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Q&A SESSION 06 OCTOBER 2011 – I INTERNATIONAL SYMPOSIUM ON DENGUE, FMUSP, SÃO PAULO

Jean LANG(1), Lucia F. BRICKS(2) & Giovanini COELHO(3)

Since the acknowledgement of the reintroduction of the dengue virus in Brazil early in the eighties, the local population has been exposed to scenarios of extensive virus transmissions. The dengue epidemiology in Brazil during the last decade has been characterized by the occurrence of bursting epidemics, increase in the number of serious cases, displacement in the patient's age group and simultaneous circulation of serotypes 1, 2 and 3 and the recent introduction of serotype 4[1-3].

In this epidemiologic scenario, the potential availability of a vaccine that immunizes against the four dengue virus serotypes is a promissory condition, capable of reverting the worsening of the problem trend in this country. This assessment is based on two basic points:

1. Difficulty to implement current measures to control the *Aedes aegypti* vector, due to its low effectiveness or high cost[4].
2. Recognition of the capacity of the Immunization National Program in insuring high vaccine coverage, which is responsible for the reduction and even for the elimination of some immunopreventable diseases.

However, issues about safety, immunogenicity, efficacy and effectiveness, which are basic pre-requisites for the development of any vaccine, become more important when we deal with candidate vaccines against dengue. The peculiar aspects of the disease physiopathogeny, especially the potential risk of Antibody Enhancement Dependence (AED) further contribute to the complexity of such vaccines development.

This subject was recently given priority by the Health Ministry in Brazil that set up a workgroup composed of experts in different fields, whose main objective is to develop strategies for the introduction of the dengue vaccine in the Sistema Único de Saúde (Government health program). Among this group's tasks, the definition of studies for the identification of priority areas and target groups who will receive the vaccine is outstanding, and should include a permanent channel for discussion about dengue candidate vaccines including public and private manufacturers.

This initiative of the Health Ministry matches other initiatives taken by different sectors. The most recent one occurred during the I International Symposium on Dengue sponsored by the Faculdade de Medicina da Universidade de São Paulo (São Paulo Medical School) in October 2011. In that symposium, the main findings concerning the recombinant dengue vaccine (YF17D) developed by the Sanofi Pasteur have been discussed.

The results of the discussions on the issues raised by the Symposium participants are described hereafter. Among the questions raised, the aspects connected with the vaccination schedule, adverse events associated with the vaccine, viscerotropism risk, immunogenicity degree for each dengue serotypes, reactogenicity to the vaccine in populations of endemic and non-endemic areas, possibility of immunization against the yellow fever virus and many others were marked issues.

1. The candidate TDV is a tetravalent recombinant live vaccine. How we can guarantee that vaccine strains will not revert to wild dengue virus?

In contrast to what has been observed with live, classically-attenuated dengue vaccines, the four recombinant CYD dengue vaccine viruses (CYD-1, CYD-2, CYD-3 and CYD-4) are very stable. The YF17D vaccine genome, upon which the CYD viruses are based, is in fact remarkably stable, both *in vivo* and *in vitro*, which may be attributed to the low error-rate of the viral RNA polymerase, the enzyme responsible for replication. Moreover, the many attenuations in the non-structural genes of YF17D make the reversion to virulence impossible in practice. The full sequence of each of the CYD-1–4 genomes was established at various stages throughout the vaccine lot production process, the results of which demonstrate that the four CYD viruses display very high genetic stability[5,6].

2. What are the most frequent adverse events observed in immunized people? Can it cause dengue-like syndrome?

The most frequent adverse events are mild-to-moderate injection site pain, erythema, edema, headache, fever, malaise, asthenia and myalgia (14-40% after each vaccination). Injection site reactions were reported by a comparable proportion of participants after each injection of TDV. Systemic reactions appeared to be more frequent after the first TDV vaccination, and there is a trend towards progressively reduction of adverse events after each subsequently dose. Overall, adverse reactions are similar when compared to other single or multiple dose licensed vaccine given to control groups. No adverse events resembling dengue-like syndrome have been reported[5-7].

3. The Sanofi Pasteur dengue vaccine is based on a YF 17D backbone. What is the risk of viscerotropism and neurotropism after vaccination?

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(1) Associate Vice-President, R&D Dengue Vaccine Program Head, Sanofi Pasteur, Lyon, France
(2) Public Health Director Sanofi Pasteur, Vaccines Division Sanofi, Brazil. Pediatrician, Doctor in Medicine by Universidade de São Paulo.
(3) Coordinator, National Program for Dengue Fever Control, Ministry of Health /Brazil.

Given that the tropism of a flavivirus is associated with its envelope proteins, and that the CYD viruses have the envelope genes of dengue rather than those of the YF17D vaccine strain, these very rare adverse events after YF vaccination are not expected to occur after vaccination with the CYD dengue vaccine[5,6]. However, given the rarity of these events after YF vaccination, post-licensure studies will be able to provide the necessary statistical power to eliminate this theoretical risk.

4. Is the immunogenicity for each dengue ST the same?

After three doses of TDV given six months apart, consistent and balanced antibody responses to all four serotypes are observed[5,6]. Some variability between serotypes are seen after first of the three doses, particularly in populations with no prior flaviviral immunity.

