Public Health Ontario | Santé publique Ontario

SYNTHESIS

COVID-19 Correlates of Protection – What We Know So Far

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Introduction

Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Please find additional details including eligibility criteria, study characteristics and key results for each included study in the Appendix to COVID-19 Correlates of Protection – What We Know So Far.

"What We Know So Far" documents provide a rapid review of the evidence related to a specific aspect or emerging issue related to COVID-19. This rapid review summarizes evidence related to potential correlates of protection (CoPs) that may indicate protection from SARS-CoV-2 infection among people with vaccine or infection-induced immune markers.

Key Findings

- A CoP is an immune marker associated with protection from an infectious agent. In our rapid review, no studies identified a humoral or cellular immune marker that represented an absolute CoP against SARS-CoV-2-infection (prevents an infection at a certain threshold); however, studies identified several potential immune markers representing relative CoPs (levels of response variably correlated with protection).

- Humoral immune markers identified as potential relative CoPs were serum concentrations and titers of anti-spike (S) protein/anti-receptor-binding domain (RBD) immunoglobulin G (IgG), anti-S/anti-RBD IgA and neutralizing antibodies (NAbs). Given the high heterogeneity in immune marker levels and association with protection from infection, providing specific immune marker thresholds or even protective ranges is not appropriate.

- Studies investigating cellular immune markers as CoPs were less common, with some noting the potential of SARS-CoV-2 specific T cells as CoPs against SARS-CoV-2 infection.

- Further research, including randomized controlled trials (RCTs) for vaccine effectiveness (VE) and longitudinal cohort/case-control studies, will refine our understanding of potential immune marker CoPs against SARS-CoV-2. While out of scope for this review, CoPs for other endpoints (e.g., severe disease, need for intensive care) likely differ from those examined in this review, namely polymerase chain reaction (PCR)-confirmed asymptomatic or symptomatic infection. Efforts to identify a relative CoP have improved our understanding of the immune response against SARS-CoV-2; however, these potential relative CoPs have limited public health and clinical utility as they lack readily quantified and actionable thresholds.

Abbreviations

aHR: adjusted hazard ratio

aOR: adjusted odds ratio

aRR: adjusted risk ratio

AU: arbitrary units

BAU: binding antibody units

CI: confidence interval

CoP: correlate of protection

COVID-19: coronavirus disease 2019

ct: cycle threshold

ED_{50}: effective dose 50%

HCW: healthcare workers

HR: hazard ratio

IC_{50}: 50% inhibitory concentration

IFN-γ: interferon gamma

IgA: immunoglobulin A

IgG: immunoglobulin G

IgM: immunoglobulin M

IL-2: interleukin-2

IU: international unit

LTCH: long-term care home

LV-N: live virus neutralization

ml: milliliter

n: sample size

N: Nucleocapsid protein

NAb: neutralization antibody

NT_{50}: neutralization titer 50

OECD: Organization for Economic Co-operation and Development

OR: odds ratio

p: p-value

PBMCs: peripheral blood mononuclear cells

PCR: polymerase chain reaction

PRNT: plaque reduction neutralization test

PV-N: pseudovirus neutralization

Q: quartile

qRT-PCR: quantitative reverse transcription polymerase chain reaction

RAT: rapid antigen test

RBD: receptor-binding domain protein

RCT: randomized controlled trial

RR: relative risk

RT-PCR: reverse transcription polymerase chain reaction

S: spike protein

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SD: standard deviation

sfu: spot-forming unit

sVNT: surrogate virus neutralization test

$TCID_{50}$: median tissue culture infectious dose

U: unit

UK: United Kingdom

US: United States

VE: vaccine effectiveness

VOC: variant of concern

WT: wild-type virus

R_S: Spearman's rank correlations coefficient

µL: microlite

Background

Immune protection from SARS-CoV-2 infection can be infection-induced, vaccine-induced or a combination of both (hybrid immunity) and decreases the occurrence of reinfections and/or breakthrough infections.[1] A CoP is an immune marker associated with protection from an infectious agent when it is present at a certain threshold.[2,3] The need for a SARS-CoV-2-specific CoP has been ongoing since the beginning of the pandemic, particularly immune marker CoPs for COVID-19 vaccines.[4] When established, an immune marker CoP (concentrations, titers or simply, levels) facilitates our understanding of immunity and durability of immunity in populations (e.g., population-level serosurveys).[2] Further, a CoP could help inform policies on vaccine schedules and public health measures in response to new variants of concern (VOCs), in order to maintain manageable levels of SARS-CoV-2 transmission and infection.[5] A readily quantified CoP for SARS-CoV-2 may allow healthcare providers to identify when patients with immune-compromising conditions or other risk factors for severe disease should receive a booster vaccine (e.g., when antibody or NAb levels drop below a protective threshold). Additionally, if immunobridging studies identify sufficient levels of an immune marker CoP, then the CoP could represent a primary endpoint for vaccine approvals.[3]

Different types of immune markers can serve as CoPs, including humoral or innate markers and cellular or adaptive markers.[6,7] CoPs may be directly responsible for protection from infection, such as mechanistic or functional CoPs; e.g., mucosal anti-S/anti-RBD-specific IgA NAbs bind to SARS-CoV-2 and prevent entry into cells via angiotensin-converting enzyme 2 (ACE2) receptors.[8,9] In contrast, CoPs may act as proxy measures for the true correlate, such as non-mechanistic CoPs that correlate to mechanistic CoPs (e.g., serum anti-S IgG levels).[6,10] CoPs may be absolute, meaning a given CoP provides complete protection from infection at a certain threshold. Alternatively, CoPs can be relative, meaning higher levels of the marker are associated with increased protection from infection or protect a proportion of the population. Cellular immunity also plays an important role in identifying CoPs, particularly T cells and antigen-specific memory B cells; however, studies targeting T cells (e.g., cluster of differentiation 4 glycoprotein T cells [$CD4^+$], $CD8^+$) are not widely used for CoP studies, largely due to the assay complexity and costs, leading to their limited use in high throughput clinical and public health laboratories.[11-14] Research into SARS-CoV-2 immunology remains in the early stages and is dominated by small, uncontrolled observational studies of immune responses.

