DENGUE VACCINE IMPLEMENTATION (Screen & Vaccinate) GENERAL INFORMATION

INFORMATION FOR SKATEHOLDERS

The purpose of this module is to summarize, for decision makers and program planners, key accessible information on dengue disease and burden, and on the characteristics and specificities of Dengvaxia®, the first dengue vaccine manufactured by Sanofi Pasteur. This module serves as an introduction for the Dengue Vaccine Toolkit.

1. DENGUE : A GLOBAL PUBLIC HEALTH CHALLENGE

1.1. Dengue epidemiology

- Dengue fever is the most prevalent and widespread mosquito-borne viral disease. It is transmitted to human through the bites of infected Aedes mosquitoes, principally *Aedes aegypti*. Dengue virus is a small single-stranded RNA virus comprising four distinct serotypes (DEN-1 to DEN-4). These closely related serotypes of the dengue virus belong to the genus Flavivirus, family Flaviridae. The geographical spread of all four serotypes from Asia to the rest of the world represents a global pandemic threat.
- The mosquito vectors become infected when they feed on infected humans during the initial five-day period of viraemia. After the extrinsic incubation period (4-10 days), mosquito bites result in infection. Infected humans are the main carriers and multipliers of the virus.
- The primary vector, *Aedes aegypti,* lives in urban habitats and breeds mostly in man-made containers. Aedes albopictus is a highly adaptive secondary dengue vector that has spread from Asia to Africa, the Americas, and Europe. Both are day-time feeders.
- Usually found in urban environments from tropical and subtropical regions, dengue is increasingly reported from rural areas, and an increasing number of cases have been reported outside endemic areas in recent years.
- Urbanization and travel greatly facilitate the dissemination of dengue viruses and therefore the re-emergence and growth of dengue fever.
- Dengue transmission is heterogeneous between countries, over time, and even at small-scale local levels, which makes country-wide generalizations difficult.

1.2. Dengue burden

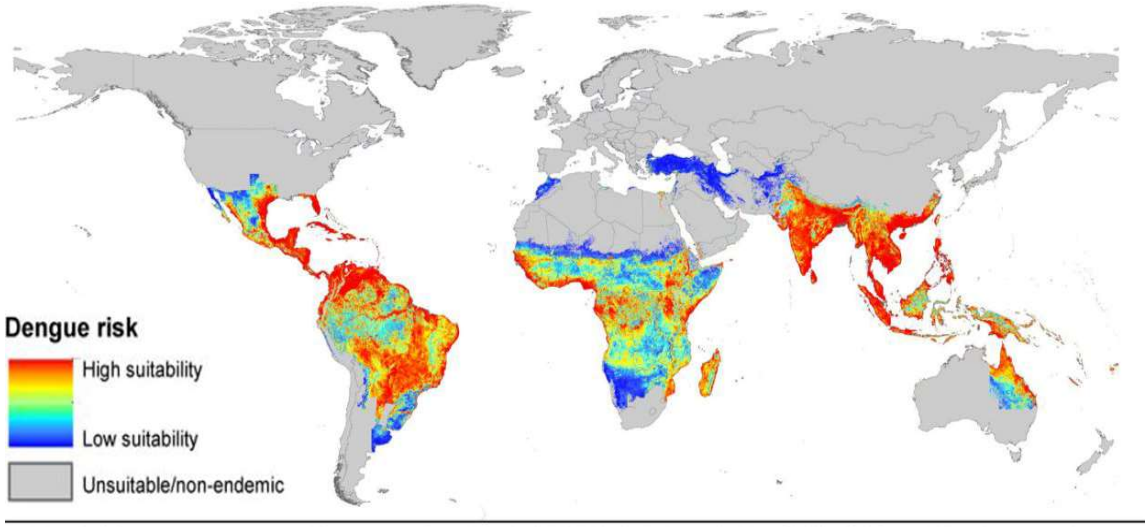
- Half the population worldwide is at risk for dengue and the disease is now endemic in 129 countries. Today, severe dengue affects most Asian and Latin American countries, and become a leading cause of hospitalization and death among children in these regions. The disease is endemic in the WHO regions of Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific and spreads to new areas including Europe. Asia represents ~70% of the global burden of disease. There is a diversity of dengue risk between regions and within countries (FIGURE 1A).
- Between 100 and 400 million infections may occur each year. One modelling study estimate indicates 390 million dengue virus infections per year (95% credible interval 284–528 million), of which 96 million (67–136 million) manifest clinically (with any severity of disease) and 500,000 people develop dengue hemorrhagic fever (DHF) requiring hospitalization. More recent studies using the Global Burden of Diseases, Injuries, and Risk factors Study (GBD) 2017 estimates that 104 771 911 (95% UI 63 759 019 - 158 870 031) dengue cases occurred in 2017, of which 40 467 died from the disease.
- The largest number of dengue cases ever reported globally was in 2019, with all WHO Regions affected.

The American Region alone reported 3.1 million cases, with more than 25,000 classified as severe, while Asia reported high number of cases: Philippines (420 000), Vietnam (320 000), Malaysia (131 000) and Bangladesh (101 000).

- During the past five decades, dengue incidence has increased 30-fold, making it one of the fastest-spreading vector-borne diseases and one of the few infectious diseases with increasing mortality trend. In 2017, globally, the estimated incidence rate was 1 371.3 (834.5 - 2 079.3) per 100 000 population (FIGURE 1B).
- Dengue virus can strike anyone, regardless of age or socioeconomic status. In endemic countries, highest incidence of dengue is generally seen in children and adolescents, but in some settings, dengue incidence peaks in adulthood. Once thought to be a disease of poverty, it is now known to also affect wealthy neighborhoods and cities.
- DHF is a leading cause of hospitalization, straining medical resources during outbreaks and having a heavy economic and societal impact. Globally, dengue caused approximately 2 922 630 (1 629 424 - 3 967 492) disability-adjusted life years (DALYs) in 2017.

