DENGUE VACCINE IMPLEMENTATION (Screen & Vaccinate) IMPLEMENTATION STRATEGIES

INFORMATION FOR SKATEHOLDERS

This module summarizes information related to the implementation of the dengue tetravalent vaccine (recombinant, live-attenuated) developed by Sanofi Pasteur (commercial name Dengvaxia®), in the context of a Screen & Vaccinate strategy. It includes considerations for determining target population for vaccine use, and implementation approaches and strategies. It refers to manufacturer current label, scientific studies, global organizations and expert committees' recommendations, as well as countries data and feedback.

1. CONTEXT OF DENGUE VACCINATION

- Dengvaxia®, the live recombinant tetravalent dengue vaccine developed by Sanofi Pasteur, is the first and only dengue vaccine approved worldwide. It has been licensed in more than 20 countries including the United States (US), and in the European Economic Area (EEA), and has been granted prequalification by the World Health Organization.
- Dengvaxia® is indicated for the prevention of dengue disease in people 9-60 years of age (up to 45 years in most countries) with prior dengue virus infection and living in endemic areas. Target age groups may vary depending on national indication (e.g., 9-16y or 12-45y). The vaccine is given as a 3-dose series with 6-month intervals between each dose. The indication is subject to change (e.g., indication from 6 years of age, see EMA 2022).
- Dengvaxia® has been shown in clinical trials to be efficacious and safe in persons who have had a previous dengue virus infection (seropositive individuals). However, it carries an increased risk of severe dengue in those who experience their first natural dengue infection after vaccination (those who were seronegative at the time of vaccination). Individuals who have not been infected by dengue virus in the past, or for whom this information is unknown, should not be vaccinated.
- For countries considering vaccination as part of their dengue control program, the World Health Organization (WHO) recommends a pre-vaccination screening strategy, in which only dengue-seropositive persons are vaccinated. Another WHO recommended – although less preferred – option, is vaccinating without individual prescreening in highly endemic settings (seroprevalence ≥80% at 9 years of age).
- Dengue risk is highly variable between and within countries and thus the priority for using vaccine will vary accordingly. As dengue epidemiology and existing public health capacity differ by country, any vaccine introduction plans should be country specific. Decisions about implementing a Screen and Vaccinate (S&V) strategy require careful assessment at the country level, including consideration of the sensitivity and specificity of available tests, local priorities, dengue epidemiology, country-specific dengue hospitalization rates, and affordability of both the vaccine and screening tests.
- Dengue vaccine introduction should be a part of a comprehensive dengue control strategy, including a well-executed and sustained vector control, the best evidence-based clinical care for all patients with dengue illness, and robust dengue surveillance.
- Dengue vaccine introduction must be accompanied with a strong targeted communication strategy [See Module COMMUNICATION].

2. APPROACHES TO DENGUE VACCINATION

- Approaches to implementing dengue vaccination depend on the program goals and objectives as well as country specificities. The goals specify expected targets in terms of reducing and controlling dengue burden (e.g. morbidity, mortality, outbreak). Based on these aspects and according to specific organizational and economic parameters, a country will determine how to launch the dengue vaccination program, e.g., implement large-scale Screen and Vaccinate (S&V) campaigns targeting a broad age group and/or routine Screen and Vaccinate for a reduced target.
- The transmission intensity in the target areas and the age at vaccination inform on the likelihood of having had past dengue infection and are therefore critical factors for all approaches.
  - > A Screen and Vaccinate program can be implemented in various and heterogeneous transmission settings
    - In settings with high transmission, both the disease burden and the pre-test probability are high so the dengue vaccination will have the greatest impact.
    - In moderate to low transmission settings, the expected population impact of the intervention is lower than in high transmission settings since less individuals are eligible for vaccination. However, in those settings, screening is more efficient than no screening since it enables selecting the individuals who will benefit the most from vaccination. As a result, S&V is generally more cost-effective than vaccination without screening in moderate to low transmission settings.
  - > Individuals who had only one past dengue infection (monotypic past infection) will benefit most from the dengue vaccine. The age groups should therefore be selected based on recent local epidemiological data, for maximizing the probability to target individuals who had one past dengue infection. The optimal age group to be targeted is just before the age at which the incidence of severe dengue is highest, and this can be ascertained from national and subnational routine hospital data.
- The timing of vaccination after a natural infection is important considering, although it will have no impact on vaccine reactogenicity/safety.
  - > Antibody response induced by natural dengue infection may interfere with immunogenicity of the live attenuated dengue vaccine in the first weeks, hence leading to a "refractory period" during which the efficacy of vaccination could be lower or even absent. Therefore, for optimal efficacy, when the date of natural infection is known, it is recommended that the vaccine is administered at least 3 months, and preferably 6 months after dengue diagnostic (FIGURE 1). In the case the actual date of infection is unknown or if for practical reasons, vaccination needs to be performed during the refractory period, first dose administration should not be postponed because the second and third doses of Dengvaxia® will be able to induce an effective immune response: although not optimal, performing vaccination after 3 months will provide some benefit.
  - > On the other hand, vaccination should start soon enough after natural infection to offer maximum benefit before a subsequent natural infection may occur. However, waiting up to one year after a confirmed natural infection to administer the first dose may be acceptable since the natural infection induces a 6 to 12-month cross-protection. The time frame for vaccination after a first natural infection depends on local dengue epidemiology and the probability of getting a second natural infection.

