# Supplementary Appendix

Supplement to: Brown PE, Hang Fu S, Bansal A, et al. Omicron BA.1/1.1 SARS-CoV-2 infection among vaccinated Canadian adults. N Engl J Med. DOI: 10.1056/NEJMc2202879

This appendix has been provided by the authors to give readers additional information about the work.

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**Investigators List: Ab-C Study Collaborators**

Patrick Brown, PhD[1]; Sze Hang Fu, MSA[1]; Aiyush Bansal, MD[1]; Leslie Newcombe, BSc[1]; Karen Colwill, PhD[2]; Geneviève Mailhot, MSc[2]; Melanie Delgado-Brand, BSc[2]; Anne-Claude Gingras, PhD[2]; Arthur S. Slutsky, MD[1]; Maria Pasic, PhD[1]; Jeffrey Companion[1]; Isaac I. Bogoch, MD[3]; Ed Morawski, MA[4]; Teresa Lam, BA[4]; Angus Reid, PhD[4]; Xuyang Tang, PhD[1]; Abha Sharma, MPH[1]; Hellen Gelband, MHS[1]; H. Chaim Birnboim, MD[1]; Nico Nagelkerke, PhD[1]; Justin Slater, MSc[1]; Peter S. Rodriguez, MSA[1]; Guowen Huang, PhD[1]; Catherine Meh, MPH[1]; Daphne C. Wu, MSc[1]; Rupert Kaul, MD[3]; Marc-André Langlois, PhD[5]; Andy Hollander, BA[4]; Demetre Eliopoulos, BSc[4]; Benjamin Aloi, MPP[4]; Kento T. Abe, BSc[2]; Bhavisha Rathod, BSc[2]; Mahya Fazel-Zarandi[2]; Jenny Wang, MSc[2]; Mariam Iskilova, MSc[2]; Adrian Pasculescu, PhD[2]; Lauren Caldwell, BSc[2]; Miriam Barrios-Rodiles, PhD[2]; Zahraa Mohammed-Ali, PhD[1]; Nandita Vas[1]; Divya Raman Santhanam, BSc[1]; Eo Rin Cho, PhD[1]; Kathleen Qu, MPH[1]; Shreya Jha, BMus[1]; Vedika Jha[1]; Wilson Suraweera, MSc[1]; Varsha Malhotra, PhD[1]; Kathy Mastali, MSc[1]; Richard Wen, MSA[1]; Samir Sinha, MD[2]; Pranesh Chakraborty, MD[5]; Prabhat Jha, MD, DPhil[1]; for the Ab-C Study Investigators

[1] Unity Health Toronto, Toronto, Ontario, Canada
[2] Network Biology Collaborative Center, Sinai Health, Toronto, Ontario, Canada
[3] Toronto General Hospital, University Hospital Network, Toronto, Ontario, Canada
[4] Angus Reid Institute, Vancouver, British Columbia, Canada
[5] University of Ottawa, Ottawa, Ontario, Canada

## Methods (Section S1)

### Subject Recruitment

The Action to Beat Coronavirus (Ab-C) study received ethical approval from Unity Health Toronto (REB 20-107). In Phase 1, from May through September 2020, we invited 44,270 members (out of about 78,000 total members) of the Angus Reid Forum,[1] an established nationwide polling panel of Canadian adults aged 18 and older, to complete an online survey about SARS-CoV-2 symptoms and testing histories. The sampled population was stratified by age groups (18-34, 35-54, 55+); sex (male, female); education (high school education or lower, some college or college or technical degree, some university, or university degree); and region, by census metropolitan area to match the national demographic distribution, with oversampling of adults 60 years or older. In August 2021, we invited about 3100 additional Forum panel members from 17 high-burden regions (of 93 total regions nationwide), based on a regression analysis of SARS-CoV-2 case counts.[2] At the end of the online survey, respondents indicated their willingness to self-collect a blood sample from a finger prick, and we sent consenters a dried blood spot (DBS) collection kit. From December 2020 through January 2021, we invited all 19,994 Phase 1 participants to join Phase 2, retaining the same sampling frame. Phase 3 and 4 recruitment used similar approaches. In Phase 4, we conducted additional outreach to 2587 additional members from marginalized groups at higher risk of COVID infection (2045 visible minorities and 542 Indigenous individuals). Of these, 1229 agreed to provide DBS and were included in Phase 4 mailouts (919 visible minorities and 310 Indigenous individuals).

