WHO Secretariat

Updated Questions and Answers related to the dengue vaccine Dengvaxia® and its use

Published 22 December 2017

This document takes into account new and unpublished data that were communicated by Sanofi Pasteur to WHO in November-December 2017.

WHO published the recommendations of the Strategic Advisory Group of Experts on Immunization (SAGE) on the use of Dengvaxia® on 27 May 20161, and subsequently a WHO position paper on dengue vaccine on 29 July 2016.2

Following the disclosure to WHO of new data on Dengvaxia® by its manufacturer, Sanofi Pasteur, as described in more detail below, WHO has initiated a process engaging independent external experts to review the data in detail. This process is expected to lead to revised recommendations from SAGE in April 2018, and to an updated WHO position paper on dengue vaccine thereafter.

The purpose of this document, prepared by the WHO Secretariat, is to supplement the WHO position paper on Dengvaxia® of July 2016 until WHO has issued an updated position paper on dengue vaccine, based on advice by SAGE. WHO Secretariat recommends that the July 2016 position paper be read in conjunction with this document.

This document replaces a questions and answers document web-posted by WHO on 30 November 2017.

What is dengue?

Dengue is a febrile illness caused by a mosquito-borne virus, for which there is no specific anti-viral treatment. Many dengue virus infections produce no or only mild clinical symptoms (i.e. they are clinically inapparent). The global annual incidence of clinically apparent dengue has been estimated at about 50-100 million cases, predominantly in Asia, followed by Latin America and to a lesser extent Africa. Dengue may be caused by any one of four dengue viruses (serotypes 1-4). In most cases, dengue is a self-limiting illness, but may require hospital admission, where supportive care can modify the course of the illness. Recovery from infection by one serotype is thought to provide lifelong immunity against that particular serotype, but susceptibility remains to the other 3 and hence a person can be infected by up to four serotypes during his or her lifetime. After infection with one serotype, cross-immunity provides temporary partial protection against the other serotypes. There is a small risk of severe disease after any dengue infection, but the second infection by a different serotype to the first is thought to be associated with the highest risk of severe dengue, while the third and fourth infections are usually associated with a milder clinical course.

What is severe dengue?

Severe dengue is a relatively rare but serious complication following dengue infection due to plasma leaking, fluid accumulation, respiratory distress, severe bleeding or organ impairment. Severe dengue may be life-threatening, but early diagnosis and prompt and

1 http://www.who.int/wer/2016/wer9121.pdf
2 http://www.who.int/immunization/policy/position_papers/dengue/en/
judicious fluid replacement therapy can decrease fatality rates to far below 1\%\(^3\).

**What is dengue serostatus?**

Serostatus refers to whether a person has experienced a dengue infection in the past. A seronegative individual has not had a previous dengue infection. A seropositive individual has had a previous dengue infection with at least one serotype. A person may not know whether he or she was infected in the past, because many dengue infections are clinically inapparent. Among those who are seropositive, some individuals will only have been infected with one dengue serotype and these individuals are at higher risk of severe dengue when infected with a second dengue serotype. Of note, only few secondary infections will lead to severe disease.

**What is Dengvaxia® (CYD-TDV)?**

Dengvaxia® (also referred to as CYD-TDV), developed by Sanofi Pasteur, is a live recombinant tetravalent dengue vaccine, based on the yellow fever 17D vaccine strain, given as a 3-dose series with 6 months between each dose. The vaccine has 4 components, encoding for antigens of the four dengue virus strains. Dengvaxia is the first dengue vaccine to be licensed. Licensure means that a national regulatory authority reviewed all of the data on the vaccine, found that the benefits outweigh the risks, and permitted the company to have a marketing authorization to sell the product in that country.

**When was Dengvaxia® licensed and for which age group?**

Dengvaxia® was first licensed in December 2015 and has now been approved by regulatory authorities in 19 countries for use in endemic areas in persons ranging from 9-45 years of age. Dengvaxia® was licensed based on the results of two large clinical trials (called Phase 3 trials). The CYD14 trial was conducted at sites in five countries in Asia and the CYD15 trial at sites in five countries in Latin America. Together, these trials included over 30,000 participants aged 2 to 16 years. The efficacy of the vaccine against laboratory confirmed dengue, measured for 12 months after the last dose and pooled across both trials, was 59.2\% in the year following the primary series, and 79.1\% against severe dengue. Efficacy varied by infecting serotype, age and serostatus. These results were published in 2014 and 2015.\(^4\)\(^5\)

