HUMAN VACCINES & IMMUNOTHERAPEUTICS
2021, VOL. 17, NO. 1, 84–87
https://doi.org/10.1080/21645515.2020.1787074

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COMMENTARY

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Neutralizing and cross-reacting antibodies: implications for immunotherapy and SARS-CoV-2 vaccine development

Samuel A. Cohen [a,b], Caitlyn Kellogg [b,c], and Ozlem Equils[b]

[a]Department of Preventive Medicine, Keck School of Medicine of USC, Los Angeles, US; [b]MiOra, Public Health Nonprofit (www.miora.org); [c]MiOra Covid-19 Response, University of California San Diego School of Medicine, Los Angeles, US

ABSTRACT

The novel coronavirus SARS-CoV-2 emerged in China in 2019 and quickly spread globally, causing a pandemic. There is an urgent need to develop vaccines against the virus, and both convalescent plasma and immune globulin are currently in clinical trials for treatment of patients with COVID-19. It is unclear whether antibodies induced by SARS-CoV-2 have neutralizing capacity and whether they can protect from future infection. Seasonal human coronaviruses (HCoV) have been circulating for decades. It is currently unknown whether antibodies against seasonal HCoV may cross-neutralize SARS-CoV-2. Data from neonates suggest that trans-placental antibodies against HCoV may have neutralizing capacity. Here we briefly review the epidemiologic observations on HCoV and discuss the potential implications for neutralizing and cross-neutralizing antibodies against SARS-CoV-2.

ARTICLE HISTORY
Received 25 May 2020
Accepted 13 June 2020

KEYWORDS
COVID-19; vaccine; immunotherapy; pregnancy

As states across America prepare to reopen, one of the critical questions in the management of COVID-19 is the individual susceptibility to infection. SARS-CoV-2 is a novel coronavirus that emerged in China in December 2019 and has since created a public health crisis (COVID-19) globally. While symptoms of SARS-CoV-2 infection may be milder than those seen in previous pandemics caused by other coronaviruses, including Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS-CoV), worldwide, SARS-CoV-2 has killed more people than MERS and SARS-CoV combined. This is thought to be due to the efficient person-to-person transmission of SARS-CoV-2 and lack of population-level immunity.[1] SARS-CoV-2 infection appears to induce an antibody response in the patient; however, it is not clear whether these antibodies prevent re-infection.

Based on their serological relationships, human coronaviruses (HCoV) fall into two groups (Table 1).[2] Serological cross-reactivity has been reported between viruses in the same group.[3] HCoV-229E (group 1) and HCoV-OC43 (group 2) were identified in 1962 and 1967, respectively.[4,5] Although HCoV-NL63 (group 1) was first discovered in 2004, serology data from pregnant women and their infants suggest that it was circulating before 1999.[6,7] SARS-CoV (group 2) emerged in 2002, HCoV-HKU1 (group 2) was identified in 2004, and in 2012, MERS-CoV (group 2) was identified.[8–10] SARS-CoV-2 (group 2) emerged in late 2019 and, as of May 2020, is still resulting in high death rates globally.[11]

Although SARS and MERS caused short-lived pandemics, seasonal human coronaviruses (OC43, 229E, NL63, HKU1) have been circulating in the community for decades;[12] these viruses can cause upper and lower respiratory tract infections, and are considered to be the second-most frequent cause of the common cold.[13] Similar to SARS-CoV-2, seasonal HCoVs are enveloped, positive-sense RNA viruses with four distinct structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N).[12] Antibodies directed against S protein are proposed to have neutralizing capacity.[14] Although there is a striking homology between S protein of SARS-CoV and SARS-CoV-2, it is divergent from seasonal HCoV S protein.[15]

Data on HCoV-induced antibody response and neutralizing capacity come from studies of natural infection and human challenge studies.[14] Infants less than 1 year old consistently account for the smallest proportion of cases due to seasonal coronaviruses (Table 2).[16–20] The rate of infection peaks among children ages 1–5 years, followed by those between 6 and 17 years of age (Table 2).[16–20] The low rate of HCoV infection in infants less than 1 year of age was attributed to the placental transfer of maternal antibodies and their neutralizing capacity.[3] In a longitudinal serological survey study of 25 newborns, Dikjman et al.[3] showed that all infants had antibodies directed to the N protein of seasonal HCoVs (OC43, 229E, NL63, HKU1) at birth, but the antibody levels decreased to low detectable levels within a few months. In a separate experiment with a larger cohort of children, the investigators confirmed that the majority (64%) of infants younger than 6 months of age had antibodies against both NL63 and 229E, which decreased over time.[7] Approximately 22% of those who were 12 months old were seropositive.[7] The seropositive rate increased with time, and among children 3.5 to 5 years of age, the seropositivity rate rose to 65% for HCoV-229E and 75% for HCoV-NL63. The investigators concluded that maternal antibodies protect infants from seasonal HCoV and most children become susceptible to infection between 18 and 42 months of age.[7] The observations from SARS-CoV-2 exposed infants are similar; transmission of SARS-CoV-2 to

CONTACT Ozlem Equils ozlem@miora.org MiOra

Table 1. Group 1 and Group 2 Human coronaviruses.