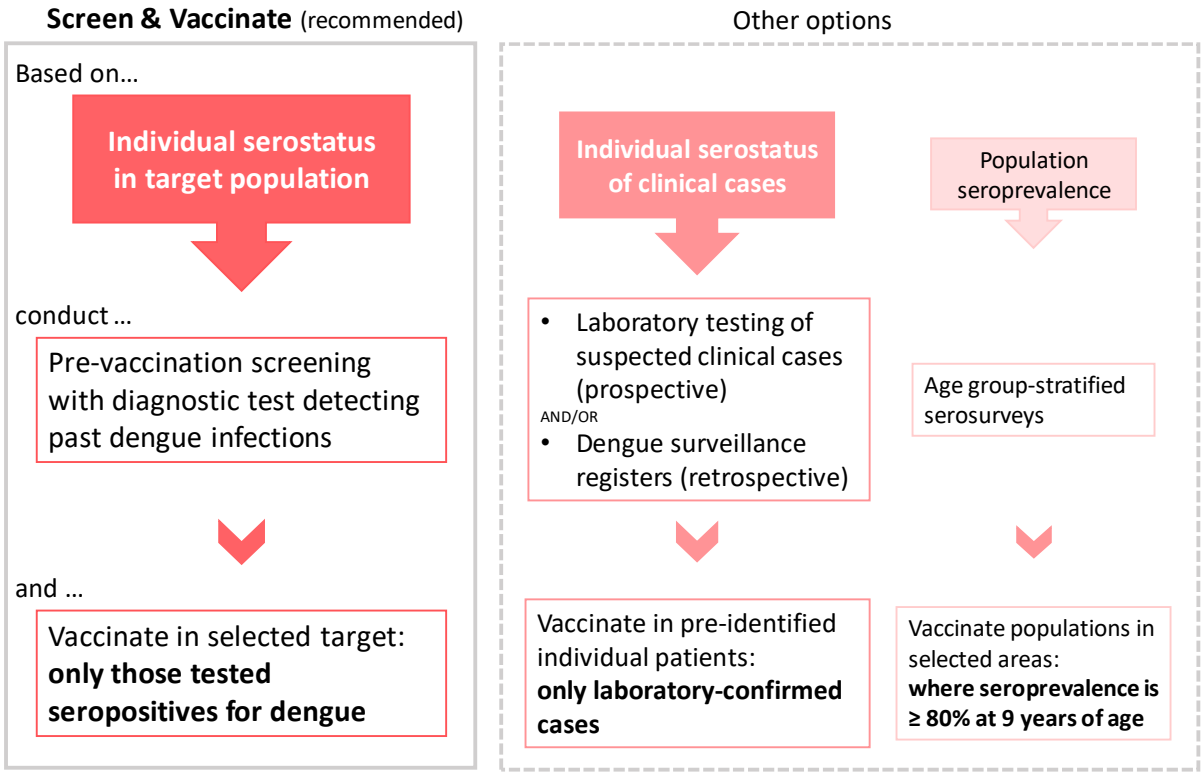
FIGURE 1.

Timing for vaccination: the optimal window for administering the first dose after a natural infection.

- A range of approaches can be considered when implementing the dengue vaccination. Only those complying with the product label and the WHO recommendations are detailed (FIGURE 2).

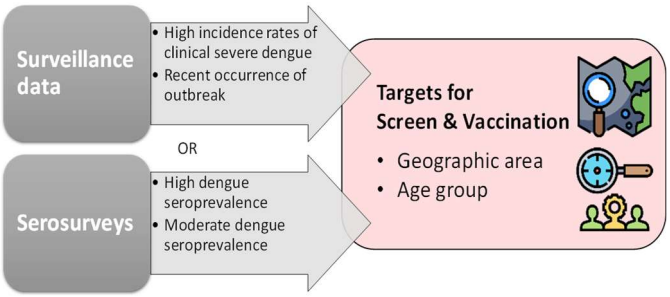
FIGURE 2.

Approaches to implement dengue vaccination.



2.1. Implementation based on individual serostatus in a target population

- The Screen and Vaccinate strategy is the WHO preferred option: it implies screening every potential vaccine recipient to determine serostatus, and only vaccinate persons tested positive for prior dengue infection, or those with a documented history of dengue with a nominal proof of a positive laboratory test.
- <u>Target population:</u>
  - > Areas and age groups with a high proportion of individuals with primary infections. The likelihood of having had only one past dengue infection depends on age and transmission intensity. Recent age-stratified seroprevalence data (already available or obtained through new seroprevalence surveys) can be used to guide the intervention to specific geographic areas and age groups.
  - > Alternatively, the optimal age target for S&V can be informed by the age at which hospitalization due to severe dengue peaks, and this can be ascertained from national and subnational routine hospital data. In this case, the optimal age target for vaccination is just before the age group in which the highest dengue hospitalization incidence is observed.



- <u>Diagnostic tests:</u>
  - > Screening tests should be highly specific (able to identify true seronegatives) to reduce the possibility of wrongly vaccinating seronegative persons,

- Screening tests should be highly sensitive (able to identify true seropositives) to maximize vaccine impact by ensuring that most of the eligible population will benefit from vaccination.
- For programmatic feasibility, dengue rapid diagnostic test (RDT) should be used for large-scale point-of-care, quick and easy identification of seropositives.
- However, the characteristics and performance of most dengue RDTs are limited since they are calibrated to detect recent or acute infection and therefore may miss past infections (low sensitivity). In settings with co-circulation of other flaviviruses such as Zika, chikungunya or yellow fever, there are issues of antibodies cross-reaction when using an IgG serological diagnostic test, leading to false positive results for dengue (low specificity).
- The *OnSite*® Dengue IgG RDT has been specifically designed to identify individuals in the age range for vaccination who have had a past dengue infection, and with performance characteristics within the expected ranges to enable safe and efficient implementation of pre-vaccination screening and dengue vaccination. This test is CE-marked and registered for use in certain countries.
- Conventional serological testing for dengue (e.g. dengue IgG ELISA) can also be used if the samples collected are tested in a laboratory (Two-step implementation).

- Implementation:
  - **One-step implementation**: where possible, both sampling, diagnostic and vaccination of seropositives can be performed on the same day and at the same place such as schools, community S&V out-reach posts, and health centers. This requires carefully anticipating waiting times and areas, management of registers, patient flow, communication including risk communication, tests and vaccines logistics including transport, and cold chain and waste management.
  - **Two-step implementation**: for various reasons a One-step approach might not be possible or desirable, in which case the test and the vaccination can be dissociated. Samples are taken first, either at school or through community outreach, and tested either on site or in a laboratory, depending on the type of test used. Registers are carefully filled and a master list of seropositives is used to contact people who are offered vaccination, either at school, health center or community outreach.
  - The pre-vaccination screening of the eligible population may be repeated over time:
    - For new cohorts reaching the selected age indication
    - For those previously tested with a negative result
  - The first dose may not be given to a person who has a positive result but who has had reported clinical dengue or dengue symptoms in the last 3-month. In this case, it would be desirable to postpone the vaccination outside the refractory period.