Participants were not compensated financially by the study for participating, but earned modest redeemable points from the Angus Reid Forum.[3] Figure S1 provides the timeline for Phases 1 to 4, in relation to Canada's national weekly averages of confirmed COVID cases, and in relation to weekly averages of vaccination including the third "booster" doses. Figure S2 illustrates the study recruitment and flow; there were few (about 1%) exclusions, mostly from incomplete testing.

### IgG Serology

Participants collected five small circles of blood on special bar-coded filter paper, dried the sample for at least two hours, placed it in a two-layer protective pouch, and returned it to St. Michael's Hospital in Toronto, postage prepaid. Mailing time across Canada ranged from about 3 to 6 days. Upon arrival, samples were scanned, catalogued, and stored at 4 °C in larger boxes with additional desiccant, and monitored for humidity levels (kept <20%).

Antibodies were then eluted from a 4.7 mm punch in 99 µL of PBS + 0.1% Tween (PBS-T) and 1% Triton X-100. The use of 99 µL was to ensure sufficient eluate to test three antigens (spike protein, receptor binding domain (RBD) of the spike, and nucleocapsid protein (NP)). Punches were incubated in elution buffer for 4 hours with gentle shaking (150 RPM) at room temperature or overnight at 4ºC. The samples were then centrifuged at 1000 g for 30 seconds.

The Network Biology Collaborative Centre at Sinai Health, Toronto, conducted a high-throughput, highly sensitive chemiluminescence-based ELISA targeting the spike protein, RBD, and NP. Automated chemiluminescent ELISA assays were performed as previously described on a ThermoFisher Scientific F7 robotic platform[4,5] with a few modifications. Briefly, LUMITRAC 600 high-binding white polystyrene 384-well microplates (Greiner Bio-One #781074, VWR #82051- 268) were pre-coated overnight with 10 µL /well of antigen (50 ng spike (SmT1), 20 ng RBD and 7 ng nucleocapsid, all supplied by the National Research Council of Canada (NRC)). After washing (all washes were 4 times with 100 µL PBS-T), wells were blocked for 1 hour in 80 µL 5% Blocker BLOTTO (ThermoFisher

Scientific, #37530) and then washed. 10 µL of sample (2.5 or 0.156 µL of DBS eluate diluted in 1% final Blocker BLOTTO in PBS-T) was added to each well and incubated for 2 hours at room temperature. After washing, 10 µL of a human anti-IgG fused to HRP (IgG#5, supplied by NRC, final of 0.9 ng/well) diluted in 1% final Blocker BLOTTO in PBS-T was added to each well followed by a 1-hour incubation at room temperature. After 4 washes, 10 µL of SuperSignal ELISA pico chemiluminescent substrate (diluted 1:4 in MilliQ distilled $H_20$) was added to each well and incubated for 5-8 min at room temperature. Chemiluminescence was read on an EnVision (Perkin Elmer) plate reader at 100 ms/well using an ultra-sensitive detector.

Each 384-well assay plate included replicates of a standard reference curve of a human anti-spike IgG antibody (VHH72-Fc supplied by NRC)[5] or an anti-nucleocapsid IgG antibody (Genscript, #A02039), positive and negative master mixes of pooled serum samples, human IgG negative control (Sigma, #I4506), and blanks as controls. Negative and/or positive DBS controls (defined using plasma serology results) were included in runs in each phase.

For each antigen, raw values (counts per second) were normalized to a blank-subtracted point in the linear range of the standard reference curve to create a relative ratio (hereinafter referred to as titer). The samples were processed at a 1:4 dilution of the DBS eluate (2.5 ul/well of sample) and 1:64 dilution. We used the former to derive positivity threshold based on NP and the latter to display titer distributions for Spike protein and RBD.

