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Letter to the Editor

Early seasonal coronavirus seroconversion did not produce cross-protective SARS-CoV-2 antibodies

To the Editor,

We read with interest a recent article by Aran et al. on the reduced odds of SARS-CoV-2 infection among those with a recent diagnosis of common cold.[1]

Endemic human coronaviruses (HCoV) are common causes of respiratory infection and typically cause mild illnesses in young children. Most epidemiological studies of HCoV infections have focused on acute infections in young children[2] although infections in adults have been reported.[3] Natural immunity to HCoV infection is believed to wane with age, and re-infections have been reported although without confirmation by molecular epidemiology.[4] The prevalence of HCoV seropositivity among young and older age groups in the general population is not well studied.

Interest in immunological responses to HCoVs has been triggered by age-related disparities in the severity and prevalence of the novel human coronavirus SARS-CoV-2. COVID-19 infection at advanced age is strongly associated with increased risk of severe disease and death while pediatric COVID-19 infection has been consistently associated with clinically milder disease phenotypes.[5] We thus hypothesized that seropositivity to endemic coronaviruses such as HCoV-OC43, NL63, 229E and HKU1 increases in young adults due to cumulative exposure to seasonal coronaviruses but declines in late adulthood, and that loss of cross-protective neutralizing antibodies may explain the increased risk of severe disease in advanced adulthood. We also hypothesized that multipositivity (seropositive to 2 or more HCoVs) may confer greater cross protection against SARS-CoV-2 compared to monopositivity.

259 de-identified banked serum samples from Singaporean institutional ethics review board approved studies collected from non-infected healthy individuals across three different age groups were studied: 139 1-year-old infants (2004–2008); 57 adolescents aged 17–21 (2018); and 63 adults aged 22-62 (2011–2013). All sera were screened for antibodies to endemic CoVs HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1 through their binding affinity to individual HCoV-specific spike S1 protein subunit antigens (Sino Biological, Beijing, China) in enzyme-linked immunosorbent assays performed according to manufacturer's instructions. Ethics approval was obtained from the institutional review board (NHG DSRB Ref: 2020/00304).

The optical density (OD) of the final solutions were measured in terms of absorbance which was proportionate to the amount of seasonal HCoV IgG present in the original sera. Anti-human serum albumin (HSA) levels were used as a baseline to determine cutoffs for seasonal HCoV IgG antibody levels present in each sample. As HSA is the most plentiful protein found in human plasma, this was regarded as the baseline and any IgG antibodies beyond this range were determined to be positively detected. A validated surrogate viral neutralization assay[6] (sVNT) to epidemic HCoVs (SARS-CoV, SARS-CoV-2 and MERS-CoV) was performed on all samples to assess cross-neutralizing capabilities.

There were high seropositivity rates to seasonal HCoVs overall (Fig. 1). In the infant age group, 55% of samples were seropositive, of which 35·3% were positive to OC43 followed by NL63 (30·9%), HKU1 (26·6%) and 229E (20·9%). 39·6% of these samples were multi-positive and 2·9% of samples had positive serology to all four endemic HCoVs.

Among the adolescents, 96% were seropositive to at least one HCoV (Table 1). In contrast to the infant age group, NL63 was the most common HCoV identified (93%), followed by OC43 (71·9%), 229E (68·4%) and HKU1 (57·9%). A similarly high percentage (94%) of adult samples were seropositive to at least one HCoV: OC43 (68·3%) and NL63 (66·7%) were the most common, followed by 229E (49·2%) and HKU1 (46%). Among the four endemic HCoVs, seropositivity to NL63 was highest with 53·3% of total samples, followed by OC43 (51·4%), HKU1 (38·2%), and 229E (38·2%). Seropositivity to multiple HCoVs was common with 59·5% of all samples demonstrating seropositivity to two or more HCoVs. The trend of multi-positivity increased from infancy (39·6%) to adolescence (91·2%) with a slight decline in adulthood (69·8%). Surrogate viral neutralization assays against SARS-CoV-2 performed on all HCoV seropositive samples were all negative, indicating the absence of cross-neutralization to SARS-CoV-1, MERS and SARS-CoV-2.

Despite the high prevalence of endemic HCoV seropositivity in the general population especially in young adults and adolescents, no cross-neutralizing activity against MERS, SARS-CoV-1 and SARS-CoV-2 was detected. This suggests neutralizing antibodies from prior endemic HCoV infections are unlikely to protect against COVID-19 infection or to explain the differences in clinical phenotype between young children and older adults.

