DENGUE VACCINE
PUBLIC HEALTH IMPACT EVALUATION

INFORMATION FOR STAKEHOLDERS

The purpose of this document is to help decision makers and program planners identify key parameters regarding the impact assessment of CYD-TDV, the dengue tetravalent vaccine (live, attenuated).

1. REFERENCES

A number of resources are available which provide an insight on impact evaluation issues that could relate to CYD-TDV implementation.


- The Dengue Vaccine Initiative (DVI) published a series of statements on CYD-TDV, including on SAGE Dengue Vaccine recommendations. They are available at: http://www.denguevaccines.org/resource_library

2. WHY EVALUATE VACCINE IMPACT

Countries that introduce CYD-TDV should plan continuing and in some cases strengthening dengue surveillance to allow evaluation of vaccine impact. This will serve several purposes:

Measuring true vaccine performance:
CYD-TDV vaccine efficacy (VE) may inaccurately predict impact because of:

- Imperfect programmatic implementation compared to the trial settings
- Differences in disease epidemiology, since VE may vary by age groups and geographical settings.
- Differences in serotype distribution, since VE varies by dengue serotype
- Differences in dengue prevalence, since VE is higher among dengue seropositive individuals
- Clinical trial design, since with vaccines that have measureable indirect protection at immunization
coverage of less than 50% (e.g., Hib vaccine), individually randomized trials such as were conducted for CYD-TDV may underestimate true VE

Assessing program implementation:
Lower than expected reductions in disease burden may indicate problems with vaccine delivery, including lower than reported immunization coverage or problems in vaccine storage.

Strengthening program support:
Documenting and publicizing dengue vaccine impact may provide important public and political support for routine immunization programs; this is likely to be particularly the case where vaccine first is introduced during an outbreak.

Countering rumors:
Vaccine impact data can help to counter anti-vaccine messaging, including that related to rumors about side effects or lack of efficacy.

Identifying unexpected effects:
CYD-TDV is a new vaccine. While it has been tested in large-scale clinical trials across a wide range of settings, questions remain:
- Potential for an increase in serotypes for which CYD-TDV has a lower efficacy;
- Safety issues on very rare serious adverse events following immunization (post-licensure surveillance of an early rotavirus vaccine led to withdrawal from the market after identifying an increased risk of intussusception);
- Indirect impact of CYD-TDV on disease burden (Hib vaccine showed much greater reductions in disease than predicted based on immunization coverage, eventually confirmed as due to profound indirect protection).

3. DENGUE CASE DEFINITIONS

- Suspected dengue cases: clinical diagnosis without laboratory confirmation
- Probable dengue case: clinical diagnosis with a positive serologic test (antibody detection - ELISA)
- Confirmed dengue case: clinical diagnosis with positive viral nucleic acid detection (molecular testing - RT-PCR)
- Before 2009, WHO dengue case definitions included three categories: undifferentiated fever, dengue fever (DF) and dengue hemorrhagic fever (DHF). DHF was further classified into four severity grades, with grades III and IV being defined as dengue shock syndrome (DSS)
- Under the revision proposed in 2009, dengue cases are now classified according to the level of severity and includes three categories: dengue, without or with warning signs, and severe dengue:

4. CLINICAL SURVEILLANCE OUTCOMES

- Clinical outcomes selected for post-licensure impact assessments should be those that reflect the main objectives of dengue vaccine introduction. The following could be considered (by age group):
  - Suspected dengue (and severe dengue) case counts
  - Suspected dengue (and severe dengue) incidence
  - Laboratory confirmed dengue case counts/incidence
  - Confirmed severe dengue case counts/incidence
  - Dengue related mortality cases/incidence
- The selection of criteria for dengue impact assessment depends on country laboratory capacities, the additional burden on the surveillance system and health professionals’ activities, the cost of data collection, and outcome specificity.
• Using confirmed dengue cases as outcomes would prevent confusing dengue with other febrile illnesses.
• Standardization of laboratory diagnosis (e.g. moving to virological confirmation whenever possible) and harmonizing case definitions within and across countries in the same region will facilitate rapid impact assessment, data sharing and comparability across regions. WHO regional offices may provide further guidance.
• Capacity is needed to assess whether dengue cases occur among unvaccinated persons or resulted from vaccine failure. Consequently, immunization surveillance should be coordinated with dengu surveillance and vaccine pharmacovigilance.
• In resource-limited settings, the following options should be considered:
  o Strengthening dengue disease surveillance system prior to vaccine introduction. This may be appropriate where long-term surveillance is needed.
  o Conducting epidemiological studies to assess dengue disease burden prior to vaccine introduction. This may be appropriate where the need or capacity for long-term surveillance is uncertain or known to be low. These studies can be costly, and therefore their added value should be carefully assessed.
  o Strengthening surveillance simultaneously with vaccine introduction. This may be appropriate in low-resource settings where clinical data support high dengue prevalence.
• For dengue vaccination coverage data, population-based surveys may complement estimates based on administrative data.
• Considering assessing indirect vaccine effects by incorporating non-vaccinated control groups in dengue surveillance would be an asset.
• Estimating CYD-TDV coverage:
  o CYD-TDV coverage surveys are necessary to determine 1) if the target population was correctly vaccinated, 2) if other populations were vaccinated, and 3) what the percentage of vaccinees is by age group, by geographical locations, and by other variables of interest for vaccine assessment.
  o Vaccination coverage for each of the three doses should be assessed, as well as the compliance with recommended schedule, in terms of timing of doses 2 and 3. Consequently, the immunization information system should capture individual data, with accurate records of vaccine dose and date at vaccination for each dose.

