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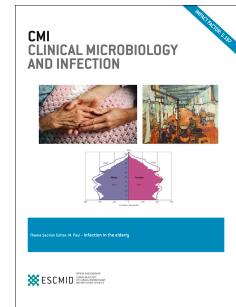
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Four-year safety follow-up of the tetravalent dengue vaccine CYD-TDV

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Several decades of dengue vaccine research have shown the difficulties to develop a highly efficacious and safe vaccine that protects against all four serotypes.¹ The main challenge is the viral interference between the four serotypes in a tetravalent vaccine resulting in the potential of one serotype being immune-dominant thereby leading to an imbalanced efficacy against the remaining serotypes.² Imbalanced antibody levels or an imbalanced waning of protective antibody levels over time may then sensitize vaccinees to develop more severe dengue upon subsequent exposure to wild-type dengue viruses.³ Natural studies indicate a titer-dependent and time-dependent role of cross-protective anti-dengue antibodies.⁴ After an initial window of protection, cross-reactive antibodies wane from higher-titer, protective levels to lower-titer, disease-enhancing levels.⁴ Using multiple statistical approaches to study a long-term pediatric cohort in Nicaragua, disease enhancement was highest within a narrow range of preexisting anti-DENV antibody titers.⁵ Experiences from Cuba highlighted that the incidence of severe dengue disease increased as the interval between heterologous infections increased from 4 to 20 years.⁶ Hence, longer observation times are needed to conclusively rule out an increased risk of antibody dependent enhancement in vaccine recipients. In 2012, the World Health Organization (WHO) issued guidelines on the clinical development of dengue vaccines that included a plan for follow-up of subjects for safety for at least 3–5 years from the time of completion of primary vaccination.⁷ Therefore, the a priori planned long-term follow up to 6 years of the first licensed tetravalent dengue vaccine, CYD-TDV (Dengvaxia®) developed by Sanofi Pasteur, is to be commended. This month's issue in *Clinical Microbiology and Infection* provides important interim 4 year follow up data on protection and safety of CYD-TDV.⁸

Arredondo-Garcia et al report the relative risk (RR) of hospital admission for virologically-confirmed dengue (VCD) and the risk of clinically-severe hospitalised VCD occurring up to four years post-first dose in vaccinated versus un-vaccinated children. The follow up data of three randomised clinical trials comprised of 23,429 participants randomised to the CYD-TDV group and 11,694 randomised to the control group. Consistent with previous reports, a higher risk of hospitalized dengue was found in the younger age group from 2 to 8 years. In the age group of interest, the age group for which CYD-TDV is licensed in 19 countries, CYD-TDV reduced the risk of confirmed severe dengue and hospital admissions throughout the 4 years observation time. The overall cumulative RR in those aged 9 and above was favorable at 0.242. As efficacy equals $1 - RR$, this finding translates into a 76% efficacy cumulatively over 4 years in terms of reducing hospitalized VCD. However, the RR increased in year 3 and 4, hence efficacy decreased: in the first two years after the first dose the RR was 0.172 (efficacy of 83%) and in the years 3 and 4 it was 0.676 (efficacy of 32%). There are two plausible explanations for the decreasing efficacy over time: (1) rapidly waning vaccine

efficacy and/or (2) a subset is experiencing a higher risk of hospitalized dengue thus increasing the overall RR.

There is no need to speculate anymore. We now know the explanation. Not long after this manuscript was submitted to *Clinical Microbiology and Infection*, on 29 November 2017, Sanofi Pasteur made a press release highlighting new findings based on additional analyses.⁹ They found a significant differential performance of CYD-TDV depending on serostatus. Serostatus refers to whether a person has experienced a dengue infection in the past; a seronegative person has not had a previous dengue infection. By utilizing a novel NS1 antibody IgG ELISA on sera obtained at month 13 of the trial, combined with imputation methods, the company retrospectively analyzed the trial data separately in participants inferred to be seronegative or seropositive at baseline to estimate the long-term safety and efficacy of the vaccine by serostatus. The new analyses showed an increased risk of severe and hospitalized dengue in the subset of seronegative children vaccinated with CYD-TDV, irrespective of age and throughout the observation period of 5 years, while the vaccine was efficacious and safe in seropositive children. These findings are corroborated by the results published in this issue: In the small immunogenicity subset (eg the subset of about 10% of children where baseline blood samples were taken to check for serostatus) those who were seronegative at baseline, irrespective of age, the RR was 1.327 for hospitalised VCD for all trials combined for the 4 year follow up. Given the small numbers in the immunogenicity subset, the RRs had wide 95% confidence intervals that included 1, and were hence not significant. It appears that the larger sample size and longer observation time of Sanofi Pasteur's new analyses released on 29 November 2017 consolidate these findings. However, at this point in time, the exact magnitude of the risk and more detailed statistical analyses are yet to be published in a peer reviewed scientific journal.

In seronegative individuals the vaccine enhances the severity of a subsequent dengue infection. Sanofi Pasteur has stated its intention to change the label so that individuals who have not been previously infected by dengue virus (those who are seronegative) should not be vaccinated. WHO's Global Advisory Committee on Vaccine Safety (GACVS) and the WHO Secretariat published interim statements on December 7, 2017¹⁰, and December 22, 2017¹¹, respectively. 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.

CYD-TDV finds itself again at a crossroad.¹² With dengue incidence poised to only increase, and highly effective vector control measures remaining elusive, the world still needs a dengue

vaccine. WHO acknowledges that in high seroprevalence settings, CYD-TDV 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.¹¹

Will disease enhancement in seronegative vaccinees following CYC-TDV also be a problem for second-generation dengue vaccines? The answer to this question depends on the underlying mechanism of vaccine-induced enhancement observed for CYD-TDV. The most plausible hypothesis is that the live attenuated CYD-TDV initiates a first immune response to dengue in seronegative persons 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 akin to the antibody-dependent enhancement theory.^{11,13} We do not know whether the second-generation dengue vaccines will exhibit a similar mechanism, hence we need to await the results of the two currently ongoing Phase 3 trial results for the two leading second-generation dengue vaccine candidates (one developed by Takeda¹⁴, and one by NIH/NIAID together with Butantan¹⁵). But the bar for second-generation dengue vaccines is now clearly higher than ever before. WHO convened a technical consultation in June 2017 to guide dengue vaccine developers on trial design and duration of observation to enable broader public health recommendations for second-generation dengue vaccines.⁷ The clinical development of second generation vaccines would be greatly facilitated if we had established correlates of protection¹⁶, and the lessons from CYD-TDV are that we need to study both correlates of protection and correlates of enhancement.⁵

Disclaimer:

AWS is Consultant for Arboviral Diseases at the Initiative for Vaccine Research, WHO. The author alone is responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of the World Health Organization.

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