Which Dengue Vaccine Approach Is the Most Promising, and Should We Be Concerned about Enhanced Disease after Vaccination?

The Risks of Incomplete Immunity to Dengue Virus Revealed by Vaccination

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Immune enhancement of dengue disease continues to be a concern for those with incomplete immunity in endemic areas. Advanced testing and follow-up of a newly available live attenuated dengue vaccine has recently shown the ability of vaccination to predispose some recipients for a severe outcome on subsequent infection. To improve safety, recommendations have been made to restrict use of the vaccine to those who are likely to have had prior exposure to dengue virus (DENV). Researchers continue to investigate dengue immunity and seek evidence that dengue vaccines can be safely administered to all populations needing protection.

GREAT DEBATES

What are the most interesting topics likely to come up over dinner or drinks with your colleagues? Or, more importantly, what are the topics that *don't* come up because they are a little too controversial? In ***Immune Memory and Vaccines: Great Debates***, Editors Rafi Ahmed and Shane Crotty have put together a collection of articles on such questions, written by thought leaders in these fields, with the freedom to talk about the issues as they see fit. This short, innovative format aims to bring a fresh perspective by encouraging authors to be opinionated, focus on what is most interesting and current, and avoid restating introductory material covered in many other reviews.

The Editors posed 13 interesting questions critical for our understanding of vaccines and immune memory to a broad group of experts in the field. In each case, several different perspectives are provided. Note that while each author knew that there were additional scientists addressing the same question, they did not know who these authors were, which ensured the independence of the opinions and perspectives expressed in each article. Our hope is that readers enjoy these articles and that they trigger many more conversations on these important topics.

Editors: Shane Crotty and Rafi Ahmed

Additional Perspectives on Immune Memory and Vaccines: Great Debates available at www.cshperspectives.org

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Dengue virus (DENV) remains the leading cause of arthropod-borne viral disease around the world. Although it is impossible to accurately quantify the number of cases and impact of dengue, about half of the world's population lives in areas at risk for dengue transmission (Beatty et al. 2009). It is estimated that there are at least 390 million DENV infections per year and about a quarter of those infections manifest some level of apparent disease (Bhatt et al. 2013), with 2 million cases of severe disease and >20,000 deaths per year (WHO 2012). Dengue infection results in a range of clinical outcomes: asymptomatic (most common) or mildly symptomatic illness, uncomplicated dengue fever, or more severe disease including plasma leakage, hemorrhage, and vascular collapse (dengue hemorrhagic fever/shock syndrome). All four DENV serotypes are known to cause the full spectrum of disease and, although severe disease can occur following primary infection, epidemiologic studies have shown that preexisting immunity to one DENV serotype is the greatest risk factor for severe disease on secondary DENV infection (Burke et al. 1988), although other factors such as virus strain, genetic susceptibility, and age certainly play a role in disease outcome (Guzman et al. 2016).

Immunity to DENV includes an early immunoglobulin M (IgM) antibody response that later shifts to IgG, directed primarily against surface glycoproteins prM and E and nonstructural protein 1 (NS1) secreted from cells during virus replication and a robust CD4/CD8 T-cell response to epitopes distributed mainly within the NS3 and NS5 proteins (Weiskopf et al. 2015). Neutralizing antibodies and CD8 T cells are thought to be the immune effectors of viral clearance. In nature, DENV serotypes are generally encountered sequentially, as the predominant serotype circulating in a region changes over time and this serotype-by-serotype presentation influences the subsequent antibody response. Thus, following a first infection with DENV that usually occurs during early childhood in endemic areas, polyclonal homotypic-neutralizing antibodies develop against the infecting serotype with

minimal and short-lived cross-neutralization of other serotypes. Subsequent encounters with the same DENV serotype are neutralized, with no apparent infection. However, encounters with a different DENV serotype can lead to infection and stimulation of three types of antibody responses: homotypic neutralizing antibodies specific for the newly infecting serotype, a boost in the neutralizing antibody response to the prior infecting serotype, and the production of heterotypic antibody capable of cross-neutralizing the remaining serotypes. This phenomenon has been shown experimentally in well-controlled sequential infection studies (Durbin et al. 2011b). Therefore, following infection with two different serotypes of DENV, an individual generally develops complete immunity, that is, a broad immune response sufficient to provide protection against any DENV serotype (Fig. 1). This hypothesis is also supported by the low frequency of hospital admissions for dengue illness observed in people who have been infected by more than two DENV serotypes (Gibbons et al. 2007).