5. PUBLIC HEALTH SURVEILLANCE OUTCOMES

Public health goals are best achieved by assessing dengue incidence rates. This requires knowledge of the population denominator, rather than only knowing the proportional or absolute case count reduction. A number of key indicators should be computed in this perspective, amongst which the vaccine-preventable disease incidence and the number needed to vaccinate.

Vaccine-preventable disease incidence (VPDI)
• VPDI is also known as an absolute rate reduction or incidence rate reduction. Mathematically, it is equivalent to the incidence in the control group minus the incidence in the intervention group, which is equivalent to control group incidence multiplied by VE.
• The VDI can be calculated directly through a non-randomized cohort design or a before-and-after study. In a cohort design, vaccinated persons are followed over time so VPDI is expressed as outcomes prevented per 100 persons vaccinated per year. In a before-and-after study, no cohort is followed and VPDI is expressed as outcomes prevented per 100 population (either total or target population) per year.
• An example of a public health message might be: “Following vaccine introduction, dengue disease incidence decreased from 5% per year to 1% per year for a reduction of 4 cases for every 100 persons per year.”

Number needed to vaccinate (NNV)
• The number needed to vaccinate expresses how many people need to be vaccinated to prevent a single disease outcome. While VPDI is a rate, NNV is not.
• In a cluster randomized trial (RCT) setting, and more generally cohort designs, NNV is relatively easy to calculate because a cohort is followed over time, and at least one dose of vaccine usually is a requirement for inclusion in analysis; in this case, and where VPDI is presented as outcomes prevented per 100 persons per year of follow, NNV can be expressed mathematically as (100 divided by VPDI divided by length of follow-up or known duration of immunity). In a before-and-after study, a cohort is not followed over time. In this case, NNV is calculated as [[100 divided by VPDI] x (fraction of population under study that received vaccination)].
• Using the previous example and based on a before-and-after study with 80% coverage in the target
population, an example of a public health message might be: “Following vaccine introduction, one case of dengue was prevented for every 20 persons vaccinated.

Proportional reduction in cases
- Most crudely, the proportional reduction in cases can be estimated based on the overall CYD-TDV vaccine efficacy. This estimate can be refined further by using the serotype distribution locally and serotype-specific vaccine efficacy from the clinical trials. This can be expressed mathematically as:
  \[(ST1 \times VE1) + (ST2 \times VE2) + (ST3 \times VE3) + (ST4 \times VE4)\]
  Where ST = percentage of all dengue due to that serotype and VE = serotype specific vaccine efficacy.
- For example, if one uses reported pooled data against clinical dengue, VE1=58%, VE2=47%, VE3=74%, and VE4=83%, and assumes ST1 through ST4 equal, respectively, 10%, 20%, 30%, and 40%, overall direct reduction in dengue among the vaccinated population is estimated as 71%.
- In addition to estimated proportional reduction estimates, proportional reduction can be calculated directly from a before-and-after study by focusing only on case counts. Accurate interpretation of proportional reduction in case counts is heavily dependent on having a static population in place over the study period.
- An example of a public health message might be: “Based on our serotype distribution, we estimate that CYD-TDV will reduce dengue by 71% among the vaccinated 9 and 10 year old population.”