- Communication:
  - The Screen and Vaccinate strategy is new to immunization programs and may impede vaccine acceptance. A dedicated tailored-made communication strategy must be developed and put in place to answer the various challenges.
  - A strong communication crisis plan needs to be developed prior to program launch to resolve any issue accurately and promptly.
- More information can be found in Module ORGANIZATION OF S&V SESSIONS, Module COMMUNICATION and Module LOGISTICS.

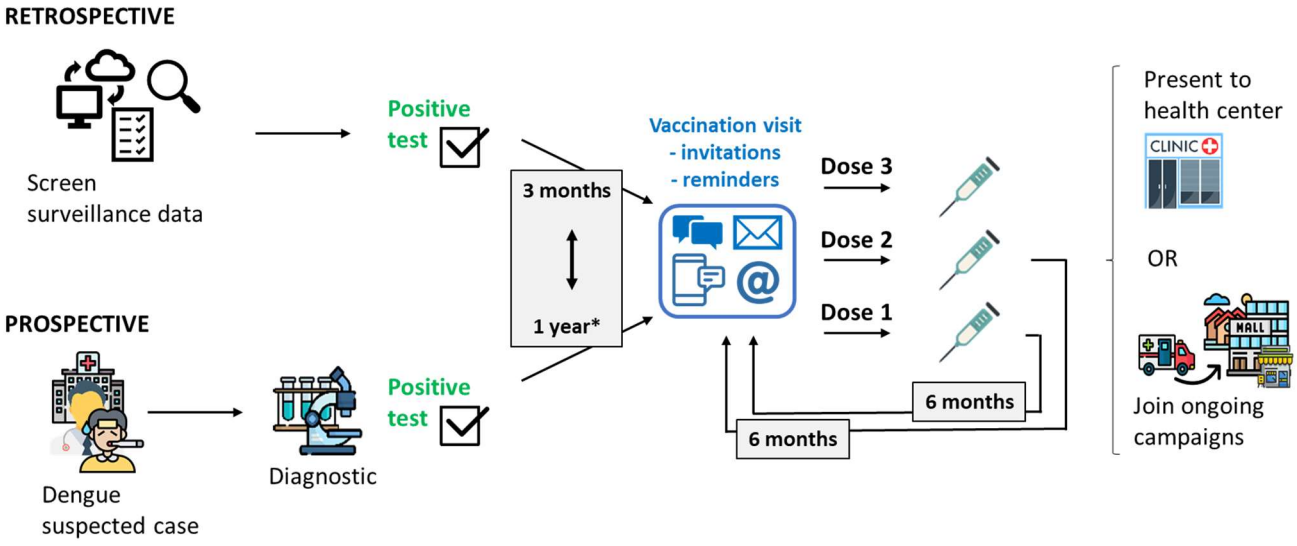
2.2. Implementation based on individual serostatus of dengue clinical cases

- This approach is not exclusive of other strategies and can be implemented as part of the routine procedure for clinical dengue case management in the country (FIGURE 3). It can apply to any eligible person within the age of indication.
- In this case, the diagnostic for dengue is highly specific because the tests are performed during the febrile phase of the disease, which allows detection of the dengue virus by molecular testing for viral RNA (RT-PCR), direct viral isolation, or NS1 antigen detection. Diagnostic is also possible using indirect methods such as serological testing for anti-dengue IgM and/or IgG antibodies (ELISA), or Plaque Reduction and Neutralization Test (PRNT).
- Patients tested positive for dengue infection and in the age indication are systematically offered dengue vaccination with Dengvaxia®. Invitation to present to health centers for vaccination or to join ongoing vaccination campaigns should be given with the positive result, together with an information notice summarizing facts on dengue, dengue vaccination, and why this vaccination is offered to people who have already been infected by the dengue virus.

- Vaccination should be given at least 3 months after and ideally 6 months to one year after the symptoms to allow induction of a secondary immune response before a natural second infection. Each country should determine the timing of vaccine delivery after a positive test, depending on programmatic aspects and epidemiological context, including local endemicity and occurrence or threat of outbreaks in the area or in surrounding areas. Vaccine age indication must be followed.
- National surveillance data can also be used to retrospectively identify laboratory-confirmed patients. In this case, surveillance data including electronic databases and health care centers registries are screened to establish a master list of seropositives for dengue and targeted for vaccination in the age indication. Based on the information collected, invitations can be sent to identified individuals to attend vaccination campaigns or present to the health centers.
- Both retrospective and prospective approaches require strong monitoring and effective tracking of subjects for subsequent dose administration. Depending on what has proved most effective in the local context, different means of communication are considered for the first invitation and the reminders, e.g. phone voice or text messaging, email, post mail, interpersonal or group communication.
- Although this is not recommended by manufacturer and WHO, and depending on the approved label in a given country, it is the country choice to allow vaccination of a person with a documented clinical diagnosis of dengue without laboratory confirmation.

FIGURE 3.

Retrospective and prospective approaches for dengue vaccination of laboratory-confirmed clinical cases.



** The optimal time period for vaccination after infection with the dengue virus is defined by countries. A 3-month delay after natural infection corresponds to the refractory period, during which vaccination would not be recommended (see text).*

2.3. Notes on other approaches for dengue vaccine implementation

- <u>Dengue vaccine implementation based on population seroprevalence.</u>
  - > This approach has been identified as the less preferred – although acceptable - option by the WHO.
  - > Modeling studies from the WHO expert group estimate that vaccination would benefit the population in areas where seroprevalence at the age of 9 is equal or above 80%.
  - > In 2017, the WHO developed a comprehensive guide for serosurveys: "Informing vaccination programs: a guide to the design and conduct of dengue serosurveys".
  - > Dengue transmission maps, at district and sub-district levels, would be useful for identifying

geographical areas in which populations would benefit the most from public dengue vaccination campaigns.

