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## Dengue vaccine: the need, the challenges and progress

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With regard to scientific progress on dengue, it could be said that we are living in the best of times and the worst of times. As recently as the 1980s, dengue was considered among the “neglected tropical diseases.” Initiatives through the NIH, World Health Organization, and Bill and Melinda Gates Foundation, among others, greatly increased the visibility of dengue and the financing of basic and translational research. These initiatives, along with advances in scientific technology, have led to an explosion of knowledge and remarkable progress in the development of novel approaches to prevention, diagnosis, and treatment of dengue. Within just the past 5 years, the first dengue vaccine entered phase III clinical trials, demonstrated efficacy against both the primary endpoint of virologically-confirmed dengue and important secondary endpoints including hospitalized dengue and dengue hemorrhagic fever, and reach licensure in several dengue-endemic countries. The challenges overcome in reaching these milestones should not be understated [1]. In addition to the complexity of developing a vaccine against all four dengue virus (DENV) serotypes, the potential to induce harmful immune responses has been a major impediment to translation from basic vaccine concept to advanced clinical testing. Protective immunity induced by natural DENV infection is predominantly serotype-specific after the first few months. However, such individuals have an increased risk for more severe dengue illness,

dengue hemorrhagic fever and dengue shock syndrome, during a second DENV infection with a heterologous DENV serotype compared to individuals who have never had a prior DENV infection. The increased risk for severe disease appears to be most strongly associated with the second DENV infection, and it is clear that broadly protective immunity can eventually be generated. It was uncertain whether such protective immunity could be induced by a vaccine without a period of increased risk. The lack of reliable immunological markers distinguishing fully protected individuals from those at elevated risk, along with the absence of faithful animal models of this phenomenon, has required something of a leap of faith on the part of vaccine developers, investigators, and participants. With a tool now in hand with the potential to reduce the risk of dengue, and particularly more severe dengue illness, we have some cause to celebrate.

The magnitude and urgency of the need for an effective dengue vaccine temper any celebration, however. DENV and its *Aedes* mosquito vectors have proven not only highly resilient but extraordinarily well-suited to exploit human economic development. The past few decades have seen an expansion of areas considered endemic for dengue, with half the human population now at risk of infection [2]. The average number of dengue cases reported annually has increased alarmingly in each of the past 4 decades. Health care systems are overloaded on a regular basis by the case load, especially in resource-limited countries, but even highly developed countries including the United States, Japan, and Singapore have proved to be susceptible to chains of local transmission. Despite the much enhanced profile for dengue among researchers, funding agencies, pharmaceutical and vaccine companies, and the lay public, we have clearly been losing the battle against the virus and the mosquito.

Against this backdrop, the Sanofi vaccine that was recently licensed, a tetravalent live attenuated vaccine formulation comprised of chimeric flaviviruses containing the structural protein genes of DENV and the non-structural protein genes of the yellow fever virus 17D vaccine strain, while

an important step, leaves much to be desired. The licensed regimen involves 3 doses given at 6-month intervals, a logistical challenge, particularly in resource-poor countries. Efficacy against serotype 2 viruses was at best suboptimal. More concerning, efficacy against the primary endpoint was significantly lower in children 2-5 years of age and in those subjects who were seronegative for dengue at baseline (i.e., had no previous DENV infections); during the first year of long-term safety monitoring (the second year after completion of the vaccination series), there was even a statistically significant increase in hospitalized dengue cases in children in the youngest age stratum who received the vaccine [3]. As a result, the vaccine has been licensed only for use in children 9 years of age or older, missing an important segment of the population at risk. While no adverse safety signals were observed in the vaccine trials among this older age group, follow up has been relatively short, and there are remaining concerns about the durability of vaccine-induced protective immunity and the potential for enhanced risk if protective immunity wanes over time.

The weaknesses in the Sanofi dengue vaccine create both the need and the opportunity for other dengue vaccine candidates. One of the candidates in advanced clinical development is the product of over 20 years of intramural NIAID research that involved the production and testing of dozens of candidate DENV vaccine strains attenuated by targeted mutation and/or chimerization [4]. Through extensive pre-clinical and phase I clinical testing, these dozens of strains were winnowed down to select a single representative of each DENV serotype with favorable safety and immunogenicity profiles. A tetravalent live-attenuated vaccine formulation referred to as TV003 has recently entered phase III clinical testing. Studies to date show an acceptable safety profile notable for the frequent occurrence of very minor rashes and an encouraging neutralizing antibody response profile after a single immunization. But will this vaccine be protective, and, if so, will protective immunity be durable?

In the current issue of the Journal, Durbin et al provide a further piece of evidence to support the potential efficacy of the TV003 vaccine [5]. The authors provide a brief summary of the neutralizing antibody responses detected one year after a first dose and then after a second dose. There were no significant adverse effects in this small study and the results suggest that the vaccine is immunogenic for one year for all 4 DENV serotypes and that a second dose after 1 year does little to enhance the antibody response to the first dose. In this and other studies the vaccine appears to be very attenuated with very little viremia detected after dose 1 and none after dose 2. The authors are performing 5 year efficacy trials to determine if the vaccine induces protection. In interpreting their current results, they acknowledge that it “not possible to unequivocally equate resistance to re-vaccination with protection against natural infection.” Even greater caution is warranted, however. From studies with another live virus vaccine, we know that antibody levels sufficient to provide protection against a dose of measles vaccine are inadequate for protection against wild-type measles virus infection by the respiratory route in infants with persistent maternal antibodies [6]. Thus, levels of antibodies that may prevent viremia in response to a live attenuated vaccine may not protect against natural virus infection. Especially with the complexity of 4 DENV serotypes and the known increased risk for severe dengue during secondary infections, it will be very important to determine if a dengue vaccine induces a balanced long-term protection against all 4 serotypes and to see whether a booster dose may be needed at some point.

Unlike other viral diseases, e.g., poliomyelitis [7], Yellow Fever, or mumps [8], dengue can occur in the presence of detectable levels of serum neutralizing antibodies [9, 10]. Overall, the dengue literature suggests that higher levels of neutralizing antibodies correlate better with protection than low or undetectable levels of antibodies. The planned longer term studies should help to determine if a balanced neutralizing antibody response is maintained and identify correlates with protection. In an endemic region exposure to DENV may boost vaccine-induced immune responses, which would not occur in individuals living in areas that are dengue free.

In conclusion, dengue is a major and increasing public health burden causing high levels of morbidity and significant mortality in much of the world. Progress in dengue vaccine development over the last 50 years has been limited. Recently, a first generation vaccine has been developed which induces significant but serotype-variable protection after multiple doses. Several other candidate vaccines are being developed. The article by Durbin et al in this issue shows convincing, robust antibody responses to all 4 serotypes of DENV after a single dose of a candidate live attenuated vaccine. These are promising results in the search for a safe and effective dengue vaccine for general use in dengue endemic areas. Long term safety and efficacy data will be awaited with interest.

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Conflict of interest: ALR has received compensation from Sanofi Pasteur as a Scientific Advisory Board member for the dengue vaccine program.

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