The Phase 3 trials included the age range of 2 to 16 years. While the vaccine was protective against hospitalization due to dengue and severe dengue in all trial participants in the first two years of follow-up after the first vaccine dose, an excess of cases of hospitalization due to dengue and severe dengue cases was seen in those receiving Dengvaxia® in the third year after the first dose, notably in the age group below 9 years, and mainly in those aged 2-5 years.\(^6\) Whether the increased risk was due to age or because this age group contains a higher proportion of seronegative individuals (which is inversely correlated with age), could not be determined with the data available at the time. For children aged 9 years and above, in the first two years of

---

\(^3\) [http://www.who.int/denguecontrol/faq/en/index2.html](http://www.who.int/denguecontrol/faq/en/index2.html)


the phase 3 trials, the data showed a reduction in severe dengue by 93% and a reduction in dengue hospitalizations by 82%. Based on these findings, licensure was obtained for those aged 9–45 year (with different age ranges in some countries). The vaccine was not licensed in children younger than 9 years because of the less favorable safety and efficacy results in young children.

What was WHO’s position on the use of Dengvaxia® as published in July 2016?

The decision of whether to introduce a new vaccine in a country is a decision of governments, not of WHO. However, WHO provides recommendations in the form of position papers to help country decision-making. These recommendations are based on the advice of SAGE,7 WHO’s principal independent expert advisory committee on vaccination. Based on their advice and the data available as of April 2016, a position paper on the dengue vaccine was published in July 2016.8 This position paper presents a conditional recommendation on the use of the vaccine for areas in which dengue is highly endemic as defined by seroprevalence in the population targeted for vaccination. Seroprevalence refers to the proportion of people in a population who have already been infected with a dengue virus, i.e. the proportion of seropositive individuals. Based on the difference in performance of Dengvaxia® in seropositive and seronegative individuals, seroprevalence thresholds were considered the best approach to define target populations for vaccination. Trial results and mathematical modeling suggested optimal benefits of vaccination if seroprevalence in the age group targeted for vaccination was in the range of ≥70%. WHO developed guidelines on how to determine the seroprevalence in an area to help countries that were considering use of the vaccine.9

Although at the time of the policy formulation no evidence of an increased risk of severe dengue in seronegative individuals aged 9 years and above was apparent from the limited available data, the possibility of low efficacy and an elevated risk of severe dengue in vaccinated seronegative individuals was mentioned in WHO’s position paper because of the observations in the younger age group. This possibility was considered in the mathematical models used to inform the WHO position. SAGE considered further research into the efficacy and safety of the vaccine in seronegative persons a high priority.8,10,11 Hence, WHO requested that Sanofi Pasteur provides more data on efficacy and safety in seronegative vaccine recipients.

What additional analyses did Sanofi Pasteur do in 2017?

Sanofi Pasteur reanalyzed the trial data separately in participants classified as seronegative and seropositive to estimate the long-term safety and efficacy of the vaccine by serostatus prior to vaccination using new diagnostics tools. Since only a subset of participants in the large Phase 3 trials had blood samples collected before vaccination, the serostatus of most trial participants (i.e., whether they were seropositive or seronegative at the time of receiving the first vaccine dose), was not

---

7 http://www.who.int/immunization/policy/sage/en/
8 http://www.who.int/wer/2016/wer9130.pdf
9 http://www.who.int/immunization/research/development/Dengue_Serosurveys_020617.pdf
known. Therefore, it was hitherto not possible to analyze the efficacy and long-term safety data of Dengvaxia® according to serostatus. To overcome this obstacle, the company utilized a new assay developed by the University of Pittsburgh to perform additional testing to infer pre-vaccination serostatus based on samples that had been collected from all trial participants at month 13, one month after the 3rd dose was administered. Without the new test, participants who were vaccinated in the trial had antibodies against dengue at month 13, but it was not known if these antibodies were induced by the vaccine, or from having being infected by dengue viruses before vaccination, or both. Participant samples were re-tested using this yet unpublished assay that identifies antibodies against the dengue non-structural protein 1 (NS1). The Dengvaxia® non-structural proteins code for yellow fever vaccine proteins, rather than for dengue and thus the new test was able to distinguish immune responses due to past dengue infection from those due to vaccination. This test, combined with imputation methods, allowed trial participants to be categorized retrospectively into those who were likely to have been seropositive or seronegative at the time of receiving the first dose of the vaccine.

What were the results of these additional analyses?