**IgG Cutoffs**

We derived a positivity threshold in Phase 4 of 0.25 titer value at the 1:4 dilution for NP by assuming infected and uninfected samples have logged NP titer values which follow skew-Normal distributions. Although infection status is unknown for most samples, we validated this among 113 individuals in Phase 4 reporting a positive COVID-19 test between 21 and less than 90 days prior to the sample being received. A number of control samples were measured from uninfected groups, and these were used to estimate a skew parameter for the uninfected state. We estimated the six remaining parameters (two location and scale parameters, skew parameters for the infected state, and proportion of samples which are infected) by maximizing the likelihood function of all Phase 4 samples (and 113 known infections). We adopted the cutoff value of 0.25 as it incorrectly classifies 10% of samples as false positives and 10% as false negatives. Thus, the overall number of samples classified as positive is expected to be correct. We implemented a similar procedure to minimize false positives and negatives to the Phase 3 NP titers, yielding a slightly higher threshold of 0.307. This higher threshold is due mostly to the lower prevalence in Phase 3. Indeed, the 0.25 threshold from Phase 4 yielded more false positives than false negatives in Phase 3 simply because there are fewer positive samples to detect. For unvaccinated individuals, infection status also considered spike and RBD proteins, with infection being inferred from cutoff values of 0.48 for spike or 0.32 for RBD.[5]

**Analyses**

This analysis focused on Phases 3 and 4 of the Ab-C study, which correspond to the pre-Omicron (Aug 15 to Oct 15, 2021) and Omicron (BA.1/1.1) period (Jan 24 to Mar 15, 2022), respectively. To confirm the Ab-C data is representative of the Canadian population, we calculated the proportion of participants who filled out the survey and provided DBS by demographic characteristics (province, household size, age, sex, education, ethnicity, weight, smoking status, diabetes, hypertension) and vaccination status, and compared these to the Canadian national data (Table S1).

As we have already reported,[2] the demographic and health characteristics of those who completed surveys and provided DBS were generally comparable to the Canadian census population, with the exception of fewer adults with an educational level of some college or less in the Ab-C study compared with the census population. Hence, we adjusted for educational level in the regression analyses and when calculating all subsequent estimates of cumulative incidence or national numbers of adults infected. Moreover, the Ab-C study has had fewer racial or ethnic minority adults (which is defined by Statistics Canada, the national lead statistical agency, as "Visible Minorities") but more Indigenous Canadian adults than the census population. Compared with the census populations or nationally representative surveys, study participants had a similar prevalence of obesity, current or former smoking, diabetes and hypertension.

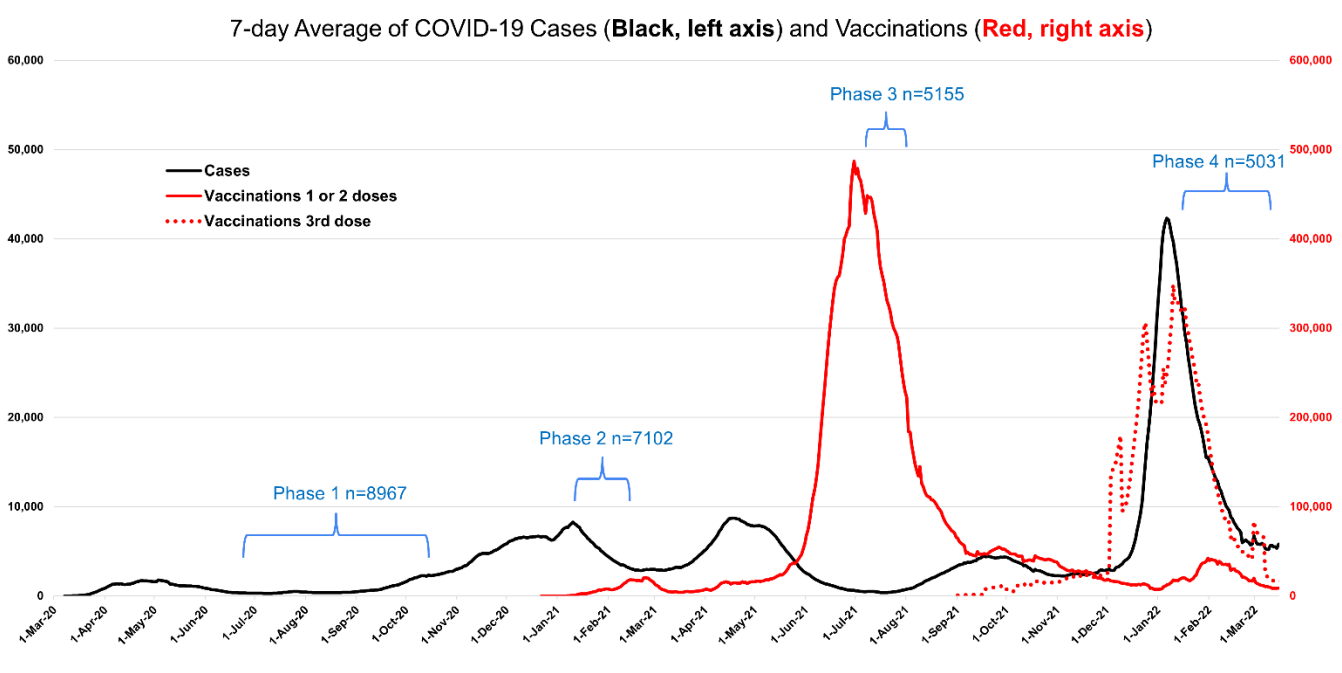
The phase 3 and 4 population distributions, which are most directly relevant to estimating cumulative and period-specific Omicron incidence are broadly similar among those who completed surveys and those who provided a DBS. In Phase 4, the proportion of adults unvaccinated was similar in the Ab-C surveyed population (10%) as in Canada overall (8%). However, the unvaccinated rates were lower in the DBS sample (5%). The absolute contribution of unvaccinated to the overall cumulative incidence is small however, and we stratify our national estimates of infected adults by vaccination status. Moreover, the characteristics of the unvaccinated were mostly defined by lower levels of education[6] and we adjusted for education and applied education-specific survey weights. Finally, a comparison of those invited who participated and did not in the Phase 1 of the study showed a bias towards greater female participation. However, differences by sex were not important predictors of cumulative incidence (data not shown), so this bias does not materially affect the overall estimates of cumulative infection.