Case count reduction
- Case count reduction expresses the absolute number of dengue outcomes prevented through vaccine introduction. This value usually is extrapolated from a study population to an area of interest, such as a district or country, and as such is limited by the representativeness of study data for the larger population. It is defined as: VPDI x population of interest.
- Alternatively, and similar to proportional reduction, case count reduction can be estimated by applying the calculated vaccine efficacy to the number of cases in the target population pre-vaccine.
- An example of a public health message for a district with one million people might be: “Following vaccine introduction among children age 9 and 10 years, vaccine prevented an estimated 5,000 cases of dengue in District X.”

6. POSSIBLE DESIGNS FOR CYD-TDV IMPACT EVALUATION

- Long-term follow-up and future post-licensure studies on safety and effectiveness are ongoing, with results available in the coming years. This will help further assessing the overall benefit of the vaccine for human health.
- The WHO/SAGE emphasizes that:
  - As the vaccine is rolled out in endemic countries, vaccine effectiveness by dose, duration of protection, and long-term impact of vaccine programmes are research priorities
  - Using surveillance data to monitor population impact of a vaccination programme may be challenging as the year-to-year variability in dengue virus transmission may be greater than the expected impact of CYD-TDV on dengue illness.
  - Long-term monitoring for severe dengue illness should be done in selected areas, and for seronegative persons in particular in special studies
  - Using surveillance data to monitor population impact of a vaccination programme may be challenging as the year-to-year variability in dengue virus transmission may be greater than the expected vaccine impact on dengue illness. Special studies should be conducted to monitor the occurrence over time of severe dengue illness in vaccinees

DESIGN 1: Randomized clinical trial
- Post-licensure, an individually or community randomized clinical trial within the licensure age range maybe considered difficult on ethical ground, and will not be considered further.

DESIGN 2: Non-randomized prospective cohort study
- This design allows the determination of dengue incidence rates between vaccinated group and control groups (e.g. area where vaccine was not introduced), and in turn dengue incidence rate differences.
- Strengths:
  - The vaccine can be delivered in the routine immunization program, which limits cost and may provide a better estimate of real life vaccine impact.
Limitations:
- Similar to case-control studies, the non-randomized approach can lead to substantial confounding, since risks for disease and lack of vaccination may be similar.
- Sufficient data to adjust for all potential confounders is unlikely to be available.
- Where immunization programs are strong, it may be difficult to identify sufficient unvaccinated persons.
- With high vaccine coverage, the unvaccinated population becomes increasingly likely to represent a marginalized group.
- In some settings target outcomes may be rare (e.g., hospitalization for severe dengue) requiring enrollment of a large number of subjects to achieve adequate study size.

DESIGN 3: Before-and-after study
- Before and after vaccine introduction, informative data can be obtained by tracking outcome case numbers, incidence over time or by conducting an interrupted time series analysis.
- Generally a minimum of two years pre-introduction and three years post-introduction are recommended.
- Design options:
  - Prospective surveillance throughout.
  - Retrospective review of records pre-vaccine or during both periods.
  - Use of administrative databases.
- Ideally a control condition unaffected by vaccine should be included as well to adjust for changes in health seeking behaviors.
- The study results can be made even stronger by conducting an evaluation over the same time period in an epidemiologically similar area where vaccine was not introduced.
- Strengths:
  - This design provides data on vaccine preventable disease incidence.
  - It enhances and can be incorporated into national surveillance systems.
  - Any of the outcomes of interest can be used.

DESIGN 4: Case-control studies
- The primary outcome is vaccine effectiveness, which can be interpreted as the proportional reduction in disease due to vaccine.
- Strengths:
  - For rare outcomes such as severe dengue, the efficiency will be greater than cohort studies.
  - Once CYD-TDV is introduced, these studies can be done over a relatively short period.
  - Case control studies do not require pre-vaccine data.
  - By applying vaccine effectiveness to existing incidence estimates, one can model burden reduction.
- Limitations:
  - Case control studies are highly susceptible to confounding due to differences between dengue cases and controls in health seeking behaviors, likelihood of vaccination with CYD-TDV, and likelihood of receiving a diagnostic test for dengue.
  - These studies can be relatively expensive, particularly when community controls are used.
  - With high vaccine coverage, the unvaccinated population becomes increasingly likely to represent a marginalized group.
  - Case control studies do not provide a direct measure of burden reduction, which is the outcome of most interest to public health decision makers.

An accompanying tool is available for estimating dengue vaccine impact in terms of reduction of disease and public health burden – Worksheet 3: Vaccine impact.