Verified infections with endemic common cold coronaviruses do not entail significant protection against SARS-CoV-2

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Letter to the editor

Several recent studies have proposed the existence of immune cross-reactivity between human common cold coronaviruses (CCCoV) and SARS-CoV-2. Humans unexposed to SARS-CoV-2 may harbor antibodies that neutralize SARS-CoV-2 in cell culture (1) along with T-cells that recognize epitopes shared between SARS-CoV-2 and CCCoVs (2,3). Henns *et al*. (4) detected neutralizing antibodies against the NL63 CCCoV in serum from subjects with mild COVID-19, but not in those with severe disease. On the other hand, Schwaiger *et al*. (5) reported that antibodies against CCCoVs had low functional avidity for SARS-CoV-2, which argues against clinically relevant cross-reactivity. These and other recent reports (6) emphasize that additional studies are required to determine whether or not cross-reactivity translates into clinically relevant cross-immunity.

Previous studies suggest that prior verified human respiratory infections with any of the four endemic CCCoV (HKU1, OC43, NL63 and 229E) induce long-term protection against infection with the same (homologous) strain of CCCoV (7,8). In accordance, we reported that homologous infections of humans with CCCoV are approximately 10 times less common than heterologous infections (9), thus implying that infection with CCCoV entails significant protective immunity against the homologous virus. Analysis of the risk and severity of SARS-CoV-2 infection in patients with verified previous CCCoV infections might, therefore, inform the degree of clinically relevant cross-immunity.

We interrogated a database of >75,000 respiratory samples from >50,000 patients with respiratory tract infection diagnosed during 2013-2020. The database contains results from analyses of 18 respiratory pathogens using real-time PCR (rtPCR), including the four

endemic CCCoV described elsewhere (10). Among patients in the database, we assessed the risk of subsequent SARS-CoV-2 infection, as determined by rtPCR detection of SARS-CoV-2 RNA in respiratory specimens or by the presence of IgG antibodies in blood against the nucleocapsid (Architect, Abbott, Abbott Park, IL, USA) and the nucleocapsid/spike protein (iFlash, YHLO, Shenzhen, China) of SARS-CoV-2. More than 100,000 patients were tested for SARS-CoV-2 at our department during February to November 2020 and of those, 8,298 had at least one previous result in the above-referenced respiratory tract infection database prior to the COVID-19 pandemic. We also utilized hospital records to determine the severity of COVID-19 disease (hospitalization/intensive care unit referral or not). The proportion of SARS-CoV-2 positivity among patients with previous respiratory infections was compared against patients with no previously verified infection using chi2-tests. The study was approved by the Swedish Ethical Review Board (application no. 2020–03276).

As shown in Table 1, verified previous infections with CCCoV did not predict significantly reduced risk of SARS-CoV-2 infection. Similar results were observed when patients were grouped by previous infections with alpha-coronaviridae (CCCoV NL63 and 229E) or beta-coronaviridae (HKU1 and OC43). The incidence of SARS-CoV-2 infection was similar in patients with a history of CCCoV infection as in those with a previous common and immunologically unrelated respiratory infection (rhinovirus infection). The severity of COVID-19, as reflected by hospitalization and/or referral to intensive care, was not significantly reduced by previously verified CCCoV infections (Table 1).

Additionally, the amount of SARS-CoV-2 in respiratory samples of patients with previously confirmed CCCoV infections [7.2 ± 2.07 $\log_{10}$ viral particles/swab (mean ± standard error of the mean, range 2.9-9.6)] did not differ significantly from that of patients with previous

rhinovirus infections (6.0 ± 1.95 $\log_{10}$ viral particles/swab, range 0.7-10.61, P=0.1, Student's t-test). Logistic regression analysis identified patient age as a risk factor for SARS-CoV-2 infection (P=0.007) and hospitalization for COVID-19 (P<0.0001). In the adjusted analyses, previously verified infections, including those caused by CCCoV, did not confer significant protection against SARS-CoV-2 infection or hospitalization. Unexpectedly, patients with previously verified infection with alphacoronaviruses showed significantly higher risk for hospitalization after adjustment for age (odds ratio 2.82, P=0.03; Supplementary table 1).

A limitation to these analyses is that serial, systematic monitoring of CCCoV infections was not available. Our study, thus, likely underestimates the incidence of CCCoV infections in this patient cohort. Nevertheless, our results support the conclusions by Schwaiger *et al*. suggesting that past infection with the four endemic CCCoV does not entail clinically significant protection against SARS-CoV-2.

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Table 1. Infection with SARS-CoV-2 in patients with previously verified common cold coronavirus (CCCoV) infection, rhinovirus infection or any respiratory infection and coherent odds ratios.

Previous infection[a]	Tested[b]	SARS-CoV-2 Positive	OR [95% CI][d]	P[e]	Hospitalized[f]	OR [95% CI][g]	P[e]
Any CCCoV	434 (22%)	41 (9%)[c]	0.92 [0.66-1.28]	0.68	20 (49%)	1.35 [0.70-2.62]	0.40
Alphacoronavirus	183 (22%)	21 (11%)	1.14 [0.72-1.81]	0.54	13 (61%)	1.98 [0.80-4.86]	0.18
Betacoronavirus	264 (22%)	21 (8%)	0.76 [0.48-1.19]	0.29	8 (38%)	0.97 [0.38-2.51]	1
Rhinovirus	1,242 (18%)	113 (9%)	0.88 [0.71-1.09]	0.26	47 (42%)	0.95 [0.62-1.46]	0.83
Any positive	3,752 (16%)	390 (10%)	1.02 [0.89-1.18]	0.80	155 (39%)	0.88 [0.67-1.17]	0.39
Negative for all	4,546 (14%)	464 (10%)	1		199 (43%)	1	

[a]Patients were tested for 18 airway pathogens from February 2013 to February 2020, prior to SARS-CoV-2 testing by rtPCR or serology.

[b]Number of patients tested for SARS-CoV-2 and percentage of all patients with indicated previous infections.

[c]One patient had co-infection with an alpha- and a betacoronavirus prior to SARS-CoV-2 infection.

[d]Odds ratio (OR) and 95% confidence interval (CI) for SARS-CoV-2 infection where the OR for patients with no previous infections ("negative for all") was set to 1.

[e]P-values from Chi2 test comparing patients with indicated previous infections with patients with no previous infections.

[f]Hospitalized after at least one positive respiratory sample of SARS-CoV-2 (RT-PCR). Forty-five patients were SARS-CoV-2-positive but had no information regarding hospitalization.

[g]OR and 95% CI for hospitalization after diagnosis of SARS-CoV-2 where the OR for patients with no previous infections was set to 1.