Gilbert et al. (2022a) identified five sources of evidence that support a given immune marker CoP: 1) observational studies correlating immune marker levels and clinical outcomes; 2) vaccine challenge studies in human trials and animal models; 3) measuring mechanistic causation by altering the immune marker; 4) RCTs assessing VE and immune marker levels among study participants; and 5) meta-analyses of multiple RCTs that correlate mean immune marker levels and VE.[3] While not abundant early in a pathogen's emergence due to logistical challenges and required expertise, RCTs and meta-analyses of RCTs offer the highest quality of evidence for assessing potential CoPs. Observational cohort and case-control studies offer a more immediate and feasible methodology for gaining evidence for immune markers as CoPs against SARS-CoV-2 infection.

This rapid review builds on the systematic review by Perry et al. (2022),[15] identifying and synthesizing the new evidence on potential immune marker CoPs published since January 1, 2022. This review will concentrate on answering the research question: **Are there humoral and/or cellular CoPs against SARS-CoV-2 infection?**

Methods

PHO Library Services conducted searches of the indexed literature in Medline, Embase and Global Health from January 1, 2022 to January 11, 2023. These databases also captured multiple preprint studies. Preprints are research papers that have not undergone peer review but are made publicly available to provide the latest data; these provide important evidence in the context of the evolving COVID-19 pandemic. However, lack of peer review is a limitation to keep in mind when interpreting results. We conducted additional targeted searching in the preprint server medRxiv and PubMed on February 22, 2023 for relevant articles. Formal critical appraisal of published and preprint COVID-19 literature was out of scope for this rapid review. Search strategies are available on request.

We included English language full text systematic reviews or primary studies published after December 31, 2021 that investigated immune markers that are potential CoPs against SARS-CoV-2 infection. A key requirement for inclusion in this rapid review was reporting of specific SARS-CoV-2 infection outcomes (i.e., breakthrough infection or reinfection). Please see the Appendix document for the full list of all inclusion and exclusion criteria.

We performed single-author screening, with checks from a second author for any records where eligibility was uncertain. Key data extracted from eligible studies included: study period and jurisdiction; VOC-context; population details (sample size, sex, age, race, immune-compromising conditions); vaccination regimens; previous infection detection; immunity marker quantification and sampling; breakthrough/reinfection detection; analyses; primary endpoints and outcome measures. For data extraction, we conducted single-author extraction with a double check by a second author. Meta-analysis was outside the scope of this rapid review, and we synthesized results narratively.

Findings

Overview of Results

We screened 3,177 records from the database searches for eligibility. After screening all records, 32 studies were included in this rapid review. Please see the Appendix document for detailed characteristics of each included study. We included three RCTs,[16-18] 26 observational studies (cohort, case-control),[19-44] and three modelling studies (included meta-analyses and cohorts).[45-47] In an exception to the eligibility criteria, we included two RCTs that used two vaccines approved for use in Canada but not widely used in Ontario, namely Janssen Jcovden COVID-19 vaccine (viral-vector based, 1 dose) and Novavax Nuvaxovid COVID-19 vaccine (protein-based, 2 doses plus booster).[16,17] These two RCTs were included due to the lack of large RCT studies overall and they provided useful evidence related to CoPs. The other included RCT examined the more commonly administered Moderna Spikevax COVID-19 vaccine.[48] COVID-19 vaccines will be referred to by their manufacturer brand name through the remainder of this report (i.e., Spikevax, Comirnaty, Jcovden, Nuvaxovid and Vaxzevria). Six studies were preprint articles and as these have not undergone peer review, results should be interpreted with caution.[26,29,34,36,40,43]

Here, we provide an overview of study and population characteristics for literature included in this review:

- **Study size**: 37.5% (12/32) of studies included less than 500 participants,[20,21,23,24,27,28,30,35,37,41,46,47] 18.75% (6/32) included between 500 and 999 participants[16,17,29,31,34,36] and 43.75% (14/32) included at least 1,000 participants.[18,19,22,25,26,32,33,38-40,42-45]

- **Participant selection**: Two of 32 studies (6.3%) selected participants at random from the general population (e.g., using address lists).[43,44] Three RCT studies (9.4%) selected participants randomly for an **immune** marker sub-study from a larger VE trial cohort,[16-18] and three observational studies (9.4%) invited participants from other larger cohorts (e.g., COVIDENCE UK).[25,34,42] Fifteen of 32 studies (46.9%) used convenience samples to recruit participants from healthcare or long-term care home (LTCH) settings.[20-24,27-30,32,33,36-38,41] Two studies (6.3%) used a combination of random selection (i.e., using address lists) from the general population as well as other recruitment methods such as social media advertisements or invitations from general practitioners to participate.[19,26] Four studies (12.5%) recruited participants using print, electronic or social media advertisements, newsletters or invitations at vaccination appointments.[31,35,40,46] One study (3.2%) used de-identified laboratory samples from multiple United States (US) states, [39] and finally two studies (6.3%) used data from multiple studies in modelling/meta-analyses and did not report the selection methods for the data.[45,47]

- **Age**: Half of included studies (16 of 32) included adults with median/mean ages >50 years.[16,18,19,22-26,28,35,37,38,41-44] Three of these studies included exclusively older adults residing in LTCHs with median/mean ages ≥80 years.[23,24,41] For the remaining 16 studies, 13 included participants with mean/median ages ≤50 years,[17,20,21,27,29,30,32-34,36,39,40,46] seven of these 13 studies included exclusively HCWs[20,21,27,29,30,32,33] and one study included data from any age group including children (≤18 years).[39] Three studies did not report the ages of participants.[31,45,47]

