Proving Etiologic Relationships to Disease

Another Look at the Common Cold Coronaviruses

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Key words: pneumonia, infants, coronaviruses, causation

(*Pediatr Infect Dis J* 2022;41:e102–e103)

Ten years ago, I wrote an Editorial for the Pediatric Infectious Diseases Journal commenting on the difficulty of proving the pathogenicity of the common cold human coronaviruses (ccHCoVs) when asymptomatic infections were so common.[1] The particular article that my comments related to was by Prill and colleagues[2] in that issue of the journal and described a study conducted in 3 large Mid-Western centers including almost 1500 children hospitalized with respiratory disease. The authors also included about 750 well control children of the same ages sampled at roughly the same time and in the same areas. The results of the study showed that there was essentially no difference in the incidence of ccHCoV infection in the sick (7.6%) and the well (7.1%). The authors' conclusion was that ccHCoV infections were "not associated" with hospitalization in the infected children, with the implication that, at least by these criteria, they likely had no role in producing the associated respiratory illnesses.

My Editorial traced some of the history of efforts to prove that various micro-organisms caused the diseases where they were found, starting with Koch's postulates and including volunteer studies, microscopic and microbiologic biopsy studies, as well as associative studies similar to the one conducted by Prill and her colleagues. The conclusion of these many considerations was that, at least for babies and young children, it was going to be very difficult to "prove" that the common cold coronaviruses caused respiratory illness. This was in spite of the fact that, at the Common Cold Research Unit in Salisbury, England, all of the known HCoVs had been administered to adult volunteers in the 1960s and early 1970s and were shown to cause colds.[3]

Ten years have passed, and now, in the midst of a major pandemic due to a coronavirus of undoubted human pathogenicity, I am again addressing the subject, "Do the ccHCoVs have pathogenicity for small infants?" The article in this issue of the Pediatric Infectious Disease Journal by Heimdal and colleagues[4] concerns ccHCoVs and has some findings that I believe may add to the consideration of their possible pediatric pathogenicity.

Interestingly, the same Norwegian group, with most of the same authors, published a previous article that also adds to the ccHCoV pathogenicity argument. This previous article described 9 years of a comprehensive study of viruses in children hospitalized in Trondheim, Norway, with acute respiratory tract illness.[5] The study contained a small contemporaneous control group of children admitted for surgery and without respiratory illness of any kind. As in the study by Prill and colleagues quoted above, the ccHCoV infection rates were the same in the ill and well children (9.1% and 10.2%, respectively). In this article, however, the authors went on to *quantify* the viral RNA found in the ill and control subjects and showed that the samples from children with respiratory illness contained higher quantities of viral RNA (polymerase chain reaction cycle threshold value <28) than those from the control children (odds ratio, 3.12 in adjusted analysis; $P = 0.016$). In subjects under 2 years of age, the adjusted odds ratio was 15.32 ($P < 0.001$).

Heimdal's article in this issue of the Pediatric Infectious Disease Journal[4] contains the same study group as in the earlier Journal of Infectious Disease article, plus clinical data and respiratory samples from 2 more years. In addition, the focus in this analysis was on virus-virus coinfections. The authors chose the two most common ccHCoV coinfections: those with respiratory syncytial virus, a virus with a high pneumonia "severity score," and those with rhinovirus (RV), a virus with a lower pneumonia severity score, about the same as that of ccHCoV. Perhaps the most intriguing finding in this study was that, whereas respiratory syncytial virus–ccHCoV coinfected infants had illness much more severe than those infected with ccHCoV alone, with a severity score almost identical to that for respiratory syncytial virus alone, the severity score of RV-ccHCoV coinfected children was *lower* than that in children with RV infection alone and *significantly lower* than that in children infected with ccHCoV alone.

The authors point out that, in vitro, RV infection is accompanied by a vigorous interferon-mediated antiviral cellular response.[6] Moreover, similar suppression by RV appears to occur between it and influenza virus both *in vitro* and *in vivo*[7,8] and also, *in vitro*, between RV and SARS-CoV-2.[9] In view of these findings, it seems very likely that the loss of virulence was a manifestation of the suppression of ccHCoV growth by RV, indicating that, by itself, the coronavirus was capable of causing lower tract respiratory disease in these infants.

Thus, there are now 2 pieces of evidence that the common cold coronaviruses may actually *cause* pneumonia in infants. Neither fragment seems, at least to me, completely persuasive, and the findings may not be reproducible. Higher viral loads seen in infants with ccHCoV infection and pneumonia, as described in Heimdal's earlier article in the Journal of Infectious Disease, may have nothing to do with the presence of the respiratory disease. In Heimdal's current article, the *P* value for RV-ccHCoV combined infections' loss of severity in comparison to ccHCoV infection alone was of borderline significance ($P = 0.04$); the reduced severity may not be due to a reduction in ccHCoV growth by RV but rather to RV growth by ccHCoV (ie, the other way around). Despite these caveats, however, it does appear that evidence of ccHCoV pathogenicity in infants is gradually accumulating.

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ISSN: 0891-3668/22/4103-e102

DOI: 10.1097/INF.0000000000003443

REFERENCES

1. McIntosh K. Proving etiologic relationships to disease: the particular problem of human coronaviruses. *Pediatr Infect Dis J.* 2012;31:241–242.

2. Prill MM, Iwane MK, Edwards KM, et al; New Vaccine Surveillance Network. Human coronavirus in young children hospitalized for acute respiratory illness and asymptomatic controls. *Pediatr Infect Dis J.* 2012;31:235–240.
3. Bradburne AF, Somerset BA. Coronavirus antibody titres in sera of healthy adults and experimentally infected volunteers. *J Hyg Camb.* 1972;70:235–244.
4. Heimdal I, Valand J, Krokstad s, et al. Hospitalized children with common Human Coronavirus: clinical impact of co-detected respiratory syncytial virus and rhinovirus. *Pediatr Infect Dis J.* 2022;41:e95–e101.
5. Heimdal I, Moe N, Krokstad S, et al. Human coronavirus in hospitalized children with respiratory tract infections: a 9-year population-based study from Norway. *J Infect Dis.* 2019;219:1198–1206.
6. Wolsk HM, Følsgaard NV, Birch S, et al. Picornavirus-induced airway mucosa immune profile in asymptomatic neonates. *J Infect Dis.* 2016;213:1262–1270.
7. Wu A, Mihaylova VT, Landry ML, et al. Interference between rhinovirus and influenza A virus: a clinical data analysis and experimental infection study. *Lancet Microbe.* 2020;1:e254–e262.
8. Nickbakhsh S, Mair Ca, Matthews L, et al. Virus–virus interactions impact the population dynamics of influenza and the common cold. *PNAS.* 2019;116:27142–27150.
9. Dee K, Goldfarb DM, Haney J, et al. Human rhinovirus infection blocks severe acute respiratory syndrome coronavirus 2 replication within the respiratory epithelium: implications for COVID-19 epidemiology. *J Infect Dis.* 2021;224:31–38.