

## Letter to the Editor

### 17D Yellow Fever Virus Vaccine

Dear Sir:

In a recent article, Edupuganti and others reported a clinical study of co-administration of subcutaneous yellow fever (YF) 17D vaccine (YF-VAX<sup>®</sup>; Sanofi Pasteur, Lyon, France) and intramuscular immune serum globulin (ISG) (amaSTAN S/D<sup>®</sup>; Talecris Biotherapeutics, Research Triangle Park, NC) or saline placebo.<sup>1</sup> The study was designed to test whether co-administration of vaccine and ISG containing YF antibodies would reduce replication (viremia) of the live 17D vaccine. The rationale for the study was the hypothesis that administration of ISG containing YF-neutralizing antibodies to travelers for hepatitis A prophylaxis might have attenuated YF vaccine-associated viscerotropic adverse events; these events emerged as ISG was replaced by hepatitis A vaccine in 1996. In a previous study published in 1984, lots of ISG contained high titers of YF neutralizing antibodies, and co-administration with vaccine had no effect on immunogenicity; however viremia measurements were not evaluated.<sup>2</sup>

The current study was statistically powered and many parameters were investigated, including viremia, antibody response, T cell activation, and cytokine responses to YF vaccine. No differences were observed between groups receiving ISG or placebo in the incidence, time-course, or magnitude of viremia measured by quantitative polymerase chain reaction. More importantly, viremia was also assessed by infectivity (plaque) assay; no differences were reported across groups, although only the proportions positive (and not titers of virus or area under the curve) were reported. The authors concluded that cessation of globulin prophylaxis was not responsible for increased reporting of YF vaccine-associated viscerotropic adverse events.

This conclusion is complicated by several problems with the design and conduct of the study, none of which, unfortunately, are discussed by the authors. The ISG was administered at the recommended dose for hepatitis A prophylaxis (0.06 mL/kg). However, the lot used had a low titer (1:20–1:40) of YF-neutralizing antibody determined by a 90% plaque-reduction neutralization assay. The passive titers of neutralizing antibody after administration to the volunteers were not determined, but even assuming 100% distribution to a 5-liter blood volume, would be undetectable (< 1:1). As the authors note, passive titers  $\geq$  1:20 are required for protection against wild-type YF virus infection,<sup>3</sup> although the level of antibody needed to abrogate infection with attenuated 17D virus is unknown.

In the previous study published in 1984,<sup>2</sup> we found that contemporary lots of ISG contained much higher titers of YF antibody (1:320– $\geq$  1:640) by the same 90% plaque-reduction neutralization assay. This finding suggests that the proportion of plasma donors with YF vaccination contributing to the pool of ISG may have previously been higher, or that the interval

between vaccination and plasma donation was shorter. The number of doses of YF vaccine distributed in the United States has decreased by 50–67% since the 1980s. Thus, the dose of antibody given in the days of hepatitis A prophylaxis may have been  $\geq$  32 times higher than that used in the current study. Dose (passive titer) is obviously critical to efficacy of passive antibody.<sup>3</sup>

Finally, the globulin was administered in the upper outer quadrant of the buttocks, but no mention is made of the needle length or procedure for injection. Such injections are often inadvertently subcutaneous,<sup>4</sup> and subcutaneous injection of globulin in the buttocks results in slow and incomplete uptake of antibody (33% of injected dose at 4–6 days),<sup>5</sup> which may have missed the critical period for abrogating virus replication. Obesity has increased since use of ISG for hepatitis A prophylaxis, making dorsogluteal intramuscular injection more difficult.

For these reasons, the hypothesis tested was not refuted by the study. Dose-ranging studies of passive antibody (which could probably be performed even with low titer lots of intravenous globulin) to mimic doses given in the pre-1996 era would be needed to clarify the role of antibody in modulating 17D infections. Such studies would also be helpful in addressing the practical question of how to manage patients with contraindications who may require immunization, and whether antibody has a role in treating patients with adverse events.

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