5. Does the reactogenicity differ when TDV is given to people living in endemic or non endemic areas?

No, the local and systemic reactogenicity is very similar between participants living in non-endemic and endemic regions. Similarly, reactogenicity is not affected by whether the participants have a history of vaccination against another flavivirus.

6. Will the Sanofi Pasteur vaccine protect against both yellow fever and dengue?

No, the Sanofi Pasteur vaccine candidate is designed to protect only against dengue infection. The envelope and pre membrane genes that induce antibodies expressed by CYD strains are from dengue virus.

7. The formulation and schedule of vaccination recommended to children is the same of that indicated for adolescents and adults?

Yes, the formulation will be the same, and the vaccine will be licensed according the schedule used in PIII studies, with three doses (0-6 and 12 months).

8. Are any differences in immunogenicity observed after 3rd dose of TDV when we compare children and adults?

Immunogenicity is robust and balanced after 3rd dose in both children (> two years) and adults.

9. Why is the vaccination schedule not offered with a shorter interval between the doses?

The immune response to dengue is serotype specific, but short-lasting cross-reactive antibodies (IgM or even IgG) triggered by the responding serotypes after one dose of live recombinant CYD dengue vaccine can still block at the time of a second dose vaccine serotypes which did not respond initially. A too short interval of time may then result in the inactivation of the booster dose because of these cross reactive antibodies, and/or by persistent innate responses (type I IFNs)[8].

10. Does the immune response to dengue vaccine differ in dengue endemic versus non-endemic areas?

Yes: a significant proportion of a population residing in an area where dengue is endemic will have developed an antibody response against dengue from natural infection prior to vaccination. This pre-existing response favors quicker and higher immune responses to CYD TDV, compared to the responses observed in a population who has not been exposed to dengue.

11. Can the vaccine be used in children? What is the age for registration?

After approval, the initial indication will be for children aged two years or older. The possibility of vaccinating children younger than two years will depend on the outcome of co-administration studies.

12. Can dengue vaccine be administered with other vaccines recommended for children, adolescents and adults?

Clinical studies designed to answer this question are ongoing or are planned. For example, a study assessing the co-administration of tetravalent dengue vaccine with a combined measles-mumps-rubella vaccine is ongoing. The results of this study are expected in 2012.

13. Is there interference between yellow fever (YF) and dengue vaccines when used simultaneously? What is the immune response for each vaccine?

The potential interference between these two vaccines will be assessed. Ongoing safety and immunogenicity studies include co-administration of TDV, YF and measles at nine months (Colombia and Peru) and MMR at 12 months of age, to evaluate. A study of Sanofi Pasteur's recombinant, live, attenuated Japanese encephalitis vaccine, developed using the same recombinant technology as that used to develop the CYD vaccine (i.e., also based on the YF-17D backbone), designed specifically to assess the potential for interference between the two vaccines, concluded that they could be successfully co-administered simultaneously or 30 days apart. Of course, the outcome may differ for dengue, which is a tetravalent vaccine[9].

14. What is the efficacy and duration of protection for each ST DEN 1, 2, 3, 4?

As there is no known correlate of protection, the level of protective efficacy can only be determined in efficacy studies. Results from the first efficacy study are expected to be known before the end of 2012. Pre and post licensure clinical studies will provide data on long-term immune responses.

15. Does SP intend to conduct new studies with two doses for people previously vaccinated with YF?

The program of development of the vaccine has focused on a three dose schedule to conservatively cover those individuals who may or not have had previous exposure to dengue or another flavivirus (natural or post-immunization).

16. How many dengue cases (DF and DHF) or deaths were confirmed after each dose of DTV?

In the initial studies already completed, there was no dengue like syndrome associated with DTV. Dengue cases are being followed in the efficacy studies in a blinded manner, and there is an Independent Monitoring Committee that analyses the signs for serious adverse events in clinical trials. In a recent study including children, adolescents and adults, four serious adverse events occurred (fatal traffic accident, partial seizures, hepatitis A infection, and upper respiratory tract infection), none of with were considered related to the vaccine by the investigators, the sponsor, or the independent monitoring committee[7]. Until now, with more then 11,000 people immunized, there was no alert sign to open the codes of studies[5,10].

17. Will a booster be necessary after three doses? When?

For "travelers" living in non-endemic areas (no further contact with

the wt viruses), this is most likely (long-term follow up is needed to know when).

In endemic regions, natural boosters caused by wt infections may be sufficient (again, data will come from long-term follow up studies in different areas)

18. What would be the best age to start vaccination?

As dengue affects people of all ages, the best age to start vaccination will be as soon as possible. The initial submission dossier will provide information about the vaccine for people > two years of age.

19. What are the contra indications for this vaccine?

As it contains live virus, it will be contraindicated to immunocompromised people and pregnant women. It has not been studied in infants, and should not be administered for children < 24 months of age.

20. Can the vaccine be used during outbreaks?

This question only can be answered after registration, because the phase III studies were developed to evaluate the efficacy after three doses (schedule 0, 1 and 6 months). We do not have data about efficacy using partial schedule.

Note - *The opinions expressed by participants not necessarily have support by Ministry of Health.*

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