The strength of this study is the large number of pre-pandemic samples from different age groups in a general population cohort. However, our study is limited by its focus on cross-neutralizing antibodies. We did not look for other potentially cross-reacting epitopes outside of the S1-spike protein so cross protection may have come through other epitopes. We were also unable to identify banked serum from teenagers or older children although we do have a group of adolescents, young adults and older individuals for comparison with infants. We also were not able to assess T-cell responses. Investigators have found that vaccination using the BNT162b vaccine in individuals who have recovered from SARS-CoV-1 infection initiated development of broad antibodies against a spectrum of sarbecoronaviruses.[7] We have demonstrated here that this is not present in those with prior seasonal coronavirus infection. Other mechanisms such as differences in innate immune

Abbreviations: HCoV, Human coronavirus.

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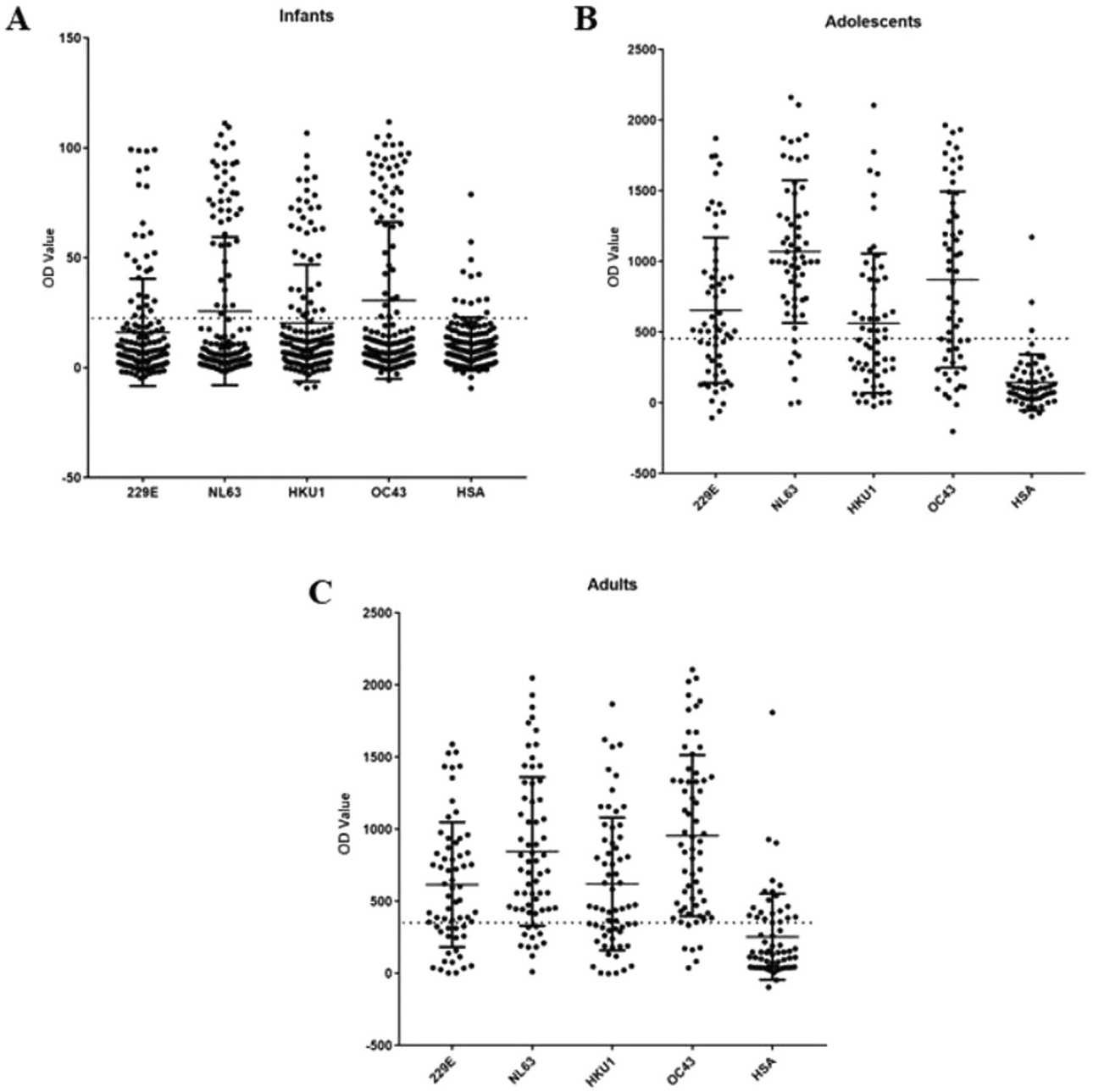

Fig. 1. Scatter plots showing optical density (OD) for each HCoV across all samples. OD values of cohorts are measured in terms of absorbance proportionate to the amount of seasonal HCoV IgG present in the original sera of the infant (Fig. 1a), adolescents (Fig. 1b) and adults (Fig. 1c) samples. The dotted line in each scatter plot represents the mean+SD of HSA used as a threshold level to differentiate positive and negative samples.

