

## Dengue Serostatus and Dengue Vaccine Safety and Efficacy

POSFAY BARBE, Klara, L'HUILLIER, Arnaud

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## Reference

POSFAY BARBE, Klara, L'HUILLIER, Arnaud. Dengue Serostatus and Dengue Vaccine Safety and Efficacy. *New England Journal of Medicine*, 2018, vol. 379, no. 20, p. 1968-1969

DOI : 10.1056/NEJMc1811986

PMID : 30428291

Available at:

<http://archive-ouverte.unige.ch/unige:128284>

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**UNIVERSITÉ  
DE GENÈVE**

Mario Gaudino, M.D.

Weill Cornell Medicine  
New York, NY  
mfg9004@med.cornell.edu

Umberto Benedetto, M.D.

Bristol Heart Institute  
Bristol, United Kingdom

David P. Taggart, M.D.

University of Oxford  
Oxford, United Kingdom

Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1813097

## Dengue Serostatus and Dengue Vaccine Safety and Efficacy

**TO THE EDITOR:** Post hoc analysis of Sanofi's Dengvaxia (CYD-TDV) vaccine by Sridhar et al. (July 26 issue)<sup>1</sup> provides evidence for an increased risk of severe dengue virus (DENV) disease among DENV-seronegative vaccinees. The authors address the possibility of antibody-dependent enhancement, but T-cell-mediated immunopathology represents another plausible explanation for this clinical outcome.

Vaccine efficacy among young children is lost within 3 to 4 years after Dengvaxia immunization.<sup>2</sup> If levels of protective antibodies decline and DENV envelope-specific T-cell memory remains intact, then a proportion of persons may become susceptible to infection in the presence of an overly robust T-cell response; this would lead to increased immunopathology, as observed with influenza.<sup>3</sup> T-cell-mediated immunopathology is implicated in dengue hemorrhagic fever,<sup>4</sup> and anecdotal evidence from a phase 1 trial suggests a trend toward increased disease symptoms among Dengvaxia-immunized yellow fever-immune persons who probably had T-cell memory to the yellow fever nonstructural proteins contained within Dengvaxia in the absence of DENV-specific neutralizing antibodies.<sup>5</sup> We propose that excessive T-cell responses in the context of inadequate neutralizing antibodies may explain increased DENV-associated adverse events among Dengvaxia-immunized children.

Mark K. Slifka, Ph.D.

Oregon Health and Science University  
Portland, OR  
slifkam@ohsu.edu

Ian J. Amanna, Ph.D.

Najit Technologies  
Beaverton, OR

Oregon Health and Science University and Dr. Slifka have a financial interest in Najit Technologies. Dr. Amanna is an employee of Najit Technologies. No other potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1811986

**TO THE EDITOR:** Sridhar and colleagues showed that the tetravalent dengue vaccine, although protective in previously seropositive children, increased the admission rates for virologically confirmed dengue (VCD) and the risk of severe VCD among seronegative children. This is consistent with the role of previous DENV exposure on vaccine efficacy and on the subsequent risk of severe disease.

Antibody-dependent enhancement is the postulated immunopathogenic mechanism explaining the increased risk of severe dengue among

patients previously infected with another serotype. Preexisting nonneutralizing heterotypic antibodies bind to DENV and facilitate infection of monocytes, which triggers an inflammatory cascade that is eventually responsible for enhanced disease severity.<sup>1</sup> Recently, Katzelnick et al. found that patients with anti-DENV titers of 1:21 to 1:80 were at the highest risk for severe dengue.<sup>2</sup> The importance of antibody concentration is particularly relevant, because postvaccination anti-DENV titers wane with time in patients without natural reexposure.<sup>3,4</sup>

Consequently, children who were seronegative before vaccination and whose postvaccination antibody titers wane are most at risk for severe disease. Studies should therefore evaluate whether booster doses could protect these patients from subsequent severe disease.

Klara M. Posfay-Barbe, M.D.

Arnaud G. L'Huillier, M.D.

Geneva University Hospitals  
Geneva, Switzerland  
arnaud.lhuillier@hcuge.ch

No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1811986

## H4:IC31 Vaccine or BCG Revaccination for Tuberculosis

**TO THE EDITOR:** Nemes and colleagues (July 12 issue)<sup>1</sup> examined the effects of bacille Calmette-Guérin (BCG) revaccination on reducing the rate of sustained QuantiFERON-TB Gold In-tube assay (QFT) conversion among adolescents in a high-risk setting. One aspect that received relatively little attention in the trial regards the immunologic mechanisms responsible for these effects, which were assessed only by measurement of interferon- $\gamma$  and interleukin-2 T-cell responses. Studies have shown a combination of improved long-term innate or trained immunity (through epigenetic reprogramming of myeloid cells) and adaptive responses after BCG vaccination, which leads to more effective control of mycobacterial and unrelated infections.<sup>2-4</sup> These mechanisms can also explain the decrease in unrelated respiratory tract infections after BCG revaccination that was observed by the authors. This decrease is consistent with the nonspecific beneficial effects after BCG vaccination that have been observed repeatedly in persons included in epidemiologic studies,<sup>5</sup> especially in infants, and warrants sustained attention in future investigations.

Charlotte de Bree, M.D.

Reinout van Crevel, M.D., Ph.D.

Mihai G. Netea, M.D., Ph.D.

Radboud University Medical Center  
Nijmegen, the Netherlands  
charlotte.debree@radboudumc.nl

No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1811046