- **Sex/gender**: Female participants comprised a greater proportion of participants in most studies; 26 of 32 studies (81.3%) had populations that were >50% female. The majority of studies (22 of32, 68.8%) reported the sex (i.e., male or female) of participants.[16-20,22-25,28,31-40,43,44] Some studies interchanged the terms sex/gender, and female/woman. Three studies (9.4%) included "other" in addition to the sex/gender options woman/man or male/female.[21,26,29]

- **Race**: Eleven of 32 studies (34.3%) reported the race/ethnicity of participants;[16-19,21,25,31,38,42-44] the majority of these 11 studies (63.6%) included >90% White participants.[19,25,31,38,42-44] The other 21 studies did not report the race of participants.

- **Immune-compromising conditions**: Nine of 32 studies (28.1%) excluded participants with immune-compromising conditions,[16-18,28-30,34,35,41] six studies (18.8%) reported the proportion of included participants with immune-compromising conditions (range: 0% to 30.2%)[19,21,25,26,31,42] and the remaining studies did not report on inclusion of patients with immune-compromising conditions.

- **Setting**: Nearly half of study settings were healthcare facilities or LTCHs, including patients, residents and/or healthcare workers (HCWs) as participants (15 of 32 studies, 46.9%);[20-24,27-30,32,33,36-38,41] nine of 32 studies (28.1%) included exclusively HCWs.[20-22,27-30,32,33] Fourteen of 32 studies (43.8%) used community volunteers and invited members of the public.[16-19,25,26,31,34,35,39,40,42-44]

- **VOC context**: Most studies (20 of 32, 62.5%) examined potential immune marker CoPs and infection risks in study periods that included Omicron circulation,[20,22,24-29,31-36,38,40-44,47] nine study periods (28.1%) included Delta circulation but not Omicron,[16-19,30,39,44-46] and three study periods (9.4%) preceded Delta circulation.[21,23,37]

- **Type of immunity**: Twelve of 32 studies (37.5%) included participants with vaccine-induced immunity (i.e., 100% of participants were vaccinated and those with previous infection were excluded from study participation).[16-19,22,29,30,32,35,42,44,46] Fifteen of 32 studies (46.9%) examined participants with vaccine-induced or hybrid immunity (i.e., 100% of participants were vaccinated and variable proportions of participants had a previous infection).[20,24-28,33,36-38,40,41,43,45,47] Four of 32 studies (12.5%) included participants with any mix of immunity (i.e., less than 100% were vaccinated, variable proportions had a previous infection).[23,31,34,39] Finally, one study (3.1%) specifically investigated infection-induced immunity (i.e., 0% of participants were vaccinated and 100% had a previous infection).[21]

- **Vaccines**: Most studies (20 of 32, 62.5%) included participants who received the three vaccines commonly used in Ontario (Comirnaty, Spikevax, Vaxzevria) for the primary series and/or booster doses;[19,20,24-26,28,31,32,34-38,40,42-47] seven studies (21.9%) included participants vaccinated with Comirnaty only.[22,23,27,29,30,33,41] One study did not report the vaccine status of participants,[39] one included unvaccinated participants only,[21] and three RCTs were for Spikevax, Jcovden and Nuvaxovid.[16-18] Vaccine dosage regimens varied widely among studies, from a single vaccine dose to four or five doses (primary series and boosters).

- **CoPs**: All 32 studies investigated humoral immune markers as CoPs. The most commonly studied humoral immune markers were anti-S/anti-RBD IgG (20 of 32 studies, 62.5%),[16-18,22-27,29,30,32,33,36-38,40,43,44,46] followed by NAbs (15 of 32 studies, 46.9%),[16-18,20,21,24,27,30-32,35,36,41,45,47] anti-S total antibodies (five of 32 studies, 15.6%),[19,21,31,39,42] anti-S/anti-RBD IgA (three of 32 studies, 9.4%),[28,29,37] anti-RBD total antibodies (two of 32 studies, 6.3%)[34,41] and anti-nucleocapsid (N) antibodies (one of 32 studies).[21] Two studies investigated cellular immune markers (SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cells) and humoral immune markers as CoPs.[20,41]

- **Outcome measures**: Key results were reported as hazard ratios (HRs), odds ratios (ORs) and relative risks (RRs) in most studies (18 of 32 studies, 56.3%),[16-19,21,22,25,26,28,29,31-34,36,39-41] while the remainder used various other metrics, such as correlations, mean/median differences and positive predictive values (PPVs)/negative predictive values (NPVs).

In the following sections, we briefly describe high-level findings for potential humoral and cellular immune marker CoPs, further organized by specific immune marker. Please see the Appendix document for characteristics of each study (e.g., jurisdiction, study period, VOC context, population demographics, vaccination and previous infection status, immune markers examined, outcomes measured and analyses) and for key results extracted from each study. Unless otherwise noted, all immune marker measures reported here are within the context of vaccine-induced or hybrid immunity.

Updates since Perry et al. (2022)

Perry et al. (2022) searched the scientific literature up to December 31, 2021 and identified 25 studies related to potential humoral CoPs.[15] We include an additional 32 studies in this rapid review, showing a rapid increase of investigations into potential immune marker CoPs. Perry et al. (2022) did not identify any studies investigating Omicron-specific CoPs; however, we identified 20 studies that included estimates of immune marker CoPs during Omicron circulation.

