DENGUE VACCINE IMPLEMENTATION (Screen & Vaccinate)
SAFETY OF DENGVAXIA®

INFORMATION FOR SKATEHOLDERS

The purpose of this module is to summarize current information and issues on vaccine safety for decision-making, relevant to the implementation in endemic areas of Dengvaxia® (CYD-TDV), the dengue tetravalent vaccine (live, attenuated).

1. TECHNICAL SPECIFICATIONS OF DENGVAXIA

- Dengvaxia® is indicated for the prevention of dengue disease caused by all four dengue virus serotypes in people 9-60 years of age (up to 45 years in most countries) with prior dengue virus infection and living in endemic areas. The indication is subject to change (e.g., from 6 years of age, EMA 2022). Individuals who have not been infected by dengue virus in the past, or for whom this information is unknown, should not be vaccinated.
- Dengvaxia® is a recombinant yellow fever-17D–dengue virus, live, attenuated, tetravalent dengue vaccine.
- The vaccine consists of a powder and solvent for suspension (NaCl 0.4% for unidose and NaCl 0.9% for multidose) and must be stored between +2°C and +8°C (35°F to 46°F), i.e., in a refrigerator.
- For single dose vials, the vaccine must be used promptly after reconstitution. For multidose vials, the suspension must be used as soon as possible and discarded at the end of the immunization session or within 6 hours after reconstitution, whichever comes first. During this period, open vials must be kept between 2°C and 8°C and protected from light.
- The vaccine is to be administered subcutaneously in the deltoid region of the upper arm in a volume of 0.5mL. Ideally, subjects should be kept under observation for 30 minutes after each vaccination to ensure vaccine safety.
- Before administration, vaccine must be inspected visually for cracks, broken seals, correct label content, and extraneous particulate matter or discoloration.
- The vaccination schedule is three doses at 0-6-12 months.

2. VACCINE SAFETY ASSESSMENT IN CLINICAL TRIALS

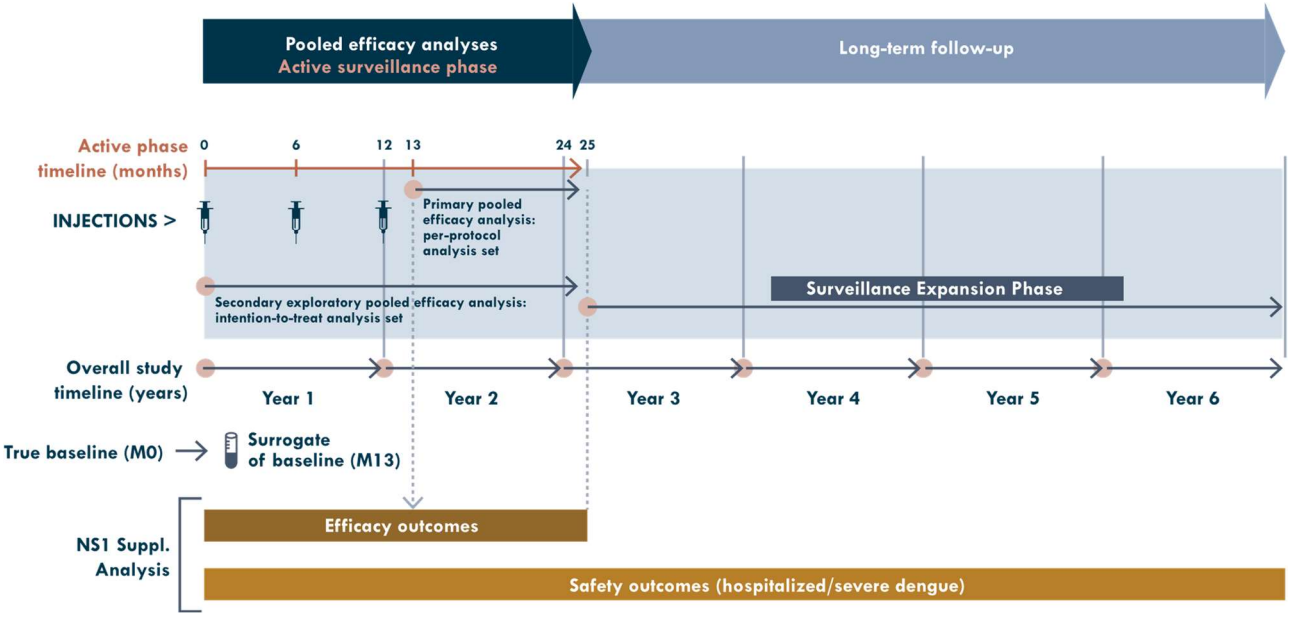
- Dengvaxia® was evaluated in a large, robust clinical trial program, involving 31 studies and more than 41,000 children, adolescents, and adults from endemic and non-endemic countries.
- Vaccine long-term safety has been assessed in trial participants during two phase 3 trials in five Asian–Pacific countries (CYD14; participants aged 2–14 years) and five Latin American countries (CYD15 trial; participants aged 9–16 years), and during a phase 2b in Thailand (CYD23/57; participants aged 4–11 years).
- In compliance with WHO guidelines, hospitalized and severe dengue has been documented.
- An Independent Data Monitoring Committee (IDMC) was in charge of regular review of safety data including assessment of severity. Any related serious adverse event – including serious adverse events of special interest or death – was promptly reviewed by the IDMC throughout the trial period.
- Clinical development allowed to gather immunogenicity and reactogenicity data.
- Efficacy studies were initially designed in 2 phases:

