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Age specific differences in efficacy and safety for the CYD-tetravalent dengue vaccine

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Summary

CYD-TDV is the first dengue vaccine to have completed Phase 3 efficacy trials. Efficacy was consistently higher in those aged 9 and above for all variables studied: efficacy against virologically confirmed dengue of any severity and serotype, serotype specific efficacy, efficacy dependent on baseline seropositivity, efficacy against hospitalizations and efficacy against severe disease. Because of the higher efficacy and the absence of a safety signal, the age group with the best benefit of the use of CYD-TDV is individuals aged 9 and above – the age group for which licensure is now being sought.

Keywords: dengue, vaccine, efficacy, age indication, efficacy

The CYD tetravalent dengue vaccine candidate (CYD TDV) is composed of four recombinant, live, attenuated vaccines (CYD-1-4) based on a yellow fever vaccine 17D (YFV 17D) backbone, each expressing the pre-membrane and envelope genes of one of the four dengue virus serotypes. The first such chimeric vaccine to be approved for marketing is a vaccine against another flavivirus, Japanese encephalitis (JE), which also employs yellow fever 17D (1) as backbone. The dengue vaccine is, however, more complex than JE in that it requires a mixture of four live viruses each expressing one of the four dengue serotypes(1), hence issues of interference and homo, hetero- and multitypic immunity pose additional challenges(2). CYD-TDV is the first dengue vaccine to have completed Phase 3 efficacy

trials. Conducted in ten endemic countries in Asia and Latin America these two multi-centre efficacy trials involved more than 31,000 subjects with an age range from 2 to 16 (3, 4) and observations from the first three years after the first dose are now available (5). In addition, approximately 4000 subjects between the ages of 4 and 11 from the phase 2b CYD23 trial in Thailand (6) are being followed in the CYD57 trial with currently four years of follow-up published (5). The primary objective of the two multi-center trials was to assess protective efficacy against symptomatic, virologically confirmed dengue, irrespective of disease severity or serotype, 28 days after the third injection. The primary endpoint was for the lower boundary of the 95% CI of vaccine efficacy to be greater than 25%. The Phase 3 trials met the a priori endpoint, with an overall efficacy of 56.5% (95% CI 43.8–66.4) in Asia(3), and 64.7% (95% CI, 58.7 to 69.8) in Latin America(4). In parallel to clinical development, Sanofi Pasteur has put strategies into place for scale up and industrialization to anticipate and facilitate supply and access to vaccine in the countries where the dengue disease burden makes it an urgent public health priority(7). In the second quarter of 2015 Sanofi Pasteur submitted the dossiers to the National Regulatory Authorities of several dengue endemic countries. In July 2015, a technical consultation with National Regulatory Authorities on the dengue vaccine dossier hosted by the World Health Organization in partnership with the Dengue Vaccine Initiative (www.denguevaccines.org) was held, during which Sanofi Pasteur made known that they seek licensure with an age indication from 9-60 years of age. The objective of this short report is to explore the rationale for the proposed age indication for CYD-TDV for those aged 9 and above based on the efficacy and safety results from the pooled analysis published in the week prior to the NRA meeting in Geneva(5).

Efficacy: The efficacy results of the phase 3 trials have shown varied performance depending largely on baseline seropositivity, serotype and age. The relative lack of vaccine efficacy in participants who were dengue-virus naive may suggest that this vaccine boosts and broadens pre-existing immunity more than raising de novo protective antibodies (8). The resulting protective efficacy could thus be explained by serotype cross-protective immunity rather than serotype-specific immunity. In other words, a prior infection with one serotype boosted by the vaccine could drive a previous primary infection into a tertiary or quaternary infection. As third and fourth infections are known to be associated with milder disease(9), such a shift could explain the relatively higher protection against severe disease seen in the trials.

Although the geometric mean titers of the antibody response were relatively high across all four serotypes after 3 vaccine doses(10), recent modeling of the immunological response has shown that serotype 4 was the most immune-dominant, in particular after the first dose(11). This observation would also explain the imbalanced efficacy in favor of serotype 4. Older age was associated with better efficacy, plausibly driven by baseline seropositivity as older

children will have had more exposure to dengue. Analyses of the pooled data from both trials allow for a more robust analysis of age effects, and suggest that age also had an effect independent of baseline seropositivity (5). In seronegative children younger than 9, the vaccine showed no efficacy at all (efficacy 14.4 with confidence interval ranging from -111 to 63.5), but efficacy was 52.5% (5.9-76.1) in those seronegative subjects aged 9 and above. The table shows that the efficacy was consistently higher in those aged 9 and above for all variables studied: efficacy against virologically confirmed dengue of any severity and serotype, serotype specific efficacy, efficacy dependent on baseline seropositivity, efficacy against hospitalizations and efficacy against severe disease. The result of the studies in Asia and Latin America are remarkably consistent for efficacy by age, serotype, severity and other analyses when looking at same age groups of 9 years and above. Of particular note in the age group of 9 years and above is the high efficacy against hospitalization (81%) and severe disease (93%)- the two parameters most important for individual and public health.

