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Detection of dengue cases by serological testing in a dengue vaccine efficacy trial: Utility for efficacy evaluation and impact of future vaccine introduction

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ABSTRACT

Background: Dengue diagnosis confirmation and surveillance are widely based on serological assays to detect anti-dengue IgM or IgG antibodies since such tests are affordable/user-friendly. The World Health Organization identified serological based diagnosis as a potential tool to define probable dengue cases in the context of vaccine trials, while acknowledging that this may have to be interpreted with caution.
Methods: In a phase IIb randomized, placebo-controlled trial assessing the efficacy of a tetravalent dengue vaccine (CYD-TDV) in Thai schoolchildren, case definition was based on virological confirmation by either serotype-specific RT-PCRs or by NS1-antigen ELISA (Clinicaltrials.gov NCT00842530). Here, we characterized suspected dengue cases using IgM and IgG ELISA to assess their utility in evaluating probable dengue cases in the context of vaccine efficacy trials, comparing virologically-confirmed and serologically diagnosed dengue in the vaccine and placebo groups. Serologically probable cases were defined as: (1) IgM positive acute- or convalescent-phase samples, or (2) IgG positive acute-phase sample and ≥4-fold IgG increase between acute and convalescent-phase samples.
Results: Serological diagnosis had good sensitivity (97.1%), but low specificity (85.1%) compared to virological confirmation. A high level of false positivity through serology diagnosis particularly in the 2 months post-vaccination was observed, and is most likely related to detection of the immune response to the dengue vaccine. This lack of specificity and bias with vaccination demonstrates the limitation of using IgM and IgG antibody responses to explore vaccine efficacy.
Conclusion: Reliance on serological assessments would lead to a significant number of false positives during routine clinical practice and surveillance following the introduction of the dengue vaccine.
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1. Introduction

Dengue is a viral disease caused by four antigenically distinct dengue virus (DENV-1, -2, -3 and -4) serotypes, transmitted by *Aedes* mosquitoes, primarily, *Aedes aegypti*. Although most dengue infections are asymptomatic/subclinical [1], primary symptomatic infection with any one of the four virus serotypes usually presents with an undifferentiated acute febrile illness with no specific clinical features that can reliably distinguish it from other febrile illnesses. There is currently a high unmet medical need for a dengue vaccine to halt the increasing number of epidemics in endemic transmission settings. While the course of the disease may be self-limited and fairly benign in most cases, a significant number may develop complications, and further deteriorate to severe, incapacitating or life-threatening disease, such as dengue hemorrhagic fever or dengue shock syndrome, and death [2]. The wide variability of clinical illness associated with dengue underlies the need for laboratory confirmation using antigen detection and serological tests to confirm clinical diagnosis [2,3]. In addition, laboratory confirmation is an integral component of most national epidemiological surveillance systems.

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Laboratory confirmation is based on direct detection of viral nucleic acid, antigens or, isolation of the virus in cell cultures (known as virologically-confirmed dengue infection) or indirectly through the detection of dengue-specific antibodies [4]. Virus isolation or detection of viral components such as non-structural glycoprotein-1 (NS1) using ELISA and nucleic acid using reverse transcriptase polymerase chain reaction (RT-PCR) is more sensitive in the early acute stages of the disease, typically corresponding to the duration of fever. Serological assays, which include anti-dengue immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies, are generally easier and cheaper to perform than the other methods. Tests based on IgG and IgM are commonly used for clinical screening and surveillance activities. In a clinical setting, a single IgM positive sample may be deemed sufficient for laboratory diagnosis as it would be highly suggestive of dengue infection. However, paired sera, collected within the time frame of acute and convalescence phases of the disease to demonstrate seroconversion in serological assays would be required to confirm ongoing or recent dengue infection. Unfortunately, collection of paired-samples in routine clinical practice is a challenge — samples may not be collected within the required time window which limits the clinical value of the results, or the patient recovers and fails to return for convalescent tests. The timing of the collection of the acute sample can impact the results of the test (false negative results are common with samples collected too early and/or too late), and responses differ according to primary/first vs. second/subsequent dengue infections [4,5]. IgM response to a second/subsequent dengue infection may be low or indeed absent; similarly IgG may be low or indeed absent in the acute phase of primary infection but high in the acute phase of a second/subsequent dengue infection. Additional tests may also be needed to exclude cross-reactivity of IgG and IgM responses to other flaviviruses (false positives) [6–8]; for example, in Asia, cross-reactivity with Japanese encephalitis following exposure to wild-type infection or vaccine.