- an active phase of 2 years (years 1-2) allowing the detection of all symptomatic virologically-confirmed dengue (VCD) cases, regardless of the severity,
- and a hospital phase allowing the detection of dengue cases in hospitalized febrile patients, for a period of 4 years (years 3-6).

- Because the incidence of hospitalized VCD cases was higher in the group receiving Dengvaxia® compared to the control group (driven by subjects aged below 6 years of age at enrolment who are more often seronegatives), active surveillance of all symptomatic dengue cases (hospitalized or not) was reactivated during years 5-6. This period of the hospital phase is called the "surveillance expansion period" (FIGURE 1).

FIGURE 1.

Study design of the long-term follow-up of the CYD14 and CYD15 studies:



Source: Dayan GH, et al. Assessment of the long-term efficacy of a dengue vaccine against symptomatic, virologically-confirmed dengue disease by baseline dengue serostatus. Vaccine 2020;38:3531–6.

- In order to further evaluate the safety and efficacy of Dengvaxia® according to dengue serostatus prior to vaccination, a supplemental exploratory analysis (post-hoc) was conducted based on data and samples collected from efficacy studies (CYD23/57, CYD14, CYD15). Because only 10–20% of study participants (immunogenicity subsets) had information on serostatus at baseline, dengue serostatus was retrospectively inferred using a dengue anti-NS1 IgG ELISA assay.
- The NS1 assay measures total IgG antibodies against the NS1 structural protein of the dengue virus that is not expressed by Dengvaxia® recombinant viruses, and thus evaluates previous exposure to wild infection. The full methodology is described in Sridhar et al, 2018 published in N Engl J Med.

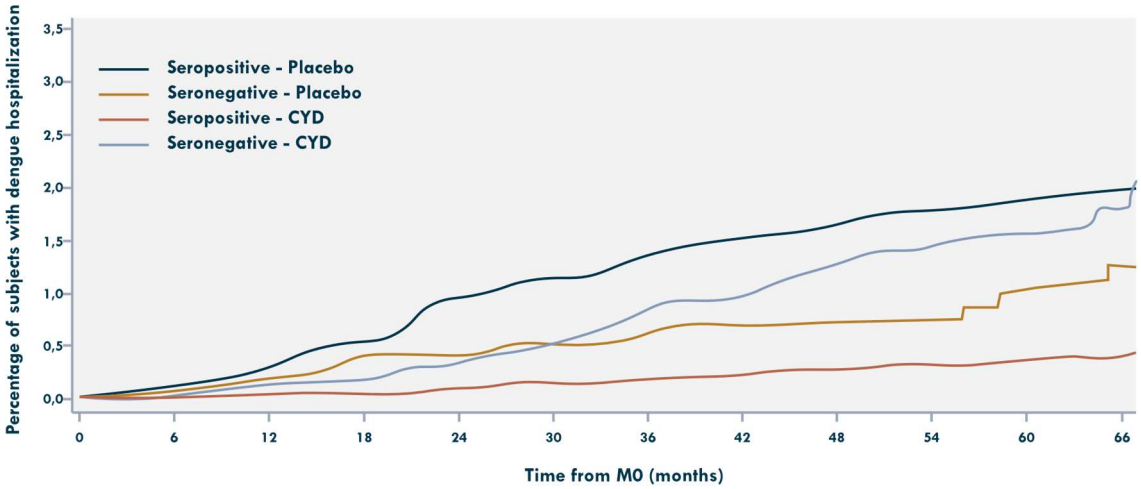
3. VACCINE SAFETY PROFILE IN CLINICAL TRIALS