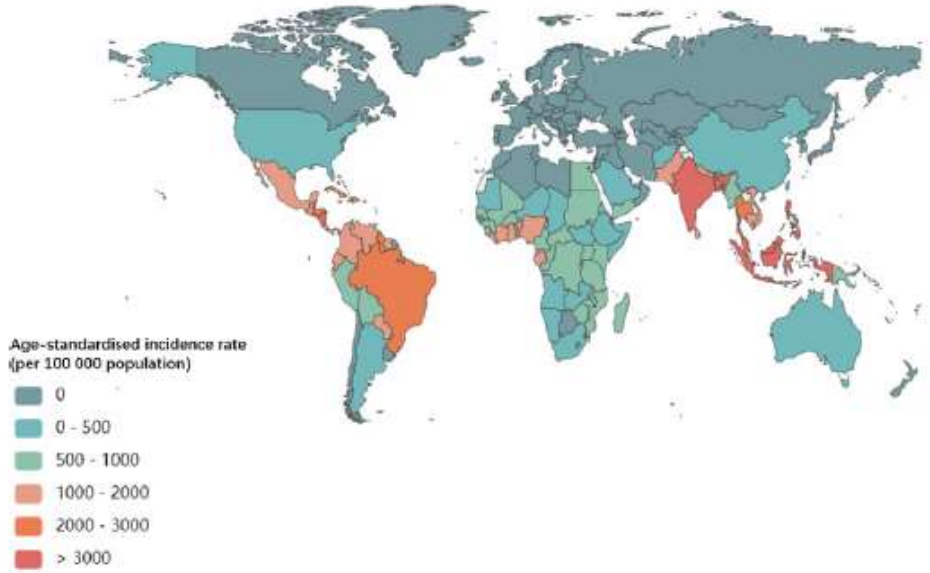
FIGURE 1. A&B

A. Distribution of global dengue risk (from Simmons et al., 2012; Bhat et al., 2013).



Global strategy for dengue prevention and control 2012-2020, World Health Organization, ISBN 978 92 4 150403 4, page 2, 2012

B. Dengue incidence rates (Zeng et al., 2021)



1.3. Dengue, a life-threatening disease

- Dengue, also known as break bone fever, is usually presenting as an influenza-like illness; it has a wide clinical spectrum that includes both severe and non-severe manifestations. In most patients, after an incubation period of 4 to 10 days, the illness begins abruptly with a self-limiting symptomatic phase, usually during 2 to 7 days.
- Severe manifestations are however observed in a small proportion of patients (2 to 4 % of symptomatic cases), including severe bleeding, shock, respiratory distress and organ impairment. The case fatality ratio typically varies from 0.1 to 1%.
- Warning signs may be observed during the febrile phase; they usually announce the transition to critical phase and the occurrence of a severe form of dengue.
- The dengue virus can infect people up to four times. While first infections are typically asymptomatic or mild, secondary infections carry an increased risk of severe disease. The longer the interval between the first and second infection, the higher the risk of developing severe disease.
- Recovery from infection by one serotype usually provides lifelong immunity against that particular serotype. However, cross-immunity to other serotypes is partial and temporary.
- The pathogenesis of dengue and the leading causes for disease severity are very complex and still not understood. The current hypothesis includes the integration of several responses: humoral immunity with possibility for antibody-dependent enhancement (ADE); cellular immunity with subsequent cytokine storm mediated by the T cell response; and the viral component with viruses impairing the function of target cells. Other risk factors for severe dengue include age, pregnancy near the term, chronic diseases, and dengue immune status.
- There is no specific treatment for dengue. Clinical management is based on supportive therapy. Early diagnostic, early recognition of warning signs, optimization of triage, and appropriate case management (including rational use of intravenous rehydration therapy) are crucial in the perspective of dengue mortality reduction.
- The clinical presentation of dengue shares similarities with up to 12 major pathogens making misdiagnosis common, particularly in areas with high incidence of febrile illnesses.

1.4. Dengue outbreaks

- The past 25 years have also seen the emergence and re-emergence of epidemic dengue, with explosive outbreaks which are larger and more frequent. Outbreaks are often unpredictable, making difficult to control the disease.
- The threat of a possible outbreak of dengue now exists in Europe, with local transmission and autochthonous cases now observed on an almost annual basis in many European countries.
- During dengue epidemics, very large numbers of patients are admitted every day and due to the scarcity of resources, close monitoring of all dengue patients become impossible. Case management of dengue cases diverts limited health care resources away from other routine preventive and curative activities.
- Dengue outbreaks generate significant economic burden; these affect tourism and other economic drivers, and lead to substantial losses in productivity.
- Dengue morbidity can be reduced by:
  - > Vaccinating against dengue
  - > Enhancing outbreak prediction and detection through the implementation of a coordinated epidemiological and entomological surveillance
  - > Promoting and deploying context-specific vector management and control strategies
  - > Optimizing communication strategies to achieve behavioral outcomes in prevention programs
  - > Improving disease diagnosis and case management
- Dengue mortality can be reduced by:
  - > Vaccinating against dengue
  - > Identifying early warning signs for a timely management of cases and reducing the risk of progression to severe dengue
  - > Implementing early case detection and appropriate hospital referral of severe patients
  - > Managing severe cases with appropriate treatment
  - > Reorganizing health services for the purpose of dengue outbreaks preparedness
  - > Training personnel at all levels of health system
- Vector control strategies include:
  - > Preventing mosquitoes from accessing egg-laying habitats through environmental cleansing
  - > Removing man-made vector habitats
  - > Covering, emptying, and cleaning regularly domestic water storage containers
  - > Treating outdoor water storage containers with larvicides as complementary to environment management
  - > Using personal household protection such as window and door screens, clothing that minimize skin exposure, using bed-nets, mosquito repellents including mosquito coils and other insecticides vaporizers reducing biting activity

- Improving community participation and mobilization for sustained vector control interventions
- Insecticides spraying during outbreaks
- Active entomological surveillance to determine effectiveness of vector control interventions
- New alternative vector-control tools such as the release of Wolbachia-infected *Aedes aegypti* in dengue-affected communities (www.worldmosquitoprogram.org)

Since 2016, dengue is a vaccine-preventable disease.

