

References of Dengue Vaccine Position Paper, September 2018.

- 1.) Guidance for the development of evidence-based vaccine related recommendations. Available at http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf, accessed April 2018.

No abstract available.

- 2.) See No. 30, 2016, pp. 349–364.

See: <http://www.who.int/wer/2016/wer9130/en/>

- 3.) Sanofi Pasteur. Press release Sanofi updates information on dengue vaccine. Available at <http://mediaroom.sanofi.com/sanofi-updates-information-on-dengue-vaccine/>, accessed May 2018.

- 4.) Brady OJ. et al. Refining the global spatial limits of dengue virus transmission by evidence-based consensus. PLoS Negl Trop Dis. 2012;6:e1760.

Abstract

BACKGROUND:

Dengue is a growing problem both in its geographical spread and in its intensity, and yet current global distribution remains highly uncertain. Challenges in diagnosis and diagnostic methods as well as highly variable national health systems mean no single data source can reliably estimate the distribution of this disease. As such, there is a lack of agreement on national dengue status among international health organisations. Here we bring together all available information on dengue occurrence using a novel approach to produce an evidence consensus map of the disease range that highlights nations with an uncertain dengue status.

METHODS/PRINCIPAL FINDINGS:

A baseline methodology was used to assess a range of evidence for each country. In regions where dengue status was uncertain, additional evidence types were included to either clarify dengue status or confirm that it is unknown at this time. An algorithm was developed that assesses evidence quality and consistency, giving each country an evidence consensus score. Using this approach, we were able to generate a contemporary global map of national-level dengue status that assigns a relative measure of certainty and identifies gaps in the available evidence.

CONCLUSION:

The map produced here provides a list of 128 countries for which there is good evidence of dengue occurrence, including 36 countries that have previously been classified as dengue-free by the World Health Organization and/or the US Centers for Disease Control. It also identifies disease surveillance needs, which we list in full. The disease extents and limits determined here using evidence consensus, marks the beginning of a five-year study to advance the mapping of dengue virus transmission and disease risk. Completion of this first step has allowed us to produce a preliminary estimate of population at risk with an upper bound of 3.97 billion people. This figure will be refined in future work.

- 5.) Jentes ES. et al. Evidence-based risk assessment and communication: a new global dengue-risk map for travellers and clinicians. *J Travel Med.* 2016 Sep 13;23(6).

Abstract

BACKGROUND:

International travel can expose travellers to pathogens not commonly found in their countries of residence, like dengue virus. Travellers and the clinicians who advise and treat them have unique needs for understanding the geographic extent of risk for dengue. Specifically, they should assess the need for prevention measures before travel and ensure appropriate treatment of illness post-travel. Previous dengue-risk maps published in the Centers for Disease Control and Prevention's Yellow Book lacked specificity, as there was a binary (risk, no risk) classification. We developed a process to compile evidence, evaluate it and apply more informative risk classifications.

METHODS:

We collected more than 839 observations from official reports, ProMED reports and published scientific research for the period 2005-2014. We classified each location as frequent/continuous risk if there was evidence of more than 10 dengue cases in at least three of the previous 10 years. For locations that did not fit this criterion, we classified locations as sporadic/uncertain risk if the location had evidence of at least one locally acquired dengue case during the last 10 years. We used expert opinion in limited instances to augment available data in areas where data were sparse.

RESULTS:

Initial categorizations classified 134 areas as frequent/continuous and 140 areas as sporadic/uncertain. CDC subject matter experts reviewed all initial frequent/continuous and sporadic/uncertain categorizations and the previously uncategorized areas. From this review, most categorizations stayed the same; however, 11 categorizations changed from the initial determinations.

CONCLUSIONS:

These new risk classifications enable detailed consideration of dengue risk, with clearer meaning and a direct link to the evidence that supports the specific classification. Since many infectious diseases have dynamic risk, strong geographical heterogeneities and varying data quality and availability, using this approach for other diseases can improve the accuracy, clarity and transparency of risk communication.

- 6.) Bhatt S. et al. The global distribution and burden of dengue. *Nature.* 2013;496(7446):504–507.

Abstract

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.

- 7.) WHO. Fact sheet Dengue. Available at <http://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue>, accessed July 2018.

No abstract available.

- 8.) Stanaway JD. et al. The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. *Lancet Infect Dis.* 2016 Jun;16(6):712-723.

Abstract

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.

FUNDING:

Bill & Melinda Gates Foundation.

- 9.)** Wilder-Smith A. et al. Epidemic arboviral diseases: priorities for research and public health. *Lancet Infect Dis* 2017; 17(3): e101-e6.

Abstract

For decades, arboviral diseases were considered to be only minor contributors to global mortality and disability. As a result, low priority was given to arbovirus research investment and related public health infrastructure. The past five decades, however, have seen an unprecedented emergence of epidemic arboviral diseases (notably dengue, chikungunya, yellow fever, and Zika virus disease) resulting from the triad of the modern world: urbanisation, globalisation, and international mobility. The public health emergency of Zika virus, and the threat of global spread of yellow fever, combined with the resurgence of dengue and chikungunya, constitute a wake-up call for governments, academia, funders, and WHO to strengthen programmes and enhance research in aedes-transmitted diseases. The common features of these diseases should stimulate similar research themes for diagnostics, vaccines, biological targets and immune responses, environmental determinants, and vector control measures. Combining interventions known to be effective against multiple arboviral diseases will offer the most cost-effective and sustainable strategy for disease reduction. New global alliances are needed to enable the combination of efforts and resources for more effective and timely solutions.

- 10.)** Ferguson RW. et al. Dengue in Peace Corps Volunteers, 2000-14. *J Travel Med.* 2016 Mar;23(3).

Abstract

BACKGROUND:

Dengue is an arboviral disease estimated to cause 50-100 million infections each year in >100 tropical and subtropical countries. Urbanization, human population growth and expanded global travel have resulted in an increase in the incidence of dengue worldwide. International travellers to areas with endemic dengue are at risk of contracting dengue and US Peace Corps Volunteers are one specific group of long-term travellers who are exposed to environments where dengue can be contracted.

METHODS:

Cases of dengue among Peace Corps Volunteers, defined as clinically apparent infections with laboratory-confirmation by a positive NS1 antigen test, demonstration of IgM antibodies or by a 4-fold increase in IgG antibodies, between 1 January 2000 and 31 December 2014, reported to the Peace Corps' Epidemiologic Surveillance System were analyzed.

