.who.int/immunization/sage/meetings/2016/april/3_Ferguson_Comparative_Dengue_Modelling_SAGE.pdf?ua=1, accessed July 2017
(No abstract available.)

(No abstract available.)

Flasche S et al., Comparative modelling of dengue vaccine public health impact.

http://www.who.int/immunization/sage/meetings/2016/april/2_CMDVI_Report_FINAL.pdf, accessed July 2017. A manuscript is in preparation that will provide updated figures.
(No abstract available.)


http://www.who.int/entity/immunization/sage/meetings/2016/april/2_Smith_Clinical_Trial_Results_SAGE.pdf, accessed July 2016
(No abstract available.)

Dengue is a major public health concern in pediatric populations in endemic regions. A recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV) is under development for the control of dengue with a 3-dose (0-6-12 month) vaccination schedule.

METHODS: In this controlled phase II trial conducted in the Philippines, 210 toddlers aged 12-15 months were randomized to 4 groups: 3 groups received the CYD-TDV vaccination schedule and a measles, mumps and rubella (MMR) vaccine given either concomitantly with the first CYD-TDV dose or 1 month earlier; 1 group received 3 active control vaccines. Safety and reactogenicity were assessed after each dose. Immunogenicity was assessed 30 days after vaccinations using the plaque reduction neutralization test against dengue and enzyme-linked immunosorbent assay methods against MMR antigens.

RESULTS: Injection site and systemic reactions occurred at similar rates across CYD-TDV groups, except for fever, which was more frequent after CYD-TDV and MMR coadministration (28.8%) compared with other groups (12-20%). Reactogenicity did not increase with subsequent CYD-TDV injections. There were no safety issues with the study vaccine. CYD-TDV achieved a balanced antibody response to all 4 dengue serotypes across the study groups, with geometric mean titers in the range of 105-124, 147-213, 311-387 and 127-160 for serotypes 1, 2, 3 and 4, respectively. CYD-TDV coadministration did not affect MMR immunogenicity (≥95% seroprotection against MMR) and vice versa.

CONCLUSIONS: The CYD-TDV has an acceptable safety and immunogenicity profile in toddlers and when coadministered with MMR.

(No abstract available.)

(No abstract available.)

BACKGROUND: Dengue diagnosis confirmation and surveillance are widely based on serological assays to detect anti-dengue IgM or IgG antibodies since such tests are affordable/user-friendly. The World Health Organization identified serological based diagnosis as a potential tool to define probable dengue cases in the context of vaccine trials, while acknowledging that this may have to be interpreted with caution.

METHODS: In a phase IIb randomized, placebo-controlled trial assessing the efficacy of a tetravalent dengue vaccine (CYD-TDV) in Thai schoolchildren, case definition was based on virological confirmation by either serotype-specific RT-PCRs or by NS1-antigen ELISA (Clinicaltrials.gov NCT00842530). Here, we characterized suspected dengue cases using IgM and IgG ELISA to assess their utility in evaluating probable dengue cases in the context of vaccine efficacy trials, comparing virologically-confirmed and serologically diagnosed dengue in the vaccine and placebo groups.

Serologically probable cases were defined as: (1) IgM positive acute- or convalescent-phase samples, or (2) IgG positive acute-phase sample and ≥4-fold IgG increase between acute and convalescent-phase samples.

RESULTS: Serological diagnosis had good sensitivity (97.1%), but low specificity (85.1%) compared to virological confirmation. A high level of false positivity through serology diagnosis particularly in the 2 months post-vaccination was observed, and is most likely related to detection of the immune response to the dengue vaccine. This lack of specificity and bias with vaccination demonstrates the limitation of using IgM and IgG antibody responses to explore vaccine efficacy.

CONCLUSION: Reliance on serological assessments would lead to a significant number of false positives during routine clinical practice and surveillance following the introduction of the dengue vaccine.