- WHO is promoting the "Integrated Vector Management (IVM)" as a key strategy for vector control; however, and despite governments efforts, vector control programs are costly and have failed to halt dengue's advance.

2. DENGVAXIA®: THE FIRST VACCINE AGAINST DENGUE

2.1. The first licensed dengue vaccine

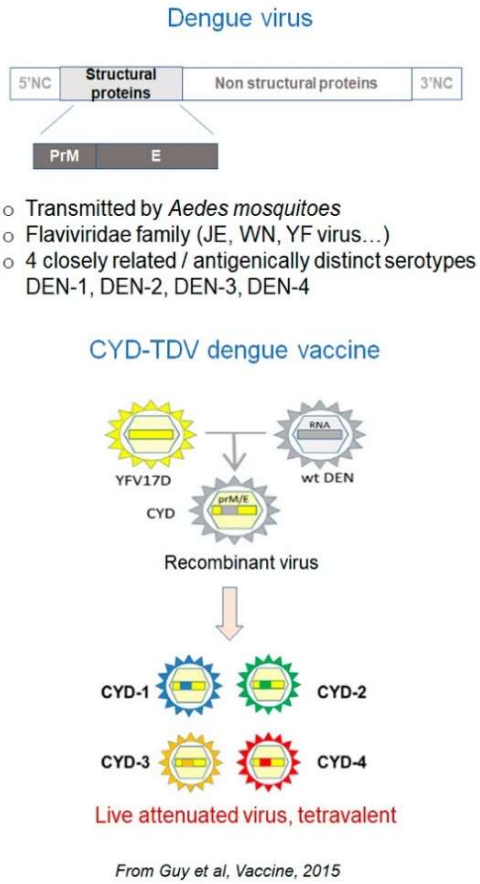
- Since December 2016, dengue is a vaccine-preventable disease. The CYD-TDV vaccine, developed by Sanofi Pasteur, and licensed under the name Dengvaxia®, is the first and only dengue vaccine approved worldwide. The vaccine was evaluated in a large, robust clinical trial program which led to its licensure in EU, US and in several endemic countries in Latin America and Asia.
- In June 2019, Dengvaxia® was added to the WHO EML (Model List of Essential Medicines) and EMLC (Model List of Essential Medicines for Children) for use in some high-risk populations.
- In March 2020, WHO awarded prequalification status to Dengvaxia®, underlying the vaccine's quality, safety, and efficacy.
- Dengvaxia® has been implemented in private markets in Asia and Latin America and in two public health programs.

2.2. Dengvaxia® vaccine characteristics

- Dengvaxia® is a prophylactic, tetravalent, live recombinant viral vaccine. Based on the yellow fever 17D vaccine strain, the vaccine is a mix of four viral recombinant, encoding for membrane and envelop proteins antigens of the four dengue virus strains (FIGURE 3). There is no adjuvant.
- Dengvaxia® is indicated for the prevention of dengue disease caused by all four dengue virus serotypes in people 9-45 years of age (up to 60 years in some countries) with prior dengue virus infection and living in endemic areas. The indication is subject to change (e.g., indication from 6 years of age, see EMA 2022).
- Dengvaxia® is given as a 3-dose series with 6 months between each dose. The injection is given under the skin, preferably in the upper arm.
- It is not indicated for outbreak control, since immunization requires the administration of three doses over a period of 12 months. Nevertheless, an outbreak remains a signal for the potential public health interest for vaccine use.

FIGURE 3.

Dengvaxia®, the dengue vaccine



From Guy et al, Vaccine, 2015

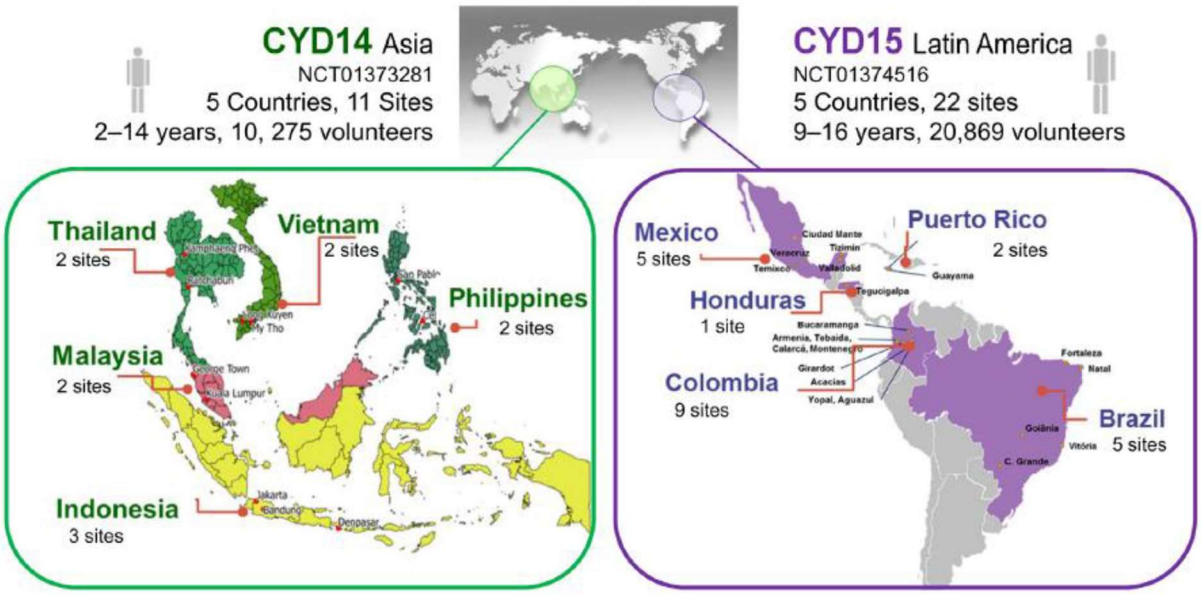
2.3. Dengvaxia® (CYD-TDV) characteristics