Although sequential infection by DENV serotypes leads to complete immunity, it is responsible for severe dengue complications in a proportion of patients (Fig. 1, left panel). Immune enhancement of secondary DENV infections mediated by both antibody and T-cell mechanisms is postulated to be responsible for increased disease severity. Antibody-dependent enhancement (ADE) of disease is based on the observation that DENV infection elicits antibodies with varying capacity to neutralize virus (Halstead 2003). Antibody with poor neutralizing activity binds heterotypic virions at a suboptimal occupancy threshold and, rather than achieving neutralization, the opsonized particle has increased ability to infect Fc γ -receptor-bearing cells. This functional increase in infectivity leads to an increased viremia associated with enhanced pathogenesis and disease severity (Vaughn et al. 2000). ADE is thought to be the mechanism by which newborn infants with maternally derived DENV antibodies are at risk for severe disease when infection occurs before maternal antibody levels decline (Halstead et al. 2002). In addition to

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Figure 1. General model for the development of dengue virus (DENV) antibody responses by natural infection or vaccination. Sequential exposure to different DENV serotypes eventually leads to a complete antibody response to all four serotypes after two or more heterotypic exposures. However, partial immunity acquired along this pathway can predispose individuals to antibody-dependent enhanced (ADE) disease in some cases but is not necessarily related to specific serotype pairs (*left side of figure*). Numbers indicate DENV serotype. Vaccination with a fully tetravalent vaccine (serotypes 1234) can induce a rapid comprehensive antibody response without predisposition to ADE in both dengue-naïve and experienced individuals (*right side of figure*). Vaccination with an incomplete vaccine (serotypes 3 and 4 in this case) can leave an individual with only partial immunity and susceptibility to ADE owing to their lack of preexisting DENV immunity. Of course, catch-up vaccination in those with preexisting immunity would be expected to lead to a complete immunity regardless of the vaccine breadth. DHF, Dengue hemorrhagic fever.

increased viremia, elevated plasma levels of proinflammatory and vasoactive cytokines, soluble receptors, and coagulation factors have also been associated with severe disease (Srikiatkhachorn and Green 2010). This “cytokine storm” can be triggered by excessive T-cell activation during secondary infection and may be the product of “original antigenic sin” as it relates to memory T cells. Memory T cells from prior DENV infection by a different serotype can be rapidly recalled and expanded following

secondary infection. However, these reactivated T cells may have lower avidity for epitopes derived from the newly infecting DENV serotype, rendering them less able to lyse infected cells and produce antiviral cytokines, while producing higher levels of inflammatory cytokines that trigger enhanced inflammation and changes in vascular permeability (Rothman 2011). In the end, a multitude of factors come together to create the perfect storm of immune-enhanced dengue disease: serological status, age, timing of

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second infection, virus strain, and sequence of DENV exposures (Mizumoto et al. 2014).

Dengue continues to be a public health emergency in many tropical regions and the need for effective control measures, including vaccines, has continued to grow over the last several decades. Vaccines are thought to be the most sustainable approach for controlling dengue, but the pathway to a vaccine has been arduous and challenging. Much of the difficulty arises from the lack of suitable animal models, the need for protection against four individual serotypes, and lack of a primary immune correlate of protection. The absence of a correlate of protection has led to the preference for development of vaccines that stimulate both cellular and humoral immune responses that mimic those elicited by natural infection, and thus live attenuated vaccines (LAVs) have received the most attention. Although LAVs potentially realize many of the elements of an ideal dengue vaccine, including ease of administration, completeness and durability of the immune response, and low cost of manufacture, significant effort is required to ensure safety and low level of reactogenicity, even distribution of infectivity, control of vaccine transmission, and thermostability of the product. A deficiency in any of these properties can be problematic and has resulted in decisions to cease further development of candidate vaccines (Kitchener et al. 2006; Thomas and Rothman 2015). In endemic areas, immunity acquired from natural DENV infections is thought to persist for a lifetime; this fostered the hope that LAVs would do the same. Although desirable, this is not without its caveats, because a prior DENV infection is known to set the stage for a more severe subsequent infection. Can protection afforded by dengue vaccination be achieved without predisposing vaccinees to the risk of enhanced disease? Can dengue vaccination proceed without harm?

The principal endpoint in the clinical evaluation of any dengue vaccine has always been and should always be safety. Above all, vaccination should do no harm. Clinical trials of dengue vaccine candidates generally begin in healthy adults who are serologically naïve to DENV and other related flaviviruses and

progress through age de-escalation cohorts to younger subjects recruited in dengue-endemic areas. The ultimate target for dengue vaccination in endemic areas is young children who are DENV “seronaïve” before their first natural exposure. However, an increased frequency of dengue hospitalization has been reported 1–2 years after vaccination with Dengvaxia (Sanofi Pasteur) in previously seronaïve children, with a more than sevenfold increase in the risk of hospitalization for dengue illness among vaccinated children 2–5 years of age (Hadinegoro et al. 2015). Although several hypotheses are being investigated to explain this increased risk (Guy and Jackson 2016), it appears that Dengvaxia is insufficiently immunogenic in populations that are DENV seronaïve at time of vaccination (Fig. 1, right panel). Additionally, the efficacy of the vaccine against dengue of any severity was 82% among subjects who were seropositive, but markedly lower at 53% for those who were seronaïve at baseline (Hadinegoro et al. 2015), suggesting that the vaccine broadens existing immunity rather than providing sufficient primary protective immunity (Wilder-Smith 2014). In other words, for Dengvaxia to be both safe and effective, an individual must have been exposed to DENV before receipt of the vaccine. The dependence on preexposure to promote vaccine efficacy is a paradigm that is unprecedented, with the noteworthy exception of the zoster vaccine to prevent shingles. Thus, the use of Dengvaxia is suitable for catch-up vaccination, in which the intent is to augment or complete one’s dengue immune profile by eliciting an immune response to DENV serotypes absent from one’s repertoire (Fig. 1, right panel). The World Health Organization (WHO) has not recommended use of the Dengvaxia vaccine in children under 9 years of age or in other age groups in which DENV seroprevalence is below 50% (WHO 2016). The WHO suggests that, ideally, DENV seroprevalence in a population should be >70% to maximize the public health impact and cost effectiveness of Dengvaxia.