The results confirmed previous findings that, overall, vaccinated trial participants had a reduced risk of virologically-confirmed severe dengue and hospitalizations due to dengue.

Trial participants who were inferred to be seropositive at the time of first vaccination had a durable protection against severe dengue and hospitalization during the entire 5-year observation period.

However, the subset of trial participants who were inferred to be seronegative at time of first vaccination had a significantly higher risk of more severe dengue and hospitalizations from dengue compared to unvaccinated participants, regardless of age at time of vaccination. Beyond an initial protective period during the first two years, the risk was highest in year 3 following the first dose, declined in the following years but persisted over the trial follow up period of about 5 years after the first dose.

How can one explain the excess cases of severe dengue in the vaccinated seronegative population?

The reasons for the excess cases are not fully understood, but a plausible hypothesis is that the vaccine may initiate a first immune response to dengue in seronegative persons (e.g. persons without a prior dengue infection) that predisposes them to a higher risk of severe disease. That is, the vaccine acts as a "primary-like" infection and a subsequent infection with the first wild type dengue virus is then a "secondary-like" clinically more severe infection. This hypothesis is illustrated in the Figure below. However, other hypotheses are possible and, at this stage, there is no definitive explanation. Of note, it is not the vaccine itself that causes excess cases, but rather that the vaccine induces an immune status that increases the risk that subsequent infections are more pronounced.
What is the risk of developing severe dengue in a vaccinated seronegative person compared to an unvaccinated seropositive person when exposed to a wild-type dengue virus infection?

The new analysis by Sanofi Pasteur suggests a similar rate of severe and hospitalized dengue between unvaccinated seropositive persons and vaccinated seronegative persons. The clinical severity in the vaccinated seronegative group was similar to that of severe cases in the unvaccinated seropositive group. In the clinical trials for those aged 9 years and above, the cases of severe dengue that occurred in initially seronegative vaccine recipients were categorized by the company as Dengue Hemorrhagic Fever Grades I and II and did not lead to shock, severe bleeding or death. All of the patients with dengue illnesses in the trial recovered.

What do the findings from the new analysis mean in real life settings?

The expected number of cases prevented or induced in a vaccinated population will depend on the seroprevalence in a particular country and on the incidence of dengue infections. For example, in the areas in the Philippines where Dengvaxia® was introduced (mainly through school programmes), the seroprevalence was estimated to be at least 85%. A seroprevalence of 85% means that 85% of the population is seropositive and will benefit from Dengvaxia®. In such a high transmission setting, every 1 excess case within a 5 year period of hospitalized dengue in vaccinated seronegatives is offset by 18 cases prevented in vaccinated seropositives, and 1 excess severe dengue in vaccinated seronegatives by 10 prevented severe cases in vaccinated seropositives.

In the dengue transmission settings of the clinical trials with varying degrees of seroprevalence in different countries, during the 5 year follow-up after vaccination, there was a reduction of about 15 cases of hospitalized dengue and 4 cases of severe dengue per 1,000 seropositive persons vaccinated. For 1,000 seronegative persons vaccinated, there was an increase of about 5 cases of hospitalized dengue and 2 cases of severe dengue.

Accounting for prevented and induced cases, if the vaccine is administered in a population with a high seroprevalence, there is still a significant benefit in terms of reduction of severe dengue and hospitalizations due to dengue.

**What is the absolute risk of severe dengue in the vaccinated and unvaccinated trial populations by serostatus?**

The risk depends on the yearly incidence of dengue. Based on the incidence in the epidemiological settings of the trials, for persons aged 9 years and above, the new analysis indicates that the 5-year risk of severe dengue in vaccinated seronegative persons (4 per 1,000 seronegative persons vaccinated) is similar to the risk of severe dengue in unvaccinated seropositive persons (4.8 per 1,000 seropositive persons unvaccinated). The risk of severe dengue is lower in unvaccinated seronegative persons (1.7 per 1,000 seronegative persons unvaccinated). The risk of severe dengue in vaccinated seropositive persons is the lowest (less than 1 per 1,000 seropositive persons vaccinated). There is no evidence that clinical manifestations of disease were more severe in vaccinated seronegative persons compared to unvaccinated seropositive persons. For the entire vaccinated population, overall, the risk of severe dengue is reduced compared to a non-vaccinated population.

**Will this elevated risk of severe dengue in vaccinated seronegative persons compared to unvaccinated seronegative persons last throughout life?**

No long-term data beyond the trial observation period of 5 years currently exist. In the trial, the highest risk was in the third year and subsequently declined. Theoretically, based on the model that the vaccine acts like a silent primary infection, it is expected that the elevated risk of severe disease in vaccinated seronegative persons should disappear after they have had a natural infection.