- Dengue vaccine implementation based on dengue burden only.
  - > This approach is not recommended by WHO, and will not guarantee that seronegatives are not vaccinated.
  - > Nevertheless, some countries may consider that the benefit of vaccination outweighs the risks, and they will base their decision on other important indicators related to burden, such as: dengue disease and mortality incidence, dengue outbreaks occurrence, dengue seroprevalence, entomological indicators, co-circulation of dengue serotypes, sustained health care access, economic impact of the intervention, notification of dengue cases for 20 weeks or more in at least one of the last 5 years, social, environmental, or climatic conditions favoring the occurrence of outbreaks.
  - > In this case, countries should be warned that implementing such a strategy may induce the distrust and non-adherence of a part of public opinion and will require strong training and communication activities to potentially address criticisms and rumors.

3. SCREEN AND VACCINATE IMPLEMENTATION PRINCIPLES

Screen and Vaccinate (S&V) strategy is a new approach to vaccination worldwide. Consequently, there is no prior experience to fully refer to or leverage to extract learnings or best practices. Key principles for dengue vaccine introduction can be applied to the followings:

- Programmatic parameters:
  - > Dengue vaccine should complement and promote existing public health interventions aiming to control dengue disease, such as the implementation of vector control strategies, community education, and proper case management, including early diagnostic and referral of severe forms.
  - > Countries should consider local priorities, dengue burden, dengue epidemiology, screening tests characteristics, logistical constraints, communication issues and affordability of purchasing both Dengvaxia® and screening tests.
  - > The levels of understanding and acceptance towards the S&V strategy should be assessed across different groups including patients or their parents, key decision makers and opinion leaders at the national and local level, health care providers and other S&V implementers, school managers and staff when a school-based program is launched.
  - > Emphasis should be placed on the implementation of sustainable strategies that are successful in achieving program goals. Programmatic feasibility should be ensured through assessment of capacities and resources. Experience of immunization programs with laboratory diagnostics is limited and different supply chains may be used. This logistic challenge needs to be evaluated and organized in advance, including all level staff training [See Module LOGISTICS].
  - > Some countries may consider vaccinating populations up to 45 or 60 years of age (depending on local label):
    - In routine programs, when they experience high disease incidence in adult population
    - During catch-up campaigns if additional and quick impact is desired
  - > The combined Screen and Vaccinate strategy is a novelty in public health; therefore, there is no specific operational document available yet, describing the procedures, and that program can rely on.
  - > Modeling may play a substantial role in assessing vaccine impact at population level; these studies might help national bodies to select the optimal programs and catch-up cohorts to achieve maximal public health benefit.
  - > Recent studies show that in baseline dengue seropositive participants, Dengvaxia® elicits comparable immunogenicity and safety profiles when administered concomitantly or sequentially with a human papilloma virus (HPV) vaccine or with a diphtheria toxoid and acellular pertussis (Tdap) vaccine. Such coadministration can increase the cost-effectiveness and coverage of the intervention but should also be considered in the interest of post-vaccination Adverse Event Following Immunization (AEFI) surveillance, which should be specific to each vaccine.
  - > Due to dengue epidemiological dynamics and vaccine impact on virus circulation, transmission and disease burden, the target age groups and geographic areas for the S&V intervention are likely to

change over time. Consequently, the program should be regularly reevaluated and adapted to the new context, based on updated data from disease surveillance and sero-prevalence surveys.

> Demonstration programs in selected areas are strongly recommended as they will help the country to define the optimal approach and strategy for various settings and increase the acceptability and long-term implementation of the program.

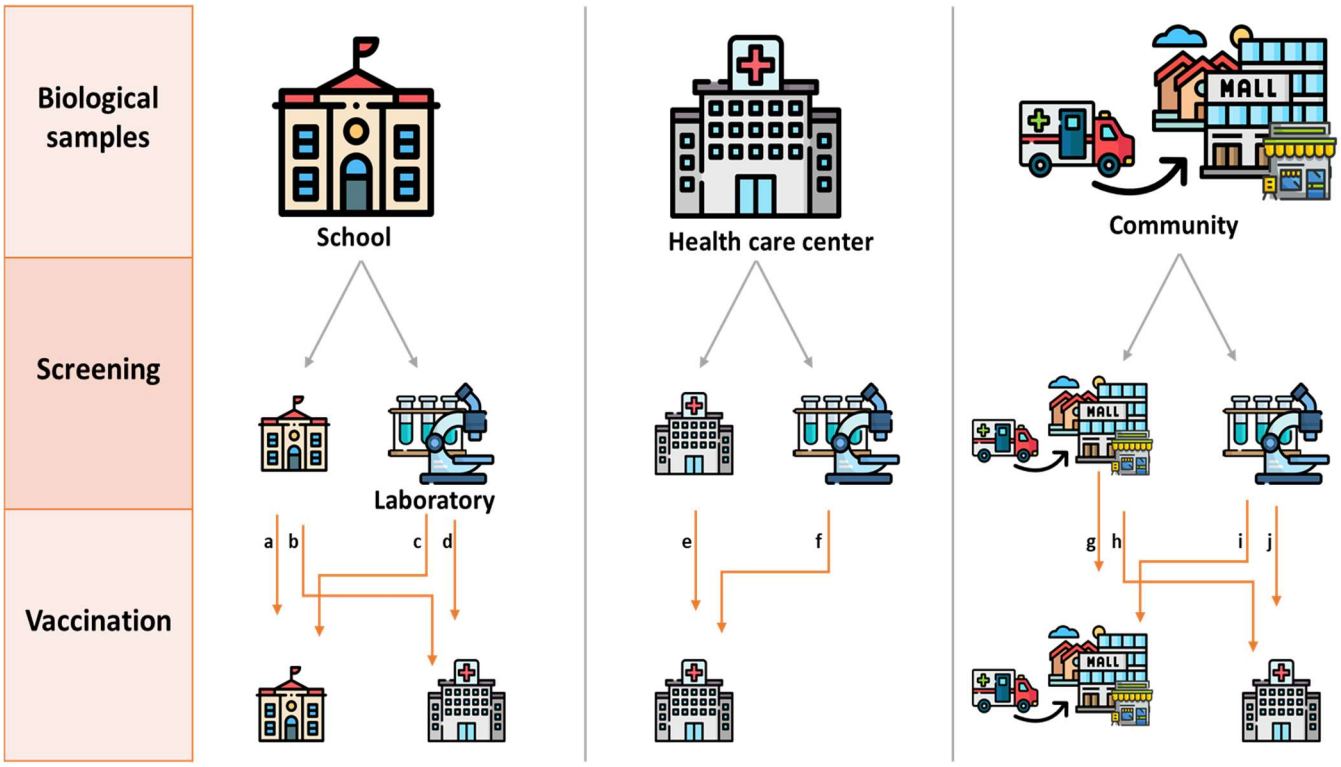
- Monitoring and evaluation:
  - > Standardized and coordinated approaches for vaccine introduction should be implemented, for the purpose of monitoring and evaluating program performance and for conducting comparisons within and between countries. This includes:
    - similar diagnosis algorithms and case definition
    - similar data collection tools
    - similar reporting process and frequencies
    - appropriate training and integrated tools and strategies
  - > The monitoring and surveillance activities should include the reinforcement and linkage of the information systems (registries and databases) dealing with individual serostatus for dengue virus infection, vaccination data, surveillance data of dengue disease (in particular severe/hospitalized), and vaccine pharmacovigilance data (AEFI).
  - > Vaccine uptake needs to be monitored at the individual level for the 3 doses to flag low coverage and drop-outs and to engage in targeted actions.
- Information and Communication:
  - > Robust and adapted Information, Education, and Communication (IEC) program needs to be developed beforehand and implemented throughout the S&V campaigns.
  - > Monitoring of rumors, flagging and reporting of issues, AEFI and raising concerns, communication crisis and risk management are paramount. Communication Rapid Response Teams must be set up in advance and be focused on media monitoring and rumor management during and after the vaccination campaign.
  - > It is critical to have trusted representatives from the community prepared to reinforce positive messages and correct inaccurate information, and ready to promptly react to any communication crises.
  - > More information can be found in Module COMMUNICATION.
- Safety and ethics:
  - > Contra-indication for dengue vaccination should be addressed during individual and private interviews. Administration should be postponed in individuals suffering from moderate to severe febrile or acute disease.
  - > Dengvaxia® vaccination requires informed consent procedures consistent with national regulations and international human rights principles. Possible strategies for children vaccination include:
    - Opt-in option: The signed consent from the caregiver or the adult vaccinee is required prior to administer the intervention.
    - Opt-out option: the child is screened and vaccinated if positive unless the caregiver signs a refusal.
  - > The child assent should be considered in the S&V procedures: he/she should not be forced to participate against his/her will.
  - > The adult vaccinee consent or the parental consent (and child assent) should be required for blood testing prior to vaccination.
  - > It is not recommended to provide one informed consent for the diagnostic test and another one for the vaccination in the event of a positive test. Consent for vaccination should be given for the full 3-dose vaccination course.
  - > More information can be found in Module VACCINE SAFETY.