Group 1 (Alpha-CoV)	Group 2 (Beta-CoV)
229E	OC43 (lineage A)
NL63	HKU1 (lineage A)
	SARS-CoV (lineage B)
	SARS-CoV-2 (lineage B)
	MERS (lineage C)

Table 2. Mean Age of Pediatric Coronavirus Infections.

Coronavirus	Mean Age of Infection ± Standard Deviation (SD)
HCoV-NL63[16]	6.4 ± 5.7 years
HCoV-HKU1[16]	8.4 ± 5.7 years
HCoV-229E[16]	8.2 ± 5.5 years
HcoV-OC43[16]	5.2 ± 4.6 years
SARS-CoV[17]	11.2 years (SD unknown)
MERS-CoV[18]	8.25 years (SD unknown)
SARS-CoV-2[19]	6.7 years*@ (SD unknown)

*Median value
@Data at the time of development of this manuscript

a newborn appears to be very rare when the mother is acutely infected.[21] In infants, in addition to the differences in angiotensin converting enzyme 2 (ACE2) receptor expression, transplacental antibodies may provide protection against SARS-CoV-2.

Data from the 2003 SARS-CoV pandemic also suggest a potential role for neutralizing antibodies in the current SARS-CoV-2 outbreak. In 2003, convalescent plasma treatment led to a shorter hospital stay and lower mortality among those with SARS-CoV.[22] Recently, in China, treatment with convalescent plasma with high titers of receptor binding domain specific IgG and IgM was reported to improve the clinical outcomes in patients with SARS-CoV-2 infection.[23] Convalescent plasma has recently been shown to be effective for the treatment of COVID-19 in clinical trials, and intravenous immune globulin is currently being tested for the treatment of pediatric patients with Multi-System Inflammatory Syndrome (MIS-C) related to SARS-CoV-2.[24,25]

Cross-neutralizing antibodies directed to N protein have been recognized among seasonal HCoV.[3] In a sequence of seroconversion study in children, prior infection with OC43 (group 2) was observed to be protective from infection with HKU1 (group 2). However, the opposite was not true; those previously infected with HKU1 were not protected against infection with OC43.[3] Longitudinal observational studies show that the incidence of different HCoVs oscillates from year to year, especially for OC43 and HKU1 (group 2), which make approximately half of all HCoV infections every year (Figure 1).[20,26] If one of the group 2 viruses dominates 1 year, the other group 2 virus appears to dominate the following year (Figure 1).[26] In addition, if it was a particularly bad season with group 2 viruses (such as 2012–13 and 2014–15), the following season, group 2 viruses did not appear to be as frequent (Figure 1).[26] A similar pattern was observed by Talbot et al.[27] who reported the incidence of human coronaviruses (OC43, NL63 and 229E) in children over a 20 year period and by Killerby et al.[20] who examined The National Respiratory and Enteric Virus Surveillance System (NREVSS) data on laboratory detected HCoV in the United States during 2014–2017. These data suggest that recent exposure and immune response to one group 2 HCoV may influence the susceptibility to infection with another group 2 virus. SARS-CoV and SARS-CoV-2 are group 2, lineage B coronaviruses.[28] Antibodies induced by infection with seasonal group 2, lineage A HCoV may provide cross-protection to infection with SARS-CoV and SARS-CoV-2 and lead to milder or asymptomatic disease.[29] So far, there are limited data on the circulating seasonal HCoV during fall/winter 2019–2020. Recently Nowak et al.[30] suggested that NL63 (n = 23) and HKU1 (n = 13) were the main group 1 and group 2 viruses circulating in the New York area between March 16 – April 20, 2020.

SARS-CoV-2 and SARS-CoV share 74.5% genome identity, and a SARS-CoV serology assay may give false-positive results in 85% of SARS-CoV-2 patients within 10 days of onset of illness.[31] In *in vitro* experiments, serum from a patient who recovered from SARS moderately inhibited the transduction by