Perry et al. (2022) included 14 descriptive papers describing immune responses in re-infection cases; our rapid review included 32 studies with similar study designs. Perry et al. (2022) included 11 studies that investigated immune responses among breakthrough infections or used statistical modelling to estimate relationships between antibodies and VE. All except one of the studies in this review examined breakthrough infections following vaccination. Two studies examined quantitative CoPs in Perry et al. (2022); however, in our review, all studies examined quantitative CoPs, through RCTs on VE, observational cohort/case-control studies or modelling studies examining relationships between immune marker levels and risk of breakthrough infection.

Potential Humoral Immunity Markers

IMMUNOGLOBULIN G

Serum anti-S IgG and anti-RBD IgG were the most frequently examined potential CoPs across studies included in this rapid review (n=20 studies examined one or both types of IgG).[16-18,22-27,29,30,32,33,36-38,40,43,44,46] There was relatively consistent evidence suggesting an association between higher levels of anti-S IgG and/or anti-RBD IgG, and lower COVID-19 infection risk. However, the magnitude of association varied greatly across studies, and the association was not always statistically significant. The evidence does not suggest a specific threshold that correlates to absolute elimination of risk of SARS-CoV-2 infection. Given the heterogeneity across studies, there were no clear trends in the data for associations of reduced infection risk and IgG levels in the context of different VOCs or vaccines. We describe findings from several key studies below to illustrate the range of results.

An RCT for VE of Spikevax by Gilbert et al. (2022b) found infection risk per 10-fold increase in anti-S IgG was reduced by 34% (aHR: 0.66; 95% confidence interval [CI]: 0.50, 0.88).[18] When comparing high anti-S IgG levels (>3,800 binding antibody units [BAU]/milliliter [ml]) to low levels (<2,190 BAU/ml), there was a significant reduction in risk (aHR: 0.23; 95% CI: 0.09, 0.60). For anti-RBD IgG, infection risk per 10-fold increase in anti-RBD IgG was reduced by 43% (aHR: 0.57; 95% CI: 0.40, 0.82), and when comparing high anti-RBD IgG levels (>5,750 BAU/ml) to low (<3,310 BAU/ml), infection risk was significantly reduced (aHR: 0.28; 95% CI: 0.12, 0.66). Two additional randomized trials studied the vaccines Nuvaxovid and Jcovden, which have not been widely used in Ontario. Fong et al. (2023) found the risk of breakthrough infection decreased by 64% for every 10-fold increase in anti-S IgG (aHR: 0.36; 95% CI: 0.20, 0.36), and decreased by 65% for every 10-fold increase in anti-RBD IgG (aHR: 0.35; 95% CI: 0.18, 0.69).[16] Fong et al. (2022) found similar trends; however, these results did not reach statistical significance.[17] These three RCTs examined data relevant up to the Delta VOC period and did not include findings relevant to Omicron.

The impact of serum IgG levels on COVID-19 infection risk was described across observational studies in various ways, including HRs, ORs, RRs, mean/median differences in antibody levels in infected compared to uninfected participants, and estimated thresholds of protection from infection. For example, Cheetham et al. (2023) grouped anti-S IgG levels into quintiles and compared risk of breakthrough infection in the context of Omicron, between vaccinated individuals (Spikevax, Comirnaty, Vaxzevria or combination) with IgG levels in the lowest quintile (0.4–18.1 BAU/ml), to those with levels in the highest quintile (>165 BAU/ml).[25] Adjusting for age, sex and number of weeks since vaccination, those with anti-S IgG levels in the lowest quintile had greater odds of breakthrough infection, compared to those with levels in the highest quintile (aOR: 2.9; 95% CI: 1.4, 6.0). De Gier et al. (2022) similarly measured anti-S IgG concentrations; however, grouped results into quartiles (lowest: <6,778 BAU/ml; highest: >32,401 BAU/ml).[26] The risk of breakthrough infection was significantly lower for those with anti-S IgG levels in the highest quartile, compared to those in the lowest quartile (aHR: 0.29; 95% CI: 0.22, 0.37). A study by Wei et al. (2022; preprint) illustrated the impact of multiple factors and the complexities involved in attempting to establish specific thresholds of protection.[43] Anti-S IgG levels associated with protection against breakthrough infection for 67% of vaccinated (Spikevax, Comirnaty or combination) participants aged 60 years (as reported in study, exact age parameters unclear) without previous infection, with pre-Alpha/Alpha infection, or with Delta/Omicron BA.1 infection were 1,520 BAU/ml, 1,080 BAU/ml and 480 BAU/ml, respectively. A previous Omicron BA.2 infection had the highest protection against Omicron BA.4/5 infection, with over 80% of participants protected regardless of antibody levels. Levels associated with 67% protection were 1,180–1,520 BAU/ml for those aged 20–50 years, 2,400 BAU/ml for those aged 75 years and 3,200 BAU/ml for those aged 80 years.

Barda et al. (2022) examined the association between serum anti-RBD IgG levels (sampled pre-fourth vaccine dose) and the risk of Omicron breakthrough infection at the 6-month follow up (post-fourth dose).[22] IgG levels >700 BAU were associated with reduced risk of infection compared to IgG levels <700 BAU (aHR; 0.65, 95% CI: 0.52, 0.80). In addition, results showed for each 10-fold increase in IgG, infection risk decreased by 46% (aHR: 0.54; 95% CI: 0.41, 0.71). An additional 12 observational studies[22-24,26,27,30,32,33,36,38,40,44] and one modelling study[46] found significant associations between higher serum IgG levels and lower infection risk to varying degrees. Two observational studies found no significant association between IgG levels (anti-S and anti-RBD) and infection risk.[29,37]

Nearly all studies examined antibodies detected in serum and only one study examined mucosal IgG with samples collected from nasal swabs. Havervall et al. (2022) found WT-S-specific mucosal anti-S IgG levels and Omicron BA.1-S-specific mucosal anti-S IgG levels in the 75th percentile or higher, compared to levels below the 75th percentile (exact IgG measure not reported), did not have a significant effect on risk of breakthrough Omicron infection.[28]

IMMUNOGLOBULIN A

Three observational studies examined IgA levels, specifically serum anti-S IgA,[29,37] serum anti-RBD IgA,[29,37] and mucosal anti-S IgA.[28] Overall, the evidence consistently suggested an association between higher IgA levels and lower COVID-19 infection risk.