Safety: The vaccine was found to be safe for all age groups in the first two years of the trial. However, in the third year a higher number of hospitalizations were observed in the vaccinated group compared to the unvaccinated group for those individuals below the age of 9, with a relative risk (RR) of 1.58(5). This reverse risk benefit ratio was more evident in the very young - aged 2-5 - where the relative risk was as high as 8. This safety signal precludes the use of this vaccine in this age group. No increased risk was observed in subjects aged 9 and above who all had a more stable and sustained reduction in hospitalizations into the third year, although some waning of efficacy was observed as evidenced by the increasing trend of RR from the first to the third year (RR in the first year: 0.17, second year 0.21, third year 0.53; Table). It is important to explore different hypotheses that may explain the safety signal observed in the third year in younger children. Antibody dependent enhancement (ADE) is an explanation that first comes to mind, especially as a higher number of baseline seronegative children were implicated. It is plausible that seronegative young children when vaccinated developed a low quality immune response that did not significantly protect against disease or hospitalization. Subsequently, the immune response could have resulted in enhanced disease during breakthrough dengue infections, but most efficiently during the third year post-vaccination, similar to sequential natural dengue infections where hospitalized dengue disease occurs only two or more years after a first dengue infection(12). However, cytokine profiles or higher viremia levels indicative of immune enhancement were not found in these children compared to their hospitalized controls (5). Furthermore, the increased risk of hospitalizations was only transient and waned in the fourth year (5). If it were true ADE, then the increased incidence of hospitalizations would have not only continued but increased in the fourth year, given the experiences from Cuba showing that the incidence of severe dengue with secondary

infections (thought to be due to ADE) increased as the interval between heterologous infections increased from 4 to 20 years (13). Other explanations for the transient reversed risk benefit need to be entertained. A lower immunogenicity in younger children for CYD-TDV, similarly observed for many other vaccines at younger age, could have led to rapid waning immunity and a consequent shift in disease occurrence to later age groups rather than immune enhancement. Then the short-lived higher incidence in the third year would be indicative of rebound, as also seen in the case of the RTS/S malaria vaccine where young children experienced a higher incidence of malaria attacks at the time of waning vaccine efficacy compared to the unvaccinated controls(14). As the quality and quantity of the immune response to the CYD-TDV was lower in seronegatives, waning efficacy is expected to occur earlier and faster in seronegatives, which could explain the higher proportion of baseline seronegatives in the hospitalized cases in the third year. Given the small numbers, and the limited subset of immunogenicity data in the CYD trial, any explanation will remain speculative. However, the safety signal in the third year has major implications: first of all, the study protocol was changed to revert to the active surveillance in all the trial sites over the next years; second, for the time being the vaccine should not be used in young children.

In children aged 9 and above, the efficacy against virologically confirmed dengue of any severity was 64%, against hospitalizations 81% and against severe disease 93%; no safety signal was seen. Efficacy declined over the years, as seen in the increasing RR—which could be either due to waning vaccine efficacy or an increase in enhanced disease seen in seronegatives in the third year. Because of the higher efficacy and the absence of an obvious safety signal the age group to best benefit of the use of this vaccine is individuals from the age of 9 to 16—the age group for which licensure has been filed. Sanofi Pasteur is also seeking licensure for individuals aged 16 and above, up to age 60. Good immunogenicity and safety data exist for up to the age of 45 (10), but no efficacy data exist for the age above 16, and the rationale for expanding the age group beyond 16 is mainly based on immunobridging. Expanding the age indication beyond the age range studied in trials is not new, and has been done frequently for other vaccines. National regulatory authorities (NRA) of individual countries will need to make the decision on the age indications they will want to include in their local labels based on the currently available data.