The age-specific "immunity wall" in Figure 1B defines infection as either having tested positive on polymerase chain reaction or antigen rapid test or with antibodies to the NP antigen (which is appropriate among the largely vaccinated cohort). NP antibodies reflect infection and would not arise from Canadian-approved vaccines that only contain the spike protein. In unvaccinated participants, spike and RBD positivity would be indicative of infection and would capture additional cases where a person did not seroconvert for NP antibodies. Hence, spike or RBD seropositivity with NP seronegativity were also considered as infection among the unvaccinated (this does not apply to the vaccinated since vaccination would induce spike and RBD seropositivity). For the pre-Omicron period, we used cumulative prevalence of infection, which is defined as any positive COVID test within two months of DBS testing and any NP seropositive. For the Omicron period, cumulative incidence included any positive COVID test after December 1, 2021, or any NP seropositive.

Using the infection and vaccination status, we grouped all adults into six categories: 1) no infection history or vaccination, 2) infection only or one vaccine dose and uninfected, 3) two vaccine doses and uninfected, 4) three vaccine doses and uninfected, 5) one or two vaccine doses and infected, and 6) three vaccine doses and infected. We calculated the proportion of participants belonging to each category, separated by age groups, for the pre-Omicron and Omicron periods.

We obtained the overall cumulative incidence of SARS-CoV-2 infections based on NP seropositivity and derived the 95% confidence intervals using the Delta method.[7] In order to examine the level of antibody response from infection and vaccination (by vaccine doses), we display the distributions of antibodies to spike antigens (at the 1:64 dilution) using box plots with jitter (Figure 1A). Results for antibodies to RBD are similar (Figure S3). All analyses were performed using Stata 16 and R 4.0.5.

**Figure S1. 7-day rolling averages of confirmed COVID cases in Canada (black line) and SARS-CoV-2 vaccinations, either first or second dose (solid red line) or third dose (dotted red line), from March 2020 to March 2022**




Notes: Testing and vaccination data were derived from the Public Health Agency of Canada as of April 20, 2022: https://www.canada.ca/en/public-health/services/diseases/coronavirus-disease-covid-19/epidemiological-economic-research-data.html

