Dengue virus (DENV) represents a rapidly expanding global health threat, with approximately 40% of the world’s population now living in >100 countries at risk for DENV transmission, including the United States [1, 2]. In 2010, an estimated 390 million DENV infections occurred worldwide, of which 96 million were symptomatic [3]. DENV infections produce a spectrum of clinical disease. This includes mild undifferentiated fever, classical dengue fever, and severe dengue [4]. Severe dengue is characterized by hemorrhage and/or plasma leakage (dengue hemorrhagic fever and dengue shock syndrome) and organ failure. Approximately 500 000 severe cases and 20 000 deaths are estimated to occur each year [1]. These syndromes can be caused by each of 4 antigenically distinct serotypes (DENV-1–4) that cocirculate throughout the Western Pacific, Southern and Southeast Asia, Africa, and the Americas [5, 6].

Owing to global warming, spread of the Aedes vector to many parts of the world, uncontrolled urbanization, and human travel, dengue continues to intensify in DENV-endemic areas and spread to previously unaffected areas. Multiple serotypes frequently cocirculate in areas of endemicity, and epidemics of different serotypes occur unpredictably from year to year. Because of the growing economic burden associated with DENV infections and the lack of effective vector-control measures or specific therapy, a licensed DENV vaccine has become an urgent need [7].

The safety of DENV vaccines has been a vexing problem primarily because of concerns about disease enhancement. Following infection with a single DENV serotype, an individual will develop lifelong homotypic immunity and transient heterotypic immunity, which wanes after several months [8, 9]. Epidemiological evidence suggests that the risk of severe dengue is higher following a subsequent infection with a heterologous serotype. Although the precise mechanisms of disease enhancement are unknown, poorly neutralizing heterotypic antibody is believed to play a role via antibody-dependent enhancement [10]. Antibody-dependent enhancement occurs when poorly neutralizing heterotypic antibodies bind to virus and increase viral uptake by Fc receptor–bearing cells (eg, macrophages), resulting in increased viral replication [11]. Additionally, cross-reactive heterotypic T cells may produce a cytokine storm resulting in increased disease severity [12]. Additionally, the nonstructural protein (NS1)–antibody complexes bind to plasma complement, generating anaphylatoxin [13, 14]. Regardless of the mechanism(s), immune-mediated enhancement has raised significant concerns about the safety of DENV vaccines. However, there has been no evidence of disease enhancement in the field following immunization, although follow-up has been no longer than 25 months [15–17]. A general consensus holds that a tetravalent DENV vaccine protecting against all serotypes simultaneously will be required.

The article by Kirkpatrick et al in this issue of The Journal of Infectious Diseases highlights a potentially important advance in dengue vaccine development offered by a candidate, live attenuated tetravalent dengue vaccine (LATV) administered as a single subcutaneous injection [18]. Each of the 4 monovalent vaccine components, designed by the Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, is composed of a DENV genetic background with a shared core–attenuating 30-nucleotide deletion in the 3’ untranslated region of the viral genome. The DENV-2 component (rDEN2/Δ30) is a chimeric virus with the structural proteins of DENV-2 replacing those of DENV-4. Two formulations (TV003 and TV005) of the LATV candidate were tested in phase 1 randomized, double-blind, placebo-controlled trials in 168 healthy,
flavivirus-seronegative adult volunteers. The TV005 had a DENV-2 component concentration of 4 log_{10} plaque-forming units (PFU), compared with 3 log_{10} PFU in the TV003 admixture. The safety and immunogenicity of both admixtures was tested to determine whether there was benefit to the increased DENV-2 concentration in TV005. Additionally, a second dose of vaccine administered 6 months after the first dose was tested, and the kinetics of the neutralizing antibody responses and vaccine viremia were studied. Both formulations of the vaccine showed excellent safety profiles, with the principal adverse reaction being a nonpruritic maculopapular rash in 62% of vaccinees. Importantly, after a single dose, 90% of TV003 vaccinees developed a tetravalent neutralizing antibody response, compared with 74% of TV003 recipients. Furthermore, a single dose appeared to induce sterilizing immunity to a booster dose at 6 months. Interestingly, racial differences were noted, with African American volunteers having significantly lower tetravalent seroconversion rates (57%) than non–African Americans (86%) in the combined TV003 and TV005 trials.

