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Minimal Impact of Prior Common Cold Coronavirus Exposure on Immune Responses to Severe Acute Respiratory Syndrome Coronavirus 2 Vaccination or Infection Risk in Older Adults in Congregate Care

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Background. Common cold coronaviruses were a frequent cause of respiratory infections in older adults living in congregate care homes before the coronavirus disease 2019 pandemic, which may influence immune responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination and infection. We investigated humoral and cellular immune responses to prior common cold coronaviruses and SARS-CoV-2, how they are affected by SARS-CoV-2 vaccination and infection, and their associations with Omicron BA.1 SARS-CoV-2 infections in residents of long-term care and retirement homes.

Methods. In SARS-CoV-2 infection–naive residents with 3 monovalent messenger RNA SARS-CoV-2 vaccinations, we measured serum anti–receptor binding domain (RBD) immunoglobulin (Ig) G and IgA antibody titers against SARS-CoV-2 and common cold human coronavirus (HCoV) NL63, HCoV-OC43, and HCoV-229E; ancestral and Omicron BA.1 neutralizing antibodies; and $CD4^+$ and $CD8^+$ T-cell activation responses to membrane, nucleocapsid, and spike proteins. We examined the relationships of common cold coronavirus and SARS-CoV-2 humoral immune responses, whether antibody and T-cell responses changed after SARS-CoV-2 messenger RNA vaccination or infection, and their associations with Omicron BA.1 infection.

Results. Anti-RBD IgG HCoV-OC43 titers were positively correlated with SARS-CoV-2 anti-RBD IgG and neutralizing antibody titers. Common cold coronavirus anti-RBD IgA titers, but not anti-RBD IgG titers, increased after SARS-CoV-2 vaccination or infection, and many residents had cross-reactive T cells. Common cold coronavirus humoral immunity was similar in residents without and those with subsequent Omicron BA.1 infection.

Conclusions. Despite frequent exposure, and associations of common cold coronavirus and vaccine-induced SARS-CoV-2 humoral immunity, preexisting common cold coronavirus immunity was not associated with Omicron BA.1 infection in residents of long-term care and retirement communities.

Keywords. common cold coronavirus; COVID-19; older adults; SARS-CoV-2; seasonal coronavirus.

Common cold respiratory infections in humans are often caused by alphacoronaviruses (ie, human coronavirus [HCoV] NL63 and HCoV-229E) as well as phylogenetically related betacoronaviruses (ie, HCoV-OC43 and HCoV-HKU1) [1]. These infections are typically self-limiting and rarely require medical intervention, but they may cause pneumonia or bronchitis, particularly in older adults [2]. Surveillance for common cold coronavirus infections has been minimal, even in regions where there are annual seasonal outbreaks, so estimating infection rates is difficult. However, most people seroconvert (ie, develop anticoronavirus antibodies) in early childhood [3, 4], and high antibody titers are maintained throughout life due to frequent reinfections [5–7]. In addition, common cold coronaviruses cause a significant number of respiratory virus outbreaks in long-term care

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facilities [8], accounting for up to 32% of annual respiratory infections [9].

Common cold coronaviruses are closely related to the pandemic coronavirus SARS-CoV-2, which causes coronavirus disease 2019 (COVID-19) [1]. Evolution of SARS-CoV-2 since its emergence in 2019 has also led to multiple variants of concern, including Alpha, Beta, Gamma, Delta, and, most recently, Omicron (B.1.1.529) and its subvariants (eg, BA.1). SARS-CoV-2 is more transmissible and virulent in humans [1] and is associated with significant mortality rates in older adults [10, 11]. Despite variations in transmission and severity, however, all coronaviruses that cause disease in humans have evolutionarily conserved and immunogenic structural proteins, such as the nucleocapsid (N), membrane (M), and spike (S) proteins [12, 13]. Accordingly, up to about 60% of individuals unexposed to SARS-CoV-2 have memory T cells to these conserved proteins [14–16] and about 20% of pre–COVID-19 pandemic serum samples have antibodies that recognize SARS-CoV-2 [17, 18]. It has therefore been hypothesized that prior exposure to common cold coronaviruses modifies immune responses to SARS-CoV-2 infection and vaccination [19].

To date there have been conflicting reports as to whether preexisting common cold coronavirus immunity is beneficial [20–23], neutral [24–26], or detrimental [27, 28] in preventing SARS-CoV-2 infection. Effects of prior common cold coronavirus exposure on SARS-CoV-2 infection and vaccination responses may be further modified by aging of the immune system, which is associated with progressive impairments of humoral and cellular immunity [29]. Despite the high rates of both pre–COVID-19 pandemic common cold coronavirus infections and subsequent SARS-CoV-2 infections in long-term care facilities [8, 9], there has been little consideration of interactions between common cold coronavirus and SARS-CoV-2 immunity in this population.

In the current study we investigated humoral and cellular immune responses to prior common cold coronavirus exposure and SARS-CoV-2 vaccination and infection in residents of long-term care and retirement communities. We evaluated (1) associations of common cold coronavirus and SARS-CoV-2 antibody titers in SARS-CoV-2–vaccinated infection-naive individuals; (2) whether SARS-CoV-2 vaccination or infection affected titers of anti–receptor-binding domain (RBD) immunoglobulin (Ig) G and IgA antibodies to common cold coronaviruses and $CD4^+$ and $CD8^+$ T-cell responses to conserved N, M, and S proteins; and (3) whether common cold coronavirus immune responses differed between individuals who remained uninfected and those who developed COVID-19 during the early Omicron BA.1 wave of infections.

METHODS

Patient Consent Statement

All protocols were approved by the Hamilton Integrated Research Ethics Board (project no. 13059) and site-specific ethics boards. Informed consent was received from participants or their substitute decision makers.