Sheikh-Mohamed et al. (2022) compared antibody levels detected in vaccinated (Comirnaty or Spikevax) participants who developed breakthrough infections, compared to those who remained uninfected, in the context of circulating Alpha and Gamma variants.[37] Results showed a trend of lower anti-S IgA levels in breakthrough cases versus uninfected participants (152.8 BAU/ml versus 471.4 BAU/ml, $p<0.05$), and lower anti-RBD IgA levels in breakthrough cases, compared to uninfected participants (162.31 BAU/ml versus 495.68 BAU/ml; $p<0.01$). Hertz et al. (2022; preprint) found that lower levels of anti-S IgA, compared to higher levels (i.e., lowest versus highest quartile), were associated with greater risk of

infection among vaccinated participants.[29] This was the case for anti-S IgA binding to WT (aHR: 3.19; 95% CI: 1.21, 8.38; p=0.019) and anti-S IgA binding to VOCs (aHR: 4.45; 95% CI: 1.51, 13.02; p=0.006). In addition, this study examined the impact of the combination of low baseline IgA binding to WT and low IgA binding to VOCs, and found this combination had a greater association with infection risk among low levels compared to high levels (aHR: 5.73; 95% CI: 1.54, 21.26).

Havervall et al. (2022) examined mucosal IgA levels specific to WT and Omicron strains.[28] Those with WT-S-specific mucosal IgA levels in the 75th percentile (exact IgA measure not reported) or greater had significantly reduced risk of breakthrough infection when compared to those with levels below the 75th percentile (aRR: 0.35; 97.5% CI: 0.11, 0.91). Those with Omicron BA.1-S-specific mucosal IgA in the 75th percentile or greater did not have a significantly reduced risk of breakthrough infection when compared to those with levels below the 75th percentile (aRR: 0.63; 97.5% CI: 0.22, 1.49).

SERUM ANTI-S ANTIBODIES (MULTIPLE IMMUNOGLOBULINS)

Five observational studies examined multiple combined or unspecified anti-S antibodies. Specific markers examined included total antibodies to the S1 subunit of the S protein,[19] anti-S antibodies (unspecified),[21,31] or anti-S IgG/A/M.[39,42] Evidence across studies was consistent in finding significant associations between higher anti-S antibody levels and reduced risk of COVID-19 infection; however, the outcome measures and magnitude of effects varied.

For example, in a study with a large data set (n=22,204) collected during Alpha and Delta circulation in the US (vaccination history not reported), Sullivan et al. (2023) categorized anti-S IgG/A/M titers as low (0–250 BAU) or high (>250 BAU).[39] Subjects who developed COVID-19 had significantly greater odds of being in the low anti-S antibody group prior to infection compared to patients who did not contract COVID-19 (aOR: 2.77; 95% CI: 2.23, 3.43). A study by Vivaldi et al. (2022) was conducted during Delta and Omicron circulation and examined anti-S IgG/A/M responses.[42] Those with breakthrough infections had significantly lower antibody titers (mean [standard deviation, SD]) than those without breakthrough infections (177 [102] BAU/ml versus 222 BAU/ml [113]); mean difference: 55 BAU/ml (95% CI: 50, 61). The remaining three studies associated anti-S levels with infection risk using HRs, ORs and significant differences in titer levels, all supporting the trend that higher anti-S antibody levels were associated with decreased infection risk, compared to lower levels.[19,21,31]

SERUM ANTI-RBD ANTIBODIES (MULTIPLE IMMUNOGLOBULINS)

Two observational studies examined multiple or unspecified anti-RBD antibodies (note: RBD is part of S; thus, there is some epitope overlap).[34,41] Results were mixed and more evidence is needed to understand the impact of anti-RBD total antibodies on infection risk. Torres et al. (2022) reported median levels of anti-RBD antibodies in infected (Omicron period) versus uninfected participants, and found no significant differences in antibody levels between groups (21,123 BAU/ml versus 24,723 BAU/ml; p=0.34).[41] Perez-Saez et al. (2022; preprint) measured total antibodies (IgG/A/M) against the RBD portion of SARS-CoV-2 S protein among participants with largely hybrid immunity (80% were vaccinated and 90% had previous infection), and estimated hazard of infection.[34] The hazard of having an Omicron BA.1/BA.2 infection was significantly reduced for individuals with anti-RBD binding antibody levels higher than 800 IU/ml, compared to those with levels below that threshold (aHR: 0.30; 95% CI: 0.22, 0.41).

SERUM ANTI-N ANTIBODIES (MULTIPLE IMMUNOGLOBULINS)

One case-control study by Atti et al. (2022) examined the association between anti-N antibodies and reinfections, finding no significant impact (all participants unvaccinated).[21] Among previously infected and unvaccinated subjects, there was no significant difference in anti-N IgG levels between reinfection cases and controls (p=0.29). Doubling of anti-N levels were not significantly associated with reduced risk of reinfection.

NEUTRALIZING ANTIBODIES

A total of 15 studies examined NAb levels and their association with risk of infection, this included three RCTs,[16-18] 10 observational studies,[20,21,24,27,30-32,35,36,41] and two modelling studies.[45,47] Overall, the evidence supported a trend toward an association between higher NAb levels and decreased risk of COVID-19 infection, to varying degrees.

