We thank Dr. Saitoh for the comments (1) on our article “Severe Human Parechovirus Infections in Infants and the Role of Older Siblings” (2). We would like to elaborate further on this interesting subject and clarify certain important points.

In the response to our study, Dr. Saitoh describes a human parechovirus type 3 (HPeV-3) epidemic in Niigata, Japan, in 2014 that was evaluated using polymerase chain reaction analysis of serum and/or cerebrospinal fluid samples from 43 neonates and young infants (3). The data from that outbreak support our finding that the presence of an older sibling is a risk factor for HPeV-3 infection. The approach used by Aizawa et al. (3) was a more clinical approach than was our epidemiologic modeling approach. They furthermore tested stool samples from asymptomatic siblings of the clinical HPeV-3 cases for HPeV-3 and then conducted sequencing, which resulted in 100% identical gene sequences between siblings. This finding indicates that the sick neonates and young infants likely contracted the virus from shedding of HPeV-3 in the stool/secretions of their asymptomatic siblings.

Regarding the development of measures to prevent HPeV-3 infection in neonates, we agree that it presents a challenge and requires varied approaches and strategies, which was our point exactly. However, taking into consideration the very low age of the Danish children infected with HPeV-3 (median age, 37 days), we believe that although handwashing likely will reduce the viral load, it is not sufficient as a stand-alone preventive measure to control spread of HPeV among children, particularly during an epidemic, because the nature of this virus (i.e., shedding of high viral titers in the stool). Thus, we maintain our view that that in “high-risk” infants (i.e., vulnerable neonates at high risk for a fatal outcome of severe disease), further isolation measures might be beneficial. Preventing symptomatic siblings (and even siblings younger than 5 years of age irrespective of symptomatology) access to the high-risk infants during their most vulnerable age window might actually be the only effective preventive strategy. After all, the most vulnerable age window for the majority of infants affected by HPeV-3 is limited to the first 2 months of life.

Last, we find that the suspicion that “some diagnoses of HPeV-3 infection based on the presence of virus in stool from patients with a nonstandard presentation might have been erroneous” (1, p. 000) is unlikely. We find it more likely that because of the design of our study, we obtained more information about the real clinical spectrum of HPeV-3 infection, because there is a tendency—at least in Denmark—for the pediatricians to not sample material that requires invasive sampling methods, including cerebrospinal fluids, when a nonspecific, treatable, “benign” illness such as sepsis-like illness due to enterovirus/HPeV is suspected. Instead, the pediatricians send a stool sample because it is less invasive to acquire and therefore more readily obtainable. We suspect that only testing material that requires invasive sampling methods, like serum and cerebrospinal fluid samples, will lead to underestimation of the true scale of the epidemic, because it is very likely that for HPeV infection (as for enterovirus infection), only a minor fraction actually present with severe sepsis-like illness/meningitis. We hope that this response will clarify the major issues presented by Dr. Saitoh (1).

ACKNOWLEDGMENTS
Conflict of interest: none declared.

REFERENCES

Alex Christian Yde Nielsen1, Nete Munk Nielsen2, Sofie Elisabeth Midgley1, Claus Bohn Christiansen3, and Thea Kølsen Fischer1,4 (e-mail: AYN@ssi.dk)

1 Department of Microbiological Diagnostics and Virology, Statens Serum Institut, Copenhagen, Denmark
2 Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark
3 Department of Clinical Microbiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
4 Global Health Center and Department of Infectious Diseases, University of Southern Denmark, Odense, Denmark