



## Letter to the Editor

## Reply to “A comment on ‘Current status of hepatitis E virus infection at a rhesus monkey farm in China’”



Dear Editor,

We would like to thank Dr. Ibrahim M. Sayed for his letter to the Editor and appreciate the discussion of our manuscript on Hepatitis E virus (HEV) infection in rhesus monkeys.

This is a primary study focusing on the current status of HEV infection in rhesus monkey because there is a lack of information about the natural infection of monkeys with HEV. In this study, samples were collected from rhesus monkeys; after reaching a certain point, we did not detect HEV RNA in the samples. To understand the degree of HEV infection in rhesus monkeys, long-term monitoring is required. Unfortunately, before the submission of this article, we could not obtain a good HRP-conjugated anti-monkey IgM antibody; therefore, we were unable to detect anti-HEV IgM antibodies in the rhesus monkeys in this study. Recently, we analyzed HEV infection in cynomolgus monkeys that were imported from China and Cambodia to Japan. Although no HEV RNA was detectable in any of the serum samples, anti-HEV IgG and IgM were detected with positive rates of 97.5% and 54.5%, respectively (Zhang et al, JJID, *in press*). Thus, we consider that anti-IgM-positive serum could be detectable in rhesus monkeys, and it is important to clarify the duration of IgM antibody availability after natural infection.

We agree with Dr. Ibrahim M. Sayed's opinion that virus dose, immune response, and genotype are important factors that influence HEV infection in monkeys. In addition, the infection route is also an important factor for HEV infection. In natural infection, HEV is mainly

transmitted to monkeys by oral–fecal route. In contrast, most studies conducted in monkeys have used intravenous inoculation to initiate HEV infection, because the infectious dose of HEV needed is significantly lower than that required for the oral–fecal route. In fact, there is no successful report on oral inoculation of HEV. To clarify how the infection route influences HEV infection in monkeys, long-term monitoring of natural HEV infection in monkeys is required.

As the monkeys were susceptible to G1 to G8 HEV infection, it was justifiable to use monkeys as an animal model for HEV studies. Experimental HEV infection in monkeys presents in different patterns: sub-clinical infection, acute hepatitis, and persistent infection. Almost all acute hepatitis cases have been diagnosed based on elevation of alanine transaminase (ALT). However, other clinical signs are not clear. In our observation, none of the HEV-infected monkeys showed significant clinical signs, and we considered that the pathogenicity of HEV in monkeys and humans is largely different.

As Dr. Ibrahim M. Sayed pointed out, the cause of HEV infection is not completely known. Further research on experimental HEV infection in monkeys is required, and monkey farms need to control HEV infection and keep the monkeys free from HEV infection.

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