2.3.1. 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. The two major Phase 3 clinical trials were conducted in 10 endemic countries – five in the Asian-Pacific region (CYD14; Capeding et al, 2014) and five in Latin America (CYD15; Villar et al, 2015). A smaller phase 2b study (CYS23/57) was conducted in Thailand. All together, these 3 efficacy and safety trials totaled more than 35,000 subjects aged 2 to 16 years in the vaccine and the control groups (FIGURE 4). Phase 3 trials were randomized, placebo-controlled, observer-blind and multicenter. Randomization was 2:1 vaccine group: placebo, and the primary endpoint for vaccine efficacy was symptomatic virologically confirmed dengue (VCD).
- Using a case cohort sampling design, the trial data were reanalyzed to evaluate the long-term safety and efficacy of the vaccine by dengue serostatus of participants prior to vaccination (i.e., whether they were seropositive or seronegative at the time of receiving the first vaccine dose).
- Because the serostatus of most trial participants was not known, pre-vaccination serostatus was inferred, based on samples that had been collected from all trial participants one month after the 3rd dose was administered. Participant samples were re-tested using a new diagnostic assay that allows distinguishing immune responses due to past dengue infection from those due to vaccination. This test, combined with imputation methods, allowed retrospective categorization into seropositives and seronegative at time of first vaccination.

FIGURE 4.

CYD-TDV large phase 3 trials. Source: Adapted from Guy et al., 2015.



Source: Hadinegoro et al., 2015

2.3.2. DENGVAXIA® EFFICACY

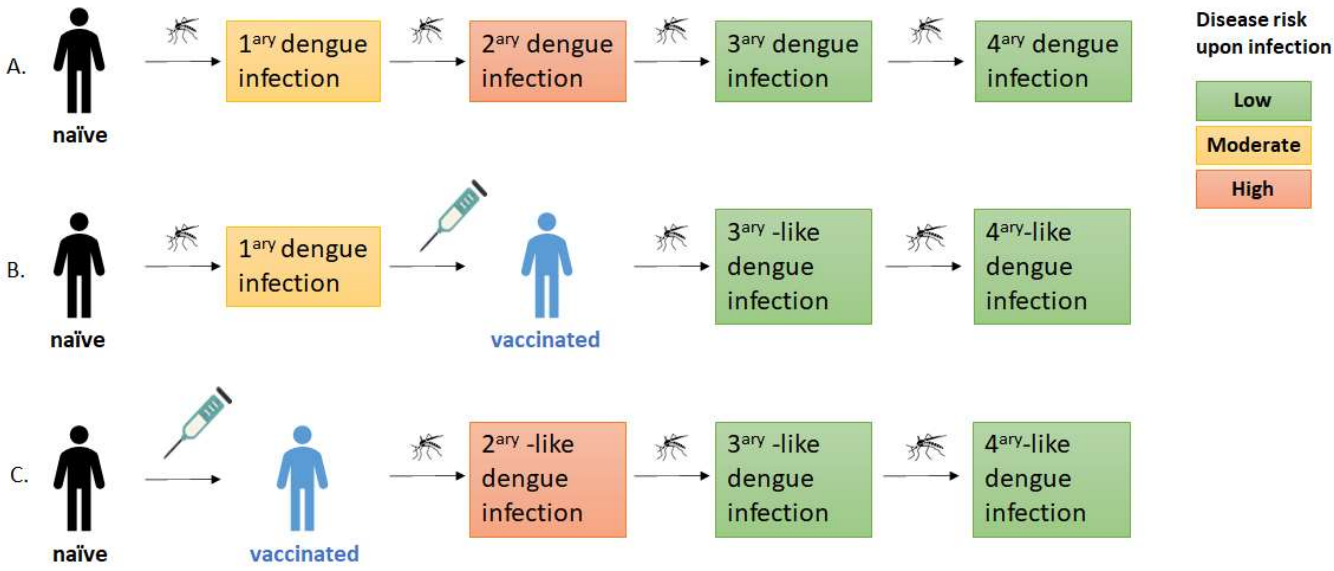
- Dengvaxia® provides efficacy across all four dengue virus serotypes, and is effective at reducing the risk of symptomatic, severe and hospitalized dengue in people with a past dengue infection (prevents approximately 8 out of 10 cases of severe and hospitalized dengue) with long-term protection up to 6 years.
- Over the entire 6-year follow-up period, in participants who were seropositive and ≥9 years old, Dengvaxia® demonstrated robust protection against hospitalized dengue (hazard ratio (HR) = 0.19 [95% CI: 0.12–0.30]) and against severe dengue (HR = 0.15 [95% CI: 0. 06–0.39]).

- The risk for hospitalized VCD was reduced across all dengue serotypes, being lowest for serotype 4.
- The use of Dengvaxia® in individuals up to 60 years of age is supported by immunogenicity and safety data collected in the clinical trials in adults.
- Since Dengvaxia® was licensed, additional data became available from several clinical studies which allowed to further assess the benefit risk profile of the vaccine. Data show that children with a past dengue infection aged 6–8 years have a 62% risk reduction in hospitalized dengue up to 6 years after the first injection, showing benefit in this age group. Data is being reviewed by National Regulatory Authorities with regard to a possible extension of the vaccine indication.