Recruitment and Identification of SARS-CoV-2 Infection

Participants were part of the COVID in Long-Term Care Study, a longitudinal observational study designed to examine SARS-CoV-2 infection and vaccination in a cohort of long-term care and retirement home residents in Ontario, Canada. Residents of these congregate care homes often have multiple comorbid conditions, including frailty [8, 30]. Participant recruitment began in March 2021. The current study is a secondary analysis of data and biospecimens from 114 participants with 3 monovalent ancestral variant messenger RNA (mRNA) vaccinations before January 2022 (ie, BNT162b2 [Pfizer-BioNTech Comirnaty] and/or mRNA-1273 [Moderna Spikevax]). Following Province of Ontario vaccination guidelines, most participants received their third mRNA vaccine dose ≥6 months after their second dose [31], and some participants received a fourth monovalent mRNA vaccine dose in 2022, ≥3 months after their third dose [32].

Participants either had no infections before or during the study or a SARS-CoV-2 infection confirmed using nasopharyngeal polymerase chain reaction (PCR) from 1 January to 8 February 2022. Infections were assumed to be caused by the Omicron BA.1 variant as it accounted for >98% of cases during this period by provincial genomic surveillance [33, 34]. To identify infections that were asymptomatic or not detected by PCR test, seroconversion was assessed by a validated anti-N antibody enzyme-linked immunosorbent assay (ELISA) protocol [35]. No participants had seroconverted before a positive PCR test. Demographics are summarized in Supplementary Tables 1–3.

Sample Collection

Venous blood was drawn in anticoagulant-free vacutainers for serum antibody assays or in heparin-coated vacutainers for blood T-cell activation assays, per published protocols [36]. Samples were collected approximately 3 months after third-dose vaccinations beginning on 16 November 2021 and from the same participants approximately 4 months later after no event (ie, neither vaccination nor infection), fourth ancestral monovalent mRNA vaccination, or SARS-CoV-2 infection, through 8 August 2022 (see Supplementary Figure 1 for study and sample collection timeline and Supplementary Figure 2 for participant populations by event and immune assay).

Anti-RBD IgA and IgG Titers

Recombinant coronavirus RBD proteins were produced using plasmids encoding mammalian RBD in Expi293 cells [37]. First, 96-well NUNC Maxisorp ELISA plates (Thermo Fisher Scientific; no. 44–2404-21) were coated with 50 mmol/L carbonate-bicarbonate buffer (pH 9.6) containing 2 μg/mL coronavirus RBD protein (ie, SARS-CoV-2, HCoV-NL63, HCoV-OC43, or HCoV-229E) and incubated overnight at 4°C. After blocking in phosphate-buffered saline with 0.05% Tween 20 and 5% skim milk (blocking buffer) for 1 hour at room temperature, participant serum samples were 2-fold serially diluted from a 1:20 dilution in blocking buffer. Plates were incubated for 1 hour at room temperature and washed 3 times with phosphate-buffered saline with 0.05% Tween 20. A secondary horseradish peroxidase–conjugated donkey anti–human IgG antibody (diluted 1:4000 for SARS-CoV-2 and 1:2000 for HCoV-NL63, HCoV-OC43, and HCoV-229E; BioLegend no. 410902) or goat anti–human IgA antibody (diluted 1:2000 for SARS-CoV-2 and 1:1000 for HCoV-NL63, HCoV-OC43, and HCoV-229E; BioLegend no. 411002) was added.

Samples were incubated and washed as before and then incubated with o-phenylenediamine dihydrochloride substrate (Sigma-Aldrich no. P9187) for 10 minutes (SARS-CoV-2) or 15 minutes (HCoV-NL63, HCoV-OC43, and HCoV-229E), before quenching with 3 mol/L hydrochloric acid (Sigma-Aldrich no. 320331). The optical density was measured at 490 nm using a Spectramax i3 Microplate Reader (Molecular Devices). IgG and IgA end-point titers were calculated as the reciprocal of the lowest dilution at which the optical density exceeded 3 SDs above the mean of control wells with only secondary antibody.

Microneutralization Titers

Vero E6 cells (ATCC CRL-1586) were incubated with participant serum and live ancestral (SB3) or Omicron BA.1 SARS-CoV-2, following established protocols to determine microneutralization titers (MNTs) [38]. Data were reported as geometric mean MNT at 50% (MNT_{50}), from below detection (MNT_{50}, 5; 1:10 dilution) to a maximum MNT_{50} of 1280.

Activation-Induced Marker T Cells

Antigen-specific T-cell responses against the SARS-CoV-2 complete M and N proteins and immunodominant regions of the S protein were measured using an established activation-induced marker assay and flow cytometry protocol [35]. Samples were analyzed using a CytoFLEX LX flow cytometer (Beckman Coulter) and FlowJo software (version 10.9.0; BD Life Sciences). Activated T cells were identified by their coexpression of CD25 and CD134 (OX40) on $CD4^+$ T cells and coexpression of CD69 and CD137 (4-1BB) on $CD8^+$ T cells. Data were reported as a proportion of total $CD4^+$ or $CD8^+$ T cells, after subtraction of an unstimulated medium-only control.

Statistical Analysis

Statistical analyses were performed using Prism (version 10; GraphPad Software) or RStudio (version 2024.09.0 + 375; R Core Team) software with packages from CRAN. Differences in immune measures were assessed using Wilcoxon matched-pairs signed rank tests for intraindividual assessments or Student *t* or Mann-Whitney *U* tests according to data normality. Differences in categorical group distributions were assessed by means of Fisher's exact test. Immune measure associations were assessed using Spearman rank correlation. Multiple logistic regression analyses were performed using the binomial family glm function (*glm* package) to examine the influence of coronavirus humoral immune responses, age, and sex on the outcome of SARS-CoV-2 Omicron BA.1 infection. Differences were considered significant at $P < .05$.

RESULTS

Humoral and T-cell responses to coronaviruses were examined in residents of long-term care and retirement homes in Ontario, Canada, after 3 doses of monovalent mRNA SARS-CoV-2 vaccines and after no event (neither vaccination or infection), monovalent vaccine dose 4, and/or Omicron BA.1 SARS-CoV-2 infection (Supplementary Figures 1 and 2). The mean participant age (SD) was 84.4 (10.1) years, and female participants comprised 67.5% of the cohort (77 of 114). The majority of residents received either 3 ancestral SARS-CoV-2 BNT162b2 (52.6% [60 of 114]) or mRNA-1273 (44.7% [51 of 114]) vaccines. Between sample collections, 76.3% of participants (87 of 114) had no SARS-CoV-2 infection, and 23.7% (27 of 114) had a PCR-confirmed SARS-CoV-2 infection. Further participant demographics are summarized in Supplementary Tables 1–3.

