Editorial

Dengue vaccine: Re-visited

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I wrote an editorial titled "Dengue vaccine: Light at the end of the tunnel" in the 2012 September issue of the *Sri Lanka Journal of Child Health*[1]. At that time the Sanofi Pasteur dengue vaccine was undergoing field trials on thousands of children in Thailand with initial efficacy results expected in September 2012[2]. Currently, the only dengue vaccine commercially available is the Sanofi Pasteur vaccine, called Chimeric Yellow-fever Dengue - Tetravalent Dengue Vaccine (CYD-TDV), sold under the brand name Dengvaxia[3]. It is a chimeric live attenuated tetravalent vaccine, produced using recombinant deoxyribonucleic acid (DNA) technology by replacing the pre-membrane (PrM) and envelope (E) structural genes of the yellow fever attenuated 17D strain vaccine with those from the four dengue serotypes[4,5].

Phase I clinical trials showed that CYD-TDV was well tolerated and manifested a 100% seroconversion rate to all four serotypes after receiving three doses[6,7]. However, phase IIb and III clinical trials showed limited efficacy against dengue virus (DENV)-2 (34.7% efficacy against virologically confirmed dengue), which unfortunately is also most commonly associated with severe dengue. Efficacy against DENV-1, 3 and 4 was 54.5%, 65.2% and 72.4% respectively[8,9]. A large phase III clinical trial recruited over ten thousand children aged 2-14 years in five Asia-Pacific countries to evaluate the efficacy of the vaccine. Overall, a 56.5% (95% CI 43.8-66.4) reduction of polymerase chain reaction (PCR)-confirmed dengue cases was observed in the vaccine recipients compared to the control group[9]. However, vaccine efficacy was consistently lower in children below 9 years of age, compared to older participants (44.6% versus 67.8%)[10], most probably because these younger children were less likely to be seropositive. For these reasons CYD-TDV has been licensed for use only in individuals 9 years of age and above[11].

An additional limitation to the use of Dengvaxia is that it appears to sensitize dengue naïve participants, acting like a natural primary infection, thereby putting them at a greater risk of developing secondary dengue, which tends to be more severe. The reason why this occurs is not fully understood, but may be explained by the mechanism of antibody-dependent enhancement (ADE), combined with an imbalanced immunogenicity against the different serotypes[12].

Lower efficacy for baseline seronegative patients was observed for all participants and not only the younger group. CYD-TDV is safe and effective in patients with antibodies against at least one dengue serotype, but its administration is potentially dangerous in seronegative individuals. Thus, the Strategic Advisory Group of Experts (SAGE) on immunization from the World Health Organisation recommends a pre-vaccination screening to assess the serostatus of the recipients, in order to immunize exclusively individuals who had a previous dengue virus infection. In environments where this screening is not feasible, the vaccine should be administered only in those countries where the seroprevalence has been shown to be 80% or greater in children aged 9 years or more[13].

It is apparent that Dengvaxia is not the 'ideal' dengue vaccine. The 'ideal' dengue vaccine should be safe and effective against all 4 serotypes and ensure a solid protective immunity from dengue infection, regardless of the age or serological status of the recipients[14]. The increasing global burden of dengue has motivated researchers and pharmaceutical companies to invest a lot of resources towards developing new vaccines. The most advanced candidates are two live-attenuated vaccines, Tetravalent Dengue Vaccine (TDV), manufactured by Takeda Vaccines (Singapore). and TDV 003/005, developed by the United States National Institute of Health, which are both currently in phase III clinical trials.

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G N Lucas orcid.org/0000-0002-4005- 5618
Joint Editor

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