2.3.3. DENGVAXIA® SAFETY

- Over 41 000 subjects participated in the Sanofi Pasteur dengue vaccine clinical study program (phases 1, 2 and 3), of whom 29 000 volunteers received the vaccine. The overall safety profile of Dengvaxia® is similar to that of placebo.
- In the long-term follow-up of Phase 3 clinical trials, an increased risk of severe dengue has been observed in vaccinated seronegatives (with no dengue infection prior to vaccination) compared to unvaccinated seronegatives. The risk of severe dengue in vaccinated seronegatives is the same as the risk in unvaccinated seropositives (5 out to 1000 upon secondary infection). The symptoms of dengue hemorrhagic fever (DHF, grade I or II) observed in seronegative individuals vaccinated are a temperature over 38°C for 2 days or more, coupled with abnormal laboratory. In the study, all individuals recovered fully after symptomatic treatment.
- The vaccine does not cause any known disease and does not cause dengue but would act like a silent natural dengue infection. In seronegative individuals, the response to the first natural infection following vaccination may act as a second infection, which has typically been associated with a higher risk of serious severe disease. In seropositive individuals, the response to the first natural infection following vaccination is as if it was a third second or later infection and not associated with a higher risk of serious severe disease (FIGURE 5).
- Of the 2.9 million doses of Dengvaxia® distributed worldwide, 2.3 million were administered in two vaccination public programs in Asia and in Latin America. Post marketing safety data showed that the vaccine is safe in individuals with past dengue infection. There is no clusters of events in any of the two countries.

FIGURE 5.
Proposed Dengvaxia® mode of action (adapted from Laydon et al., 2021).
A: with no vaccine; B: vaccine administered to seropositive; C: vaccine administered to seronegative.



- The risk of disease during a natural infection with dengue fever varies depending on the number of infections one individual has suffered and his/her vaccination status (FIGURE 5). In unvaccinated (naïve) individuals, disease risk is moderate during their first dengue infection, high during their second natural infection, and low during subsequent natural infections (5A). Vaccine may work as a silent infection. In individuals who have previously been infected once, the vaccination mimics a subsymptomatic immune response. If a second natural infection occurs, the individual is protected, and the disease risk will be low, similar to that caused by a tertiary infection (5B). In seronegative individuals who receive vaccination, a subsequent first natural infection will resemble a second natural dengue infection, thus carrying a higher risk of severe disease (5C).

Dengvaxia® demonstrated robust protection against hospitalized and severe VCD over the entire 6-year follow-up in participants who were seropositive and ≥9 years old.

2.3.4. DENGVAXIA® PUBLIC HEALTH IMPACT

- In the current indicated age population (≥9 years), over the 6-year follow-up, the decreased attributable risk translated into 1 320 to 1 570 hospitalized dengue cases prevented and 340 to 410 severe dengue cases prevented per 100 000 vaccinees seropositive at baseline.
- A screen and vaccinate approach targeting those at highest risk of severe dengue and hospitalization has the potential to be cost-effective in most dengue-endemic settings. By selecting individuals at greatest risk, pre-vaccination screening translates into a higher proportion of severe and hospitalized dengue cases prevented per vaccination.
- High-resolution maps of dengue seropositivity are now available, to help optimal deployment of the vaccine. Such tools could help reducing the worldwide burden of dengue disease by as much as 30%. Therefore, targeting seropositive recipients with Dengvaxia® is an increasingly viable public health strategy.

2.4. Policy and recommendations

- The implementation of public dengue vaccination programs using Dengvaxia® should be in accordance with official recommendations and consistent with current approved labelling in each country where it is approved, as well as in line with WHO position for the vaccine.
- Following the release of the long-term safety data stratified by serostatus, the World Health Organization (WHO) has issued in 2018 an updated position paper on Dengvaxia® that addresses modifications to the initial indication (BOX 1). The WHO recommended the use of Dengvaxia® with pre-vaccination screening to identify people with prior dengue infection for countries incorporating Dengvaxia® into their dengue control program. Vaccinating people with a past dengue infection targets those at greatest risk of severe disease and hospitalization and mitigates the risk of vaccinating those without prior infection.
- Individuals who have not been infected by dengue virus in the past, or for whom this information is unknown, should not be vaccinated (EMA, 2020).
- A series of recommendations and position papers are published by national experts' bodies and global organizations to help country decision-making. As usually done, the evaluation process is constantly fed with the latest evidence, including new scientific results, epidemiological data and vaccine implementation information, and recommendations are updated accordingly.

2.5. Dengvaxia® implementation

- Dengvaxia introduction should complement existing effort to optimize dengue surveillance, mosquito vector control, and dengue case management. Use of dengue vaccine should follow an integrated approach and help invigorating existing programs.
- Administering Dengvaxia® to people with a past dengue infection targets those at greatest risk of severe disease and hospitalization and mitigates the risk of vaccinating those without prior infection. Consequently, for countries considering vaccination as part of their dengue control program, the World Health Organization (WHO) recommends a "Screen and Vaccinate" strategy, in which only dengue-seropositive persons are vaccinated.
- Sanofi Pasteur co-developed with CTK Biotech the *OnSite*® Dengue IgG RDT, specifically designed to identify individuals in the age range for vaccination who have had a past dengue infection, and with specificity and sensitivity criteria within the targeted range. Although less optimal, other options may be chosen to assess dengue seropositivity before vaccination, such as using other RDTs for dengue diagnostic or ELISA testing.

- Depending on local epidemiology and context, a range of Screen and Vaccinate strategies can be considered to obtain optimal impact. Both the Screening and the Vaccination of seropositives can be performed on the same day (One-step approach) or two different days (Two-step approach). The Screening and the Vaccination can be performed in schools, community outreach posts, and/ or health care facilities.
- Countries wishing to maximize short-term vaccination impact may consider catch-up campaigns.
- Countries should ensure they have adequate supply chain capacity at national level and in targeted dengue endemic areas.
- Dengvaxia® introduction should be accompanied with a careful documentation of vaccine impact and safety. This includes the implementation of robust post-introduction dengue surveillance, as well as regular assessments of vaccination coverage and the close monitoring of adverse events following immunization (AEFI), and dengue surveillance. Comprehensive evidence-based cost effectiveness studies should also be conducted.
- Vaccine introduction must be accompanied with a targeted communication strategy. Effective and coordinated communication and advocacy on dengue and dengue vaccine should be organized across the governments, international organizations, donor community, independent research organizations, and vaccine advocacy agencies such as the Dengue Vaccine Initiative (DVI).
- Existing coalitions of dengue endemic countries and international stakeholders should be consolidated under one strategic umbrella. In Latin America, the Integrated Management Strategy (IMS) has incorporated the dengue vaccine as one of the fundamental initiatives to prevent and control dengue.
- Dengue fever control may be achievable by integrated prevention and control strategies, including sustained vector control programs, efficient evidence-based clinical management, and vaccination.