Association of Common Cold Coronavirus Antibody Titers With SARS-CoV-2 Antibody Titers

To examine the potential interactions of humoral immune responses to common cold coronaviruses and SARS-CoV-2, serum anti-RBD IgG and IgA titers of SARS-CoV-2 as well as common cold coronaviruses HCoV-NL63, HCoV-OC43, and HCoV-229E were measured approximately 3 months after third-dose SARS-CoV-2 mRNA vaccinations in SARS-CoV-2 infection–naive participants. The RBD is an immunodominant region within the S protein of SARS-CoV-2 and common cold coronaviruses, which is encoded within the SARS-CoV-2 mRNA vaccines, and >90% of SARS-CoV-2–uninfected adults have preexisting cross-reactive antibodies to the SARS-CoV-2 S RBD [39]. We assessed associations of anti-RBD IgG and IgA titers

(Figure 1). Significant positive correlations were observed between SARS-CoV-2 and common cold coronavirus anti-RBD IgG titers (HCoV-NL63, $P = .005$ and $r = 0.3288$; HCoV-OC43, $P < .001$ and $r = 0.5397$; HCoV-229E, $P = .02$ and $r = 0.2823$) but not anti-RBD IgA titers.

We next measured neutralizing antibodies against the ancestral and Omicron BA.1 variants of SARS-CoV-2 in the same residents and assessed their associations with common cold coronavirus anti-RBD IgG and IgA titers (Table 1 and Supplementary Figure 3). Neutralizing antibodies block viral entry into host cells and promote immune cell removal of virions, and they are considered to be protective against SARS-CoV-2 infection [40]. All participants had ancestral monovalent vaccinations, so it was expected that they would have high levels of neutralizing antibodies to the ancestral virus but not against the Omicron BA.1 variant. There were significant positive correlations between HCoV-OC43 anti-RBD IgG titers and ancestral ($P = .04$; $r = 0.2476$) and Omicron BA.1 ($P = .03$; $r = 0.3652$) SARS-CoV-2 neutralizing antibodies, whereas a negative correlation was noted between HCoV-NL63 anti-RBD IgA titers and ancestral SARS-CoV-2 neutralizing antibody titers ($P = .009$; $r = -0.3112$). There were no other significant associations. Therefore, our data suggested that there may be cross-reactive influences of common cold coronaviruses and SARS-CoV-2 on humoral immunity in vaccinated SARS-CoV-2 infection–naive residents of long-term care and retirement homes.

Increase in Common Cold Coronavirus Anti-RBD IgA Antibodies After SARS-CoV-2 Vaccination and Infection

The antigenic similarity of the major structural proteins of common cold and pandemic coronaviruses may lead to SARS-CoV-2 vaccination or infection boosting preexisting common cold coronavirus humoral immunity. To investigate this possibility, serum anti-RBD IgG and IgA titers of SARS-CoV-2 as well as common cold coronaviruses HCoV-NL63, HCoV-229E, and HCoV-OC43 were compared between participant samples collected 3 months after third monovalent SARS-CoV-2 mRNA vaccinations and samples from the same participants collected 4 months later after no vaccination or infection (no event), fourth-dose monovalent mRNA vaccination, or PCR-confirmed SARS-CoV-2 infection (Figure 2*A* and 2*B* and Supplementary Table 4).

As expected, participants had similar SARS-CoV-2 IgG and IgA antibody titers across sample collections in absence of SARS-CoV-2 vaccination or infection, though we noted increases in HCoV-OC43 anti-RBD IgA MNTs (median [range], increased from 240 [20–1280] to 320 [40–2560]; $P = .047$) and HCoV-229E anti-RBD IgA titers (from 160 [40–1280] to 640 [40–5120]; $P = .047$), as well as a decrease in HCoV-229E anti-RBD IgG titers (from 1280 [160–10 240] to 320 [160–2560]; $P = .03$). In participants vaccinated between collections, anti–SARS-CoV-2 anti-RBD IgG and IgA titers did not change significantly, nor did HCoV-NL63 IgG titers or HCoV-229E or HCoV-OC43 IgA titers, but anti-RBD IgA HCoV-NL63 titers increased (median [range], increased from 320 [20–2560] to 1280 [20–81 920]; $P < .001$), while there was a decrease in titers of both anti-RBD IgG HCoV-OC43 (decreased from 1280 [40–5120] to 320 [80–5120]; $P = .01$) and anti-RBD IgG HCoV-229E (from 320 [40–40 960] to 320 [40–5120]; $P = .04$).

After SARS-CoV-2 infection there was an increase in titers of anti–SARS-CoV-2 anti-RBD IgG (median [range], increased from 10 240 [80–327 680] to 327 680 [1280–2 621 440]; $P < .001$) and anti-RBD IgA (from 1280 [80–20 480] to 20 480 [80–1 310 720]; $P < .001$), but common cold coronavirus anti-RBD IgG titers remained similar (HCoV-NL63 and HCoV-229E) or decreased (HCoV-OC43) (decreased from 640 [40–20 480] to 320 [160–2560]; $P = .03$). Common cold coronavirus anti-RBD IgA antibodies remained similar (HCoV-NL63 and HCoV-OC43) or increased (HCoV-229E) after SARS-CoV-2 infection (median [range], increased from 160 [20–5120] to 320 [40–5120]; $P = .02$). These data imply that exposure to live SARS-CoV-2, as well as the SARS-CoV-2 S protein (via mRNA vaccination), may influence anti-RBD IgA titers of some common cold coronaviruses.

We next assessed SARS-CoV-2 neutralizing antibodies in the paired serum samples (Figure 2*C* and Supplementary Table 4). Participants with neither vaccination nor infection had similar ancestral and Omicron BA.1 variant neutralizing antibody titers between sample collections. SARS-CoV-2 infection during the Omicron BA.1–dominant period, but not vaccination, increased neutralizing antibody titers against both the ancestral variant (median [range], increased from 40 [5–320] to 320 [5–1280]; $P < .001$) and the Omicron BA.1 variant (increased from 10 [5–80] to 320 [5–1280]; $P < .001$). Therefore, Omicron BA.1 SARS-CoV-2 infection, but not vaccination, increased SARS-CoV-2 neutralizing antibody titers.

