Article

Not peer-reviewed version

Risk Factors for Infection with SARS-CoV-2; a Prospective Cohort of Teachers and Education Workers, 2021–2023

Brenda Coleman *, Susan Bondy, Kailey Fischer, Iris Gutmanis, Veronica Zhu, Kanchan Kanchan, Sharon Straus, John Kim, Sharon Simon, Allison McGeer

Posted Date: 21 April 2025

doi: 10.20944/preprints202504.1572.v1

Keywords: SARS-CoV-2; educators; Canada; infection; risk factors

 doi:10.20944/preprints202504.1572.v1

Article

Risk Factors for Infection with SARS-CoV-2; a Prospective Cohort of Teachers and Education Workers, 2021–2023

Brenda Coleman [1,2,*], Susan Bondy [2], Kailey Fischer [1], Iris Gutmanis [1], Veronica Zhu [1], Kanchan [1], Sharon Straus [2,3], John Kim [4], Sharon Simon [4] and Allison McGeer [1,2]

[1] Sinai Health, 600 University Ave, Toronto, ON M5G 1X5 Canada
[2] University of Toronto, 27 King's College Cir, Toronto, ON M5S 1A1 Canada
[3] Unity Health, 30 Bond St, Toronto, ON M5B 1W8 Canada
[4] National Microbiology Laboratory, 1015 Arlington St, Winnipeg, MB R3E 3R2 Canada
* Correspondence: b.coleman@utoronto.ca

Abstract: Objectives: to determine factors associated with rates of SARS-CoV-2 infection and to determine whether anti-receptor-binding domain (RBD) IgG levels were associated with the rates of infection. Design: prospective cohort of 34 months' duration (February 2021 to December 2023). Setting: teachers and education workers working ≥8 hours per week in the Canadian province of Ontario. Participants: 3155 education workers were eligible for the risk factor analysis; 2977 for the serological analysis. Primary outcome measure: SARS-CoV-2 infection, symptomatic or asymptomatic. Results: 1909 SARS-CoV-2 infections were reported (0.93 per 1000 participant-days); the highest incidence occurred during the period dominated by the Omicron BA.2 variant (2.01/1000 participant-days). After a median of 740 (interquartile range 361, 971) days of follow-up, participants who received three (adjusted hazard ratio (aHR) 0.24; 95% CI 0.11, 0.50; p<0.001), four (aHR 0.14; 95% CI 0.07, 0.30; p<0.001), or five or more (aHR 0.14; 95% CI 0.06, 0.30; p<0.001) doses of COVID-19 vaccines had lower rates of infection than participants who received <2 doses. Likewise, those who had immunity from a previous infection had lower rates of infection (aHR 0.05; 95% CI 0.04, 0.07) than those without. Participants 30 years of age or older had a lower rate of infection than participants 20-29 years old and those with Caucasian/European ancestry had a lower rate of infection (aHR 0.83; 95% CI 0.71, 0.96; p=0.01) than others. Also, compared to participants without known contact with an infected person, those in close contact with an infected household member (aHR 1.54; 95% CI 1.39, 1.71; p<0.001), coworker or student (aHR 1.22; 95% CI 1.04, 1.42, p=0.012), or individuals from more than one setting (aHR 1.45; 95% CI 1.29, 1.63; p<0.001) had higher rates of infection. Blood samples with anti-RBD antibody levels in the highest quintile (≥5850 BAU/mL) were associated with a lower rate of subsequent infection (aHR 0.40; 95% CI 0.23, 0.72) compared to samples with RBD levels below the threshold of detection. Conclusions: COVID-19 vaccines continued to provide protection against infection with SARS-CoV-2 through December 2023. Infection following exposure to people with SARS-CoV-2 occurred in a variety of venues indicating the need to practice intervention strategies when the potential for transmission is high.