- The overall safety profile of Dengvaxia® was similar to that of placebo.
- The safety profile of Dengvaxia® after any injection was acceptable and was comparable across the populations studied, regardless of age group, gender, region (non-endemic, endemic Asia-Pacific or endemic Latin America), and dengue immune status.
- No severe immediate hypersensitivity or allergic reactions were related to vaccination.
- Dengvaxia® was well-tolerated, with mild to moderate local and systemic adverse reactions. The most common are those usually observed with any vaccines: injection-site reactions (most frequently injection site pain); headache; myalgia; malaise; asthenia; and fever.

- No causal-related deaths were reported in 15 countries after clinical trials conducted for more than a decade with 41,000 subjects involved.
- No differences were observed between groups with regard to length of hospitalization, frequencies and signs of symptoms, duration of fever and clinical symptoms, and viremia and cytokine patterns. The degree of severity of the disease in vaccinated individuals responded well to medical care and all individuals recovered fully.
- There is a hypothetical risk of acute viscerotropic or neurotropic disease due to the YF 17D backbone of the recombinant dengue vaccine. After examination of non-clinical and clinical evaluations, the WHO Global Advisory Committee on Vaccine Safety (GACVS) found no evidence of such association.
- The long-term data from post-hoc study assessing vaccine performance by baseline dengue serostatus, showed that Dengvaxia® demonstrated robust protection against hospitalized and severe VCD in previously dengue exposed individuals. This confirmed the absence of risk due to waning protection against severe and non-severe dengue disease over time.
- In participants who were dengue seropositive at baseline and ≥9 years old:
  - the risk for hospitalized VCD was reduced across all dengue serotypes, being lowest for serotype 4;
  - the risk for severe VCD was reduced (about 84% reduction);
  - vaccine protection was maintained over the 6-year follow-up, being highest during the first 2 years;
  - the attributable risk of dengue hospitalization per 1,000 vaccinees over the 6-year follow-up ranged from –15.7 to –13.2 for hospitalized VCD and from –4.1 to –3.4 for severe VCD.
  - Of note: protection was also observed in seropositive 6–8-year-olds (significant hazard ratio of about 0,4 over the 6-year period).
- In participants who were dengue seronegative at baseline and ≥9 years old:
  - there was an increased risk of hospitalized VCD for Dengvaxia® versus placebo (hazard ratio of about 1.4), although the difference was not statistically significant (95% confidence interval crossed 1);
  - there was a similar pattern for severe VCD;
  - the estimated attributable risk over the 6-year period ranged from 4.8 to 6.2 per 1000 vaccinees for hospitalized VCD, and from 2.4 to 3.8 per 1000 vaccinees for severe VCD.
- These results corroborate the 2018 WHO recommendations that the vaccine should only be proposed to people with evidence of prior dengue infection.
- Cumulative incidence data of hospitalized VCD from month 0 to month 66 (FIGURE 2.), shows the protective effect of the vaccine in seropositive subjects. Vaccinated seronegative subjects develop less hospitalized VCD than non-vaccinated until month 30. At month 30, the cumulative incidence of seronegative vaccinees starts exceeding that of unvaccinated seronegatives, and progressively increase to reach incidence values comparable to those observed in unvaccinated seropositives by month 66.
- The relative risk of getting severe dengue from a mosquito bite post-vaccination for a study participant 9 years of age or older who had no prior infection was similar to that seen in an unvaccinated person who gets a secondary infection.

FIGURE 2.

Cumulative incidence of hospitalized VCD, month 0 to month 66 in age group 9-16 years old (Sridhar et al, 2018).