RESULTS:

Overall there were 1448 cases of dengue reported among Volunteers, with an incidence rate of 1.12 cases per 1000 Volunteer-months (95% CI 1.06-1.17). The highest rate of dengue among Volunteers was reported in the Caribbean region, with a rate of 5.51 cases per 1000 Volunteer-months (95% CI 4.97-6.10), followed by the East Asia/South Asia region (3.34, 95% CI 2.96-3.75) and Central America (2.55, 95% CI 2.32-2.79). The rate of dengue peaked in 2007, 2010 and 2013. Each peak year was followed by a trough year.

CONCLUSIONS:

Globally, there appears to be a 3-year cyclical pattern of dengue incidence among Volunteers, with differences by region. Dengue continues to be a priority health issue for travellers to endemic areas, and enhanced surveillance of dengue among international travellers may result in improved patient education and prevention efforts.

- 11.)** Lalani T. et al. A comparison of compliance rates with anti-vectorial protective measures during travel to regions with dengue or chikungunya activity, and regions endemic for *Plasmodium falciparum* malaria. *J Travel Med.* 2016;23(5).

Abstract

Background. There is limited information on compliance rates with anti-vectorial protective measures (AVPMs) during travel to countries with risk of dengue and chikungunya. We evaluated differences in mosquito exposures, and factors associated with AVPM compliance in travellers going to countries where the principal mosquito-borne infectious disease threat is *falciparum* malaria and those where risk of dengue or chikungunya predominates.

Methods. Department of Defence beneficiaries with planned travel to regions where the predominant mosquito-borne infection is *falciparum* malaria, and those with predominantly dengue or chikungunya risk, were included. Regions were divided into three groups: 'high-risk *falciparum* malaria', 'low-risk *falciparum* malaria' and 'chikungunya/dengue risk'. Demographics, trip characteristics, arthropod exposure and AVPM compliance were captured using pre- and post-travel surveys. Skin repellent compliance was defined as self-reported use, categorized as 'often/every day'. A logistic regression model was used to estimate factors associated with AVPM compliance.

Results. 183 (9%), 185 (9%) and 149 (7%) travelled to high and low *falciparum* malaria risk regions, and chikungunya/dengue risk regions, respectively. Overall, 53% (95% CI: 48–57%) and 16% (95% CI: 12–19%) were compliant with repellent use on skin and clothing, respectively. Daytime bites were reported more frequently in chikungunya/dengue risk regions than high malaria risk regions (37% vs. 10%), while night time bites were frequently in high malaria risk regions (53% vs 20%; $P < 0.001$). Compliance with skin repellents was associated with female gender [RR: 1.54 (95% CI: 1.05–2.28)], observing mosquitoes during travel [RR: 2.77 (95% CI: 1.76–4.36)] and travel during the rainy season [RR: 2.45 (95% CI: 1.66–3.71)].

Conclusions. Poor AVPM compliance was observed in the overall cohort. Compliance with skin repellent use was associated with female gender, observing mosquitoes and travelling during the rainy season, and was not associated with the risk of malaria or chikungunya/dengue at the travel destination.

12.)WHO. Informing vaccination programs: a guide to the design and conduct of dengue serosurveys.

Available at

http://www.who.int/immunization/research/development/Dengue_Serosurveys_020617.pdf,
accessed May 2018.

No abstract available.

13.)Messina JP. et al. Global spread of dengue virus types: mapping the 70 year history. Trends Microbiol. 2014;22(3):138–146.

Abstract

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.

14.)Guzman MG. et al. Dengue. Lancet. 2015;385(9966):453–465.

Abstract

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.

15.)Grange L. et al. Epidemiological risk factors associated with high global frequency of inapparent dengue virus infection. Front Immunol. 2014 Jun 11;5:280.

Abstract

Dengue is a major international public health concern, and the number of outbreaks has escalated greatly. Human migration and international trade and travel are constantly introducing new vectors and pathogens into novel geographic areas. Of particular interest is the extent to which dengue virus (DENV) infections are subclinical or inapparent. Not only may such infections contribute to the global spread of DENV by human migration, but also seroprevalence rates in naïve populations may be initially high despite minimal numbers of detectable clinical cases. As

the probability of severe disease is increased in secondary infections, populations may thus be primed, with serious public health consequences following introduction of a new serotype. In addition, pre-existing immunity from inapparent infections may affect vaccine uptake, and the ratio of clinically apparent to inapparent infection could affect the interpretation of vaccine trials. We performed a literature search for inapparent DENV infections and provide an analytical review of their frequency and associated risk factors. Inapparent rates were highly variable, but “inapparent” was the major outcome of infection in all prospective studies. Differences in the epidemiological context and type of surveillance account for much of the variability in inapparent infection rates. However, one particular epidemiological pattern was shared by four longitudinal cohort studies: the rate of inapparent DENV infections was positively correlated with the incidence of disease the previous year, strongly supporting an important role for short-term heterotypic immunity in determining the outcome of infection. Primary and secondary infections were equally likely to be inapparent. Knowledge of the extent to which viruses from inapparent infections are transmissible to mosquitoes is urgently needed. Inapparent infections need to be considered for their impact on disease severity, transmission dynamics, and vaccine efficacy and uptake.

- 16.)** Gibbons RV. et al. Analysis of repeat hospital admissions for dengue to estimate the frequency of third or fourth dengue infections resulting in admissions and dengue hemorrhagic fever, and serotype sequences. *Am J Trop Med Hyg.* 2007 Nov;77(5):910-3.

Abstract

Immunity to a single dengue virus (DENV) infection does not provide heterologous immunity to subsequent infection. In fact, the greatest risk for dengue hemorrhagic fever (DHF) is with a second DENV serotype exposure. The risk for DHF with a third or fourth dengue infection relative to a first or second exposure is not known. An analysis of our database of children admitted to the Queen Sirikit National Institute of Child Health and Kamphaeng Phet Provincial Hospital with suspected dengue illness revealed that the number of dengue admissions caused by a third or fourth DENV infection was extremely low (0.08-0.8%). Once admitted, the risk for DHF relative to dengue fever was not different for those experiencing third or fourth DENV infections over those experiencing a second DENV infection. We document new dengue serotype infection sequences leading to DHF of 1-4, 2-3, 3-1, and 3-4.

- 17.)** WHO. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva, Switzerland: 2009. Available at <http://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf>, accessed April 2018.

No abstract available.

- 18.)** WHO. Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever. Available at http://www.searo.who.int/entity/vector_borne_tropical_diseases/documents/SEAROTPS60/en/, accessed July 2018.

No abstract available.

- 19.)** Groen J. et al. Evaluation of six immunoassays for detection of dengue virus-specific immunoglobulin M and G antibodies. *Clin Diagn Lab Immunol* 2000; 7(6): 867-71.