Three vaccine RCTs examined risk of COVID-19 infection with respect to NAb titers (pseudovirus 50% inhibitory dilution, ID_{50}). Evidence was consistent across these trials in finding increased NAb levels were associated with reduced risk of infection. For example, the Spikevax trial by Gilbert et al. (2022b) found those with high NAb levels (>363 international units per ml [IU_{50}/ml]) were associated with significantly reduced risk of infection compared to those with low NAb levels (<178 IU_{50}/ml) (aHR: 0.31; 95% CI: 0.12, 0.80).[18] The hazard reduction by 10-fold increase in NAbs was also significant (aHR: 0.43; 95% CI: 0.27, 0.65). For ID_{80} assays, high NAb levels (>661 IU_{80}/ml), compared to low levels (<407 IU_{80}/ml) were significantly associated with reduced infection risk (aHR: 0.20; 95% CI: 0.07, 0.61). The hazard reduction by 10-fold increase in ID_{80} NAb levels was also significant (aHR: 0.35; 95% CI: 0.20, 0.61).

Overall, there was evidence across most observational studies (8 of 10) suggestive of a significant association between increased NAb levels and reduced COVID-19 infection risk; however, study contexts, outcome measures and suggested protective thresholds varied widely. For example, a case-control study by Mohlendick et al. (2022) conducted during the Omicron period estimated the risk of breakthrough infection at varying inhibition rates of NAbs.[32] Inhibition rates <65.9% were associated with significantly increased risk of infection compared to those with rates above this threshold (aOR: 3.61; 95% CI: 1.42, 9.01). This study also estimated the impact of inhibition rates combined with binding anti-S IgG levels, finding those with anti-S IgG level <2,621 BAU/ml and <65.9% inhibition against Omicron had a 10-fold increased risk for breakthrough infection (aOR: 10.4; 95% CI: 2.36, 47.55), compared to those with IgG and inhibition rates above these thresholds. A study by McGee et al. (2022) quantified sera NAbs using in-vitro SARS-CoV-2-specific pseudovirus assays.[31] In this study sample, 82.3% of participants were vaccinated and 14.3% had a previous infection. NAb titers >2,000 arbitrary unit (AU)/ml inhibited Delta; however Omicron, evaded neutralization. The authors suggested that antibody titer thresholds established for one variant would not apply to new variants. An additional six observational studies provided evidence to support the association between increased NAb titers and decreased infection risk.[20,21,24,27,30,35] Two observational studies did not detect significant associations between NAb levels and COVID-19 infection risk.[36,41]

Two modelling studies supported NAbs as CoPs against COVID-19; these studies also illustrated the challenges in attempting to establish a specific threshold of protection or absolute CoP. Cromer et al. (2022) found that, across vaccine types, NAb titers decreased against VOCs (Alpha, Beta, Gamma, Delta) compared to against WT, but NAb titers remained strongly correlated (Spearman's rank correlation coefficient [R_S]=0.81; p=0.0005) with protection from symptomatic infection.[45] Khoury et al. (2023) found, while the degree of protection varied across vaccine types, there was a consistent overall relationship between NAb titers and protection from COVID-19.[47] For example, in modelling a vaccine-comparison approach, the protection curve derived from vaccination with Spikevax, Comirnaty and

Vaxzevria, and the corresponding neutralization titer (fold of convalescence), are shown (Figure 3 of the study full text). For all three vaccines, there is trend showing increased neutralization titer corresponding with increased protection from infection; for Spikevax and Comirnaty, a neutralization titer >1 corresponded with >80% protection from SARS-CoV-2 infection. Due to the limitations of modelling and variability across evidence and individuals (e.g., diversity of assays used to measure neutralization and uncertainties in estimating individual neutralization titers), establishing a firm protective threshold was not possible, but the authors suggested a gradient of relative risk likely exists at different NAb levels.

Cell-mediated Immunity Markers

We identified two cohort studies with results related to cell-mediated immunity markers.[20,41] Results were mixed and more evidence is needed to understand the role of cellular markers in establishing a CoP for SARS-CoV-2 infections.

Almendro-Vazquez et al. (2022) examined SARS-CoV-2-specific T cells (interferon gamma [IFN-γ] and interleukin-2 [IL-2]) among vaccinated participants.[20] The only breakthrough infections occurred in participants without prior infection (17 infections among 70 total naive participants). A cluster analysis of individuals without prior infections showed that subjects who developed both high T cell (>700 S1 IFN-γ spot-forming units [sfu]/10^6 peripheral blood mononuclear cells [PBMCs]) and NAb levels (>1/1,206 IU/ml) after vaccination were protected against breakthrough infection. Based on these results, the authors suggested that individuals with low cellular or neutralizing responses could benefit from additional booster doses.

Torres et al. (2022) quantified SARS-CoV-2-S-specific- IFN-γ-producing $CD4^+$ and $CD8^+$ T cells, reported as the frequency of specific T cells divided by total T cells.[41] Detectable $CD4^+$ and $CD8^+$ T cell responses after vaccine dose 3 were not significantly different between those with breakthrough infections and uninfected participants ($CD4^+$: 13/13 versus 40/46, respectively; p=0.32; $CD8^+$: 12/13 versus 36/46, respectively; p=0.42). Median frequencies of both S-reactive T-cell subsets were not significantly different between participants with breakthrough infections and those without. Having detectable SARS-CoV-2-S-reactive-IFN-γ-producing $CD4^+$ or $CD8^+$ T cells after dose 3 was not significantly associated with a decreased risk of developing breakthrough infection.