We also compared $CD4^+$ and $CD8^+$ T-cell responses to conserved SARS-CoV-2 M, N, and S proteins in blood collected from SARS-CoV-2 infection–naive participants approximately 3 months after the third vaccination and samples collected from the same participants after the fourth monovalent vaccination or after SARS-CoV-2 infection followed by the fourth vaccination (Figure 2*D* and Supplementary Tables 2 and 5). Consistent with previous findings, $CD4^+$ T-cell responses were more robust than $CD8^+$ T-cell responses [35, 36]. None of the participants had prior COVID-19, so the presence of M- and N-activated $CD4^+$ T cells (90% of participants [26 of 29]) as well as $CD8^+$ T cells (M, 45% [13 of 29]; N, 52% [15 of 29]) in the first samples was considered to be from cross-reactive memory T cells generated from a prior common cold coronavirus infection. All participants had received mRNA vaccines, so it was expected that most had S-activated $CD4^+$

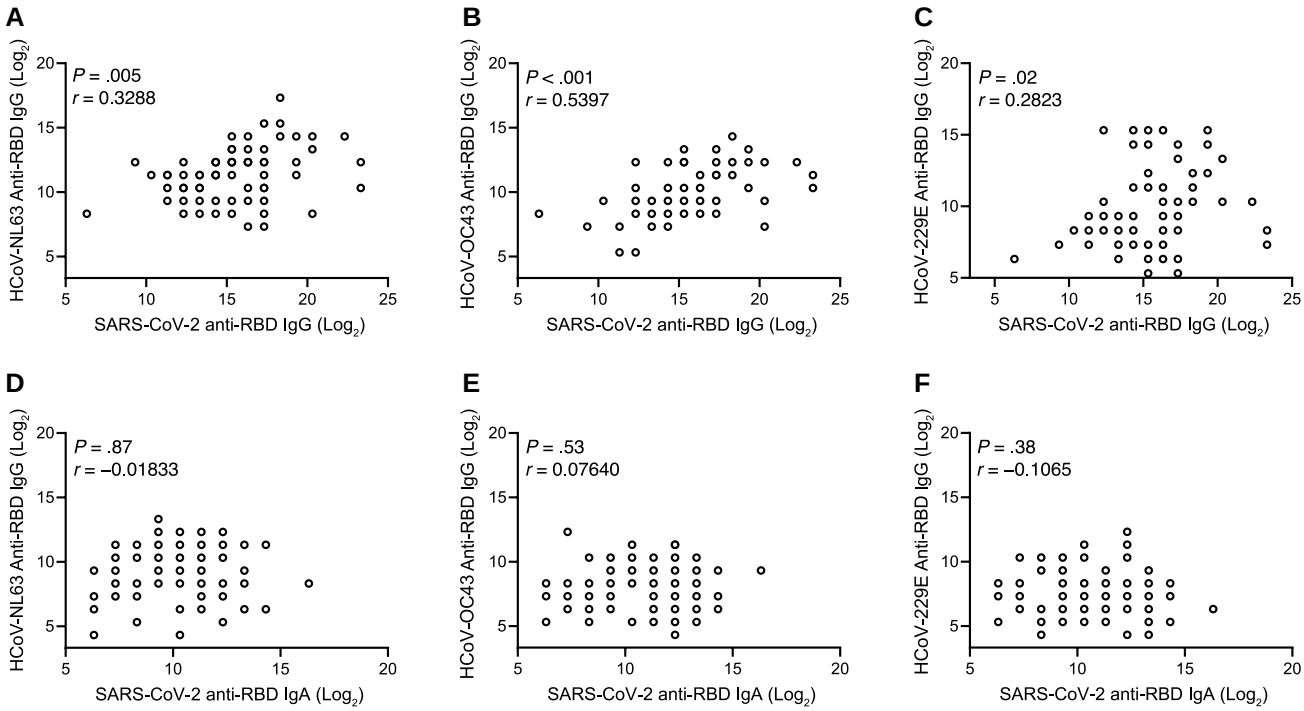

Figure 1. Common cold coronavirus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) anti–receptor-binding domain (RBD) immunoglobulin (Ig) G and IgA correlations in residents of long-term care and retirement homes. Serum anti-RBD IgG and IgA antibody titers to SARS-CoV-2 and common cold coronaviruses, human coronavirus (HCoV) NL63, HCoV-OC43, and HCoV-229E, were compared in participants after third-dose vaccinations. Displayed are the associations of SARS-CoV-2 titers with anti-RBD IgG titers for HCoV-NL63 (A), HCoV-OC43 (B), HCoV-229E (C) and anti-RBD IgA titers for HCoV-NL63 (D), HCoV-OC43 (E), and HCoV-229E (F). Each dot indicates a single assessment from an individual participant (n = 70). Statistical significance was assessed by means of Spearman rank correlation.

Table 1. Common Cold Coronavirus Anti–Receptor-Binding Domain Immunoglobulin G and A Titers and Severe Acute Respiratory Syndrome Coronavirus 2 Neutralizing Antibody Titer Correlations in Residents of Long-Term Care and Retirement Homes

		Ancestral SARS-CoV-2 MNT_{50}		Omicron BA.1 SARS-CoV-2 MNT_{50}	
Anti-RBD Antibody	Common Cold Coronavirus	*P* Value[a]	*r* Value	*P* Value[a]	*r* Value
IgG	HCoV-NL63	.28	0.1313	.64	0.08627
	HCoV-OC43	**.04**[b]	**0.2476**	**.03**[b]	**0.3652**
	HCoV-229E	.23	0.1475	.64	–0.08649
IgA	HCoV-NL63	**.009**[b]	**–0.3112**	.56	–0.1056
	HCoV-OC43	.052	–0.2352	.51	–0.1213
	HCoV-229E	.11	–0.1922	.80	0.04607

Bold text indicates statistically significant associations.