Abstract

The performance of six commercially available immunoassay systems for the detection of dengue virus-specific immunoglobulin M (IgM) and IgG antibodies in serum was evaluated. These included two IgM and IgG enzyme immunoassays (EIA) from MRL Laboratories and PanBio, a rapid immunochromatographic test (RIT) from PanBio, immunofluorescence assays (IFA) from Progen, a dot blot assay from Genelabs, and a dipstick EIA from Integrated Diagnostics (INDX). For this study a panel of 132 serum samples, including 90 serum samples from patients with suspected dengue virus infection and 42 serum samples from patients with other viral infections, was used. In addition, serial serum samples from two monkeys experimentally immunized and challenged with dengue virus type 2 were used. Results were considered conclusive when concordant results were obtained with four of the six antibody-specific assays. Based on this definition, the calculated overall agreement for the human serum samples for the respective IgM immunoassays was 97% (128 of 132), with 34% (45 of 132) positive serum samples, 63% (83 of 132) negative samples, and 3% of samples (4 of 132) showing discordant results. The calculated overall agreement for the IgG assays was 94% (124 of 132), with 49% (65 of 132) positive, 45% (59 of 132) negative, and 6% (8 of 132) discordant results, respectively. The sensitivities of the dengue virus-specific assays evaluated varied between 71 and 100% for IgM and between 52 and 100% for IgG, with specificities of 86 to 96% and 81 to 100%, respectively. The relative sensitivities of the respective IgM assays measured with the monkey serum samples were comparable with those obtained with 12 serial serum samples from humans. Overall performance, based on the sum of the agreement, sensitivity, specificity, and Kappa statistics of the IgM and IgG immunoassays, showed that the antibody detection systems from INDX and Genelabs and the MRL and PanBio EIA are useful and reliable assays for dengue virus serodiagnosis.

- 20.)** Pal S. et al. Multicountry prospective clinical evaluation of two enzyme-linked immunosorbent assays and two rapid diagnostic tests for diagnosing dengue fever. *J Clin Microbiol* 2015; 53(4): 1092-102.

Abstract

We evaluated four dengue diagnostic devices from Alere, including the SD Bioline Dengue Duo (nonstructural [NS] 1 Ag and IgG/IgM), the Panbio Dengue Duo Cassette (IgM/IgG) rapid diagnostic tests (RDTs), and the Panbio dengue IgM and IgG capture enzyme-linked immunosorbent assays (ELISAs) in a prospective, controlled, multicenter study in Peru, Venezuela, Cambodia, and the United States, using samples from 1,021 febrile individuals. Archived, well-characterized samples from an additional 135 febrile individuals from Thailand were also used. Reference testing was performed on all samples using an algorithm involving virus isolation, in-house IgM and IgG capture ELISAs, and plaque reduction neutralization tests (PRNT) to determine the infection status of the individual. The primary endpoints were the clinical sensitivities and specificities of these devices. The SD Bioline Dengue Duo had an overall sensitivity of 87.3% (95% confidence interval [CI], 84.1 to 90.2%) and specificity of 86.8% (95% CI, 83.9 to 89.3%) during the first 14 days post-symptom onset (p.s.o.). The Panbio Dengue Duo Cassette demonstrated a sensitivity of 92.1% (87.8 to 95.2%) and specificity of 62.2% (54.5 to 69.5%) during days 4 to 14 p.s.o. The Panbio IgM capture ELISA had a sensitivity of 87.6% (82.7 to 91.4%) and specificity of 88.1% (82.2 to 92.6%) during days 4 to 14 p.s.o. Finally, the Panbio IgG capture ELISA had a sensitivity of 69.6% (62.1 to 76.4%) and a specificity of 88.4% (82.6 to

92.8%) during days 4 to 14 p.s.o. for identification of secondary dengue infections. This multicountry prospective study resulted in reliable real-world performance data that will facilitate data-driven laboratory test choices for managing patient care during dengue outbreaks.

- 21.)** Simmons CP. et al. Recent advances in dengue pathogenesis and clinical management. *Vaccine*. 2015;33(50):7061–7068.

Abstract

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.

- 22.)** Achee NL. et al. A critical assessment of vector control for dengue prevention. *PLoS Negl Trop Dis*. 2015;9(5):e0003655.

Abstract

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.

- 23.)** Rodrigo WW. et al. Dengue virus neutralization is modulated by IgG antibody subclass and Fcγ receptor subtype. *Virology*. 2009;394(2):175–182.

Abstract

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 Fcγ receptors (FcγR) on monocytes, natural targets for DENV in humans. Using epitope-matched humanized monoclonal antibodies (mAbs) and stable FcγR-transfected CV-1 cells, we found that DENV neutralization by IgG1, IgG3, and IgG4 mAbs was enhanced in high-affinity FcγRIIA transfectants and diminished in low-affinity FcγRIIA transfectants, whereas neutralization by IgG2 mAbs (low-affinity ligands for both FcγRs)

was diminished equally. In FcγR-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 FcγR binding. Thus, the IgG antibody subclass profile generated by DENV infection or vaccination may independently influence the magnitude of the neutralizing response.

- 24.)** Wu RS. et al. Neutralization of dengue virus in the presence of Fc receptor-mediated phagocytosis distinguishes serotype-specific from cross-neutralizing antibodies. *Antiviral Res.* 2012;96(3):340–343.

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 FcγRIIB 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 FcγR-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 FcγR-mediated phagocytosis for complete humoral protection.

- 25.)** Montoya M. et al. Symptomatic versus inapparent outcome in repeat dengue virus infections is influenced by the time interval between infections and study year. *PLoS Negl Trop Dis.* 2013;7(8):e2357.

Abstract

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.

- 26.)** Reich NG. et al. Interactions between serotypes of dengue highlight epidemiological impact of cross-immunity. *J R Soc Interface*. 2013;10(86):20130414.

ABSTRACT

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.

- 27.)** Endy TP. et al. Prospective cohort studies of dengue viral transmission and severity of disease. *Curr Top Microbiol Immunol*. 2010;338:1–13.

Abstract

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.

28.) Sangkawibha et al. Risk factors in dengue shock syndrome: a prospective epidemiologic study in Rayong, Thailand. I. The 1980 outbreak. *Am J Epidemiol.* 1984 Nov;120(5):653-69.