Table 1
Demographics of study cohort.

	Infants (n = 139) n (%)	Adolescents (n = 57) n (%)	Adults (n = 63) n (%)
Gender			
Female	68 (48·9)	36 (63·2)	44 (69·8)
Male	71 (51·0)	21 (36·8)	19 (30·2)
Percentage Positivity to each HCoV			
OC43	49 (35·3)	41 (71·9)	43 (68·3)
NL63	43 (30·9)	53 (93·0)	42 (66·7)
HKU1	37 (26·6)	33 (57·9)	29 (46·0)
229E	29 (20·9)	39 (68·4)	31 (49·2)
Multi-Positivity			
Negative to all	63 (45·3%)	2 (3·5%)	4 (6·3%)
Single Positive	21 (15·1%)	3 (5·3%)	15 (23·8%)
Double Positive	32 (23%)	12 (21·1%)	18 (28·6%)
Triple Positive	19 (13·7%)	21(36·8%)	10 (15·9%)
Positive to all	4 (2·9%)	19 (33·3%)	16 (25·4%)

responses in the elderly, or decreased levels and binding affinity of paediatric ACE-2 (the SARS-CoV-2 target receptor) in children; may thus be responsible for the age-related disparity in COVID-19 infection.

Seropositivity to endemic coronaviruses across different age groups in the general population is not well reported. A pre-pandemic study from Beijing using an IFA assay found high levels of seronconversion (> 60%) after age 3, with > 70% seropositivity for the adult age group, similar to our findings.[8] Other studies have concentrated on PCR or serological studies of hospitalized individuals which may not reflect the immunological history of the patients and cannot determine cross protection.[9,10]

In conclusion, we have demonstrated that seroconversion to endemic HCoV begins early in life, increases significantly in adolescence with a slight decline in seropositivity in adulthood. However, despite the high prevalence of endemic HCoV seropositivity, there was no cross neutralization against epidemic HCoVs. More research is required to determine the reasons for the increased severity of SARS-CoV-2 infection in older adults.

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Declaration of Competing Interest

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CRediT authorship contribution statement

Lydia Su Yin Wong: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Evelyn Xiu Ling Loo:** Methodology, Writing – review & editing. **Chiung-Hui Huang:** Formal analysis, Data curation, Methodology. **Gaik Chin Yap:** Formal analysis, Data curation, Methodology. **Michelle Jia Yu Tay:** Formal analysis, Data curation, Writing – original draft. **Regena Xin Yi Chua:** Formal analysis, Data curation, Writing – original draft. **Alicia Yi Hui Kang:** Formal analysis, Data curation, Writing – original draft. **Liangjian Lu:** Methodology. **Bee Wah Lee:** Writing – review & editing. **Lynette Pei-Chi Shek:** Conceptualization, Data curation, Writing – review & editing. **Jinyan Zhang:** Methodology. **Wan Ni Chia:** Methodology. **Lin-Fa Wang:** Conceptualization, Data curation, Methodology, Writing – review & editing. **Elizabeth Huiwen Tham:** Conceptualization, Data curation, Writing – review & editing. **Paul Anantharajah Tambyah:** Conceptualization, Data curation, Writing – review & editing.

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Lydia Su Yin Wong*
Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore
Khoo Teck Puat-National University Children's Medical Institute, National University Health System

Evelyn Xiu Ling Loo
Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore
*Singapore Institute for Clinical Sciences (SICS), Agency for Science, Technology and Research (A*STAR)*

Chiung-Hui Huang, Gaik Chin Yap, Michelle Jia Yu Tay, Regena Xin Yi Chua, Alicia Yi Hui Kang
Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore

Liangjian Lu
Khoo Teck Puat-National University Children's Medical Institute, National University Health System

Bee Wah Lee
Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore

Lynette Pei-Chi Shek
Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore
*Singapore Institute for Clinical Sciences (SICS), Agency for Science, Technology and Research (A*STAR)*

Jinyan Zhang, Wan Ni Chia, Lin-Fa Wang
Duke-NUS Medical School

Elizabeth Huiwen Tham
Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore
Khoo Teck Puat-National University Children's Medical Institute, National University Health System
*Singapore Institute for Clinical Sciences (SICS), Agency for Science, Technology and Research (A*STAR)*
Human Potential Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore

Paul Anantharajah Tambyah
National University Hospital, Singapore
Department of Medicine, Infectious Diseases Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore

*Corresponding author at: Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, 1E Kent Ridge Road, NUHS Tower Block, Level 12, Singapore 119228, Singapore.
E-mail address: paelwsy@nus.edu.sg (L.S.Y. Wong)