Highlights

Strengths and limitations

- This prospective cohort followed participants for up to 34 months encompassing eight SARS-CoV-2 variant periods
- The use of modified survival analysis permitted the inclusion of both first and subsequent SARS-CoV-2 infections in the analysis of factors associated with infection
- Self-collected dried blood spot samples were used to assess serological response to vaccines and infections

 doi:10.20944/preprints202504.1572.v1

- Exposure information from participants without symptoms who were negative for, or not tested for, SARS-CoV-2 was used as comparators to infected participants
- Participants who withdrew may be dissimilar to those who chose to continue in the study

Keywords: SARS-CoV-2; educators; Canada; infection; risk factors

1. Introduction

Teachers and others working in education systems across the world play a vital role in social infrastructures. Their roles put them in close contact with both children and adults, and therefore at higher risk of exposure to communicable diseases, including SARS-CoV-2. Authors of studies done in England and Wales [1] and the United States [2] reported that school teachers and teaching support staff had higher rates of COVID-19 than the general working population. Despite this, there is a paucity of research into the epidemiology of communicable diseases, including respiratory pathogens, in this population.

There are numerous strategies to reduce the probability of infection with respiratory pathogens including SARS-CoV-2. The strategies are broadly categorized as pharmaceutical (e.g., vaccination) and non-pharmaceutical (e.g., masking, isolating when ill, enhanced cleaning, improved ventilation, etc.). Because vaccines were not available at the onset of the COVID-19 pandemic, many jurisdictions, including Ontario, Canada, were able to drastically reduce community transmission by isolating people through the closure of non-essential workplaces, including schools [3].

The introduction of vaccines dramatically reduced disease caused by the early variants of SARS-CoV-2, but immunity waned due to a reduction in antibody levels over time and because variants of SARS-CoV-2 escaped vaccine-and infection-induced immunity [4–6]. Following the first booster doses of vaccine, vaccine effectiveness (VE) against symptomatic infection during the Delta- and Omicron-dominated periods peaked eight weeks after vaccination at 91.8% and 67.3%, respectively, but declined to 76.5% and 46.1% by 24 weeks afterwards [7]. Studies have reported lower VE for people with recent protection from SARS-CoV-2 infection (76%) than for those without (87%) [8].

Correlates of protection are necessary to estimate the potential effectiveness of new vaccines [9] and are helpful in evaluating the immune status of populations or subgroups of populations. Antibodies against SARS-CoV-2 such as the immunoglobulin G (IgG) antibodies of the spike and receptor binding domain (RBD) are induced by vaccination while infection induces a general response against the nucleocapsid and other viral proteins. The RBD is a target for antibody-mediated neutralization making it a possible option for serological assays for SARS-CoV-2 [10]. Authors of some studies have reported that high levels of SARS-CoV-2 IgG anti-spike and anti-RBD antibodies were associated with significantly lower risks of infection [11–13] while other, generally smaller, studies found no association [14,15].

The objectives of this study were to describe the rates of SARS-CoV-2 infection (symptomatic or asymptomatic) in education workers, to determine factors associated with rates of infection, and to ascertain whether anti-RBD IgG levels were associated with the rates of subsequent infection.

2. Methods

This prospective cohort study enrolled people aged 18 to 75 years who were employed in any capacity by an Ontario public or private school board for ≥8 hours per week [16]. Recruitment occurred between 18 February 2021 and 01 June 2023 with data collection ending upon withdrawal from the study or on 22 December 2023, whichever occurred first. Participants were recruited virtually through communications from federations and unions for education workers and via social media platforms. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Sinai Health Research Ethics Board (#20-0343-A; 21 January 2021). All participants provided written consent prior to enrolment.

 doi:10.20944/preprints202504.1572.v1

Participants were eligible for the risk factor analysis if they completed ≥80% of at least one baseline questionnaire, a vaccination report, at least one illness or biweekly questionnaire, and participated for ≥30 days. To be eligible for the serological analyses, participants must have submitted at least one dried blood spot (DBS) sample of sufficient quantity and quality for laboratory analysis and have completed ≥80% of at least one baseline questionnaire, a vaccination report, and at least one illness or biweekly questionnaire. Eligibility was not restricted by vaccination status nor previous infection with SARS-CoV-2.

All questionnaires used for this study were drafted and their face validity assessed by experts in epidemiology, infectious diseases, and infection prevention and control before they were pilot-tested with education workers. All questionnaires and participant-facing documents were available online or by paper and in both English and French, with translation provided by a certified translation service.