Abstract

In January 1980, the municipal area of Rayong, Thailand, and contiguous suburban villages were chosen for a long-term study on dengue epidemiology. From 3,185 children randomly sampled in schools and households, the population prevalence of neutralizing antibody to the four dengue serotypes was estimated. To estimate the incidence of infection with each dengue virus serotype (dengue seroconversions), first grade children were re-bled in January 1981 (cohort study). Children admitted to hospital were studied for dengue virus isolation and antibody responses in paired sera. An epidemic of dengue occurred in 1980. Plaque reduction neutralization tests of 1,009 pre-epidemic sera from children aged less than 1-10 years of age determined that 3.3% were immune to dengue 1, 13.2% to dengue 2, 6.4% to dengue 3, and 5.8% to dengue 4. Examination of pre- and post-epidemic cohort blood samples revealed that the incidence of dengue infection in 251 seronegative children was 39.4% (15.1% dengue 1, 11.1% dengue 2, 2.0% dengue 3, 4.8% dengue 4, and 6.4% two or more dengue viruses). Among the 52,935 residents of the study area, there were 22 cases of virologically and clinically confirmed dengue shock syndrome, in children 15 years or younger. All 22 shock syndrome cases had secondary type antibody responses. Eight of 22 had been included in the random serologic sample prior to onset of shock; five had been immune to dengue 1, two to dengue 3, one to dengue 4, and none to dengue 2. Despite the high rate of dengue 1 infections in 1980, only dengue 2 viruses were recovered from dengue shock syndrome cases, including two dengue 1 immune children with pre-illness serum specimens. Although the pre-epidemic prevalence of antibodies to dengue 1 was the lowest to any type, children with this immunologic background contributed disproportionately to shock cases. In descending order of magnitude, risk factors for dengue shock syndrome in Rayong were secondary infections with dengue 2 which followed primary infections with dengue 1, dengue 3, or dengue 4.

29.) Graham RR. et al. A prospective seroepidemiologic study on dengue in children four to nine years of age in Yogyakarta, Indonesia I. studies in 1995–1996. *Am J Trop Med Hyg.* 1999;61(3):412–419.

Abstract

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 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.

30.) Thein S. et al. Risk factors in dengue shock syndrome. *Ibid.* 1997;56(5):566–572.

Abstract

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.

31.) 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):935–942.

Summary

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.

32.) Kliks SC et al. Evidence that maternal dengue antibodies are important in the development of dengue hemorrhagic fever in infants. *Am J Trop Med Hyg.* 1988 Mar;38(2):411-9.

Abstract To establish the role of maternal dengue-specific antibodies in the development of dengue hemorrhagic fever and dengue shock syndrome caused by dengue 2 virus in infants, we examined sera from mothers of infants and toddlers with dengue hemorrhagic fever or dengue shock syndrome and mothers of infants with pyrexia of unknown origin. The mean titers of hemagglutination inhibition, neutralization, and infection-enhancing activities against dengue 2 virus were not statistically different among the three groups. However, among infants who developed dengue hemorrhagic fever/dengue shock syndrome there was a strong correlation between the mothers' dengue 2 neutralizing titers and infant age at the time of onset of severe illness, where no such correlation was found among the other two groups. Furthermore, the actual age at which dengue hemorrhagic fever/dengue shock syndrome occurred in each infant correlated with the age at which maximum enhancing activity for dengue 2 infection in mononuclear phagocytes was predicted. This critical time for the occurrence of dengue hemorrhagic fever/dengue shock syndrome was observed to be approximately 2 months after the time calculated for maternal dengue 2 neutralizing antibodies to degrade below a protective level. In addition, sera of mothers of infants with dengue hemorrhagic fever/dengue shock syndrome enhanced dengue 2 virus infection to a slightly greater degree than did sera from mothers of infants with pyrexia of unknown origin and toddlers with dengue hemorrhagic fever/dengue shock syndrome. These data are consistent with the hypothesis that maternal dengue antibodies play a dual role by first protecting and later increasing the risk of development of dengue hemorrhagic fever/dengue shock syndrome in infants who become infected by dengue 2 virus.

33.) Simmons CP. et al. Maternal antibody and viral factors in the pathogenesis of dengue virus in infants. *J Infect Dis* 2007; 196:416-24.

The pathogenesis of dengue in infants is poorly understood. We postulated that dengue severity in infants would be positively associated with markers of viral burden and that maternally derived, neutralizing antidengue antibody would have decayed before the age at which infants with dengue presented to the hospital. In 75 Vietnamese infants with primary dengue, we found significant heterogeneity in viremia and NS1 antigenemia at hospital presentation, and these factors were independent of disease grade or continuous measures of disease severity. Neutralizing antibody titers, predicted in each infant at the time of their illness, suggested that the majority of infants (65%) experienced dengue hemorrhagic fever when the maternally derived neutralizing antibody titer had declined to $!1:20$. Collectively, these data have important implications for dengue vaccine research because they suggest that viral burden may not solely explain severe dengue in infants and that neutralizing antibody is a reasonable but not absolute marker of protective immunity in infants.

34.) Chau TN et al. Dengue virus infections and maternal antibody decay in a prospective birth cohort study of Vietnamese infants. *J Infect Dis* 2009; 200:1893-900.

Abstract

Dengue hemorrhagic fever can occur in primary dengue virus (DENV) infection of infants. The decay of maternally derived DENV immunoglobulin (Ig) G and the incidence of DENV infection

were determined in a prospectively studied cohort of 1244 Vietnamese infants. Higher concentrations of total IgG and DENV-reactive IgG were found in cord plasma relative to maternal plasma. Maternally derived DENV-neutralizing and E protein-reactive IgG titers declined to below measurable levels in >90% of infants by 6 months of age. In contrast, IgG reactive with whole DENV virions persisted until 12 months of age in 20% of infants. Serological surveillance identified 10 infants with asymptomatic DENV infection for an incidence of 1.7 cases per 100 person-years. DENV-neutralizing antibodies remained measurable for > or = 1 year after infection. These results suggest that whereas DENV infection in infants is frequently subclinical, there is a window between 4 and 12 months of age where virion-binding but nonneutralizing IgG could facilitate antibody-dependent enhancement.

35.) Olkowski S. et al. Reduced risk of disease during postsecondary dengue virus infections. *J Infect Dis.* 2013;208(6):1026–1033.

Abstract

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.

36.) Beatty RP et al. Dengue virus non-structural protein 1 triggers endothelial permeability and vascular leak that can be inhibited by anti-NS1 antibodies. *Science Translational Medicine* 2015; 7:304ra141.