Abbreviations: Ig, immunoglobulin; HCoV, human coronavirus; MNT_{50}, geometric mean microneutralization at 50%; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Statistical significance was assessed by means of Spearman rank correlation (see Supplementary Figure 3).

[b]Significant at $P < .05$.

T-cell responses (97% [28 of 29]), though fewer (62% [18 of 29]) had S-activated $CD8^+$ T cells. There was a slight increase in M-reactive $CD4^+$ T cells after the fourth vaccination (median [range], increased from 0.11% [0.00%–5.00%] to 0.30% [0.00%–5.90%]; $P = .02$). After infection and vaccination, there was a tendency toward increased $CD4^+$ T-cell responses to M and N stimulation (both $P = .06$). In summary, additional vaccination and SARS-CoV-2 infection had limited effects on T-cell responses to conserved coronavirus proteins.

Similarity of Common Cold Coronavirus–Associated Immune Responses in SARS-CoV-2 Infection–Naive Participants Who Remain Uninfected and Who Acquire Omicron BA.1 SARS-CoV-2 Infection

We next considered whether differences in humoral and cellular immunity from prior common cold coronavirus exposure and SARS-CoV-2 mRNA vaccination may underlie development of SARS-CoV-2 infection during an Omicron BA.1–dominant period. This study included measures from residents of both long-term care and retirement facilities, which share many aspects of congregate living but may differ in resident independence in daily activities and associated support services and thus the likelihood of common cold coronavirus and SARS-CoV-2 exposures [8, 30]. We compared immune parameters between the 2 residence types and considered whether participants developed an Omicron BA.1 infection (Supplementary Table 3). There were significantly more infections ($P = .003$) in long-term care homes (33.3% [23 of 69]) than in retirement homes (8.9% [4 of 45]). Residents of long-