- Within the population studied, these data suggest that during a 5-year follow-up, about 5 additional hospitalized dengue cases or 2 additional severe dengue cases per 1000 seronegative vaccinees could occur following vaccination compared to un-vaccinated seronegative children, while there is a reduction of 15 cases of hospitalized dengue and 4 cases of severe dengue per 1,000 seropositive vaccinees, compared to unvaccinated seropositives.
- In addition, a dynamic transmission model based on the NS1 study analysis data was used to assess vaccination outcomes during a 5-30 year period of time and for a range of transmission settings. This model explored the benefits and risks associated with dengue vaccination for a wide range of transmission settings and time horizons. Results indicated that vaccination of dengue-seropositive subjects translates into long-term and sustained benefits.
- According to various models used to assess benefit risk, the dengue Screen and Vaccinate (S&V) strategy is effective in reducing the number of hospitalized and severe cases prevented per vaccination performed. The impact of the intervention strongly depends on the pre-vaccination screening test performances and the dengue seroprevalence in the target population
  - > In high-transmission settings, the public health impact of the intervention, measured by the number of hospitalizations averted, is maximized when specificity is high (which minimized individual harm by vaccinating only seropositives), and sensitivity at least moderately sensitive (which increased coverage among the few who should have been vaccinated, hence maximizing population benefit)
  - > In low-transmission settings, screening tests should be both highly specific and sensitive.
- Models are available to assess public health benefit depending on the proportion of vaccinees with prior dengue virus infection and pre-vaccination screening test characteristics.

4. POST MARKETING DATA FROM IMPLEMENTING COUNTRIES

- Of the 2.9 million doses of Dengvaxia® distributed worldwide, 2.3 million were used during the mass vaccination campaigns in the Philippines and Brazil.
- Safety surveillance in the initial post-marketing stage has been key to better assess the safety profile of Dengvaxia®. Data from both countries are available and show the vaccine to be safe.
- There are no clusters of events in any of the two countries.
- The most frequently reported adverse events (pyrexia, headache, dizziness, myalgia, and vomiting) are consistent with those observed in the clinical development program and in the product label.
- Treatment-emergent allergic and anaphylactic reactions were reported at an estimated frequency of <0.01%.
- As of 7 Dec 2018, 151 dengue cases, of which 101 hospitalized, were reported post vaccination, either spontaneously from market research studies, or from the Post-authorization Safety study (PASS) conducted by Sanofi Pasteur (DNG15; NCT02948933). Among them, 51 cases were virologically-confirmed dengue and 10 suspected cases.
- As of August 2019, a total of 16 fatal dengue case were reported, 15 in the Philippines, and one in Brazil. There were all analyzed through a very efficient pharmacovigilance system and classified as vaccine failure. There continues to be no evidence that any deaths have been causally linked to the dengue vaccine, and the WHO Global Advisory Committee on Vaccine Safety (GACVS) considers indeterminate cause in fatal dengue cases.
- No cases of yellow fever vaccine-associated viscerotropic (YEL-AVD) or neurotropic (YEL-AND) disease were reported.

5. REMARKS ON THE INCREASED RISK IN SERONEGATIVES VACCINEES

- Recovery from infection by one serotype is thought to provide lifelong immunity against that particular serotype, however cross-immunity only provides temporary partial protection against the other serotypes. There is a small risk of severe disease after any dengue infection, but the second infection by a different serotype to the first is thought to be associated with the highest risk of severe dengue. The third and fourth infections are usually associated with a milder clinical course.
- A possible explanation for the excess cases in vaccinated seronegatives are not fully understood, but a

plausible hypothesis is that the vaccine primes the immune system similarly to natural infection (primary-like) infection. According to this hypothesis, the response to a subsequent natural infection following vaccination in seronegatives may act as a second infection, and consequently to a higher risk of serious disease.

- Whether this is due to first infection or vaccine priming, disease severity may be due to:
  - > An antibody dependent enhancement (ADE) favored by priming by vaccination. In this theory, primary infection leads to the formation of serotype-specific antibodies, which confer long-lasting immunity to the infecting serotype, but short-lasting immunity to other unexposed serotypes. Hence, for secondary infection with different serotypes, the antibodies produced are unable to neutralize the virus, but instead form immune complexes with the virus. These immune complexes have higher affinity towards Fcγ receptors on the surfaces of macrophages and other cells, and hence, enhance the entry of the virus into these cells, besides allowing viral replication to occur. The ADE is frequently observed in vitro for flaviviruses and other viruses. In vivo, ADE of dengue is commonly associated to a worse clinical outcome.
  - > Cellular mechanisms, in which high levels of memory T cell activation are observed, accompanied by the release of inflammatory cytokines and apoptosis.