! ***The combined impact of COVID-19 and dengue epidemics is placing immense pressure on health care and management systems worldwide and can potentially result in devastating consequences for the populations. The WHO has emphasized the importance of sustaining efforts to prevent, detect and treat vector-borne diseases such as dengue during this crucial period.***

BOX 1: SUMMARY OF CURRENT WHO SAGE and GACVS RECOMMENDATIONS

PUBLIC HEALTH VALUE OF THE VACCINE

The overall benefit of dengue vaccination is favorable in high endemic populations.

The recent long-term follow up and inferred serostatus analyzes on trial data indicate that the vaccine performs better in seropositive versus seronegative individuals, and that there is an increased risk of hospitalized and severe dengue in the seronegative individuals group starting about 30 months after the first dose.

IMPLEMENTATION

For countries considering vaccination as part of their dengue control program, the SAGE recommends two options. The preferred option is a "pre-vaccination screening strategy" in which only dengue-seropositive persons are vaccinated. which would use currently-available serotests, despite limitations. The SAGE less preferred option is vaccinating without individual pre-screening in highly endemic settings (seroprevalence ≥80% at 9 years of age).

The vaccine is recommended as a three-dose series given 6 months apart, and should be used within the indicated age range: 9 to 45 or to 60 years of age

There is a continued need to adhere to other disease preventive measures and to seek prompt medical care in the event of dengue-like symptoms

SAFETY

The vaccine is safe and efficacious in individuals who have had a primary infection with wild dengue preceding immunization.

There is no vaccine-associated deaths, and the adverse effects following dengue vaccination are mild and comparable to other vaccine interventions.

Sources: *WHO SAGE revised recommendations, June 8, 2018: WER 8 June 2018, vol. 93, no. 23 (pp. 329–344); and WHO GACVS statement on Dengvaxia® (CYD-TDV), December 7, 2017: http://www.who.int/vaccine_safety/committee/GACVS-StatementonDengvaxia-CYD-TDV/en/*

3. THE DENGUE VACCINE IMPLEMENTATION TOOLKIT

3.1. Rationale and objectives

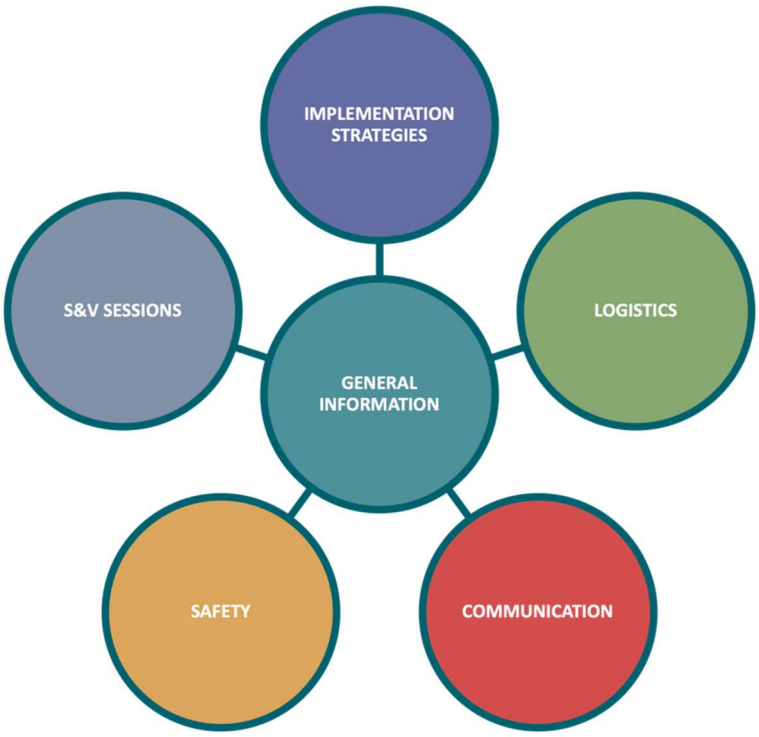
- The dengue vaccine is offered to the children from 9 and adult population previously tested seropositive for dengue, according to a schedule of 3 doses, 6 months apart. Due to this unique vaccine profile and an unprecedented vaccine implementation strategy, it is necessary to review all aspects of the implementation and adapt them to new challenges.
- Informed decision making requires understanding the products involved (diagnostic test and/or vaccine) and the recommended Screen & Vaccination strategy. The evaluation, choice of intervention and planning of activities should be supported by new specific tools covering all the themes essential to a successful introduction, as this will impact vaccine uptake, timelines of vaccination, schedule compliance, vaccine evaluation, prioritization, communication, training, etc.
- The objective of the Dengue vaccine implementation toolkit is to facilitate discussions of country decision makers, program planners (including Ministry of Health staff and National Immunization Technical Advisory Groups (NITAG) members) and implementers on the dengue vaccine implementation. It focuses on the dengue Screen and Vaccinate strategy and the use of a suitable rapid diagnostic test. It summarizes key accessible information in order to assist an informed decision-making process, plan the vaccine introduction, monitor the implementation and support pre/during/post introduction evaluation. The Toolkit is an informative and technical tool that details a variety of topics specific to vaccination with Dengvaxia® as part of a novel Screen and Vaccinate strategy.
- As much as possible, the Toolkit content aims at reflecting the range and diversity of contexts, thoughts and solutions.