4. SCREEN AND VACCINATE STRATEGIES

A range of Screen and Vaccinate (S&V) strategies (FIGURE 4) can be considered to obtain optimal impact, i.e., maximum coverage with the 3 doses of the dengue vaccine in the eligible targeted population. This will depend on the age group targeted by vaccination, the choice for the approach, a history of successful previous implementations and other contextual factors including targeted coverage, programmatic and logistical feasibility, adherence to the 3-dose regimen, S&V acceptance parameters, and operational costs including human and financial resources. More information can be found in Module S&V SESSIONS.

FIGURE 4.

Possible combinations for the Screen and Vaccinate strategies



- <u>School-based interventions</u>

Schools can be used to collect samples for screening (a – d), to apply screening test (a, b), and to deliver vaccination to seropositives (a, c).

PROGRAM	- **While rolled out in schools, the program, including the teams and all materials, should be based in the health centers, and mobile vaccinations teams should be dispatched from the vaccination centers into schools with all necessary material and equipment.** - **It provides an opportunity for integration of school-based education regarding dengue, other mosquito-borne diseases, or other health activities such as family health interventions.** - **The school-based strategy can be considered by age or by grade (see Module ORGANIZATION OF S&V SESSIONS).** - **It is strongly recommended to conduct demonstration for evaluation of S&V team size, number of visits required, students flow, etc.** - **It requires an early joint planning and strong collaboration between the health and education programs including private schools, at all levels, and throughout implementation.** • ! This strategy is only valid if vaccination targets school-age children. • ! A complementary strategy needs to be developed for reaching out-of-school children and adolescents. • ! The dengue vaccination is given as a 3-dose regimen with 6-month intervals; consequently, school activities will have to be adapted at least two days per year. The timing and organization of interventions should be chosen carefully to avoid disruption in school programs and interference with holiday and other school-based activities. • ! The principles of equity should be respected by ensuring that all children in the age group have access to the vaccination offer, regardless of the type of school administration Internal communication, planning parameters and logistical constraints may differ between private and public schools and should be taken into account. • ! Combining dengue vaccination with other health intervention such as deworming or vaccine co-administration should be carefully assessed. In previous school-based dengue vaccination campaigns,

	HPV vaccination and deworming interventions had to be postponed, to avoid possible misclassification of serious adverse events (international data).
LOGISTICS	- **Schools provide a secured and closed environment for health interventions.** - **Logistics need to consider sampling, testing and possibly vaccinating children in a school environment.** - **This requires an accurate assessment of the number and management of blood collection kits, screening tests, vaccines and other materials including all necessary documentation.** • ! Waste management and cold chain during school-based interventions can be a challenge.
ADHERENCE	- **In the case of Human Papilloma Virus (HPV) vaccination, where school attendance is high, this approach has been shown to result in higher coverage than with strategies involving only health facilities or community outreach.** - **The population targeted by the intervention is more "captive" throughout the duration of the intervention (3 doses).** • ! Where the number of out-of-school children is high, this strategy will lead to low coverage of the target population and should be complemented by other strategies. • ! Previous school-based dengue vaccination experiences have reported high drop-out rates from one dose to another, due to a change in children's school. State, or region/nation-wide registries should be implemented to allow follow-up of vaccination. • ! School-based interventions should be complemented by other strategies (such as community out-reach and health facility services) for out-of-school, absents, moving or leaving school children.
ACCEPTANCE	- **Acceptance may be increased in school-based programs, since it mobilizes advocacy from teachers, who are trusted people interacting daily with the target population.** - **School staff should be trained and equipped to provide key messages to pass on to the children, including those on dengue, the vaccine and the S&V strategy.** - **Key popular leaders should be identified in schools to advocate for the vaccination campaign.** • ! A participative approach should be put in place ahead and during the intervention to inform, discuss and train relevant school staff on the intervention. It would promote staff understanding and motivation and improve their ability to advocate for the intervention and address communication challenges.
COST	- **The school-based strategy can be cost effective since there will be less effort to reach a target population and to administer the 3-dose regimen.** • ! If not implemented previously (e.g., for HPV), it will require a new system to be put in place.