**Figure S2. Study flow including sampling and study inclusion by Phase in the Ab-C Study**

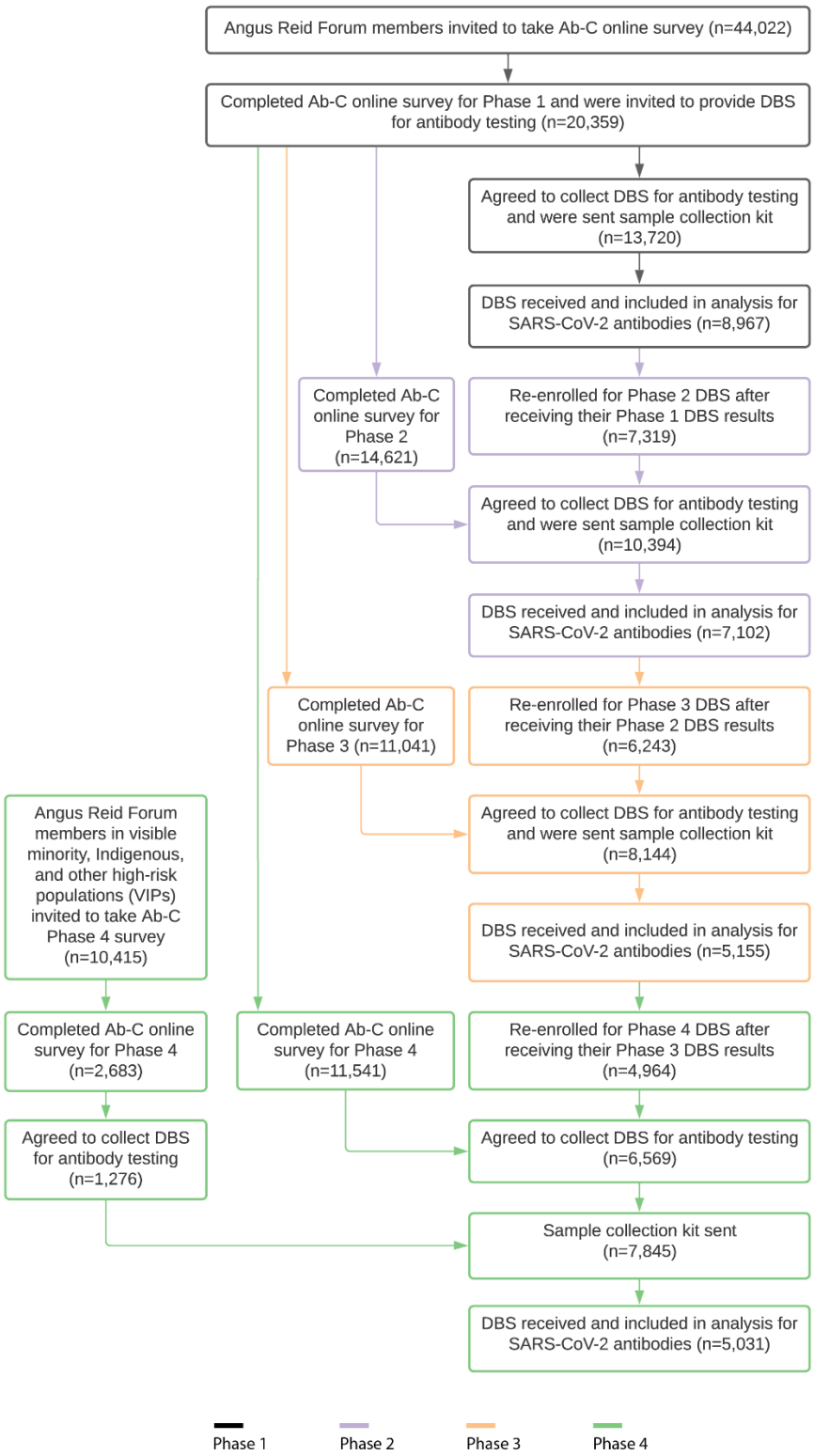


**Figure S3. RBD titers on IgG antibody testing stratified by infection and vaccination status**