Assuming that NRA will adopt a licensure indication for individuals aged 9 and above, mathematical modelling will need to estimate the public health impact dependent of various scenarios of age inclusion on national programmes to help policy-makers make evidence-informed decisions. Although annual incidence was slightly higher in the younger age groups in the published trials, an age indication of 9 and above could potentially still have some

public health impact given the fact that a shift of dengue's age distribution to older age groups has occurred in many dengue endemic countries in recent decades (15). For example, in Thailand, the country with one of the highest dengue incidences in the combined trials, a shift of the main disease burden to those aged 10–14 years and beyond has been observed for the past decade(16). The same observation was documented in Brazil, the country with highest absolute number of dengue cases in the world (17). In the year 2012, Brazil reported the highest number of dengue cases in the age group of 20-39, followed by the age group of 40-59, and then ages 15-19(18); however the highest death rates are around the age of 6 (personal communication; Eduardo Massad).

It will be important to calculate vaccine preventable disease incidence, which is a measure that takes both efficacy and burden of disease into account (19). The higher the disease burden, the higher the vaccine preventable disease incidence, and the more impact a vaccine will have even if efficacy is only moderate. Number needed to vaccinate (NNV) is another measure to gauge vaccine attractiveness. To calculate the NNV, one needs to calculate the Absolute Risk Reduction (ARR) which is the incidence in the unvaccinated group minus the incidence in the vaccinated group. The NNV is the inverse of the ARR: $NNT = 1/ARR$. A back of the envelope calculation based on the data from CYD 14 and 15 came up with an NNV that ranged from 18 to 174 for individuals aged 9 and above to prevent virologically confirmed dengue of any severity. The calculated NNV to avoid a case of hospitalized dengue ranged from 118 to 1210; such an NNV compares favorably for example with the NNV needed for the recommendation of influenza vaccination in pregnant women to avoid influenza related hospitalizations -- a recommendation that requires an NNV of 1200 (20).

The findings from the CYD 14 and 15 trials indicate the highly heterogeneous nature of dengue transmission. Such heterogeneity will have bearing on vaccine preventable dengue incidence and NNV; these will vary by geographical location, from year to year, and be highly dependent on age and serotype distribution. As the trials showed, the extent of efficacy (which will in turn also influence vaccine preventable disease incidence and NNV), varied from country to country: for example, in Colombia vaccine efficacy was found to be 67.5%, but in Mexico only 31.3%; and the main reasons for this substantial discrepancy were the baseline seropositivity (92% for Colombia versus 53% for Mexico) and serotype distribution. The implications of these findings are that this vaccine would best be used in countries with a very high dengue disease burden (as reflected by high seropositivity rates).

While the scientific community continues to actively address the reasons for the imbalanced efficacy results against the serotypes, the lower efficacy in immunologically naïve subjects

and the transient reversed risk/benefit ratio in the third year in the very young, policy-makers need to make informed decisions how best to use the CYD-TDV vaccine for the age group for which licensure is now being sought in various dengue endemic countries. In the absence of other failing control measures(21), the public health impact of CYD-TDV may still be important, despite of its age limitation and moderate efficacy. Clearly, this vaccine on its own will not be able to eradicate dengue, but it may be an important additional tool in the armamentarium for dengue prevention and control. However, with the possibility that this vaccine could enhance disease in baseline seronegative persons, vigilance and monitoring will need to be maintained over many years, in particular for dengue naïve individuals. The public health priority for this vaccine would be countries with very high dengue endemicity. The vaccine's efficacy and hence impact will be limited in countries with low dengue endemicity, and even more limited in the travel medicine context (eg dengue virus naïve international travelers). In view of the complexity of this vaccine, the global scientific and public health community will need a coordinated effort and international leadership. Indeed, in March 2015, the World Health Organization established a SAGE working group on dengue vaccine and vaccination(22). The Working Group has been asked to review the evidence, including data from mathematical modeling, and formulate proposed recommendations on the use of a licensed dengue vaccine for a SAGE review. Tentatively scheduled for April 2016, the SAGE review will lead to the publication of a WHO position paper on the use of a dengue vaccine.

Expert commentary:

CYD-TDV is the first dengue vaccine to have completed Phase 3 efficacy trials. Efficacy was consistently higher in those aged 9 and above for all variables studied: efficacy against virologically confirmed dengue of any severity and serotype, serotype specific efficacy, efficacy dependent on baseline seropositivity, efficacy against hospitalizations and efficacy against severe disease. Because of the higher efficacy and the absence of a safety signal the age group to best benefit of the use of CYD-TDV is individuals aged 9 and above-- the age group for which licensure is now being sought. While the reasons for the imbalanced efficacy results against the serotypes, the lower efficacy in immunologically naïve subjects and the transient reversed risk/benefit ratio in the third year in those aged 2-5 are being investigated, policy-makers need to make informed decisions how best to use CYD-TDV for the age group of 9 and above given it is the only vaccine available to date to control dengue in the absence of other failing control measures. As efficacy was higher in countries with high dengue seroprevalence, CYD-TDV would be best used in countries with a very high dengue disease burden (as reflected by high seropositivity rates).