- Health facility-based interventions

A target population can be invited to attend/go to a health facility for blood sampling and testing for dengue serostatus (e, f) and to receive vaccination if found seropositive (e, f, b, d, h, i).

PROGRAM	- **It allows reaching the target when school age children are not the selected age group, or when there is a high proportion of out-of-school children.** - **This is where all programs are based, including teams and materials.** - **It can be included in routine health services and consequently does not require specific planning and coordination with school or other services.** - **It allows the inclusion of eligible targets coming for other health services.** • ! It can only be effective where a large percentage of population has easy access to the health care facilities hosting the intervention. • ! It may achieve less impact where there is no history of adolescents presenting for immunization. • ! Adding extra activities to the health facility daily burden, it needs be organized to avoid disruptions in terms of human resources, patient rooms, stocking areas including cold chain, and waste management. • ! The 3-dose schedule will lead to low coverage without a strong pro-active strategy.
LOGISTICS	- **This is the option with the lowest logistical constraints as it uses health services, facilities and staff.** • ! Specific training should be given to the health staff to accurately and timely report test results, and/or vaccination status, and vaccine dose tracking.

ADHERENCE	- **People going to a health facility intervention are more likely to adhere to the intervention as it is a voluntary and pro-active process.** - **Information given by health professional is more likely to be accurate and consistent, triggering better comprehension and adherence.** • ! Specific training should be given to the health staff to accurately communicate on the Screen and Vaccinate intervention.
ACCEPTANCE	- **Acceptance is likely to be high as the intervention is given through the existing trusted health system by trusted health staff.**
COST	- **This is the least costly option, as it is already integrated into the existing system, does not require high extra transport costs, and can be added to the existing cold chain and waste management system.**

- Community out-reach interventions

Campaigns for blood sampling (g-j), sampling and testing (g, h) or sampling, testing and vaccinating (g, i) can be organized in the community for a fixed period, and in different places such as schools, colleges, universities, private companies, gymnasium, churches, pharmacies, supermarkets, restaurants and commercial areas.

PROGRAM	- **It allows reaching the S&V target age group if older than school age children.** - **It allows reaching out-of-school children.** - **It can facilitate catch-up campaigns.** • ! Additional considerations are required, such as training or experience level of staff permitted to administer vaccines. • ! Health units, vaccination rooms and mobile teams are required and should be operational where and when target population is available (potentially 7 days a weeks and mornings, days and evenings, depending on the settings). • ! AEFI should be closely monitored during the intervention. • ! Because the interventions are front-line and open in public spaces, crisis communication management skills and capacities will be critical in the event of a sudden hostile environment.
LOGISTICS	- **This is the option with the highest logistical constraints as it requires organization of S&V out-reach posts in non-medical and open community settings.** • ! Specific training should be given to the health staff in mobile teams at state and municipalities levels, to accurately and timely report test results, and/or vaccination status, and vaccine dose tracking.
ADHERENCE	- **This is a voluntary and pro-active process, so people engaging in the intervention are more likely to adhere to the full intervention.** • ! Strong social mobilization and communication is required, with committed trusted community and national actors. • ! The 3-dose schedule will lead to low coverage without a strong pro-active strategy, reminders and lost to follow-up monitoring systems.
ACCEPTANCE	- **This option can be effective and well accepted in settings having previous successful experience with community-based health interventions.** - **The intervention can be better accepted if proposed with other health intervention such as measurement of BMI and blood pressure, counsel on sport, diet, smoking, alcohol, and more generally disease prevention, including dengue.** - **Acceptance will largely rely on national and local communication campaigns as well as strong targeted social mobilization.** • ! Information and communication tools and staff training will need to address the issues related to a new intervention, the targeting of a specific age group, the 3-dose regimen, etc.
COST	• ! Implementing such a strategy can be costly because it requires sending mobile teams to set up and work in the S&V out-reach posts, in various unusual locations for days or weeks for each of the 3 doses. - **However, costs can be mitigated when using the opportunity to deliver other health related interventions.**

- Mixed strategies

Depending on the national and local context, it may be desirable to design strategies that include several components. Mixed strategies can apply at different levels:

1. Mixed settings
   - > Different intervention settings can be used within a same country or area depending on:
     - dengue epidemiology and burden - resulting in targeting different age groups
     - whether previous health interventions were successfully implemented in schools or in the community
     - access to quality health care facilities
     - whether logistical and financial capacities allow for a sustainable program, etc.
   - > In some settings, various strategies can be considered, such as a school-based program supplemented by facility- or community-based interventions for out-of-school children.