Abstract

The four dengue virus serotypes (DENV1 to DENV4) are mosquito-borne flaviviruses that cause up to ~100 million cases of dengue annually worldwide. Severe disease is thought to result from immunopathogenic processes involving serotype cross-reactive antibodies and T cells that together induce vasoactive cytokines, causing vascular leakage that leads to shock. However, no viral proteins have been directly implicated in triggering endothelial permeability, which results in vascular leakage. DENV nonstructural protein 1 (NS1) is secreted and circulates in patients' blood during acute infection; high levels of NS1 are associated with severe disease. We show that inoculation of mice with DENV NS1 alone induces both vascular leakage and production of key inflammatory cytokines. Furthermore, simultaneous administration of NS1 with a sublethal dose of DENV2 results in a lethal vascular leak syndrome. We also demonstrate that NS1 from DENV1, DENV2, DENV3, and DENV4 triggers endothelial barrier dysfunction, causing increased permeability of human endothelial cell monolayers in vitro. These pathogenic effects of physiologically relevant amounts of NS1 in vivo and in vitro were blocked by NS1-immune polyclonal mouse serum or monoclonal antibodies to NS1, and immunization of mice with NS1 from DENV1 to DENV4 protected against lethal DENV2 challenge. These findings add an important and previously overlooked component to the causes of dengue vascular leak, identify a new potential target for dengue therapeutics, and support inclusion of NS1 in dengue vaccines.

- 37.)** Modhiran N, Watterson D, Muller DA, Panetta AK, Sester DP, Liu L, et al. Dengue virus NS1 protein activates cells via Toll-like receptor 4 and disrupts endothelial cell monolayer integrity. *Sci Transl Med* 2015; 7:304ra142.

Abstract

Complications arising from dengue virus infection include potentially fatal vascular leak, and severe disease has been linked with excessive immune cell activation. An understanding of the triggers of this activation is critical for the development of appropriately targeted disease control strategies. We show here that the secreted form of the dengue virus nonstructural protein 1 (NS1) is a pathogen-associated molecular pattern (PAMP). Highly purified NS1 devoid of bacterial endotoxin activity directly activated mouse macrophages and human peripheral blood mononuclear cells (PBMCs) via Toll-like receptor 4 (TLR4), leading to the induction and release of proinflammatory cytokines and chemokines. In an in vitro model of vascular leak, treatment with NS1 alone resulted in the disruption of endothelial cell monolayer integrity. Both NS1-mediated activation of PBMCs and NS1-induced vascular leak in vitro were inhibited by a TLR4 antagonist and by anti-TLR4 antibody treatment. The importance of TLR4 activation in vivo was confirmed by the reduction in capillary leak by a TLR4 antagonist in a mouse model of dengue virus infection. These results pinpoint NS1 as a viral toxin counterpart of the bacterial endotoxin lipopolysaccharide (LPS). Similar to the role of LPS in septic shock, NS1 might contribute to vascular leak in dengue patients, which highlights TLR4 antagonists as a possible therapeutic option.

- 38.)** Whitehead SS. Development of TV003/TV005, a single dose, highly immunogenic live attenuated dengue vaccine; what makes this vaccine different from the Sanofi-Pasteur CYD vaccine? *Expert Rev Vaccines* 2016;15:509e17.

Abstract

Dengue is caused by four serotype-distinct dengue viruses (DENVs), and developing a multivalent vaccine against dengue has not been straightforward since partial immunity to DENV

may predispose to more severe disease upon subsequent DENV infection. The vaccine that is furthest along in development is CYD™, a live attenuated tetravalent vaccine (LATV) produced by Sanofi Pasteur. Although the multi-dose vaccine demonstrated protection against severe dengue, its overall efficacy was limited by DENV serotype, serostatus at vaccination, region and age. The National Institute of Allergy and Infectious Diseases has developed the LATV dengue vaccines TV003/TV005. A single dose of either TV003 or TV005 induced seroconversion to four DENV serotypes in 74-92% (TV003) and 90% (TV005) of flavivirus seronegative adults and elicited near-sterilizing immunity to a second dose of vaccine administered 6-12 months later. The important differences in the structure, infectivity and immune responses to TV003/TV005 are compared with CYD™.

- 39.)** Osorio JE et al. A recombinant, chimeric tetravalent dengue vaccine candidate based on a dengue virus serotype 2 backbone. *Expert Rev Vaccines*. 2016;15(4):497-508.

Abstract

Dengue fever is caused by infection with one of four dengue virus (DENV) serotypes (DENV-1-4), necessitating tetravalent dengue vaccines that can induce protection against all four DENV. Takeda's live attenuated tetravalent dengue vaccine candidate (TDV) comprises an attenuated DENV-2 strain plus chimeric viruses containing the prM and E genes of DENV-1, -3 and -4 cloned into the attenuated DENV-2 'backbone'. In Phase 1 and 2 studies, TDV was well tolerated by children and adults aged 1.5-45 years, irrespective of prior dengue exposure; mild injection-site symptoms were the most common adverse events. TDV induced neutralizing antibody responses and seroconversion to all four DENV as well as cross-reactive T cell-mediated responses that may be necessary for broad protection against dengue fever.

- 40.)** WHO. Guidelines on the quality, safety and efficacy of dengue tetravalent vaccines (live, attenuated) Annex 2. TRS No 979, 2013. Available at http://www.who.int/biologicals/vaccines/Dengue_DB_5_April_2012_clean.pdf, accessed August 2018.

No abstract available.

- 41.)** Vannice KS. Et al. Clinical development and regulatory points for consideration for second-generation live attenuated dengue vaccines. *Vaccine* 2018 Mar 7. pii : S0264-410X(18)302149-4.

Abstract

Licensing and decisions on public health use of a vaccine rely on a robust clinical development program that permits a risk-benefit assessment of the product in the target population. Studies undertaken early in clinical development, as well as well-designed pivotal trials, allow for this robust characterization. In 2012, WHO published guidelines on the quality, safety and efficacy of live attenuated dengue tetravalent vaccines. Subsequently, efficacy and longer-term follow-up data have become available from two Phase 3 trials of a dengue vaccine, conducted in parallel, and the vaccine was licensed in December 2015. The findings and interpretation of the results from these trials released both before and after licensure have highlighted key complexities for tetravalent dengue vaccines, including concerns vaccination could increase the incidence of dengue disease in certain subpopulations. This report summarizes clinical and regulatory points for consideration that may guide vaccine developers on some aspects of trial design and

facilitate regulatory review to enable broader public health recommendations for second-generation dengue vaccines.

42.) Capeding MR. et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. *Lancet* 2014; 384(9951): 1358-65.

Abstract

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.

43.) Villar L. et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. *N Engl J Med* 2015; 372(2): 113-23.

Abstract

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. (Funded by Sanofi Pasteur; ClinicalTrials.gov number, NCT01374516.).