This is not the first description of immune responses following a single-dose of LATV candidate in clinical trials, but it does show considerable potential as a single-dose DENV vaccine, compared with other candidates [16, 19]. A single-dose vaccine is more desirable than a multidose DENV vaccine for many reasons: (1) it would provide more-rapid protection in the field and for travelers to endemic countries; (2) it would not leave individuals unprotected who withdraw from multidose immunization programs after the first dose; (3) it would provide immunity earlier than multidose vaccines, thus eliminating the window of disease enhancement theoretically possible between repeated vaccinations; (4) it may be more affordable than a multidose vaccine; (5) it would enhance vaccine acceptance, particularly among children and travelers; and (6) it would be easier to incorporate into existing pediatric vaccine schedules.

Although currently there is no licensed DENV vaccine, multiple candidates are in preclinical and clinical trials [20]. The LATV candidates furthest along the development pipeline include CYD-TDV (Sanofi Pasteur) [15, 17], DENVax (Takeda) [19], F17/F19 (WRAIR-GSK) [21], and TV003/TV005 (National Institutes of Health), described by Kirkpatrick et al in this issue [18]. The Sanofi Pasteur YF17D/dengue chimeric vaccine candidate, CYD-TDV, has completed phase 2b and phase 3 trials in Asia and the Americas [15, 17, 22]. While a tetravalent response after a single dose of CYD-TDV was not explicitly reported, it can be inferred on the basis of seroconversion to individual serotypes that no more than 18%–26% of individuals showed tetravalent seroconversion after the first dose [16]. In the phase 3 trials of CYD-TDV, it was disappointing that protective efficacy reached only 56.5% and 64.7% in Asia and Latin America, respectively, with even lower efficacy (35.5%) in flavivirus-naive individuals [15, 17]. This relatively modest efficacy was associated with >1:10 neutralizing antibody titers against DENV-1 (95%), DENV-2 (99%), DENV-3 (100%), and DENV-4 (98%) 28 days after the third immunization. These results bring into question the plaque reduction neutralization test (PRNT) titer required for protection against each serotype and ultimately the usefulness of measuring neutralizing antibody titers as a correlate of protection, using current PRNT methods. The third LATV candidate, a chimeric recombinant attenuated vaccine (DENVax; Takeda), has completed phase 1 testing [19]. DENVax administered to flavivirus-naive adults showed a favorable safety profile but tetravalent seroconversion rates of only 20%–30% 30 days after the first dose [19]. The rederived WRAIR-GSK LATV candidates F17 and F19 were tested in a small phase 2 trial [21]. Tetravalent seroconversion rates 1 month after the first dose were modest in unprimed volunteers (37.5%–40%) [21]. In summary, we have compared tetravalent responses after a single dose of all LATV candidates for consistency and omitted discussion of trivalent seroconversion. We assume, without much evidence, that tetravalent, compared with trivalent seroconversion, will provide better protection over time.

The use of a dengue human infection model to further assess the likelihood of vaccine success in the field will potentially escalate the development of TV005 and other DENV vaccine candidates. Experimental infection of volunteers with DENV has been described since the early 20th century [23]. Recently, there has been renewed interest among dengue vaccinologists in using the dengue human infection model together with mildly attenuated DENV strains to reproducibly create uncomplicated illness with clinical, biochemical, and immunological features consistent with dengue [23]. In addition to protective efficacy, the controlled human infection model could also provide invaluable insight into the immune correlates of protection, which would greatly facilitate early phase clinical trials of other vaccine candidates.

A survey of policymakers in DENV-endemic countries identified the major determinants for the implementation of a DENV vaccine, which included (1) World Health Organization Strategic Advisory Group on Immunization recommendation of the vaccine, (2) cost of the vaccine, (3) availability of external financing for lower-income countries, and (4) the ability of the vaccine to be incorporated into the countries’ existing routine immunization schedule [24]. In addition, a successful DENV vaccine will need to safely protect young children and flavivirus-naive individuals of all ages and be safe in human immunodeficiency virus–infected and immunosuppressed individuals [20].

In conclusion, the National Institutes of Health vaccine candidate TV005 shows considerable promise. The results support the use of the vaccine in target populations unprimed by previous DENV exposure. As shown by many studies, a primed population would likely respond even more robustly [16, 21]. A major
caveat is that the tetravalent neutralizing antibody responses in 90% of volunteers and the geometric mean titers of 1:10 to 1:40 at 6 months [18] may not equate with protection in the field, as witnessed by the phase 2b trial of the Sanofi Pasteur candidate vaccine [16]. Concerns also include a significantly lower tetravalent seroconversion rate in African American volunteers [18], with the implication of possible racial differences in protective efficacy. Overall, we look forward with anticipation to efficacy trials of the TV005 vaccine.

Note
Potential conflict of interest. M. A. M. has received consulting fees from Takeda Vaccines. R. E. serves as a paid consultant for Takeda’s Tetravalent Dengue Vaccine clinical research program.
Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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