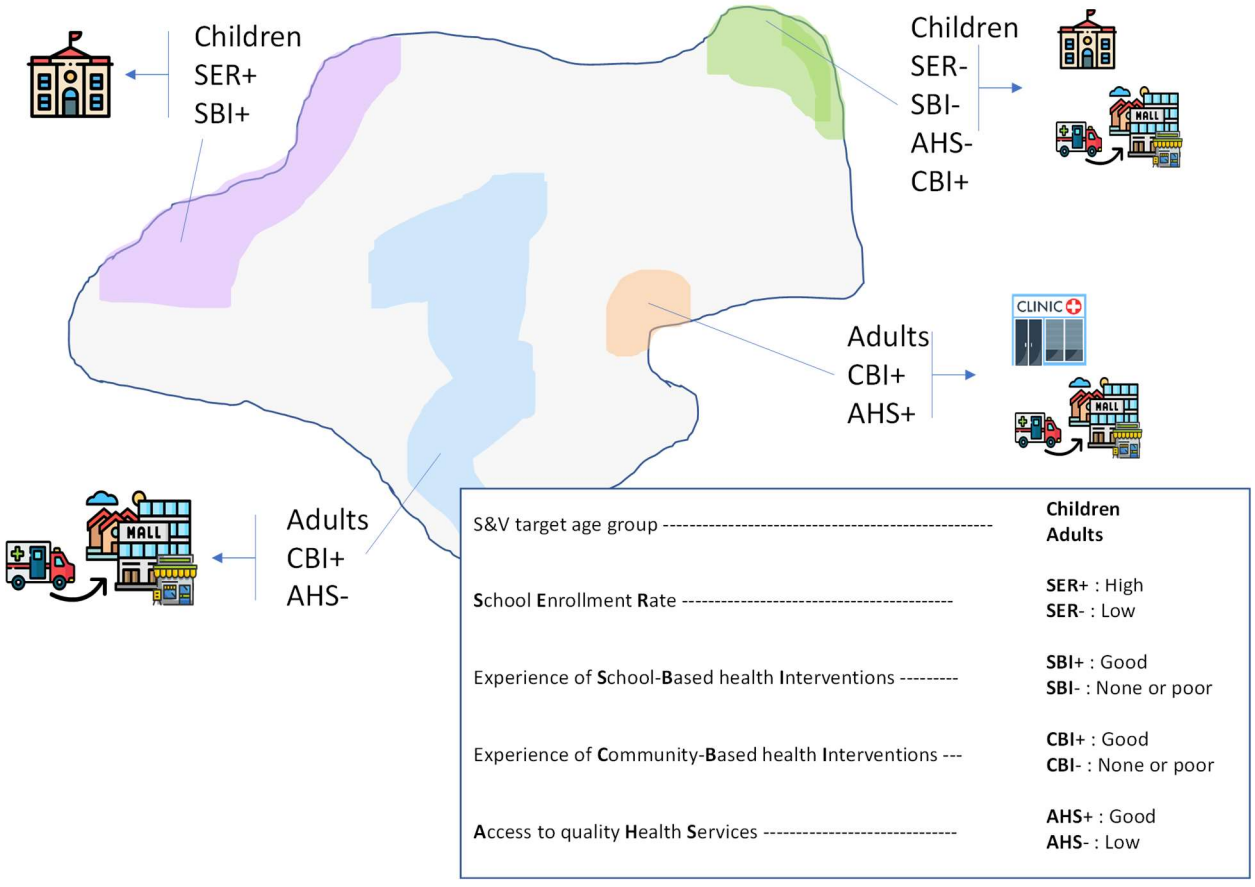
CASE STUDY

A country identified four areas of high to moderate dengue virus transmission based on good quality recent surveillance data (FIGURE 5) and decided to introduce dengue vaccination. In order to design the most appropriate implementation strategy, further analyses are conducted in each setting to identify the age group bearing the higher burden and the school enrollment rate if children are targeted, and to document experience and lessons learned from previous school- or community-based interventions, as well as local access to health services.

FIGURE 5.

Example of mixed strategies for dengue vaccine implementation in one country/area.

Four regions (pink, green, orange, blue) are targeted for vaccination. Based on local context (see legend in the figure), appropriate intervention settings are selected (schools, community out-reach posts, health care facilities).



2. One-step or Two-step

> To screen and vaccinate in the same setting on the same day would help optimizing resources, increase adherence to the intervention and avoid disruption of school or other settings activities. However, a One-step strategy may not be possible for various reasons, e.g.:

- if samples need to be tested in a remote laboratory: it will allow using different types of tests (e.g. ELISA and no RDT).
- if time constraints apply: procedures for only sampling and testing may take more than one hour, causing too much disruption during the school day, or being unrealistic and impeding voluntary S&V in com-munities and health centers.
- if vaccination cannot be given in schools or communities.

> A Two-step strategy can be implemented, where the places for sample taking and serostatus testing differ from the place for vaccination or when samples are tested in remote laboratories.

For example (see FIGURE 4):

- School age children may be sampled or prescreened at school and invited to get vaccinated at health center, based on a positive test result (b and d). These strategies would allow decreasing burden on schools and administering the vaccine in a controlled and trusted environment. However, it may decrease vaccine coverage and lead to drop off between doses.
- In a school-program were samples are tested in remote laboratories (c), other diagnostic tests could be performed, school programs would be disrupted twice instead of one (a), but for shorter periods during each visit (only sampling/testing or only vaccination time required) and for fewer children on the second visit (only those identified seropositive). Less vaccines would need to be stored, transported and handled and less staff would be required each time.
- Health facility-based strategies may also require sending samples in remote laboratories (f). The advantage would be for those seronegative, who will only spend the sampling time at the clinic and will get informed of negative results by different channels. Those seropositive will need to come twice to the health center instead of once (e), which may lead to lower vaccine coverage
- Getting the full Screen and Vaccinate intervention at the same time in communities (g) may be a too long intervention for active segments of the population such as young adults. The full procedure requires informing on the intervention and giving consent, performing the test (RDT), getting the test results, informing on test results and contraindications for those seropositives, administering the vaccine and leaving time for AEFI monitoring.
- An alternative may be to reach people through community interventions where information and other public health interventions may be given together with a rapid diagnostic test (h), and to invite seropositives to present to their nearest health center to receive vaccination. The advantage would be to reach eligible people in the communities and for reasonably short interventions and encourage them to use health services for getting vaccinated. Community interventions dissociated from vaccination - where only dengue diagnostic is proposed, may be better accepted and followed than a One-step S&V campaign. They may be less likely to elicit hostile and deleterious reactions from anti-vaccination groups. A similar strategy would be to only collect samples for remote diagnostic, communicate results when available and invite dengue seropositive people to vaccination either in health centers (i) or during ongoing vaccination campaigns (i). This would allow dissociating the vaccination from the testing and using other tests, but would add complexity for sending results, information and consents and data management.
- Vaccine coverage may be low unless strong social mobilization is implemented in the selected areas. Drop-out rates may also be important in regions with highly mobile populations.