44.) Sabchareon A. et al. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. *Lancet*. 2012;380(9853):1559-67.

Abstract

BACKGROUND:

Roughly half the world's population live in dengue-endemic countries, but no vaccine is licensed. We investigated the efficacy of a recombinant, live, attenuated tetravalent dengue vaccine.

METHODS:

In this observer-masked, randomised, controlled, monocentre, phase 2b, proof-of-concept trial, healthy Thai schoolchildren aged 4-11 years were randomly assigned (2:1) to receive three injections of dengue vaccine or control (rabies vaccine or placebo) at months 0, 6, and 12. Randomisation was by computer-generated permuted blocks of six and participants were assigned with an interactive response system. Participants were actively followed up until month 25. All acute febrile illnesses were investigated. Dengue viraemia was confirmed by serotype-specific RT-PCR and non-structural protein 1 ELISA. The primary objective was to assess protective efficacy against virologically confirmed, symptomatic dengue, irrespective of severity or serotype, occurring 1 month or longer after the third injection (per-protocol analysis). This trial is registered at ClinicalTrials.gov, NCT00842530.

FINDINGS:

4002 participants were assigned to vaccine (n=2669) or control (n=1333). 3673 were included in the primary analysis (2452 vaccine, 1221 control). 134 cases of virologically confirmed dengue occurred during the study. Efficacy was 30.2% (95% CI -13.4 to 56.6), and differed by serotype. Dengue vaccine was well tolerated, with no safety signals after 2 years of follow-up after the first dose.

INTERPRETATION:

These data show for the first time that a safe vaccine against dengue is possible. Ongoing large-scale phase 3 studies in various epidemiological settings will provide pivotal data for the CYD dengue vaccine candidate.

45.) Sridhar S. et al. Impact of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. *N Engl J Med.* 2018; 26;379(4):327-340. Abstract

BACKGROUND:

In efficacy trials of a tetravalent dengue vaccine (CYD-TDV), excess hospitalizations for dengue were observed among vaccine recipients 2 to 5 years of age. Precise risk estimates according to observed dengue serostatus could not be ascertained because of the limited numbers of samples collected at baseline. We developed a dengue anti-nonstructural protein 1 (NS1) IgG enzyme-linked immunosorbent assay and used samples from month 13 to infer serostatus for a post hoc analysis of safety and efficacy.

METHODS:

In a case-cohort study, we reanalyzed data from three efficacy trials. For the principal analyses, we used baseline serostatus determined on the basis of measured (when baseline values were available) or imputed (when baseline values were missing) titers from a 50% plaque-reduction neutralization test (PRNT50), with imputation conducted with the use of covariates that included the month 13 anti-NS1 assay results. The risk of hospitalization for virologically confirmed dengue (VCD), of severe VCD, and of symptomatic VCD according to dengue serostatus was estimated by weighted Cox regression and targeted minimum loss-based estimation.

RESULTS:

Among dengue-seronegative participants 2 to 16 years of age, the cumulative 5-year incidence of hospitalization for VCD was 3.06% among vaccine recipients and 1.87% among controls, with

a hazard ratio (vaccine vs. control) through data cutoff of 1.75 (95% confidence interval [CI], 1.14 to 2.70). Among dengue-seronegative participants 9 to 16 years of age, the cumulative incidence of hospitalization for VCD was 1.57% among vaccine recipients and 1.09% among controls, with a hazard ratio of 1.41 (95% CI, 0.74 to 2.68). Similar trends toward a higher risk among seronegative vaccine recipients than among seronegative controls were also found for severe VCD. Among dengue-seropositive participants 2 to 16 years of age and those 9 to 16 years of age, the cumulative incidence of hospitalization for VCD was 0.75% and 0.38%, respectively, among vaccine recipients and 2.47% and 1.88% among controls, with hazard ratios of 0.32 (95% CI, 0.23 to 0.45) and 0.21 (95% CI, 0.14 to 0.31). The risk of severe VCD was also lower among seropositive vaccine recipients than among seropositive controls.

CONCLUSIONS:

CYD-TDV protected against severe VCD and hospitalization for VCD for 5 years in persons who had exposure to dengue before vaccination, and there was evidence of a higher risk of these outcomes in vaccinated persons who had not been exposed to dengue. (Funded by Sanofi Pasteur; ClinicalTrials.gov numbers, NCT00842530 , NCT01983553 , NCT01373281 , and NCT01374516 .).

- 46.)**WHO. Policy Statement: Multi-dose Vial Policy (MDVP). 2014. Available at http://apps.who.int/iris/bitstream/10665/135972/1/WHO_IVB_14.07_eng.pdf, accessed April 2018.
No abstract available.
- 47.)**Vigne C. et al. Integrated immunogenicity analysis of a tetravalent dengue vaccine up to 4 y after vaccination. *Hum Vaccin Immunother.* 2017 Sep 2;13(9):2004-2016.
Abstract
Two large pivotal phase III studies demonstrated the efficacy of the tetravalent dengue vaccine (CYD-TDV; Dengvaxia®, Sanofi Pasteur) against all dengue serotypes. Here we present an unprecedented integrated summary of the immunogenicity of CYD-TDV to identify the parameters driving the neutralizing humoral immune response and evolution over time. We summarized the immunogenicity profiles of a 3-dose schedule of CYD-TDV administered 6 months apart across 10 phase II and 6 phase III trials undertaken in dengue endemic and non-endemic countries. Dengue neutralizing antibody titers in sera were determined at centralized laboratories using the 50% plaque reduction neutralization test (PRNT50) at baseline, 28 d after the third dose, and annually thereafter for up to 4 y after the third dose in some studies. CYD-TDV elicits neutralizing antibody responses against all 4 dengue serotypes; geometric mean titers (GMTs) increased from baseline to post-dose 3. GMTs were influenced by several parameters including age, baseline dengue seropositivity and region. In the 2 pivotal studies, GMTs decreased initially during the first 2 y post-dose 3 but appear to stabilize or slightly increase again in the third year. GMTs persisted 1.2-3.2-fold higher than baseline levels for up to 4 y post-dose 3 in other studies undertaken in dengue endemic countries. Our integrated analysis captures the fullness of the CYD-TDV immunogenicity profile across studies, age groups and regions; by presenting the available data in this way general trends and substantial outliers within each grouping can be easily identified. CYD-TDV elicits neutralizing antibody responses

against all dengue serotypes, with differences by age and endemicity, which persist above baseline levels in endemic countries.