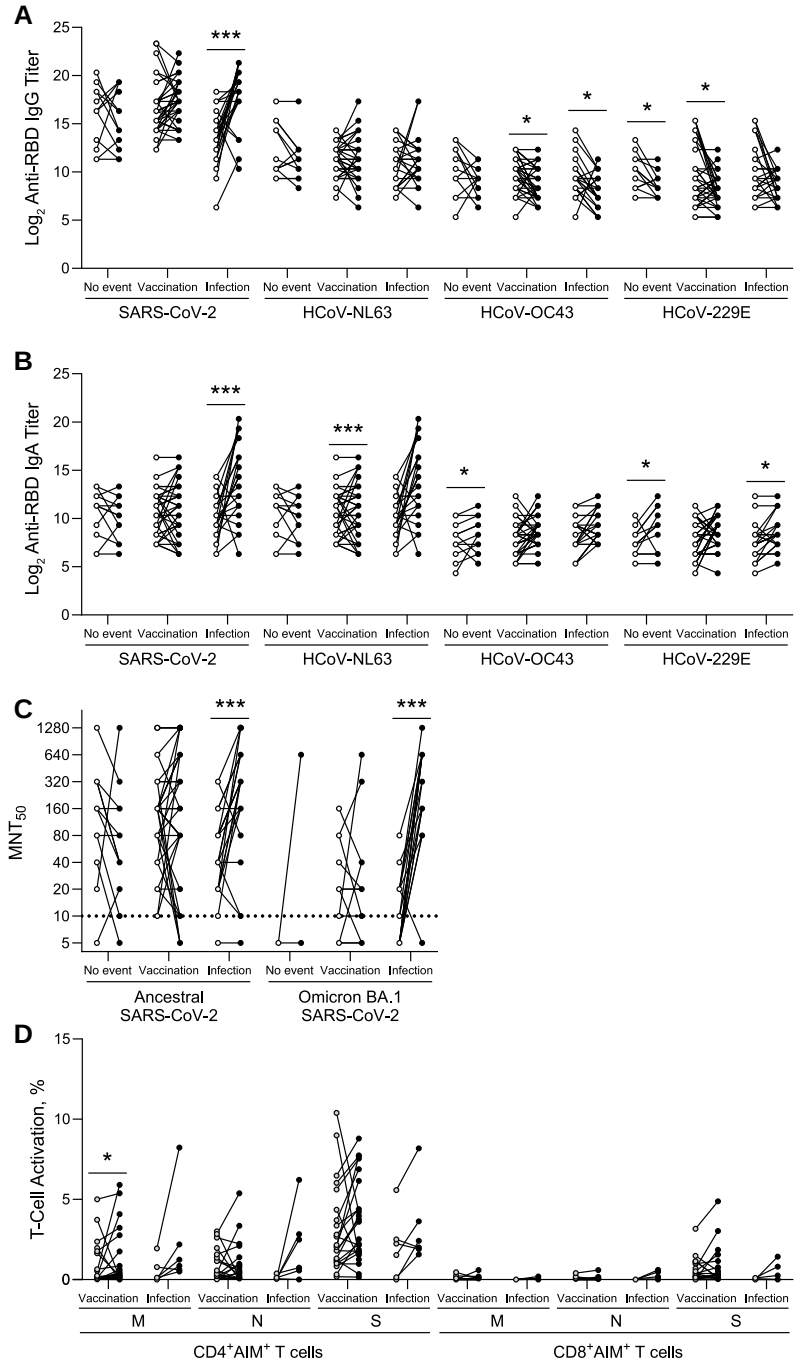

Figure 2. Coronavirus-associated humoral and cellular immunity after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination and infection in residents of long-term care and retirement homes. Anti–receptor-binding domain (RBD) immunoglobulin (Ig) G and IgA SARS-CoV-2 and seasonal coronavirus (human coronavirus [HCoV] NL63, HCoV-OC43 and HCoV-229E) antibodies were assessed by means of enzyme-linked immunosorbent assay, microneutralization assays were used to determine ancestral and Omicron BA.1 SARS-CoV-2 neutralizing antibody titers, and $CD4^+$ and $CD8^+$ T-cell responses to SARS-CoV-2 membrane (M), nucleocapsid (N), and spike (S) proteins were assessed by means of activation-induced marker (AIM) assay and flow cytometry. *A–C,* Comparisons of immune parameters after third-dose vaccinations in individuals with no prior SARS-CoV-2 infections followed by no event, fourth-dose vaccination (vaccination), or SARS-CoV-2 infection (infection). *D,* Comparisons of immune parameters after third-dose vaccinations in individuals with no prior SARS-CoV-2 infections followed by fourth-dose vaccination (vaccination) or with SARS-CoV-2 infection followed by fourth-dose vaccination (infection). *A,* Anti-RBD IgG titers to SARS-CoV-2, HCoV-NL63, HCoV-OC43, and HCoV-229E. *B,* Anti-RBD IgA titers to SARS-CoV-2, HCoV-NL63, HCoV-OC43, and HCoV-229E. *C,* Neutralizing antibodies to ancestral and Omicron BA.1 SARS-CoV-2. Abbreviation: MNT_{50}, geometric mean microneutralization at 50%. *D,* $CD4^+AIM^+$ and $CD8^+AIM^+$ T-cell responses (as proportions of total $CD4^+$ or $CD8^+$ T cells, respectively). Each dot represents a single assessment in an individual participant, with lines connecting intraindividual assessments; dotted line in *C* indicates the assay threshold. Post–third-dose samples are indicated by open circles, and post-event samples by solid circles. Statistical significance was assessed by means of intraindividual comparisons using the Wilcoxon matched-pairs signed rank test. *A, B,* n = 12 for no event, n = 35 for vaccination, and n = 23 for infection; *C,* n = 2 (Omicron BA.1) or n = 12 (ancestral) for no event; n = 12 or n = 35, respectively, for vaccination, and n = 18 or n = 23 for infection; *D,* n = 23 for vaccination and n = 6 for infection. See Supplementary Tables 4 and 5 for summary statistics. $^*P < .05$; $^{***}P < .001$.

term care homes had lower anti–SARS-CoV-2 RBD IgG titers than retirement home residents (median [range], 20 480 [80–1 310 720] for long-term care and 81 920 [2560–1 0485 760] for retirement homes; $P < .001$), lower neutralization of ancestral SARS-CoV-2 virus (80 [5–1280] and 160 [5–1280], respectively; $P = .01$), and lower anti-RBD IgG titers to HCoV-NL63 (2560 [160–163 840] and 2560 [320–40 960]; $P = .03$) and HCoV-OC43 (640 [40–2560] and 1280 [40–20 480]; $P < .001$).

To explore whether common cold coronavirus humoral immunity could be associated with SARS-CoV-2 infection, we compared common cold coronavirus and SARS-CoV-2 measures of humoral and T-cell immunity in samples collected before SARS-CoV-2 infections with contemporaneous samples from participants who were not infected. We initially assessed anti-RBD IgG and IgA titers (n = 47 for no infection and n = 23 for infection) (Figure 3*A* and 3*B* and Supplementary Table 6). Anti-RBD IgG titers against SARS-CoV-2 were lower in participants who later developed COVID-19 than in those who did not (median [range], 81 920 [2560–1 0485 760] for no infection vs 10 240 [80–327 680] for infection; $P < .001$), but anti-RBD IgG and IgA titers against all common cold coronaviruses were similar among participants, irrespective of future infection. We also assessed titers of SARS-CoV-2 neutralizing antibodies (ancestral, n = 47 for no infection and n = 22 for infection; Omicron BA.1, n = 24 and n = 18, respectively) (Figure 3*C* and Supplementary Table 6).

Ancestral SARS-CoV-2 neutralizing antibody titers were significantly lower in participants with subsequent SARS-CoV-2 infections than in uninfected participants (median [range], 40 [5–320] vs 160 [5–1280], respectively: $P = .002$). Participants had not yet received Omicron-specific vaccines (and had no prior SARS-CoV-2 infections), so low Omicron BA.1 neutralizing antibody titers were observed and did not differ between uninfected and future infection groups. In addition, measurements of $CD4^+$ and $CD8^+$ T-cell activation in response to SARS-CoV-2 M, N, and S proteins were similar between participant groups (n = 42 for no infection and n = 8 for infection; Figure 3*D*), suggesting that cross-reactive T cells did not modify the likelihood of future SARS-CoV-2 infection.

To further examine the influence of preexisting coronavirus humoral immune responses on future SARS-CoV-2 Omicron BA.1 infection outcome, we used multiple logistic regression and also considered potential modifying effects of sex and age (Supplementary Table 7 and Figure 3*E*). Individuals with higher MNTs against ancestral SARS-CoV-2 had lower odds of infection (odds ratio, 0.994 [95% confidence interval, .987–.999]; $P = .04$), but common cold coronavirus IgG and IgA titers were not associated with future infection. Therefore, we did not find evidence of differences in preexisting common cold coronavirus humoral immunity in participants with subsequent Omicron BA.1 SARS-CoV-2 infections.

DISCUSSION

In this study, we examined potential influences of prior common cold coronavirus exposure on SARS-CoV-2 vaccination and infection responses and Omicron BA.1 variant infection in vaccinated but infection-naive residents of long-term care and retirement homes. We found that titers of anti-RBD IgG and IgA from the common cold coronaviruses HCoV-OC43, HCoV-NL63, and HCoV-229E were not associated with SARS-CoV-2 infection risk. Other studies have reported similar findings across the life course. Common cold coronavirus infections are frequent in children, so it was hypothesized that cross-reactive immunity might be protective [41], especially as before the Omicron era, SARS-CoV-2 infections in children were shorter, less severe, and less frequent [42], but subsequent studies did not find that common cold coronavirus antibodies were protective in children [24, 43].

As common cold coronavirus antibody titers increase into young adulthood, when the risk of SARS-CoV-2 infection is highest, it was not unexpected to find that common cold coronavirus neutralizing antibodies were not cross-protective against SARS-CoV-2 in adolescents or adults [44, 45]. Levels of common cold coronavirus anti-N antibodies have also been reported to be similar among uninfected and infected adults early in infection [46], and similar levels of anti-RBD IgG common cold coronavirus antibodies have been observed in infected and uninfected community-dwelling adults at the point of SARS-CoV-2 exposure [47].