> A combination of approaches and strategies are therefore possible to fit best the realities of the countries:

- Screen and Vaccinate programs, new procedures for vaccination of confirmed clinical cases, or vaccination based on seroprevalence data
- One-step or Two-step implementation
- In schools, health facilities, and/or community settings

> Monitoring test result administration and vaccine dose is essential and should be organized throughout the intervention across settings. Programmatic and logistical feasibility, cost effectiveness and acceptance should be evaluated beforehand.

5. DENGUE OUTBREAK SITUATION

- Dengvaxia® is currently not indicated for outbreak response since the immunization requires the administration of three doses over a period of 12 months and given the absence of studies. Vaccination is better suited for the prevention of future outbreaks than in response to an outbreak, although there is no restriction in vaccine use during epidemics.
- Vaccine efficacy estimates in seropositive participants aged ≥ 9 years at post-dose 1 is 80,5% (95%CI 66.2-88.7) over a period of 6 months. Therefore, an outbreak may signal the potential utility of a public health preventative vaccination program as dengue vaccination can provide short-term individual protection to people at epidemic risk and identified seropositives either through a S&V strategy or through a documented serostatus.
- Dengue vaccination can also have a beneficial effect on the population by reducing the virus circulation.
- The decision and strategy to vaccinate during an outbreak must be discussed beforehand so that within the context of an outbreak the decision to vaccinate is accelerated. with special attention for the planning delivery of all three vaccine doses.
- Specific challenges need to be covered in advance, including:
  - > Choice of timing for the S&V intervention: from the alert signal or from the outbreak signal
  - > Pre-screening of those recently infected as the vaccine efficacy will be very limited or null for those infected during the previous month
  - > Sufficient provision for vaccine supply to cover administration of 3 doses to the at-risk population
  - > System ready for an emergency vaccine introduction: process of registration, program policy, procurement, health staff training, logistics, social mobilization, communication
- A comprehensive package of monitoring and evaluation (M&E) activities should consider vaccine evaluation situations where an outbreak occurs in the introduction area or when the vaccine is used as part of the outbreak response.

6. READ MORE

CONTEXT OF DENGUE VACCINATION
- Sanofi Pasteur published an update of the product label November 29, 2017, 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/
- Wilder-Smith et al. *"Deliberations of the Strategic Advisory Group of Experts on Immunization on the use of CYD-TDV dengue vaccine"*. Lancet Infect Dis. 2019;19(1):e31-e8
- Dayan 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.
- 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

APPROACHES TO DENGUE VACCINATION
- Guy et al. *"When Can One Vaccinate with a Live Vaccine after Wild-Type Dengue Infection?"* Vaccines (Basel). 2020;8(2)
- Coudeville et al. *Assessment of benefits and risks associated with dengue vaccination at the individual and population levels: a dynamic modeling approach*. Expert Review of Vaccines. 2018 Aug;17(8):753-763. doi: 10.1080/14760584
- The WHO guide for serosurveys: *"Informing vaccination programs: a guide to the design and conduct of dengue serosurveys. Geneva: World Health Organization, 2017"* is available at: http://www.int/iris/handle/10665/255650

SCREEN AND VACCINATE IMPLEMENTATION PRINCIPLES
- Arredondo et al. "Immunogenicity and safety of a tetravalent dengue vaccine and a bivalent HPV vaccine given concomitantly or sequentially in girls aged 9 to 14 years in Mexico". Vaccine. 2021 Jun 8;39(25):3388-3396. doi: 10.1016/j.vaccine.2021.04.064. Epub 2021 May 13.

- Santos et al. "Immunogenicity and Safety of a Tetravalent Dengue Vaccine Administered Concomitantly or Sequentially With Tdap Vaccine: Randomized Phase IIIb Trial in Healthy Participants 9-60 Years of Age in the Philippines". Pediatr Infect Dis J. 2021 Jun 10. doi: 10.1097/INF.0000000000003220.
- "*WHO, Consideration regarding consent in vaccinating children and adolescents between 6 and 17 years old*", publis hed in 2014, and aimed at vaccination programme managers summarizes information to consider when preparing guidance note on the consent process. It is available at: http://www.who.int/immunization/programmes_systems/policies_strategies/consent_note_en.pdf

SCREEN AND VACCINATE STRATEGIES

- 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. PMID: 34253416.* This article summarizes the discussions and outcomes of the Partnership for Dengue Control (PDC) expert meeting held in January 2020 at the Mérieux Foundation, Veyrier du Lac, France.
- Similarities exist between human papillomavirus vaccine (HPV) and Dengvaxia® implementation, including the potential target age group (children and adolescent), potential delivery through school immunization programs, and need for multiple doses over a prolonged period. The "London School of Hygiene & Tropical Medicine and PATH.*HPV Vaccine Lessons Learnt & Recommendation: Achievement and HPV Vaccine Lessons Learnt &Recommendations: delivery. 2015.*" presents findings, key lessons, and recommendations related to HPV introduction. It can be downloaded at: http://www.rho.org/files/PATH-LSHTM_HPVvacll_brief_achievements_2015.pdf and www.rho.org/files/PATHLSHTM_HPVvacll_brief_delivery_2015.pdf
- "PATH and Child Health and Development Centre (CHDC). *Shaping a Strategy to Introduce HPV Vaccines in Uganda: Formative Research Results from the HPV Vaccines: Evidence for Impact Project.*" Seattle: PATH; 2009." This document is available online at: www.rho.org/HPV-vaccine-implementation.htm. It provides research results for an HPV vaccine delivery strategy in Uganda.
- "*PATH Implementing HPV Vaccination Programs: Practical Experience from PATH. Cervical Cancer Prevention: Practical Experience Series. 2011.*" This document is downloadable from: http://www.rho.org/files/rb2/Implementing_HPV_vaccination_PATH_2011. It describes and discusses HPV vaccine delivery strategies, compiles useful web links for new vaccine introduction, and compiles HPV vaccine introduction country reports
- The WHO document "*New Vaccine Post-Introduction (PIE) Evaluation Tool. WHO, 2010*" provides a systematic method to assist countries with the evaluation of the implementation of a new vaccine introduction, and its impact on their vaccination system. It is available at: http://whqlibdoc.who.int/hq/2010/WHO_IVB_10.03_eng.pdf