Five year view:

By 2018 we will have a more than 5 years follow up of approximately 30,000 subjects who have received three doses of CYD-TDV – a time period that will allow to address questions on incidence of enhanced disease over time (if any), waning immunity and the need and optimal timing for booster doses. Assuming that CYD-TDV will be licensed and rolled out in countries with high dengue incidence, the next 5 years will also provide more insight and data on indirect vaccine effects, and hence vaccine effectiveness at population level. The next 5 years will most likely also see the completion of Phase 3 efficacy trials for other dengue vaccines thereby allowing comparisons with CYD-TDV in terms of age-specific effects, serotype specific efficacy and safety.

Key issues:

- The multi-center trials in Asia and Latin America have shown an imbalanced efficacy depending on various factors: baseline seropositivity, serotype and age
- Efficacy was consistently higher in those aged 9 and above for all variables studied: efficacy against virologically confirmed dengue of any severity and serotype, serotype specific efficacy, efficacy dependent on baseline seropositivity, efficacy against hospitalizations and efficacy against severe disease.
- Understanding the reasons for the transient reverse risk benefit ratio in the third year after vaccination in very young children is critical for further dengue vaccine development
- Mathematical modelling is important to estimate the public health impact of CYD-TDV on populationwide dengue incidence if vaccination is limited to individuals aged 9 and above.

Financial and competing interests disclosure

A Wilder-Smith is the principal investigator of a phase 2b trial on the CYD-TDV dengue vaccine. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Reference annotations

* *Of interest*

** *Of considerable interest*

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Table 1: Efficacy and relative risk (RR) by age group (data extracted from Reference 5)

	Age group (age in years)	
	2-8	9-16
Number of subjects enrolled		
Asia (CYD14)	5234	4931
Latin America (CYD15)	–	19898
Efficacy		
VCD of any severity and serotype	44.6 (31.6-55.0)	65.6 (60.7-69.9)
Serotype 1	46.6 (25.7-61.5)	58.4 (47.7-66.9)
Serotype 2	33.6 (1.3-55.0)	47.1 (31.3-59.2)
Serotype 3	62.1 (28.4-80.3)	73.6 (64.4-80.4)
Serotype 4	51.7 (17.6-71.8)	83.2 (76.2-88.2)
Seropositive at baseline	70.1 (32.3-87.3)	81.9 (67.2-90.0)
Seronegative at baseline	14.4 (-111-63.5)	52.5 (5.9-76.1)
All severity hospitalised	56.1 (26.2-74.1)	80.8 (70.1-87.7)
Severe (IDMC) hospitalised	44.5 (-54.4-79.7)	93.2 (77.3-98.0)
DHF (WHO 1997) hospitalised	66.7 (-4.7-90.2)	92.9 (76.1-97.9)
Relative Risk		
	Relative Risk (%) (95% CI) for hospitalizations of VCD of any severity	
CYD14 (Asia)		
Year 1	0.36 (0.16, 0.78)	0.44 (0.14, 1.38)
Year 2	0.53 (0.25, 1.12)	0.08 (0.01, 0.27)
Year 3	1.58 (0.61, 4.83)	0.57 (0.18, 1.86)
Cumulative Results	0.61 (0.39, 0.95)	0.27 (0.14, 0.50)
CYD15 (Latin America)		
Year 1	–	0.17 (0.05, 0.48)
Year 2	–	0.21 (0.10, 0.43)
Year 3	–	0.53 (0.25, 1.16)
Cumulative Results	–	0.28 (0.18, 0.44)
CYD23/57		
Year 1	0.50 (0.11, 2.15)	0.76 (0.09, 9.08)
Year 2	0.75 (0.36, 1.59)	0.17 (0.03, 0.68)
Year 3	1.57 (0.60, 4.80)	0.31 (0.05, 1.58)
Year 4	0.54 (0.23, 1.29)	0.31 (0.09, 0.93)
Cumulative Results	0.89 (0.54, 1.52)	0.29 (0.11, 0.69)