Cross-reactive coronavirus T cells have been reported to decrease with age, whether in unexposed, convalescent, or vaccinated individuals [16]. However, we detected $CD4^+$ and $CD8^+$ T cells that were responsive to SARS-CoV-2 N and M proteins in our SARS-CoV-2 infection–naive older adults, consistent with reports that T-cell responses to common cold coronaviruses are cross-reactive with SARS-CoV-2 [14, 15] and SARS-CoV-2 S protein encoded in mRNA vaccines [16]. Levels of N-, M-, and S-reactive $CD4^+$ and $CD8^+$ T cells did not differ between participants who subsequently did and those who did not develop Omicron BA.1 infections. Our data therefore extend prior findings and suggest that the high rate of common cold coronavirus infections in older adults living in retirement or long-term care communities does not significantly contribute to susceptibility to COVID-19. Rather, anti-RBD IgG SARS-CoV-2 titers and neutralizing antibodies against ancestral SARS-CoV-2 were lower in participants who developed Omicron BA.1 infections, most of whom were residents of long-term care homes.

While differences in preexisting common cold coronavirus humoral and cellular immunity did not appear to be associated with SARS-CoV-2 infection, our observations of increased common cold coronavirus HCoV-NL63 IgA antibody titers and M-reactive $CD4^+$ T cells after vaccination,