Detection of NS1 antigens as a surrogate marker for viremia during the acute phase of the illness has become common for laboratory diagnosis of dengue infection, and may be similar or potentially superior in certain settings to virus isolation and RNA detection by RT-PCR [9]. However, the sensitivity of NS1 detection in the acute stage of second/subsequent infections is lowered by virus–IgG immunocomplexes [4,9–11]. Overall, the sensitivity and specificity of serological based dengue diagnosis may be enhanced with concurrent evaluation of NS1 antigen in addition to anti-dengue IgM and IgG at all stages (both early and late) of the disease. The reliability of diagnostic algorithms combining both viral and serological detection for dengue diagnosis in routine practice and in disease surveillance, as well as in vaccine efficacy trials and in a post-dengue vaccine introduction surveillance setting, needs to be established [12].

The World Health Organization accepts serological based diagnosis as a potential tool to define probable dengue cases in context of vaccine efficacy trials, but recognizes that these data may have to be interpreted with caution in light of vaccine induced IgG and IgM [13]. Laboratory confirmation of dengue, by analogy of serologic confirmation of other infectious diseases, is typically defined by a 4-fold or greater increase in anti-dengue IgG or IgM antibody titers in paired serum samples (acute to convalescent), or detection of dengue virus antigens or genomic sequences [2].

This exploratory analysis was undertaken to describe the serological profile of virologically-confirmed dengue cases in the dengue vaccine phase IIb efficacy trial (ClinicalTrials.gov, NCT00842530), and to evaluate applicability of the WHO case definition for probable dengue in vaccine efficacy trials as well as to explore the impact of anticipated dengue vaccine introduction on this definition for national epidemiological surveillance. The CYD23 study was a single-site trial of schoolchildren conducted in Ratchaburi Province, Thailand, and was designed to be a proof-of-concept of vaccine efficacy to be corroborated in larger phase III studies [14]. The efficacy trial design necessitated that all children be actively followed up for any acute febrile illness to ensure a high percentage of suspected case detection, and that paired serum samples (acute and convalescent) were collected in a timely manner.

2. Methods

2.1. Study design and participants

Details of the CYD23 proof-of-concept study have been published [14]. In brief, the participants were schoolchildren aged 4–11 years who were in good health and whose families intended to stay in the study area to allow for long-term follow-up. Children with fever, immunodeficiency, or who received or planned to receive another vaccine within 4 weeks of the first study vaccination were not eligible. Eligible participants were randomized to receive a recombinant yellow fever-17D–dengue virus, live, attenuated, tetravalent dengue vaccine (CYD-TDV) or a control, with twice as many in the active vaccine group as in the control group.

2.2. Procedures

Participants received three injections of CYD-TDV or control (rabies vaccine or placebo) at months 0, 6, and 12. All children were actively followed up twice weekly to detect any acute febrile illness from the first vaccination up to at least 13 months after the third vaccination. In case of febrile illness at any time lasting for at least 1 day (defined as two temperature readings of $\geq$37.5 °C at least 4 h apart), parents were asked to return their child to the study site for diagnosis and treatment. Paired serum samples were collected at presentation (i.e., acute sample, collected no later than 7 days after fever onset) and convalescent sample collected 7–14 days later.

2.3. Laboratory analyses

The acute samples from participants with febrile illness were screened for flavivirus infection using an initial PCR assay. Positive samples were tested for wild-type dengue virus with a validated serotype-specific quantitative dengue RT-PCR and for dengue NS1 antigen using the commercially available Platelia Dengue NS1 antigen enzyme-linked immunosorbent assay (ELISA) kit (Bio-Rad). Paired acute and convalescent serum samples were tested for anti-dengue IgM and IgG antibodies with the commercially available dengue virus capture IgM (EL1500M, DxSelect Kit) and IgG (EL1500G, DxSelect Kit) ELISA kits.

2.4. Dengue cases

Virological confirmation of dengue infection was defined as an acute febrile episode with a positive dengue RT-PCR or Platelia NS1 Dengue ELISA result. A probable dengue infection was defined serologically as (1) IgM positive acute- or convalescent-phase samples, or (2) IgG positive acute-phase sample and a $\geq$4-fold IgG increase between acute and convalescent-phase samples.

2.5. Statistical analyses

All analyses undertaken (performed with SAS version 9.2) were descriptive and based on all febrile illnesses assessed, including those that occurred within 28 days after each study injection. Anti-dengue IgM and IgG levels from acute and convalescent serum samples were used to derive proportions of participants with probable dengue based on the following serological criteria: (1) IgM positive acute or convalescent-phase samples; (2) IgG positive

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