3.2. The Toolkit modules

The Toolkit is composed of six modules addressing essentials aspects of the Dengvaxia® implementation (FIGURE 6).

FIGURE 6.

The Dengue vaccine implementation Toolkit modules, as of September 2021.



3.2.1. GENERAL INFORMATION

- This Module summarizes information on dengue disease and burden, and on the characteristics and specificities of Dengvaxia®, the first dengue vaccine. It serves as an introduction for the Dengue Vaccine Toolkit and presents existing Modules and possible use.

3.2.2. IMPLEMENTATION STRATEGIES

- The Module summarizes information related to the implementation of Dengvaxia® in the context of a Screen & Vaccinate strategy. It includes considerations for determining target population for vaccine use, and describes the main implementation principles. Since each country is subject to different epidemiological and organizational contexts, there is no "one-size-fits-all" implementation solution. As a result, a range of approaches and strategies are proposed which could serve as the basis for decision making and deployment at the local level. The approaches described in the Module include the implementation in One-step (both the screening and the vaccination on the same day) versus Two-step (screening and vaccination on different days). Selected strategies consider school-based, health facility-based and community-based interventions.

3.2.3. S&V SESSIONS

- The objective of the Module is to help decision makers and program planners focusing on key questions regarding the organization and management of Screen and Vaccinate sessions with Dengvaxia®. The module summarizes how to plan, prepare and conduct S&V sessions according to the contexts (schools, health facilities and community). It describes the possible roll-out of the intervention, and the main principles of documentation of serological status and vaccination, as well as communication during the sessions. Finally, it lists the various possible challenges and suggests solutions to better meet them.

3.2.4. SAFETY

- The Module summarizes current information and issues on vaccine safety for decision-making, relevant to the implementation of Dengvaxia® in endemic areas. It summarizes the vaccine safety assessment and safety profile in clinical trials, as well as post-marketing data from implementing countries. It briefly reviews the risk management plan, vaccine implementation safety requirements and pharmacovigilance challenges.

3.2.5. COMMUNICATION

- The Module presents key information on communication for Dengvaxia® implementation, in the context of the Screen and Vaccinate strategy, including communication opportunities and challenges. It gives recommendations for a communication strategy, including planning, selection of targets, key messages by target, and communication materials and channels. A chapter is dedicated to the communication crisis management including detection of risk, response and a case study illustrating the vaccine communication experience in the Philippines.

3.2.6. LOGISTICS

- The Module summarizes the logistical implications of introducing Dengvaxia® in the context of a Screen and Vaccinate (S&V) strategy, using a Rapid Diagnostic Test (RDT) for detection of dengue past infections. It describes the measures necessary for the availability and quality of tests and vaccines to ensure safe and effective vaccination. It presents the logistic challenges and propose logistic and supply needs calculation tables. A case study illustrates the estimation of the number of units for tests and for vaccines, in the context of a five-year roll-out of the intervention. A chapter considers the estimation of storage and transport needs especially in the cold chain, as well as the planning for waste management. Practical considerations are given on the logistics of the implementation.

3.3. An interactive and evolving Tool

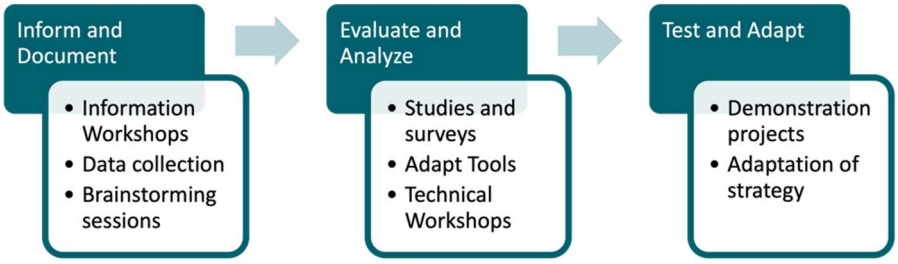
- The development of the Toolkit follows an incremental and interactive process, building up on feedback from implementing country, latest scientific evidence, international experts' meetings, manufacturer current label, and up-to-date recommendations from the WHO, other global organizations and expert committees.
- Modules are regularly updated to fit in with evolving reality and needs.
- The modules constitute working tools for deploying preparation and evaluation activities adapted to each local situation (FIGURE 7). They serve as a basis for:
  - Informing and documenting during the preparation phase - they can facilitate the sharing of information on selected topics during information workshops, country existing data collection on qualitative and/or quantitative variables and brainstorming sessions for the first steps in the decision-making process.
  - Evaluating and analyzing local data through studies and surveys to inform the choice for an approach and strategy and the planning of activities. They can help developing or adapting

implementation and monitoring tools and organizing technical workshops on any topic covered.

- Testing and adapting - modules can be used to develop protocols and monitoring tools for demonstration projects. Depending on the pilot feedback and detected challenge, the Toolkit can provide solutions for adaptation of implementation strategies and tools.

FIGURE 7.

How to use the Dengue vaccine implementation Toolkit.



4. REFERENCES

A panel of resources and publication is suggested, available online from the following websites:

DENGUE: A GLOBAL PUBLIC HEALTH CHALLENGE

- World Health Organization (WHO) Factsheets on *"Dengue and severe dengue"*, 19 May 2021. Available online at: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue
- Zeng Z., et al. *"Global, regional, and national dengue burden from 1990 to 2017: A systematic analysis based on the global burden of disease study 2017."* EClinicalMedicine vol. 32 100712. 6 Jan. 2021, doi:10.1016/j.eclinm.2020.100712. This article analyses the latest data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2017 to determine incidence of dengue and dengue related mortality and DALYs.
- Bhatt S, et.al. *"The global distribution and burden of dengue"*. Nature. 2013 Apr 25;496(7446):504-507. This article provides with dengue risk maps and infection estimates based on an exhaustive assembly of known records of dengue occurrence worldwide, and use a formal modeling framework. It is available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3651993/pdf/nihms-453763.pdf
- WHO *"Global strategy for dengue prevention and control"*, available at: http://apps.who.int/iris/bitstream/10665/75303/1/9789241504034_eng.pdf
- *"Dengue: Guidelines for Patient Care in the Region of the Americas; second edition, 2016"*, downloadable in English and Spanish at: http://www.paho.org/hq/index.php?option=com_topics&view=rdmore&cid=6134&Itemid=40734&lang=en
- Cavalcanti et al. *"Postmortem Diagnosis of Dengue as an Epidemiological Surveillance Tool"*. Am. J. Trop. Med. Hyg., 2016;94(1):187–192. DOI:10.4269/ajtmh.15-0392. This article evaluates the true mortality from dengue through active postmortem surveillance.