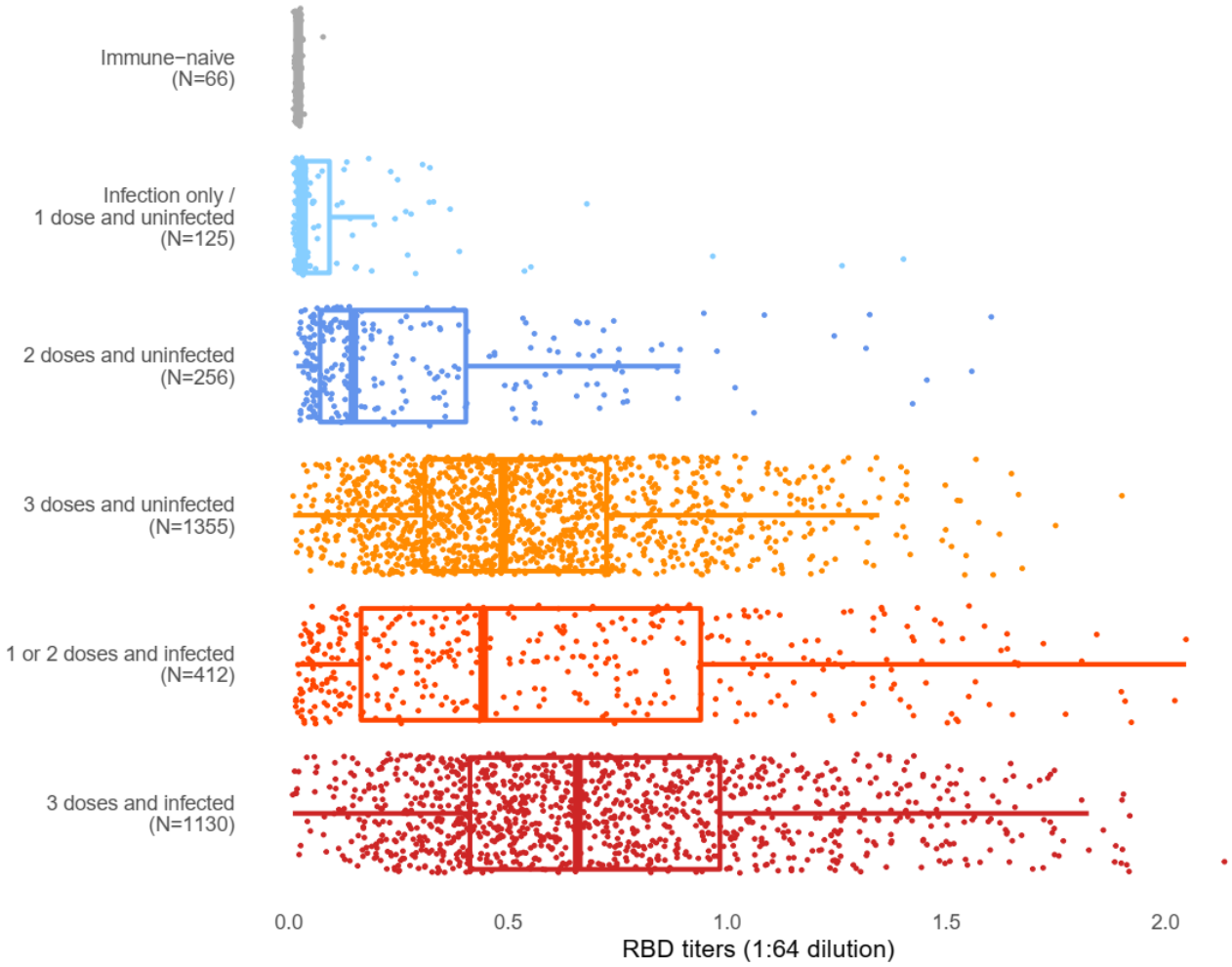


**Table S1. Sample Characteristics and Representativeness of Phases 3 to 4 (5031 adults) with Online Surveys and DBS Samples and Baseline Survey Non-Responders and DBS Non-Responders**

