Low Incidence of Reinfection With Endemic Coronaviruses Diagnosed by Real-Time PCR

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To the Editor—Monto et al recently reported results on the seasonal variation and transmission of the endemic (common) human coronaviruses (HCoV) HKU1, OC43, NL63, and 229E [1]. However, their study design did not allow for assessment of reinfection with the same HCoV. Knowledge about reinfections with common HCoV might inform the risk of recurrent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and may shed light on the efficiency of protective immunity. We interrogated a database of >75 000 clinical samples from >50 000 patients with respiratory tract infection to determine the rate of reinfection with the same HCoV (eg, NL63 followed by NL63) or a new HCoV (eg, NL63 followed by OC43).

Data were retrieved from the routine diagnostics unit at the Department of Clinical Microbiology, Sahlgrenska University Hospital with a catchment area of approximately 700 000 inhabitants. Both hospitals and primary care centers refer to this laboratory. We used a database of results obtained using an in-house real time polymerase chain reaction (PCR) panel targeting 18 respiratory pathogens [2] analyzed in 78 135 nasopharyngeal or oropharyngeal samples from 53 447 patients, mean age 47 years, between January 2013 and February 2020. We applied a lag period of >50 days from the first infection to distinguish recurrent from protracted infections. All patients with a positive initial test results for HCoV (HKU1, OC43, NL63, or 229E) and at least one additional sample analyzed >50 days later were thus included for assessment of reinfection. Ethical approval was granted by the Swedish Ethical Review Authority in Gothenburg.

The HCoV strains HKU1, OC43, NL63, or 229E were detected in 2162/78 135 (3%) samples from 1982 unique patients. HCoV accounted for 7% of samples positive for any virus. In agreement with the report by Monto et al [1], OC43 was the most prevalent HCoV (40%). Of the patients with an initial HCoV-positive test result, 470 had at least 1 additional sample taken >50 days later. In 47 samples, from 40 patients, HCoV was detected in these later samples. Six of the 40 patients tested positive for the same type of HCoV (NL63 n = 3, HKU1 n = 2, and OC43 n = 1). The mean times from first to recurrent infection with the same HCoV or a new HCoV were 676 and 566 days, respectively. One case of reinfection with the same HCoV and 18 reinfections with another HCoV were diagnosed within 1 year after the first infection.

Five of the 6 patients who were reinfected with the same HCoV were children or adolescents (mean age, 14 years; range, 2–17) and 4 of those had 1 or several comorbidities such as chronic lung disease (n = 3), cancer (n = 1), and/or compromised immunity caused by disease or therapy (n = 4). Patients who were reinfected by a new species of HCoV were older (mean age, 32 years; range, 1–82; $P = .037$). We did not observe a significant difference in the frequency of severe comorbidity between reinfected patients carrying the same versus a new HCoV.

Reinfection was significantly more likely to occur with a new rather than the same HCoV species (χ^2 goodness-of-fit $P = .012$; Table 1). While 9% of follow-up samples showed reinfection with a new HCoV, only 1% indicated reinfection with the same HCoV. These results imply that strain-specific protective immunity is achieved after HCoV infection. Notably, however, our results also suggest that recurrent infections with the same HCoV strain occur [3] and that these infections may be more common in younger immunocompromised patients.

A limitation to this study was that it did not allow for systematic long-term follow-up. Our results suggest that reinfection with the same species of HCoV

Table 1. Recurrent Human Coronaviruses (HCoV) Infections of the Respiratory Tract

	Reinfection With the Same HCoV		Reinfection With a New HCoV[a]		
HCoV	Observed	Expected	Observed	Expected	*P* Value
OC43	1	4.5	…	…	
NL63	3	5.6	…	…	
HKU1	2	3.0	…	…	
229E	0	0.4	…	…	
All	6	13.5	41	33.5	$P = .012$[b]

[a]One patient tested positive for the same HCoV in a second sample and another HCoV in a third sample.

[b]The χ^2 test was used to calculate the difference between observed and expected numbers of reinfections with the same or a new HCoV.

is infrequent and usually does not occur until >1 year after the first infection.

Notes

Financial support. This work was supported by the Swedish Cancer Society and the Swedish State through an agreement with Sahlgrenska University Hospital.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Received 11 July 2020; editorial decision 29 September 2020; accepted 6 October 2020; published online October 10, 2020.

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The Journal of Infectious Diseases® 2021;223:2013–4

DOI: 10.1093/infdis/jiaa627

Reply to Ringlander et al

To the Editor—The letter of Ringlander et al presents interesting information on observed reinfections with the same coronaviruses [1]. In the course of their observations, the authors suggest that we cannot examine this issue in our HIVE (Household Influenza Vaccine Evaluation) cohort [2], but that is not the case. The HIVE study began in 2010 following the 2009 influenza pandemic and many of the households have been participating for multiple years. Throughout, the etiology of symptomatic respiratory illnesses of any severity has been identified by reverse-transcription polymerase chain reaction. Our recent report on the occurrence of the common coronaviruses in the cohort focused on individual infections. Repeat infections in persons in our household study with the same or different viruses have been identified and are the subject of an analysis currently underway. The fact that reinfection with the same coronavirus occurs has been known at least since antibody studies were carried out with OC43 decades ago [3]. We are also currently evaluating serologic responses to the infections reported in our recent article, which will help in understanding more about the breadth and duration of coronavirus immunity.

Notes

Potential conflicts of interest. The author: No reported conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Received 21 August 2020; accepted 7 October 2020; published online October 10, 2020.

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The Journal of Infectious Diseases® 2021;223:2014

DOI: 10.1093/infdis/jiaa628

Hepatitis C Virus Vaccine Development: A Step Forward

To the Editor—I enjoyed reading the recent article by Yan et al [1], who developed a new hepatitis C virus (HCV) vaccine candidate based on the expression of soluble E2 (sE2) protein fused with *Helicobacter pylori* ferritin in *Drosophila* S2 cells. Unlike the majority of recombinant vaccine trials, this new vaccine was expressed and assembled in insect cells as nanoparticles of ferritin encompassing sE2 on the surface. Yan et al used competition enzyme-linked immunosorbent and receptor-binding assays to show the expression of sE2 in the correct conformation. Compared with their previously developed sE2 protein, the new nanoparticles showed higher B-cell immunogenicity in mice. Using a panel of prototype HCV cell culture strains from