DENGVAXIA®: THE FIRST VACCINE AGAINST DENGUE

- The WHO Model List of Essential Medicines, 2019 is available at: https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?sequence=1&isAllowed=y.
- The WHO Model List of Essential Medicines for Children, 2019 is available at: https://apps.who.int/iris/bitstream/handle/10665/325772/WHO-MVP-EMP-IAU-2019.07-eng.pdf?ua=1.
- The WHO List of prequalified vaccines 2020. Available at: https://extranet.who.int/pqweb/vaccines/list-prequalified-vaccines?nav=0&ID=329.
- Thomas SJ, Yoon IK. A review of Dengvaxia®: development to deployment. Hum Vaccin Immunother. 2019;15(10):2295-2314. doi: 10.1080/21645515.2019.1658503.
- 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

DENGVAXIA® (CYD-TDV) CHARACTERISTICS

- For long-term trials data: Forrat 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. doi: 10.1093/cid/ciab288;

and 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

- For Latin America: Villar, et al. "*Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America*" N Engl J Med. 2015 Jan 8;372(2):113-23, available at: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1411037
- For Asia: Capeding, et al. "*Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomized, observer-masked, placebo-controlled trial*" Lancet. 2014 Oct 11;384(9951):1358-65, available at: http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736%2814%2961060-6.pdf
- Long term pooled analysis: Hadinegoro, et al. "*Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease*" N Engl J Med. 2015 Sep 24;373(13):1195-206, available at: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1506223
- For Dengvaxia® safety data: 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;10:e0004821.
- Dengue transmission intensity maps and impact of preventive intervention: Cattarino et al. "*Mapping global variation in dengue transmission intensity*". Sci Transl Med. 2020 Jan 29;12(528):eaax4144. doi: 10.1126/scitranslmed.aax4144.
- The impact of a S&V strategy: Coudeville et al. "*The potential impact of dengue vaccination with, and without, pre-vaccination screening*". Vaccine. 2020 Feb 5;38(6):1363-1369. doi: 10.1016/j.vaccine.2019.12.012.)

POLICIES AND RECOMMENDATIONS

- Sanofi Pasteur update of product label published November 29, 2017 is available at: http://mediaroom.sanofi.com/sanofi-updates-information-on-dengue-vaccine/
- The 2018 World Health Organization (WHO) position paper on dengue vaccine was published in WER 7 Sept 2018, vol. 93, no. 36 (pp.457-476).
- A first WHO vaccine position paper, outlining WHO recommendations for the dengue vaccine, was published 29 July 2016: No 30, 2016, 91, 349–364, available at: http://www.who.int/wer/2016/wer9130.pdf?ua=1
- The Global Advisory Committee for Vaccine Safety (GACVS) published a revised statement on Dengvaxia® (CYD-TDV) in December 7, 2017. It is available at: http://www.who.int/vaccine_safety/committee/GACVS-StatementonDengvaxia-CYD-TDV/en/

IMPLEMENTATION

- Fongwen et al. "*Implementation strategies for the first licensed dengue vaccine: A meeting report*". Vaccine. 2021 Jul 9:S0264-410X(21)00845-8. doi: 10.1016/j.vaccine.2021.06.083.

BOX
SOME WEBSITES ON THE DENGUE VACCINE : information, statement, label, and recommendations*(by alphabetical order)*

THE DENGUE VACCINE IMPLEMENTATION TOOLKIT:
http://www.epilinks.net

BREAKDENGUE :
https://www.breakdengue.org/

DVI, THE DENGUE VACCINE INITIATIVE :
http://www.denguevaccine.org/

GACVS, THE WHO GLOBAL ADVISORY COMMITTEE ON VACCINE SAFETY :
http://www.who.int/vaccine_safety/committee/GACVS-StatementonDengvaxia-CYD-TDV/en/

GDAC, THE GLOBAL DENGUE & AEDES-TRANSMITTED DISEASES CONSORTIUM
http://preventdengue.org/category/vaccine/

PDC, THE PARTNERSHIP FOR DENGUE CONTROL:
http://www.controldengue.org/

SAGE, THE WHO STRATEGIC ADVISORY GROUP OF EXPERTS ON IMMUNIZATION:
http://www.who.int/immunization/diseases/dengue/revised_SAGE_recommendations_dengue_vaccines_apr2018/en/

SANOFI PASTEUR DENGUE INFO :
http://dengue.info/

SLIPE, SOCIEDAD LATINO AMERICANA DE INFECTOLOGÍA PEDIÁTRICA:
http://www.slipe.org/admin/files/Documento_de_posicio%CC%81n_de_SLIPE_sobre_la_vacuna_contra_el_dengue._Rev_Latinoam_Infectol_Pediatr_ENE2018_.pdf

VCP, THE VACCINE CONFIDENCE PROJECT:
http://www.vaccineconfidence.org/

WHO, THE WORLD HEALTH ORGANIZATION Q&A ON DENGUE VACCINE (DATED 19 APRIL 2018):
http://www.who.int/immunization/diseases/dengue/revised_SAGE_recommendations_dengue_vaccines_apr2018/en/index.html