Discussion

Our rapid review provides an update on potential humoral and/or cellular immune marker CoPs against SARS-CoV-2, focusing on studies published since January 1, 2022. No studies reported a candidate immune marker representing an absolute CoP, rather, the included studies identified multiple immune markers that provide relative CoPs. Humoral immune markers comprise the majority of potential relative CoPs; i.e., serum concentrations or titers of anti-S/anti-RBD IgG, anti-S/anti-RBD IgA and NAbs. Given the high heterogeneity in immune marker levels and association with protection from infection identified in this rapid review, providing specific immune marker thresholds or even protective ranges is not appropriate. Additionally, an immune marker CoP against SARS-CoV-2 infection (asymptomatic or symptomatic disease confirmed by positive PCR test) will likely differ from other CoP primary endpoints, such as severe disease or death.[49]

We build upon the published systematic review by Perry et al. (2022).[15] While adding a significant number of studies and results, we found that no studies identified an absolute immune marker CoP. Again, the literature indicated that serum anti-S IgG and NAb levels may be relative immune marker CoPs against SARS-CoV-2, with higher antibody levels associated with a decreased risk of infection (noting that few studies showed a statistically significant difference between antibody levels and either outcome; i.e., 100% protection from infection or susceptibility). An absolute CoP would offer a clinical indicator for booster dosing (e.g., for those with immune-compromising conditions), would aid in the development of vaccine schedules/policies, development of public health measures/policies and accelerates the approval process for vaccines. While identifying an absolute immune marker CoP is highly desirable, a relative CoP is an important contribution to understanding antibody and overall immune response against SARS-CoV-2.

This rapid review presents a tempered and conservative assessment of the literature on potential CoPs against SARS-CoV-2, particularly concerning vaccine-specific CoPs and CoP usefulness in the context of public health policy development. However, other work has been more definitive in their assessment and identification of CoPs, but stop short of identifying an absolute CoP. Gilbert et al. (2022a) reported that serum anti-S IgG concentrations and NAb titers are CoPs for vaccines against symptomatic SARS-CoV-2 infection, while acknowledging these CoPs are not absolute and conceding the unlikelihood of identifying an absolute CoP against SARS-CoV-2.[3] Gilbert et al. (2022a) used additional sources of data, compared to this review, such as: 1) meta-analysis of RCT data showing correlation between NAb standardized meant titers and VE; 2) NAb titers as mechanistic CoPs in challenge studies using non-human primates; and 3) COVID-19 Vaccine Correlates of Protection Program data on phase 3 trials of four vaccines showing consistent correlation of increasing NAb titers and VE. In an earlier study using data from seven vaccine trials (Comirnaty, Spikevax, Vaxzevria, Jcovden, Nuvaxovid, Sputnik V, CoronaVac), Earle et al. (2021) reported a high correlation between levels of serum NAb and VE (R_S=0.79), and even higher for levels of binding anti-S IgG and VE (R_S=0.93) (titers calibrated against convalescent sera; VE determined for each study, VE=[1-RR]x100).[50]

Antibody and NAb levels associated with increased protection against SARS-CoV-2 infection ranged widely in the included studies, noting that VOC context, methodology, population and vaccine regimens varied across studies. To highlight variability, here we report on antigen-specific CoPs associated with at least 50% protection against infection among studies that used the same unit of measurement. Compared to participants with relatively lower anti-S IgG levels (BAU/ml), antibody levels associated with at least 50% protection were as low as >94,[44] increasing to >107,[44] >154,[46] >165,[25] >168,[46] >350,[33] >480,[43] >1,080,[43] >1,520,[43] >2,528,[24] >2,816l,[32] >3,800[18] and >6,000.[27] For NAbs, two studies reported CoPs of >1.4 IU_{50}/ml[17] and >363 IU_{50}/ml,[18] compared to participants with relatively lower NAb levels.

Limitations and Challenges to Identifying CoPs Against SARS-CoV-2

Readers should take into account study-level limitations and challenges inherent to CoP studies when interpreting results presented in this review. Identification of an absolute CoP for SARS-CoV-2 is unlikely given the high heterogeneity of immune marker levels following infection and vaccination, making relative CoPs a more achievable goal. Overcoming or minimizing these limitations will reduce the uncertainty in relative CoPs, making them more useful in the context of public health policy and clinical practice.

Study characteristics and limitations hindering efforts to identify absolute CoPs include:

- **High heterogeneity.** Multiple factors contributed to high inter- and intra-study heterogeneity in immune marker levels, including previous disease severity, time since infection or vaccination, patient age and comorbidities (e.g., immune-compromising conditions), serological assay used and methodology (target antigens), circulating VOCs and vaccines used.[10-12,14,51] For example:
    - The unpredictable nature of breakthrough infections, led to high variability in pre-infection sera collection times and estimates of immune marker levels.[21,27,31,38]
    - The most commonly acknowledged caveat by authors was the need for more studies focusing on CoPs in the context of emerging VOCs and their contribution to heterogeneity.[19,24,30,39,42] We assume that the emergence of new VOCs will require increases in antibody and NAb levels to achieve an equivalent pre-VOC-emergence level of protection. VOC impact on CoPs is potentially ameliorated by research predicting VE of new vaccines and/or VE against emerging VOCs (e.g., Cromer et al. 2022).[45]
    - Small sample sizes in several of the studies limit assessments of CoPs, especially with respect to investigating additional parameters of interest such as patient age, sex, comorbidities, vaccine regimens and infection history.[24,30,31,41]
    - The included studies over-represented older ages and females, limiting the applicability of study results to the broader population.[25,37,38] This limitation is due in part to the large proportion (57.7%, 15/26) of observational studies performed in LTCHs or other healthcare facilities (HCWs, patients, residents). None of the included studies focused on immune responses in children <18 years old or pregnant women, limiting the applicability of our findings to these populations. Immune marker CoPs are only effective for public health and clinical purposes if they represent the entire population, especially those at risk of severe disease (e.g., individuals with immune-compromising conditions, pregnant women, young children and those with equity barriers such as racialized communities and people who are unhoused).
- **Assay calibration and standardization.** A noted challenge in comparing immune responses among studies is the lack of calibration against a reference standard, particularly among observational studies.[52] The World Health Organization (WHO) and collaborators developed the WHO International Standard for anti-SARS-CoV-2 immunoglobulins, which urges the reporting of international standard units (BAU/mL for binding antibodies; IU/mL for NAbs).[53,54] In addition to calibration against a reference standard, Earle et al. (2021) proposed using proficiency panels to standardize antibody quantification among laboratories.[50] In this review, reporting of antibody measurements varied among the included studies. For example, binding antibodies were measured in BAU/ml, AU/ml, BAU, and units [U]/ml; and NAbs were measured in IU/ml, 50% inhibitory concentration (IC_{50})/ml, titers, percent inhibition, AU/ml, effective dose 50% (ED_{50}),