- 48.)** Katzelnick LC. et al. Immune correlates of protection for dengue: State of the art and research agenda. *Vaccine* 2017; 35(36): 4659-69.

Abstract

Dengue viruses (DENV1-4) are mosquito-borne flaviviruses estimated to cause up to ~400 million infections and ~100 million dengue cases each year. Factors that contribute to protection from and risk of dengue and severe dengue disease have been studied extensively but are still not fully understood. Results from Phase 3 vaccine efficacy trials have recently become available for one vaccine candidate, now licensed for use in several countries, and more Phase 2 and 3 studies of additional vaccine candidates are ongoing, making these issues all the more urgent and timely. At the "Summit on Dengue Immune Correlates of Protection", held in Annecy, France, on March 8-9, 2016, dengue experts from diverse fields came together to discuss the current understanding of the immune response to and protection from DENV infection and disease, identify key unanswered questions, discuss data on immune correlates and plans for comparison of results across assays/consortia, and propose a research agenda for investigation of dengue immune correlates, all in the context of both natural infection studies and vaccine trials.

- 49.)** Hadinegoro SR. et al. Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. *N Engl J Med.* 2015;373(13):1195–1206.

Abstract

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. (Funded by Sanofi Pasteur; ClinicalTrials.gov numbers, NCT00842530, NCT01983553, NCT01373281, and NCT01374516.).

- 50.)** Nascimento EJM. et al. Development of an anti-dengue NS1 IgG ELISA to evaluate exposure to dengue virus. *J Virol Methods* 2018; 257: 48-57.

Abstract

Dengue virus infection elicits immune responses to multiple viral antigens including antibodies to dengue non-structural protein 1 (NS1) which are rapidly induced and detected within days of infection. The recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV; Sanofi Pasteur) uses the yellow fever vaccine virus as a back-bone but expresses dengue virus pre-membrane and envelop proteins. Since CYD-TDV does not express dengue NS1, we evaluated the utility of dengue NS1-specific IgG antibodies as biomarkers of dengue exposure in CYD-TDV recipients and controls. We optimized and evaluated a quantitative anti-dengue NS1 IgG enzyme-linked immunosorbent assay (ELISA). Parameters assessed included: accuracy, dilutability/linearity, precision, limit of quantitation and specificity. The assay specificity was further evaluated using Japanese Encephalitis virus, West Nile virus, Yellow Fever virus or Zika virus positive sera samples collected following confirmed infection or vaccination. Receiver-operating-characteristics (ROC) curves as well as sensitivity and specificity for discriminating previous dengue exposure were assessed using 1250 reference samples. Overall, the anti-dengue NS1 IgG ELISA was able to discriminate previous dengue exposure from non-exposure before vaccination with CYD-TDV (ROC area under the curve > 0.9). Assessment of paired samples from 2511 vaccinated participants showed high overall agreement (93%) between pre-vaccination and post-vaccination dengue serostatus classification based on the anti-dengue NS1 IgG ELISA. However, misclassification of dengue serostatus was observed after vaccination likely due to a combination of asymptomatic dengue infections, assay variability and a modest effect of CYD-TDV on the anti-dengue NS1 IgG ELISA readout.

- 51.)** Ferguson NM et al. Benefits and risks of the Sanofi-Pasteur dengue vaccine: Modeling optimal deployment. *Science*. 2016 Sep 2;353(6303):1033-1036.

Abstract

The first approved dengue vaccine has now been licensed in six countries. We propose that this live attenuated vaccine acts like a silent natural infection in priming or boosting host immunity. A transmission dynamic model incorporating this hypothesis fits recent clinical trial data well and predicts that vaccine effectiveness depends strongly on the age group vaccinated and local transmission intensity. Vaccination in low-transmission settings may increase the incidence of more severe "secondary-like" infection and, thus, the numbers hospitalized for dengue. In

moderate transmission settings, we predict positive impacts overall but increased risks of hospitalization with dengue disease for individuals who are vaccinated when seronegative. However, in high-transmission settings, vaccination benefits both the whole population and seronegative recipients. Our analysis can help inform policy-makers evaluating this and other candidate dengue vaccines.

52.) Flasche S et al. The Long-Term Safety, Public Health Impact, and Cost-Effectiveness of Routine Vaccination with a Recombinant, Live-Attenuated Dengue Vaccine (Dengvaxia): A Model Comparison Study. *PLoS Med.* 2016 Nov 29;13(11):e1002181.

Abstract

BACKGROUND:

Large Phase III trials across Asia and Latin America have recently demonstrated the efficacy of a recombinant, live-attenuated dengue vaccine (Dengvaxia) over the first 25 mo following vaccination. Subsequent data collected in the longer-term follow-up phase, however, have raised concerns about a potential increase in hospitalization risk of subsequent dengue infections, in particular among young, dengue-naïve vaccinees. We here report predictions from eight independent modelling groups on the long-term safety, public health impact, and cost-effectiveness of routine vaccination with Dengvaxia in a range of transmission settings, as characterised by seroprevalence levels among 9-y-olds (SP9). These predictions were conducted for the World Health Organization to inform their recommendations on optimal use of this vaccine.

METHODS AND FINDINGS:

The models adopted, with small variations, a parsimonious vaccine mode of action that was able to reproduce quantitative features of the observed trial data. The adopted mode of action assumed that vaccination, similarly to natural infection, induces transient, heterologous protection and, further, establishes a long-lasting immunogenic memory, which determines disease severity of subsequent infections. The default vaccination policy considered was routine vaccination of 9-y-old children in a three-dose schedule at 80% coverage. The outcomes examined were the impact of vaccination on infections, symptomatic dengue, hospitalised dengue, deaths, and cost-effectiveness over a 30-y postvaccination period. Case definitions were chosen in accordance with the Phase III trials. All models predicted that in settings with moderate to high dengue endemicity ($SP9 \geq 50\%$), the default vaccination policy would reduce the burden of dengue disease for the population by 6%-25% (all simulations: -3%-34%) and in high-transmission settings ($SP9 \geq 70\%$) by 13%-25% (all simulations: 10%- 34%). These endemicity levels are representative of the participating sites in both Phase III trials. In contrast, in settings with low transmission intensity ($SP9 \leq 30\%$), the models predicted that vaccination could lead to a substantial increase in hospitalisation because of dengue. Modelling reduced vaccine coverage or the addition of catch-up campaigns showed that the impact of vaccination scaled approximately linearly with the number of people vaccinated. In assessing the optimal age of vaccination, we found that targeting older children could increase the net benefit of vaccination in settings with moderate transmission intensity ($SP9 = 50\%$). Overall, vaccination was predicted to be potentially cost-effective in most endemic settings if priced competitively. The results are based on the assumption that the vaccine acts similarly to natural infection. This assumption is consistent with the available trial results but cannot be directly validated in the

absence of additional data. Furthermore, uncertainties remain regarding the level of protection provided against disease versus infection and the rate at which vaccine-induced protection declines.

