July 21, 2022

RE: Original research submission, “Viral genetic determinants of prolonged respiratory syncytial virus infection among infants in a healthy term birth cohort”

Dear Editor,

We are submitting our manuscript “Viral genetic determinants of prolonged respiratory syncytial virus infection among infants in a healthy term birth cohort”.

In this manuscript we tackle an observation which is of great interest in our field but not yet reported, determining if there are respiratory syncytial virus (RSV) variants associated with prolonged infection. We conducted biweekly RSV surveillance in nearly 2,000 healthy term infants and identified those with prolonged RSV infection. We applied both host and pathogen genetic association testing to detect variants that contribute to prolonged infection. This consisted of [1] a viral GWAS, [2] a human GWAS, [3] analysis of all public sequence data, and [4] assessing local immunological responses. We identified viral genetic variants associated with prolonged infection which we assessed in depth.

Our results are novel and represent an in-depth comprehensive computational statistical analysis of both host and viral genetics providing compelling evidence for RSV viral variants associated with RSV persistence in healthy human infants, a finding of significant importance to understanding the impact of RSV on chronic disease development and viral endemicity.

Thank you for your consideration of this manuscript for *Clinical Infectious Diseases*.

Sincerely yours,

Dylan Lawless, PhD, and

Tina V. Hartert, MD, MPH