median tissue culture infectious dose ($TCID_{50}$)/150 microliters (µl), 50% plaque reduction neutralization test ($PRNT_{50}$), and neutralization titer 50 (NT_{50}).

- **Binding (non-mechanistic CoPs) versus neutralization (mechanistic CoPs) assays.** An often mentioned challenge in comparing antibody levels among studies is the lack of distinction among assays that measure both binding and NAbs, or each separately.[10] The distinction is important, as NAbs represent a functional CoP involved in the inactivation of SARS-CoV-2 by preventing cell fusion and entry. PRNTs are the gold standard for NAb quantification, but require additional technical expertise and have long-turnaround times with low throughput; more feasible alternatives to PRNTs include pseudovirus and microneutralization assays.[10,55] In contrast, binding assays detect antibodies that can attach to SARS-CoV-2 and present the virus to immune cells, however, these binding antibodies do not prevent virus entry into cells. Compared to PRNTs, binding assays typically involve simpler technologies and are faster to perform with higher throughput. The studies included in this review varied in their nomenclature of binding versus neutralizing antibodies, making it difficult to interpret significance of their results.

- **Mucosal IgA.** Only one of the included studies assessed mucosal IgA responses among participants.[28] Mucosal IgA is an important target for potential immune marker CoPs, as mucosal IgA is a mechanistic CoP and provides functional neutralization of SARS-CoV-2 at infection sites such as the lungs or nasal passages. In addition, researchers are calling for more studies focusing on IgA immune responses, particularly studies incorporating easily collected specimens such as saliva.[13,21,24,37]

- **Cellular immune markers.** Researchers commonly remarked that they did not investigate potential cellular immunity markers as CoPs.[21,22,27,31,43,44] T cells and memory B cells aid in our understanding of the breadth and durability of immunity following infection or immunization, a facet of immunity especially important with the continued emergence of VOCs.[56] T cells recognize both surface and structural proteins of SARS-CoV-2, whereas antibodies recognize surface proteins (e.g., the maintenance of S-specific recognition across VOCs by $CD4^+$ and $CD8^+$ T cells).[57] Identification of SARS-CoV-2 antigen-specific T-cells will support the development of cellular immunity CoPs that will complement humoral CoPs, especially when studied in tandem with humoral immune markers (e.g., Hertz et al. 2022, preprint).[29] However, there is considerable variation in methodologies and reporting of cellular markers, similar to antibody studies, which can make consensus on cellular-mediated CoPs difficult to obtain.[58] Further, studying cellular immune responses can help improve vaccines, as they can persist longer, recognize a wider variety of viral antigens and provide protection in people that do not mount protective antibody responses.[59]

Conclusions and Public Health Implications

Currently, there is no evidence for an absolute humoral or cellular CoP against SARS-CoV-2 (and this is likely unattainable). While the heterogeneity between studies examining CoPs limits determining an absolute CoP, this review has identified several potential relative humoral CoPs against SARS-CoV-2 infection, though the evidence remains too limited to determine any specific thresholds for these potential CoPs. The best studied of these potential CoPs are serum concentrations and titers of anti-S/anti-RBD IgG, anti-S/anti-RBD IgA and NAbs. The potential relative CoPs identified here are in agreement with the larger body of evidence and consensus among researchers,[3,50] specifically that serum anti-S IgG and NAbs are CoPs for COVID-19 vaccines.

For potential relative CoPs to support public health in the development of vaccine schedules and preventative measures, along with aiding clinical decision-making surrounding booster doses, additional research is needed to decrease the uncertainty and variability in antibody levels and associated infection risk. Research could focus on variables impacting antibody levels and protection, including patient immunity type (infection, vaccination, hybrid), current VOC circulation, vaccine types and regimens, timing of sample collection and patient details (age, sex, clinical severity if previously infected, comorbidities). Larger, longitudinal RCTs, RCT meta-analyses and/or prospective cohort and case-control studies with large sample sizes will refine candidate relative CoP estimates.

Earle et al. (2021) noted that achieving consensus on any given CoP requires: 1) standardization of antibody measurements; 2) agreement on a SARS-CoV-2-specific neutralizing assay as the gold-standard for CoP and validation of secondary assays; 3) calculation of protective antibody thresholds; 4) determination of a minimum antibody level CoP for symptomatic infection (additionally severe disease and asymptomatic infection); and 5) verification that the CoP can be applied to emerging VOCs.[50]

The absence of an absolute immune marker CoP against SARS-CoV-2 emphasizes that despite meaningful progress in understanding immunity to SARS-CoV-2, important knowledge gaps remain. Minimizing SARS-CoV-2 transmission remains an important public health goal to limit acute and long-term health impacts at the population level, and the associated burdens on both health care and public health resources. Minimizing SARS-CoV-2 infections is particularly important for populations more susceptible to severe COVID-19. Ways to minimize SARS-CoV-2 infections include continuing to promote COVID-19 vaccination and other infection prevention measures that facilitate reductions in transmission and incidence of SARS-CoV-2 (e.g., paid sick time, masking, layering of measures).

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