CONCLUSIONS:

Dengvaxia has the potential to reduce the burden of dengue disease in areas of moderate to high dengue endemicity. However, the potential risks of vaccination in areas with limited exposure to dengue as well as the local costs and benefits of routine vaccination are important considerations for the inclusion of Dengvaxia into existing immunisation programmes. These results were important inputs into WHO global policy for use of this licensed dengue vaccine.

53.)WHO. Global Advisory Committee on Vaccine Safety, 6-7 June 2018. Available at http://www.who.int/vaccine_safety/committee/reports/June_2018/en/, accessed August 2018. No abstract available.

54.)Chuenkitmongkol S et al. Safety of a recombinant live attenuated tetravalent dengue vaccine: pooled analysis of 20,667 individuals aged 9 through 60 years of age. Joint International Tropical Medicine Meeting; 2015; Bangkok, Thailand. No abstract available.

55.)See No. 29/30, 2018, pp. 389–396, <http://apps.who.int/iris/bitstream/handle/10665/273010/WER9329-30.pdf?ua=1> No abstract available.

56.)Skipetrova A et al. Dengue vaccination during pregnancy - An overview of clinical trials data. Vaccine. 2018 May 31;36(23):3345-3350.

Abstract

BACKGROUND:

The live, attenuated, tetravalent dengue vaccine (CYD-TDV) is licensed in several endemic countries and contraindicated during pregnancy. Inadvertent vaccination during pregnancy may occur during clinical trials that include women of childbearing age. The potential risk associated with dengue vaccination in pregnancy remains unknown. We describe pregnancy outcomes following inadvertent dengue vaccination in pregnancy from CYD-TDV trial data.

METHODS:

Data were collected from trials conducted as part of the CYD-TDV clinical development. Women who received CYD-TDV or placebo during the pre-specified pregnancy risk window (from 30 days before the date of their last menstrual period to end of pregnancy) were considered as exposed; pregnancies occurring in non-risk periods during the trials were considered to be non-exposed. Pregnancy losses were defined as abortion (spontaneous or unspecified), death in utero, and stillbirth.

RESULTS:

615 pregnancies were reported from 19 CYD-TDV trials: 404 in the CYD-TDV arm, and 211 in the placebo arm. Exposure could not be determined for 7 pregnancies (5, CYD-TDV; 2, placebo). In

the CYD-TDV arm, 58 pregnancies were considered as exposed. Most of these (n = 47, 81%) had healthy live births; 6 (10.3%) had pregnancy losses; 3 underwent elective termination and 2 had unknown outcome. In the placebo group, 30 pregnancies were considered exposed. Most of these (n = 25, 83%) had healthy births; 4 (13.3%) had pregnancy losses; and 1 had elective termination. Among non-exposed pregnancies, most resulted in healthy live births; 23/341 (6.7%) in the CYD-TDV group and 17/179 (9.5%) in the placebo group had pregnancy losses. Most reported pregnancy losses were in women considered high-risk for adverse pregnancy outcome, primarily due to young age.

CONCLUSION:

In the small dataset assessed, no evidence of increased adverse pregnancy outcomes has been identified from inadvertent immunization of women in early pregnancy with CYD-TDV compared with the control group.

57.) Crevat D. et al. First Experience of Concomitant Vaccination Against Dengue and MMR in Toddlers. *Pediatr Infect Dis J.* 2015;34(8):884-92.

Abstract

BACKGROUND:

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 ($\geq 95\%$ seroprotection against MMR) and vice versa.

CONCLUSIONS:

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

- 58.)** WHO. Background Paper on Dengue Vaccines, April 2018. Table 7. Available at http://www.who.int/immunization/sage/meetings/2018/april/2_DengueBackgrPaper_SAGE_Apr2018.pdf?ua=1, accessed July 2018.
No abstract available.
- 59.)** Administrative level 1: national; Administrative level 2: province/state or equivalent; Administrative level 3: district or equivalent. WHO. JRF. Question 0080. Available at http://www.who.int/immunization/monitoring_surveillance/routine/reporting/WHO_UNICEF_JRF_EN.xls?ua=1, accessed August 2018.
No abstract available.
- 60.)** Imperial College London. Global Dengue Transmission map. Available at <https://mrcdata.dide.ic.ac.uk/dengue/dengue.php>, accessed July 2018.
No abstract available.
- 61.)** Zeng W. et al. Cost-effectiveness of dengue vaccination in ten endemic countries. *Vaccine*. 2018 Jan 8;36(3):413-420
Abstract
Following publication of results from two phase-3 clinical trials in 10 countries or territories, endemic countries began licensing the first dengue vaccine in 2015. Using a published mathematical model, we evaluated the cost-effectiveness of dengue vaccination in populations similar to those at the trial sites in those same Latin American and Asian countries. Our main scenarios (30-year horizon, 80% coverage) entailed 3-dose routine vaccinations costing US\$20/dose beginning at age 9, potentially supplemented by catch-up programs of 4- or 8-year cohorts. We obtained illness costs per case, dengue mortality, vaccine wastage, and vaccine administration costs from the literature. We estimated that routine vaccination would reduce yearly direct and indirect illness cost per capita by 22% (from US\$10.51 to US\$8.17) in the Latin American countries and by 23% (from US\$5.78 to US\$4.44) in the Asian countries. Using a health system perspective, the incremental cost-effectiveness ratio (ICER) averaged US\$4,216/disability-adjusted life year (DALY) averted in the five Latin American countries (range: US\$666/DALY in Puerto Rico to US\$5,865/DALY in Mexico). In the five Asian countries, the ICER averaged US\$3,751/DALY (range: US\$1,935/DALY in Malaysia to US\$5,101/DALY in the Philippines). From a health system perspective, the vaccine proved to be highly cost effective (ICER under one times the per capita GDP) in seven countries and cost effective (ICER 1-3 times the per capita GDP) in the remaining three countries. From a societal perspective, routine vaccination proved cost-saving in three countries. Including catch-up campaigns gave similar ICERs. Thus, this vaccine could have a favorable economic value in sites similar to those in the trials.
- 62.)** WHO. Evidence to recommendation Table 1: Consideration of Dengue Vaccine.
No Abstract Available
- 63.)** WHO. Evidence to recommendation Table 2: Seroprevalence and screening and vaccination strategy.