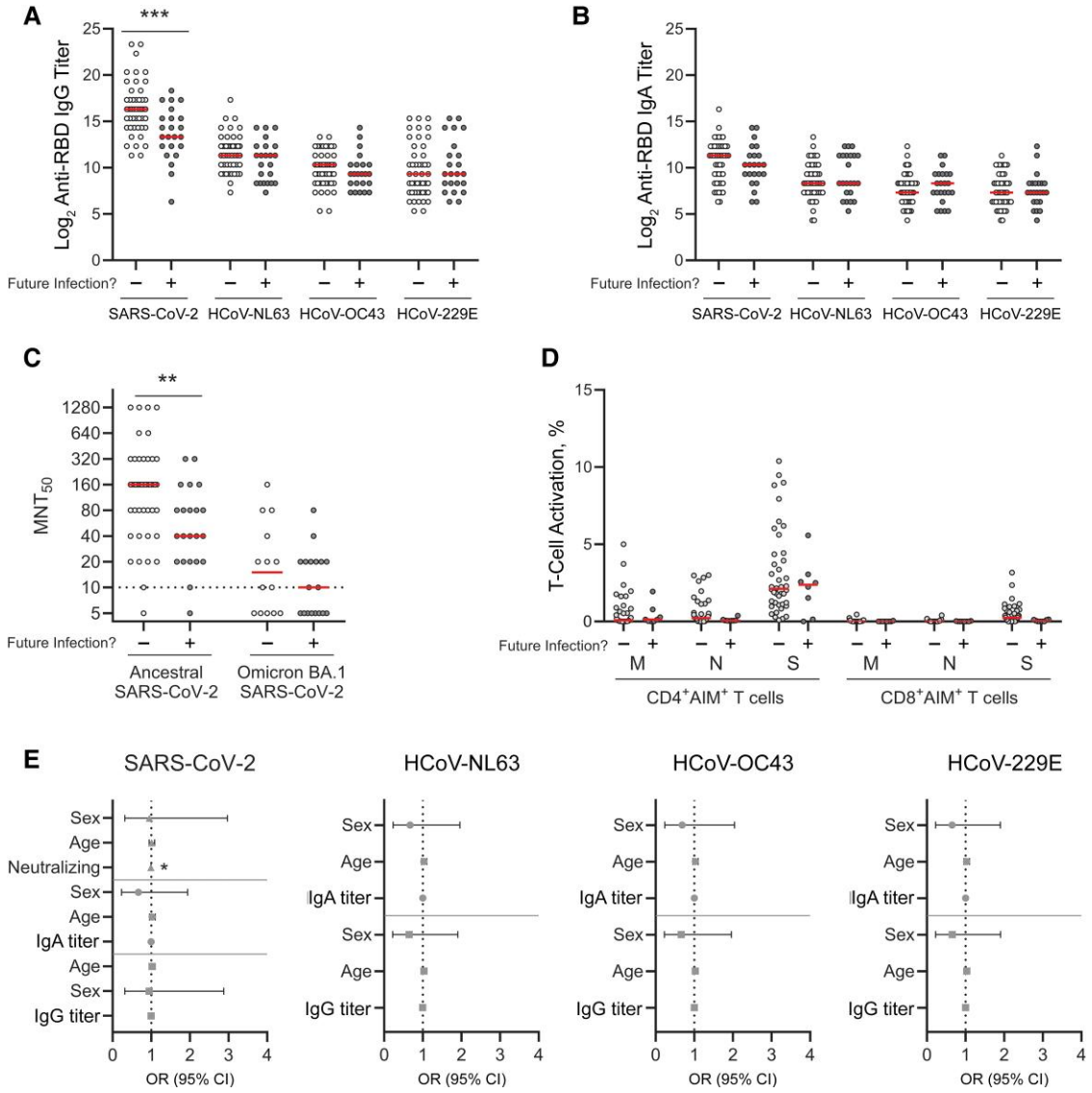

Figure 3. Coronavirus-associated humoral and cellular immunity in long-term care and retirement home residents with no later infection or with future Omicron BA.1 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Assays were performed after third-dose vaccinations in participants with no prior SARS-CoV-2 infection history, and data were stratified according to whether participants went on to have no infection (–) or future Omicron BA.1 SARS-CoV-2 infection (+). Anti–receptor-binding domain (RBD) immunoglobulin (Ig) G and IgA SARS-CoV-2 and common cold coronavirus—human coronavirus (HCoV) NL63, HCoV-OC43, and HCoV-229E—antibodies were assessed with enzyme-linked immunosorbent assay, microneutralization assays were used to determine ancestral and Omicron BA.1 SARS-CoV-2 neutralizing antibody titers, and $CD4^+$ and $CD8^+$ T-cell responses to SARS-CoV-2 membrane (M), nucleocapsid (N), and spike (S) proteins were assessed using activation-induced marker (AIM) assay and flow cytometry. *A*, Anti-RBD IgG coronavirus titers. *B*, Anti-RBD IgA coronavirus titers. *C*, Neutralizing antibodies to ancestral and Omicron BA.1 SARS-CoV-2. Abbreviation: MNT_{50}, geometric mean microneutralization at 50%. *D*, $CD4^+AIM^+$ and $CD8^+AIM^+$ T-cell responses (as a proportion of total $CD4^+$ or $CD8^+$ T cells, respectively). *E*, Multiple logistic regression models to assess the effects of SARS-CoV-2 and common cold coronavirus antibody titers, as well as sex (male vs female) and age, on the odds of SARS-CoV-2 infection. *A–D*, Dots represent single assessments from individual participants; open circles, individuals without future infection; shaded circles, individuals with future infection; red bars, medians; and dotted line in *C*, assay threshold. Statistical significance was assessed using the Mann-Whitney *U* test to compare no infection and future infection groups. *A, B*, n = 47 for no infection and n = 23 for infection; *C*, n = 14 (Omicron BA.1) or n = 47 (ancestral) for no infection and n = 18 or n = 22, respectively, for infection; *D*, n = 42 for no infection and n = 8 for infection. *E*, Point estimates of the odds ratios (ORs) with 95% confidence intervals (CIs) are depicted for microneutralization titers (*triangles*), IgA titers (*circles*), and IgG titers (*squares*). See Supplementary Tables 6 and 7 for summary statistics. $^{**}P < .01$; $^{***}P < .001$.

and HCoV-229E IgA titers after infection, are suggestive of "back-boosting". This term refers to the increase of recall responses to conserved epitopes between common cold coronaviruses and SARS-CoV-2 (or its S protein in vaccines). Similar observations have been made after SARS-CoV-2 vaccination and particularly infection in younger community-dwelling adults [16, 17, 27, 48]. This effect may also explain observations of positive correlations between anti-RBD IgG titers of common cold coronaviruses and SARS-CoV-2 anti-RBD IgG titers and neutralizing antibodies in our vaccinated

cohort, despite no associations with future Omicron BA.1 infection.

Correlations between common cold coronavirus and SARS-CoV-2 anti–S IgG reactivity were similarly observed in an uninfected community-dwelling cohort of children, adolescents, and adults [20]. Unexpectedly, we observed increased anti-RBD IgA HCoV-OC43 and HCoV-229E titers in the absence of SARS-CoV-2 vaccination or infection, which could be due to unidentified common cold coronavirus infections. As waning of common cold coronavirus immunity occurs within months [5], the reductions in some common cold coronavirus anti-RBD IgG titers observed between collections likely reflected the increased time since the last non–SARS-CoV-2 coronavirus infection.

Early in the COVID-19 pandemic it was observed that patients with severe or fatal disease had higher levels of anti–SARS-CoV-2 IgA antibodies on hospital admission [49, 50]. IgA antibodies generally do not develop early in infection (most patients were admitted within 5 days after symptom onset), so it was predicted that elevated levels of IgA were due to amplification of preexisting cross-reactive immunity. It was also reported that preexisting HCoV-OC43 antibodies contributed to COVID-19 severity [25, 28]. In contrast, recent common cold coronavirus infections have been implicated in reducing the severity of SARS-CoV-2 infection [26]. Accordingly, preexisting high antibody reactivity to common cold coronaviruses was associated with decreased susceptibility to SARS-CoV-2 infection, as well as lower likelihood of hospitalization from COVID-19 [23].

In the current study, we observed increases in HCoV-229E anti-RBD IgA titers after infection and found positive associations between HCoV-OC43 anti-RBD IgG titers and SARS-CoV-2 neutralizing antibodies in infection-naive participants. We assessed nonhospitalized participants only to ensue collection of paired samples (ie, before and after infection) and did not collect symptom data, so we cannot comment on whether preexisting common cold coronavirus immunity affected infection severity. We did not find associations of common cold coronavirus antibody titers with future SARS-CoV-2 infection, which could be an effect of SARS-CoV-2 vaccination. After vaccination, in contrast, anti–SARS-CoV-2 serum IgA was identified as a correlate of protection against pre-Omicron variants [51]. In our vaccinated cohort, we found similar SARS-CoV-2 and common cold coronavirus anti-RBD IgA titers in participants irrespective of whether they developed Omicron BA.1 infection. It remains to be determined whether this is because serum IgA is not a correlate of protection for Omicron variants or because it is not a correlate of protection in older adults.

Our observations that SARS-CoV-2 vaccination or infection increased levels of common cold coronavirus anti-RBD IgA titers may also be an indication that pandemic coronaviruses can induce broader shifts in viral ecology, which could affect future common cold coronavirus infection patterns. Before the COVID-19 pandemic, the rate of infection with common cold coronaviruses was constant across adulthood (ie, the frequency of infection did not decrease with increased exposure) [52], and reinfections occurred weeks to months apart [7], implying that there was limited cross-protection due to preexisting immunity from common cold coronavirus infection. However, both unvaccinated and vaccinated COVID-19 survivors have cross-reactive T cells against common cold coronaviruses [16, 53, 54], and SARS-CoV-2 infection has been reported to reduce the incidence of symptomatic common cold coronavirus infections [55]. While we did not observe a significant increase in SARS-CoV-2 M-, N-, and S-specific T cells after infection in our vaccinated cohort, this could be indicative of less robust T-cell responses to SARS-CoV-2 infection in older adults [29]. Therefore, SARS-CoV-2 vaccination or infection may promote resilience to future common cold coronavirus infections and reduce their severity.

A major strength of this study was that PCR testing rates, including symptomatic, surveillance, and contact testing rates, were high during the observation period due to provincial government mandates, so we were able to accurately assess whether participants had COVID-19. Limitations of our study are that we studied early Omicron BA.1 infections only in a modest sample size of participants with 3 ancestral monovalent mRNA vaccines, we were unable to exclude the possibility of common cold coronavirus infections during the study period, and we assessed immune responses only after a fourth ancestral monovalent vaccination (ie, not after bivalent or Omicron-specific vaccination or in unvaccinated participants). Despite these caveats, the evidence presented herein implies that preexisting immunity from common cold coronavirus infection is influenced by SARS-CoV-2 vaccination and infection yet is not significantly associated with SARS-CoV-2 infection in residents of long-term care and retirement homes.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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