**What can be done to reduce the risk of getting infected by a dengue virus and experiencing serious complications?**

All individuals, regardless whether they have been vaccinated or not, should take personal protective measures to avoid mosquito bites. Furthermore, for any individual who presents with clinical symptoms compatible with dengue virus infection, regardless whether they have been vaccinated or not, prompt medical care should be sought to allow for proper evaluation, monitoring and clinical management. With proper medical care, severe dengue can be well managed.

**What tests are available to determine whether a person had a previous dengue infection (i.e. to determine their serostatus)?**

There are various tests available to determine serostatus, but these are complex to use and are not yet suitable for routine practice in the context of a public vaccination programme. Dengue IgG indirect ELISA is one option to enable medical practitioners to determine if a person has had previous dengue infection, and this test is available in many dengue endemic countries. The draw-back of dengue IgG ELISA is that the results

are not immediately available. In addition, possible cross-reactivity with other flaviviruses such as Zika virus or Japanese encephalitis virus may occur, giving rise to false positive results. The preferred approach would be a rapid diagnostic test that can be used at the time of vaccination, is affordable and provides reliable immediate results. However, such a rapid diagnostic assay has not yet been evaluated for the purpose of detecting past infection. Further research is needed.

In addition to serology testing, a person’s history of dengue illness could be ascertained based on medical history or medical documentation. However, dengue infections can be asymptomatic, mild, and other infections can mimic dengue.

How many individuals have been vaccinated with Dengvaxia® to date?

Based on information available to WHO, Dengvaxia® has not been implemented in any country-wide programme to date. Dengvaxia® has been introduced in two subnational programs in the Philippines and Brazil targeting in total about one million individuals. It is otherwise available on the private market in countries where there is a marketing authorization.

Should individuals who have been partially vaccinated with Dengvaxia® (e.g. received 1 or 2 doses) complete the 3-dose series, if serostatus was unknown?

Because nearly everyone in the clinical trials received all three doses of the vaccine, there are currently no data to inform on vaccine performance in individuals partially (1-2 doses) vaccinated, either for seronegatives or for seropositives. It is not known what the long term protective effect of the vaccine is in seropositive individuals if they received fewer than 3 doses, and it is also not known if the increased risk of severe disease in seronegative individuals is different according to the number of vaccine doses they have received. Thus, there is no evidence to determine the risk and benefit of completion or suspension of the series in those who have received only one or two doses.

However, in documented high seroprevalence settings, where vaccination has started but the schedule has not yet been completed, there is likely to be an overall benefit to the population if individuals complete the schedule, hereby assuring protection of seropositive individuals who make up the majority of the vaccinated population. Programmatic and communication issues should be taken into consideration in deciding on the continuation of a vaccination programme.

Will there be a change to the license conditions?

Sanofi Pasteur has proposed a label change to the national regulatory authorities in the countries where Dengvaxia® has been licensed. The final wording of the amended label will be decided by the national regulatory authorities of the respective countries.

Are other dengue vaccines available?

Dengvaxia® is the only vaccine currently licensed against dengue. Two other candidate vaccines are currently being evaluated in large Phase 3 trials.15 The data obtained from these trials are needed before the vaccines may be licensed by national regulatory authorities. No conclusions can be drawn from the data generated from Dengvaxia® onto these two candidate vaccines.

What is WHO interim position towards the use of Dengvaxia®?

WHO has initiated a process engaging independent external experts to review the new data generated by Sanofi Pasteur in order to provide advice on revisions to the WHO policy position paper from 2016. On 6-7 December 2017, the WHO Global Advisory Committee on Vaccine Safety (GACVS) reviewed the data and subsequently published a statement related to the safety of the product.16

WHO acknowledges that in high seroprevalence settings, the vaccine can have significant population-level benefits. However, until a full review has been conducted, WHO recommends vaccination only in individuals with a documented past dengue infection, either by a diagnostic test or by a documented medical history of past dengue illness.

Any further guidance, including a review by SAGE and update of the WHO position paper on Dengvaxia®, will likely be available no earlier than April 2018 after a rigorous review of the new data and additional activities, such as population based modelling, are undertaken. Meanwhile, WHO encourages the development of a rapid diagnostic assay to determine past dengue infection.

16 http://www.who.int/vaccine_safety/committee/GACVS-StatementonDengvaxia-CYD-TDV/en/