What can be learned from the Dengvaxia experience and what are the implications? For years, the dengue research community has recognized that incomplete immunity to DENV,

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generally defined as a lack of measurable neutralizing antibody to one or more serotypes, can be dangerous. Thus, vaccine strategies to control dengue have been focused on simultaneously eliciting a response to all four serotypes in the hope of avoiding gaps that could possibly set the stage for immune-enhanced disease in the future. For live attenuated tetravalent vaccines, this could be accomplished by including vaccine components representing each DENV serotype. And, until recently, it was expected that this approach would be sufficient. However, certain newly recognized properties associated with each vaccine component are critical for success: Each component must be infectious to be immunogenic and each component must present relevant B-cell and T-cell epitopes. During the early development of Dengvaxia, there were indications that the infectivity and subsequent immunogenicity of the component strains were uneven, with the neutralizing antibody response against DENV-4 being orders of magnitude greater than the other serotypes following the first dose in seronaïve subjects (Poo et al. 2011; Dayan et al. 2013). This was confirmed by data showing that viremia following the first dose of vaccine is predominantly serotype 4 and at a higher level than measured for the other serotypes (Morrison et al. 2010). Insufficient infectivity of the remaining serotypes was also indicated by the boost in antibody titers for serotypes 1, 2, and 3 following subsequent doses of vaccine (Poo et al. 2011; Dayan et al. 2013). Ideally, for a live vaccine, a properly infectious primary dose should effectively neutralize the same virus delivered in a later dose. Sanofi Pasteur has recently acknowledged that the vaccine “induces predominantly homotypic responses dominated by specific antibodies against one or a few serotypes (usually DENV-4)” (Guy and Jackson 2016). Coupled with the lack of DENV T-cell epitopes among the yellow fever virus vaccine 17D nonstructural gene regions present in Dengvaxia, the vaccine has “different features to a true primary infection . . . so the mimicry of a primary infection could only be partial” (Guy and Jackson 2016). In summary, Dengvaxia elicits an incomplete immune response to DENV that contributes

to immune enhancement of disease in certain populations.

For many years, the question of whether dengue vaccination could contribute to disease enhancement in ways similar to natural infection was answered with a general statement of “probably no,” with the caveat that this would be confirmed by long-term follow-up of efficacy trials. This has now occurred, and the data indicate that dengue vaccination can be problematic. As the debate continues regarding how to implement a vaccine with a conditional recommendation from WHO and yet have the greatest public health benefit (Halstead 2016; Wilder-Smith et al. 2016), questions still remain: Will other candidate vaccines experience similar problems? Are there processes to predict more favorable outcomes for vaccines? What can be done differently? In the early development of Dengvaxia, vaccine components for each DENV serotype were not evaluated individually to verify acceptable infectivity before inclusion in a tetravalent formulation. This is not the case for other LAVs such as the National Institute of Allergy and Infectious Diseases (NIAID) vaccine developed at the U.S. National Institutes of Health (NIH) that is undergoing phase III evaluation by the Butantan Institute in Brazil. For this vaccine, monovalent components were administered to DENV-naïve subjects in phase I studies to select the most appropriate candidates for moving forward (Durbin et al. 2011a). In some cases, this approach identified candidates that were poorly infectious, such as rDEN3/4Δ30, as not being appropriate for further consideration (Durbin et al. 2011a). In addition, several tetravalent formulations of the NIAID vaccine were tested in clinical trials to verify that the level of vaccine viremia for each serotype was consistent, that seroconversion to each serotype was balanced, and that a second dose of vaccine was not required (Kirkpatrick et al. 2015; Durbin et al. 2016). Investigation of T-cell immunity following vaccination has also shown a robust response directed to both serotype-specific DENV epitopes as well as epitopes conserved between serotypes (Weiskopf et al. 2015). Even this methodical approach does not guarantee success. Careful evaluation in

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well-designed phase III studies with long-term follow-up, sufficient sample collection, and observation in a wide range of ages will be necessary. Most important, the dengue research community must remain vigilant and dedicated to understanding DENV immunity, searching for reliable markers of protection, and developing methods for producing vaccines that can safely protect populations most at risk for dengue disease.

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