New chapter unfolding in the fight against dengue with an unwritten ending

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Dengue is the most common and fastest growing mosquito-borne viral disease.\textsuperscript{1} Forty percent of the world’s population is at risk of contracting dengue, which is caused by four distinct yet closely related dengue virus serotypes. About 50 to 100 million dengue infections are reported annually and 500 000 people with severe dengue require hospitalization each year.\textsuperscript{2} Recovery from one serotype of dengue confers lifelong immunity against the infecting serotype but increases the risk of developing hemorrhagic fever, shock and death following infection from any one of the other three strains. Dengue causes much human suffering and economic hardship with an estimated annual cost in the Americas of US$2.1 billion per year.\textsuperscript{3}

The good news is, a vaccine is forthcoming. While this represents a new chapter in the fight against dengue, as it brings hope for a more sustainable and scalable strategy to prevent and control this disease, the ending is yet to be written.

After more than 60 years of research, the development of dengue vaccines has accelerated dramatically in recent years. Today, several vaccine candidates are in advanced development, with clinical trials underway on at least five of them.

A pivotal, recent development is the completion of the first Phase 3 trial of a dengue vaccine candidate. The trial evaluated the efficacy and safety of the Sanofi Pasteur tetravalent dengue vaccine candidate\textsuperscript{4,5} across several Asian countries. This vaccine candidate is based on live, recombinant and attenuated viruses. Sanofi Pasteur replaced the membrane and envelope genes of the yellow fever 17D vaccine virus genome with those of dengue virus, constructed four chimeric dengue viruses (one for each serotype), and combined them in a tetravalent vaccine. The vaccine was tested in a 3-dose schedule, with 6 month intervals between the doses.

The Phase 3 trial showed efficacy of 57% against any virologically confirmed dengue. Vaccine efficacy was statistically significant for all serotypes except serotype 2 (DENV2), remaining consistent with the previous Phase 2b trial,\textsuperscript{6} which also showed that the vaccine efficacy against DENV2 was lower than for the other three serotypes.

The overall efficacy is moderate compared to accustomed efficacy rates of 90% and more of other viral vaccines. Also, the variable vaccine efficacy between serotypes remains a major limitation of this vaccine candidate, as the reason behind variable vaccine efficacy is still unknown, inviting further examination.

Safety of CYD-TDV in the first 12 months following the primary vaccine series is reassuring. Researchers did not observe signals of an increase in serious adverse events in the trial during the 2 years following the administration of the first dose of the vaccine. Continued monitoring of the vaccine safety is needed, as with any other vaccine.

In addition, the trial results provided new insights in exploratory analyses: an increase in vaccine efficacy with age and a reduction of risk of severe disease in vaccinated children. These findings offer hope, as severe dengue infections leading to hospitalization represent a major public health burden. However, we need further studies to confirm the protection against severe dengue and hospitalizations given the potential confounding of age by background flavivirus exposure and the small numbers of severe disease cases.

The Dengue Vaccine Initiative (DVI) finds the results of the Phase 3 trial in Asia encouraging because they show promising indications that a safe vaccine that provides protection against dengue is technically feasible. However, key questions need to be addressed before the final chapter is written, and we hope that the sister study in Latin America will address some of those. 1. Are three doses of the vaccine needed for primary immunization? while the number of children who received only one dose in the Phase 3 study was low, efficacy after at least one dose was almost as high as that after three in a highly flavivirus-experienced population. 2. Who is going to be vaccinated, given the much lower efficacy reported in young and mostly flavivirus-naïve children? 3. Can we overcome the varying vaccine efficacy between serotypes and, in particular, the low efficacy of serotype 2 despite a solid immune response against DENV2, as measured by plaque reduction neutralization testing?
4. How can countries assess public health benefits of this vaccine candidate? 5. What will be the cost of vaccine introduction?

Investigations into some of these questions already began since the reporting of the Phase 2b data. The dengue community awaits for these results. If the vaccine is licensed and introduced in countries, Phase 4 trials will be necessary for long-term follow-up of the duration of protection, vaccine safety, impact on dengue transmission and other questions that cannot be answered with pre-licensure clinical trials.

In this way, the Phase 3 trial findings demonstrate our limited understanding of the immunology of dengue and inability to measure protective immune responses. Still, while several uncertainties remain, the results put a vaccine firmly onto the agenda for dengue control. As researchers, scientists, ministries of health, experts and the community alike answer these questions, the combined use of the various dengue control strategies, including vector control and environmental management, remains paramount and we hope to see that, in a near future, they join immunization campaigns as well to reduce the burden of dengue. The DVI commends Sanofi Pasteur’s commitment to developing a vaccine against dengue. We will continue to follow progress of their candidate, as well as other vaccine candidates as we work to lay the foundation for the adoption and rollout of a licensed dengue vaccine.

Authors’ disclaimer: The mission of DVI is to lay out the groundwork for dengue vaccine decision-making and introduction in endemic areas. We represent a consortium of organizations committed to preventing dengue.

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