**Updated Questions and Answers related to information presented in the Sanofi Pasteur press release on 30 November 2017 with regards to the dengue vaccine Dengvaxia®**

**30 November 2017**

**Q1: What is Dengvaxia®?**

There continues to be a strong public health need for effective preventive interventions against dengue, a disease caused by four viruses, termed serotypes 1-4. One dengue vaccine has been licensed, Dengvaxia® (also referred to as CYD-TDV), developed by Sanofi Pasteur. Dengvaxia® is a live recombinant tetravalent dengue vaccine developed by Sanofi Pasteur, given as a 3-dose series on a 0/6/12 month schedule. Dengvaxia® is the first dengue vaccine to be licensed and has now been approved by 19 regulatory authorities for use in endemic areas in persons typically ranging from 9-45 (in some countries 9-60) years of age. It has been introduced in two subnational programs in the Philippines and Brazil targeting about one million individuals. It is otherwise available on the private market in countries where there is a marketing authorization.

**Q2: What was previously known about the licensed dengue vaccine, Dengvaxia®?**

Dengvaxia® has been evaluated in two Phase 3 clinical trials (CYD14 trial in five countries in Asia and CYD15 trial in five countries in Latin America). Together, these trials included over 30,000 participants aged 2 to 16 years. Vaccine efficacy against confirmed dengue pooled across both trials was 59.2% in the year following the primary series, and 79.1% against severe dengue. Efficacy varied by serotype, by age at vaccination and serostatus at baseline (i.e., previous exposure to dengue prior to vaccination).

While efficacy was reported against hospitalized and severe dengue in Years 1 and 2 post-dose 1, an excess of cases of hospitalized and severe dengue cases in those receiving Dengvaxia® was seen in Year 3 in some subgroups, although it is based on relatively small numbers of cases. Whether the increased risk was due to age or serostatus at baseline, which is highly correlated with age, could not be fully clarified with the available data at the time. For subjects aged 9 and above, in the first 25 months of the phase 3 trials, there was a reduction in severe dengue by 93% and a reduction in hospitalizations by 81%. Owing to the higher efficacy among participants vaccinated at age ≥9 years, as well as an elevated risk of hospitalized dengue in the 2–5-year age group, licensure was obtained in several countries to date for those aged 9–45 or 9–60 years living in dengue-endemic settings.

**Q3: What is WHO's current position on the use of Dengvaxia®?**

Following recommendations made by the Strategic Advisory Group of Experts (SAGE) on immunization, WHO's advisory body on vaccination, a position paper was published in July 2016 based on the data available at that time. The position paper makes a conditional recommendation on the use of the vaccine for highly endemic areas. Based on considerations of superior efficacy and, possibly, safety and duration of protection in seropositive individuals, SAGE recommended seroprevalence thresholds as the best population-level strategy. Based on mathematical modeling, an optimal seroprevalence in the age group targeted for vaccination was defined in the range of ≥70%. At that time theoretical elevated risk of dengue in vaccinated seronegative subjects was noted, and research into this was considered high priority. WHO thus called on Sanofi Pasteur to provide more data on efficacy and safety in baseline seronegative vaccine recipients.

**Q 5: What are the additional analyses on efficacy and safety in baseline seronegative persons who received Dengvaxia®?**

Because the Phase 3 trials did not collect blood samples from all participants to be able to determine serostatus at baseline, the company performed additional testing to infer serostatus at the time of vaccination. However, samples were available for all trial participants at month 13, one month after the 3$^{rd}$ dose was administered. These samples were tested using an assay that identifies antibodies against the dengue non-structural protein 1 (NS1) based on the fact that the Dengvaxia® non-structural proteins code for Yellow Fever vaccine proteins, rather than for dengue. This allows differentiation between previous natural exposure to dengue and vaccination. Based on this test, Sanofi Pasteur reanalyzed the trial data stratified by seronegative and seropositive subjects to estimate the safety and efficacy of the vaccine by baseline serostatus.

**Q 6: What are the preliminary results from the recent analysis of vaccine safety in persons seronegative to dengue prior to vaccination?**

While vaccinated trial participants overall had a reduced risk of virologically-confirmed severe dengue and hospitalizations due to dengue, the subset of trial participants who had not been exposed to dengue virus infection prior to vaccination had a higher risk of more severe dengue and hospitalizations due to dengue compared to unvaccinated participants, regardless of age. This increased risk was observed after an initial protective period and persisted over the observation period of up to 66 months post primary vaccination.

**Q 7: What is WHO's interim interpretation of the data?**

WHO's interim interpretation of data is that:

- The vaccine significantly protects against hospitalized and severe dengue in subjects seropositive for dengue at time of first vaccination in all age groups studied;
- The risk of hospitalized and severe dengue is significantly increased among vaccinated subjects who were seronegative for dengue at the time of first vaccination in all age groups studied;

WHO will conduct a full review of the data through the Global Advisory Committee on Vaccine Safety and SAGE, for revised guidance of the use of Dengvaxia®.

Pending the full review of the data, *as a precautionary and interim measure*, WHO recommends that Dengvaxia® is only administered to subjects that are known to have been infected with dengue prior to vaccination.

**Q 8: What do these data mean for other dengue vaccines in clinical development?**

A more detailed analysis of the data is needed to answer this question. The two candidate vaccines in phase 3 clinical development differ significantly from Dengvaxia®, so that no conclusions on the safety and efficacy profile of these candidates should yet be drawn. However, it will be necessary to carefully monitor vaccine performance over time in both seronegative and seropositive subjects.

**References :**

WHO position paper on dengue vaccines, July 2016:

- WHO position paper on dengue vaccines
  pdf, 437kb

Previous Q&A's on Dengvaxia® study results

- **http://www.who.int/immunization/research/development/dengue_q_and_a/en/**

WHO's Dengue Control Strategy:

- **http://www.who.int/denguecontrol/resources/9789241504034/en/**