| | 2016 Canadian Census or national surveys | Baseline survey non-responders (n=23663) % | Baseline DBS non-responders (n=11392) % | Phase 3 Survey (n=11041) % | Phase 3 DBS sample (n=5155) % | Phase 4 Survey (n=14224) % | Phase 4 DBS sample (n=5031) % |
|---|---|---|---|---|---|---|---|
| **High risk regions** | | 44.6% | 37.4% | 35.5% | 34.9% | 33.6% | 34.0% |
| **Province** | | | | | | | |
| Ontario | 38.0% | 35.9% | 35.4% | 40.5% | 42.3% | 40.0% | 41.5% |
| British Columbia & Yukon | 14.0% | 13.8% | 18.1% | 19.5% | 20.3% | 20.1% | 20.9% |
| Quebec | 23.0% | 25.0% | 17.7% | 14.6% | 13.4% | 12.5% | 12.2% |
| Prairie provinces & NWT | 19.0% | 17.0% | 22.1% | 19.3% | 18.5% | 21.1% | 19.6% |
| Atlantic provinces | 7.0% | 8.3% | 6.7% | 6.0% | 5.5% | 6.2% | 5.9% |
| **Sex** | | | | | | | |
| Male | 49.0% | 45.3% | 51.1% | 45.7% | 39.2% | 45.9% | 40.1% |
| Female | 51.0% | 53.6% | 47.7% | 53.5% | 60.2% | 53.1% | 59.3% |
| Prefer to self-describe | | 1.1% | 1.1% | 0.8% | 0.6% | 1.0% | 0.6% |
| **Age group** | | | | | | | |
| 18-39 years | 49.0% | 56.4% | 33.9% | 24.4% | 20.4% | 23.9% | 19.5% |
| 40-59 years | 28.0% | 28.8% | 36.0% | 35.5% | 34.1% | 36.1% | 34.4% |
| 60-69 years | 12.0% | 10.0% | 20.0% | 26.3% | 30.0% | 24.5% | 28.3% |
| 70+ years | 11.0% | 4.8% | 10.1% | 13.8% | 15.5% | 15.5% | 17.9% |
| **Education** | | | | | | | |
| Some college or less | 45.0% | 34.4% | 36.7% | 33.9% | 31.4% | 34.0% | 30.6% |
| College graduate | 32.0% | 24.7% | 33.3% | 31.5% | 31.0% | 31.6% | 31.5% |
| University graduate | 23.0% | 33.5% | 30.0% | 34.6% | 37.7% | 34.4% | 37.9% |
| **Visible minority** | | | | | | | |
| No | | 81.2% | 82.4% | 86.3% | 90.2% | 76.5% | 84.2% |
| Yes | 22.0% | 18.8% | 17.6% | 13.7% | 9.8% | 23.5% | 15.8% |
| **Indigenous** | | | | | | | |
| No | | 90.5% | 89.1% | 91.9% | 92.3% | 89.0% | 89.8% |
| Yes | 5.0% | 9.5% | 10.9% | 8.1% | 7.7% | 11.0% | 10.2% |
| **Household size** | | | | | | | |
| Live alone | 28.0% | | 17.1% | 20.2% | 20.3% | 18.7% | 19.7% |
| Two people | 34.0% | | 39.7% | 44.8% | 47.3% | 44.0% | 47.0% |
| Three people | 15.0% | | 18.7% | 15.2% | 14.2% | 16.2% | 14.8% |
| Four people | 14.0% | | 15.0% | 13.2% | 12.1% | 13.7% | 12.3% |
| Five people or more | 8.0% | | 9.5% | 6.6% | 6.1% | 7.5% | 6.2% |
| **Smoking** | | | | | | | |
| Never | 46.0% | | 45.6% | 47.7% | 47.9% | 48.3% | 49.7% |
| Current | 54% (current or former) | | 17.5% | 12.5% | 10.0% | 13.3% | 9.3% |
| Former | | | 34.1% | 38.4% | 41.2% | 36.5% | 39.8% |
| Unknown | | | 2.8% | 1.5% | 1.0% | 1.9% | 1.1% |
| **Weight status** | | | | | | | |
| Under or normal (< 25kg/m2) | 37.0% | | 27.1% | 28.5% | 29.3% | 29.0% | 30.6% |
| Overweight (25 to < 30 kg/m2) | 37.0% | | 30.5% | 32.0% | 33.7% | 31.4% | 33.4% |
| Obese (>= 30 kg/m2) | 27.0% | | 26.5% | 27.9% | 28.5% | 27.4% | 28.1% |
| Unknown | | | 15.9% | 11.5% | 8.5% | 12.2% | 7.8% |
| **Diabetes** | | | | | | | |
| No | | | 89.1% | 88.1% | 88.5% | 88.1% | 88.5% |
| Yes | 9.0% | | 9.3% | 11.0% | 11.1% | 10.6% | 11.0% |
| Unknown | | | 1.5% | 0.9% | 0.5% | 1.3% | 0.5% |
| **Hypertension** | | | | | | | |
| No | | | 71.8% | 68.8% | 68.4% | 69.7% | 68.9% |
| Yes | 23.0% | | 25.7% | 29.8% | 30.8% | 28.4% | 30.4% |
| Unknown | | | 2.5% | 1.4% | 0.8% | 1.9% | 0.7% |
| **Vaccination as of March 13, 2022** | | | | | | | |
| Not vaccinated | 7.9% | | | 12.1% | 5.6% | 9.7% | 4.5% |
| Vaccinated | 92.1% | | | 87.9% | 94.4% | 90.3% | 95.5% |