6. RISK MANAGEMENT PLAN

- A Pharmacovigilance Risk Management Plan (RMP) has been established by Sanofi Pasteur for where the dengue vaccine is licensed and marketed. It has been designed taking into consideration all pre-clinical, clinical and post-marketing data, including observations outside the targeted age indication.
- This action plan includes Post-Authorization Safety Studies (PASS) and Post-Authorization Effectiveness Studies (PAES) plus follow-up of efficacy studies.
- The RMP serves two purposes:

1. To further characterize Dengvaxia® safety concerns (including potential adverse events and missing information). The post marketing plan has been defined as a mix between active and passive surveillance, as well as clinical trials. The data is collected from various sources, taking into account the safety surveillance systems in each country and vaccine use. Additional studies are also proposed to collect data for other anticipated uses:
   - in the population not previously exposed during clinical trials (pregnant and lactating women, immunocompromised patients)
   - regarding to co-administration of Dengvaxia® with common vaccines administered in the target population (Tetanus Diphtheria Pertussis booster and Human Papilloma Virus vaccines).
2. To minimize the risk of vaccinating seronegative patients, a communication plan (including educational material) to health care providers (HCP) can be implemented, upon agreement with the National Health Authority. The aim is to reinforce the awareness and understanding of this risk, while providing information on appropriate performance of dengue diagnostic tests to minimize the risk of false positive serological tests results -whatever the endemicity settings. This guide would support HCP in the pre-vaccination screening procedure to determine the eligibility to vaccination.

7. VACCINE IMPLEMENTATION SAFETY REQUIREMENTS

- At the time of vaccine introduction, post-licensure studies, should be considered by countries, under the primary responsibility of national public health authorities, with funding that is seen to be independent. For adverse events following immunization (AEFI)s where sufficient evidence is provided causality assessments should be promptly conducted.
- Countries should ensure robust dengue surveillance pre- and post- vaccine introduction to document Dengvaxia® impact and safety. This includes:
  - > Enhancing existing passive surveillance to identify rare events, reduce under-reporting, allow for real-time data collection, and base decision on population-based incidence data
  - > Building on and mutually strengthening any existing system of reporting information (dengue immunization coverage reports, dengue disease incidence reports, individualized data for dengue diagnostic tests results, and adverse events reports).

- Strengthening laboratory capacities for prompt and efficient diagnosis of dengue, dengue serotypes, and potential rare adverse events.
- Selecting clear and appropriate disease case definitions for AEFIs.
- Strengthening systems for data collection, reporting and data management, for dengue and Dengvaxia® Severe Adverse Events (SAE).
- Developing and implementing safety data tools including AEFI reporting and investigation forms.
- Encouraging the use of continuous "observed versus expected" analysis for signal detection and signal analysis to rapidly identify and evaluate potential risks.
- Training of health staff (vaccinators, lab technicians, GP, nurses, data managers, etc) in disease surveillance

- Vaccine program safety also needs close monitoring, including sepsis due to contaminated needles/vials, cold chain breakdown, poor injection technique, faints/panic attacks due to fear of injection, non-compliance to schedule and indication, or user errors. These program-related events should be closely monitored in the context of a new vaccine that may be given outside of health facilities, and that requires administration of 3 doses over a one-year period.
- Dengvaxia® vaccine failures will be important to document in terms of:
  - Poor or no response to vaccination
  - Waning of protection over time
  - Poor or no protection against the major circulating serotype(s)
  - Manufacturing changes and quality defects
- For AEFIs where sufficient evidence is provided Causality Assessments should be promptly conducted following the WHO recommendations for causality assessment (https://vaccine-safety-training.org/causality-assessment-of-aefis.html)".
- Vaccine introduction can be accompanied by phase 4 studies that will answer remaining questions on vaccine safety such as:
  - Safety when administered to specific populations, e.g., older individuals (above 45 years), immune-compromised individuals, or women who become pregnant between the first and third vaccine doses.
  - Possible co-administration with other age-appropriate vaccines, e.g., vaccines administered in the same target population (if no data are available).
  - Specific adverse events: severe dengue from natural infection potentially induced by incomplete vaccine protection or neurotropic and viscerotropic adverse events rarely associated with yellow fever vaccine. While none of these events have been documented with Dengvaxia®, they represent theoretical risks, the latter because vaccine has a yellow fever vaccine backbone.
  - Available optimal RDT for past dengue diagnosis based on country endemicity
  - National recommendation for available optimal RDTs to be used with the vaccine
  - Screen and vaccinate program
- A communication plan should be prepared to ensure that vaccination will be only offered to seropositive patients, and that prompt medical attention will be given to those who show early sign of dengue disease and/or early warning sign for severe dengue (proper medical attention can prevent the fatal outcome of dengue).
- When pregnant women were inadvertently administered Dengvaxia® during the clinical trials, there was no evidence of harm to the fetus or to pregnant woman. Consequently, WHO considers women of child-bearing age do not need to be tested for pregnancy.