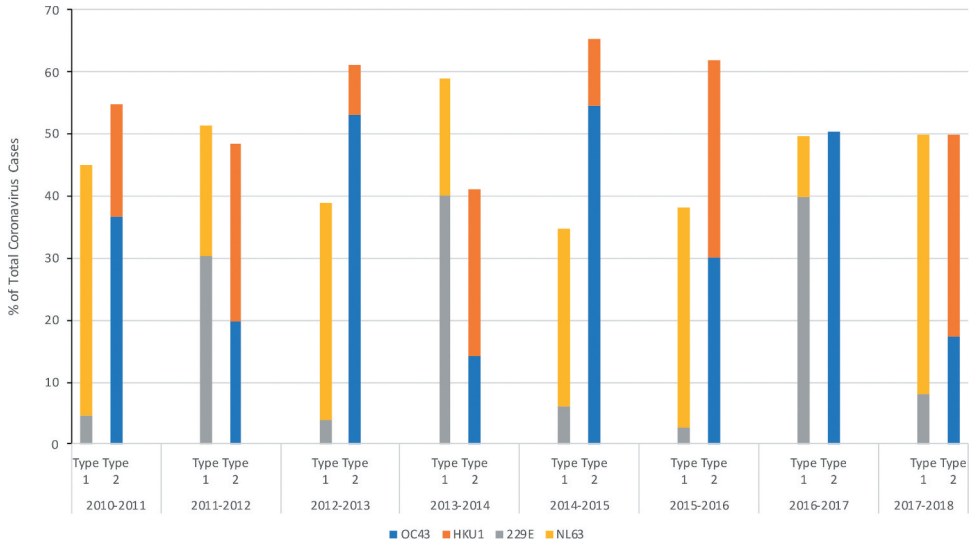

Figure 1. Incidence of 4 Seasonal Coronaviruses (OC43, 229E, NL63, HKU1) at the University of Michigan Health Care System between 2010–2018.

SARS-CoV-2 pseudovirion.[32] Pinto et al.[33] recently identified a monoclonal antibody from memory B cells of an individual who was infected with SARS-CoV in 2003; the antibody potently neutralized SARS-CoV-2 and SARS-CoV pseudoviruses as well as SARS-CoV-2 *in vitro*.[33] Sera from patients who recovered from SARS-CoV was proposed for the treatment of patients with SARS-CoV-2 infection.[34]

Recent data from de Assis, et al.[35] showed that sera from patients with SARS-CoV-2 infection (n = 7) contained IgG and IgA antibodies reacting with S protein of OC43 (group 2) and 229E (group 1). There appears to be some homology between N protein of SARS-CoV and seasonal HCoV.[36] Zhao et al.[37] showed that sera collected from two individuals 1 year prior to the SARS pandemic contained N protein specific antibodies that cross-reacted with SARS-CoV. Serum samples obtained from patients who recently recovered from SARS-CoV had antibodies that cross-reacted *in vitro* with nucleocapsid proteins of HCoV-OC43 and 229E.[38] It is important to further understand the neutralizing effect of antibodies directed against viral proteins other than S-protein on SARS-CoV-2 pathogenesis.

As vaccines and immunotherapeutics are developed against SARS-CoV-2, epidemiologic data are needed on the temporal pattern of SARS-CoV-2 and its relationship with seasonal HCoV.[14] The annual incidence of combined group 1 and combined group 2 HCoV disease appears to be stable and distributed equally over time, but the predominant group 2 virus causing disease, OC43 versus HKU1, appears to alternate from year to year (Figure 1).[26] Though SARS-CoV-2 is another group 2 coronavirus, it belongs to a different lineage as OC43 and HKU1 (Table 1) and is not known whether the immune response to circulating seasonal HCoV will have any influence on SARS-CoV-2 emergence and severity in the upcoming year. Data on seasonal HCoVs that circulated during the fall/winter of 2019–2020 will be very useful, and may be generated by using frozen patient samples stored in influenza registries.

The Center for Disease Control (CDC) has begun to track and report weekly SARS-CoV-2 activity in COVIDView.[39] Going forward, epidemiologic data on SARS-CoV-2 may be examined within the context of data on seasonal HCoV and other respiratory tract viruses, since they frequently co-infect patients.[20] Gorse et al.[40] demonstrated that in a small cohort of older adults (n = 15; 60 yr and older) with respiratory tract infections, acute infection with HCoV induced neutralizing antibodies in 46% of the individuals. The elderly in nursing homes may be isolated and less exposed to seasonal HCoV, and they may have lower level of antibodies at the beginning of a season. As we better understand the role of neutralizing and cross-neutralizing antibodies, in the future, sensitive and specific quantitative seasonal HCoV serology assays may be incorporated into patient care to help determine an individual's risk for severe SARS-CoV-2 infection.

In addition, there is an urgent need to collect longitudinal seasonal HCoV and SARS-CoV-2 serology data on all pregnant women and their infants to understand the role of antibodies to prevent neonatal infections. In pregnant women who are infected with SARS-CoV-2, it is also necessary to understand the timing and efficiency of transplacental antibody transfer, the factors that impair the transfer, as well as the half-life of the maternal antibody in the neonate.[41]

These data collected will be useful to develop safe and effective immunotherapies and vaccines against SARS-CoV-2.

Disclosure of potential conflicts of interest

The authors report no conflicts of interest.

Funding

This work was supported by MiOra public health education nonprofit.

ORCID

Samuel A. Cohen http://orcid.org/0000-0002-8816-5015
Caitlyn Kellogg http://orcid.org/0000-0002-2452-6264

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