**STROBE Statement**

| | Item No. | Recommendation | Relevant text from manuscript (page no.) |
|---|---|---|---|
| **Title and abstract** | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract | Ab-C conducted four serial assessments of SARS-CoV-2 seropositivity using the Angus Reid Forum, a nationally representative online polling platform (1, S1) |
| | | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | NA |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | The incidence of the Omicron variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which rose worldwide from December 2021, is poorly understood. (1) |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | We quantify SARS-CoV-2 incidence during the Omicron (BA.1/1.1) wave among Canadian adults and the contribution of prior infection and concurrent vaccination […] to an age-specific "immunity wall." (1) |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | Ab-C conducted four serial assessments of SARS-CoV-2 seropositivity, each of 5700-9000 adults […]. Participant-collected dried blood spots (DBS) underwent highly sensitive and specific chemiluminescence-based enzyme-linked immunosorbent assays (1) |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | The 5031 adults surveyed in Phase 4 of Ab-C whose DBS were received from Jan 24-Mar 15, 2022 (1) |
| Participants | 6 | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | Nationwide polling panel of Canadian adults aged 18 and older. The sampled population was stratified by [age, sex, education,] and region, by census metropolitan area to match the national demographic distribution (S1) |
| | | (b) For matched studies, give matching criteria and number of exposed and unexposed | NA |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | SARS-CoV-2 seropositivity […] targeting the spike protein, receptor binding domain, and nucleocapsid protein (1) |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | See no. 6. |
| Bias | 9 | Describe any efforts to address potential sources of bias | NP positivity may have under-estimated actual Omicron infection (1) |
| Study size | 10 | Explain how the study size was arrived at | NA |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | IgG Serology and Cutoffs sections, Analyses section (S1) |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding | We derived a positivity threshold […]<br>We obtained the overall cumulative incidence of SARS-CoV-2 infections based on NP seropositivity and derived the 95% confidence intervals using the Delta method. (S1) |
| | | (b) Describe any methods used to examine subgroups and interactions | NA |
| | | (c) Explain how missing data were addressed | Figure S2 |
| | | (d) If applicable, explain how loss to follow-up was addressed | Cross-sectional surveys (1, Figure S2) |
| | | (e) Describe any sensitivity analyses | We adopted the cutoff value of 0.25 as it |

| | | | |
|---|---|---|---|
| | | | incorrectly classifies 10% of samples as false positives and 10% as false negatives. Thus, the overall number of samples classified as positive is expected to be correct (S2) |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed | Figure S2 |
| | | (b) Give reasons for non-participation at each stage | Figure S2 |
| | | (c) Consider use of a flow diagram | Figure S2 |
| Descriptive data | 14* | (a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders | Table S1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Figure S2 |
| | | (c) Summarize follow-up time (e.g., average and total amount) | Figure S1 and Figure S2 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | Figure 1, Figure S1, and Figure S2 |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included | NA |
| | | (b) Report category boundaries when continuous variables were categorized | NA |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | NA |
| Other analyses | 17 | Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses | NA |
| **Discussion** | | | |
| Key results | 18 | Summarize key results with reference to study objectives | Applying the vaccinated/unvaccinated between-phase incidence to Canada's 29.7 million adults yielded an estimate of 9.0 (7.9-10.2) million adults newly infected during Omicron, of which 0.9 (0.6-1.2) million infections were among 2.3 million unvaccinated adults. (1) |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | The 5031 adults surveyed in Phase 4 […] were broadly representative of Canadian adults with similar prevalences of obesity, smoking, diabetes, and vaccination but had fewer lower-education adults (Tables S1) (1) |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | NP positivity may have under-estimated actual Omicron infection (1) |
| Generalizability | 21 | Discuss the generalizability (external validity) of the study results | […] broadly representative of Canadian adults with similar prevalences of obesity, smoking, diabetes, and vaccination (1) |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | CITF, CIHR, Pfizer, Unity Health Toronto (2) |

## Acknowledgements

We thank the thousands of Canadians who participated in the Action to Beat Coronavirus study. A full listing for the Ab-C Investigators is shown on page 1 of this supplement, and available at www.abcstudy.ca.

## Supplemental References

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