8. DENGVAXIA® PHARMACOVIGILANCE CHALLENGES

- Data do not indicate need to delay vaccine in areas where policy-makers have determined vaccine would provide benefit. However, ideally and if feasible, post-licensure studies can be conducted that augment data base of vaccine effects stratified by baseline serostatus.
- In the absence of criteria for distinguishing vaccine failure from vaccine-related immune enhancement, individual cases cannot be attributed to one or the other. As a result, such cases should be classified as indeterminate, irrespective of the time since vaccination" (The WHO Global Advisory Committee on Vaccine Safety (GACVS) published a report on 20 July 2018). Dengvaxia® will be implemented in a changing epidemiological and programmatic environment, requiring anticipation and ongoing and proactive horizon-scanning for changes, including:
  - Provision of targeted and tailored information to explain data and communicate benefits and safety.
  - Development of a national vaccine related event communication plan or manual, including rumor tracking and communication crisis management
  - Guidelines and algorithms for vaccinated patients with febrile syndrome in endemic areas for Chikungunya and Zika

- Promoting confidence in safety surveillance systems.
- Anticipating epidemiological and programmatic changes.
- Having a very proactive and tailored risk management plan in place.
- Evaluation of the risk/benefit for decision making, and especially, how many severe dengue Dengvaxia® could avert compared to how many severe dengue Dengvaxia® could potentially be responsible of.

- Countries should have a dengue safety crisis management plan in place well in advance, including:
  - A frequent, proactive, and transparent review of dengue surveillance data.
  - Ongoing analysis and interpretation of passive data.
  - Giving the public a balanced overview of Dengvaxia® safety.
  - Preparing clear and efficient guiding principles and plans for communication with the media.
  - Minimizing misuse of data by the media [see Module COMMUNICATION].

9. READ MORE

TECHNICAL SPECIFICATION

- Sanofi Pasteur update of product label published November 29, 2017 is available at: http://mediaroom.sanofi.com/sanofi-updates-information-on-dengue-vaccine/
- The WHO vaccine position paper, outlining WHO recommendations for the dengue vaccine, was published 7 September 2018: No 36, 2018, 93, 457–476, available at http://www.who.int/wer/2018/wer9336/en/
- Human medicine European public assessment report (EPAR): Dengvaxia, last updated Jan 21, 2022, available at: https://www.ema.europa.eu/en/medicines/human/EPAR/dengvaxia

VACCINE SAFETY IN CLINICAL TRIALS

- Forrat R, et al. Analysis of hospitalized and severe dengue cases over the six-years of follow-up of the tetravalent dengue vaccine (CYD-TDV) efficacy trials in Asia and Latin America. Clin Infect Dis. 2021 Apr 4:ciab288. This post-hoc analysis presents safety and efficacy data over the complete 6-year follow-up of three CYD-TDV efficacy studies.
- For latest description of long-term trials data using NS1 testing: Sridhar, et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. N Engl J Med. 2018 Jul 26;379(4):327-340. doi: 10.1056/NEJMoa1800820, available at: https://www.nejm.org/doi/pdf/10.1056/NEJMoa1800820
- In addition, these research articles describe safety and efficacy data collected during the phase 3 trials:
  - Dayan GH, et al. Assessment of the long-term efficacy of a dengue vaccine against symptomatic, virologically-confirmed dengue disease by baseline dengue serostatus. Vaccine 2020;38:3531–6.)
  - Gailhardou S, et al. Safety Overview of a Recombinant Live-Attenuated Tetravalent Dengue Vaccine: Pooled Analysis of Data from 18 Clinical Trials, PLoS Negl Trop Dis. 2016 Jul 14;10(7):e0004821. This article analyzes pooled safety data from 18 phase I, II and III clinical trials in which the dengue vaccine was administered to participants aged 2–60 years
  - Hadinegoro, et al. Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease,N Engl J Med. 2015;373(13):1195-206, available at: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1506223
  - Dayan GH, et al. Efficacy after 1 and 2 doses of CYD-TDV in dengue endemic areas by dengue serostatus. Vaccine. 2020 Sept; 38(41): 6472-6477. doi:10.1016/j.vaccine.2020.07.056. The article describes results from a post-hoc analysis of two Phase III studies showing that CYD-TDV has high efficacy against VCD from the first dose.
- The following articles describe modeling data on the risk benefit of a S&V intervention depending on transmission intensities and screening test performances:
  - Coudeville L, et al. The potential impact of dengue vaccination with, and without, pre-vaccination screening. Vaccine 2020;38(6):1363–9.
  - Wilder-Smith A, et al. Pre-vaccination screening strategies for the use of the CYD-TDV dengue vaccine: A meeting report. Vaccine, 2019; 37 (36): 5137-46.
  - Coudeville L, et al. Assessment of benefits and risks associated with dengue vaccination at the individual and population levels: a dynamic modeling approach. Expert Rev Vaccines. 2018;17(8):753-63
  - España G, et al. Model-based assessment of public health impact and cost-effectiveness of dengue vaccination following screening for prior exposure. PLoS Negl Trop Dis. 2019 Jul 1;13(7):e0007482.

POST MARKETING DATA FROM IMPLEMENTING COUNTRIES

- Rojas A, et al. 3 years of post-licensure safety data on a live attenuated tetravalent dengue vaccine (CYD-TDV). 35th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) - 24-28 August 2019 , Philadelphia, USA. Abstract on https://onlinelibrary.wiley.com/doi/full/10.1002/pds.4864 ; poster 806. This poster describes the latest post-marketing data from the Philippines and Brazil.

REMARKS ON THE INCREASED RISK IN SERONEGATIVES VACCINEES

- Rothman AL. Immunity to dengue virus: a tale of original antigenic sin and tropical cytokine storms. Nat Rev Immunol 2011; 11(8):532-543.

DENGVAXIA® PHARMACOVIGILANCE CHALLENGES

- "*Vaccine Safety Event: Managing the communications response*" is a WHO Europe resource for media communication strategies for vaccine related events. It is available at: http://www.euro.who.int/en/health-topics/communicable-diseases/poliomyelitis/publications/2013/vaccine-safety-events-managing-the-communications-response
- "World Health Organization (WHO) and the Special Programme for Research and Training in Tropical Diseases, *Dengue Guidelines for Diagnosis, Treatment, Prevention, and Control. 2009*, WHO/HTM/NTD/DEN/2009.1," available at: http://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf. This report describes and discusses current dengue diagnosis tools.
- The WHO *"Global Vaccine Safety Blueprint"*, dated 2012, proposes a set of options for ensuring safe use of vaccines, and maximum benefit from them. It is available at Global vaccine safety blueprint http://extranet.who.int/iris/restricted/bitstream/10665/70919/1/WHO_IVB_12.07_eng.pdf?ua=1
- A set of resources developed for HPV vaccine implementation are also relevant:
  - WHO Adverse events following immunization reporting form (2008)," available at: http://www.rho.org/files/rb3/AEFI_Reporting_Form_PATH_2008.pdf. This report provides an example of a simple reporting form for adverse events following immunization
  - "WHO, *Immunization Safety Surveillance: Guidelines for Managers of Immunization Programmes on Reporting and Investigating Adverse Events Following Immunization*, WPRO/EPI/99.01 (1999)," available at http://www.rho.org/files/rb3/Immunization_Safety_Surveillance_Guidelines_WHO_1999.pdf This report provides a guideline for managers of immunization programme AEFI surveillance (and others responsible for vaccine safety).
  - "WHO, *Adverse Events Following Immunization (AEFI): Causality Assessment,*" downloadable at: www.rho.org/files/rb3/AEFI_Causality_Assessment_WHO_2005.pdf . This report serves as a guide to a systematic, standardized causality assessment process for serious adverse events following immunization.
  - The revised recommendation on use of dengue vaccine from the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE). Geneva: World Health Organization, April 19, 2018. WER 8 June 2018, vol. 93, no. 23 (pp. 329–344). Are available at: http://www.who.int/immunization/diseases/dengue/revised_SAGE_recommendations_dengue_vaccines_apr2018/en/