Participant and public involvement statement: federation and association staff representing education workers in Ontario as well as current and former education workers provided feedback on the study design and questionnaires.

2.1. Setting

In Ontario, COVID-19 vaccines became available for people working and living in long term care and retirement homes, health care workers, and adults living in higher risk communities on 14 December 2020. Working age adults became eligible in March of 2021 with second doses delayed to partially protect a larger number of individuals [17]. Most doses of vaccines administered by December 2023 were either BNT162b2 (67.8%) or mRNA-1273 (29.3%); ChAdOx1-S represented 2.8% of COVID-19 vaccine doses distributed to Ontario [18] but its use was discontinued in March 2021 [19].

Ontario's schools are regularly closed for summer vacation for the months of July and August, for two weeks in December, and one week in March. During the COVID-19 pandemic, public health measures to reduce SARS-CoV-2 transmission were implemented on 15 March 2020 (the first day of the March break). Schools were closed and instruction moved online from 24 March through 30 June 2020. Schools reopened on 8 September 2021 with cohorting (students, and sometimes teachers, kept together for all subjects) and other strategies implemented to minimize virus transmission [20]. As part of these strategies, older students and all school staff were required to wear masks, with a phase-in period for masking among younger students. Subsequent school closures occurred from 4 January to 16 February 2021, 12 April to 7 September 2021 (including the summer break), and 5 January to 18 January 2022 [21]. Strategies to reduce transmission, including the mask mandate, were in effect until 19 March 2022 [22].

2.2. Data Collection

Consenting participants were linked to their individual study page on a secure, Canadian-based online platform to complete baseline, biweekly (i.e., every other week), and monitoring questionnaires as well as illness and vaccination reports (completed as needed) [23]. They then received emails every second week during the study with current COVID-19 information and reminders with links to their study page to complete questionnaires.

All participants were asked to complete a baseline questionnaire at enrolment and again every September, at the start of the new school year. Vaccination against SARS-CoV-2 was self-reported on the vaccination report that collected names and dates of receipt of COVID-19 vaccines. Participants were asked to complete illness reports if they had a respiratory illness and/or if they had a COVID-19 test. Illness reports asked for test result, test type (polymerase chain reaction [PCR] or rapid antigen test [RAT]), symptoms, and known close contact with anyone with COVID-19 in the previous 14 days. Reports could be accessed at any time using a link provided at enrolment.

Biweekly questionnaires asked about acute respiratory illness symptoms and SARS-CoV-2 tests in the previous 14 days. Participants were randomized upon enrolment to the week they would

 doi:10.20944/preprints202504.1572.v1

receive the biweekly questionnaire, with one half of the cohort asked to complete it each week. If participants reported a cough, fever, shortness of breath, or that they were tested for COVID-19, the biweekly questionnaire was closed and they were redirected to an illness report. Monitoring questionnaires, with the same questions as those asked on the illness report (except about test result/type) were assigned to occur in place of every 6th biweekly questionnaire (randomly assigned so 1/12th of participants completed it every week). Monitoring questionnaires were restricted to participants who had not submitted an illness report in the previous two weeks.

Participants were asked to provide DBS samples at enrolment, 30 days after every positive swab result and COVID-19 vaccine dose received, and every 180 days after the most recent of either (infection or vaccination). Capillary whole blood was obtained by self-collection with a lancet on 903 Whatman® protein saver cards, dried, and stored in gas impermeable bags with desiccant at ambient temperature until samples arrived at the study site. The cards were then stored at 4°C until they were couriered, in batches, to the National Microbiology Laboratory in Winnipeg, MB, Canada where they were stored at -80°C until processed for testing.

On the day the sample was processed, samples were removed from the freezer and thawed at room temperature for 30 minutes. Using the BSD Robotics (Brisbane, AU) semi-automated DBS puncher, a ¼ inch fully-saturated disc of DBS punched from the sample card into a 96-well microtitre plate. The punch was eluted overnight at 4°C in 130 uL of elution buffer (DPBS pH 7.4, 0.5% BSA, 0.05% Tween20) without shaking. The samples were then shaken at room temperature for 30 minutes and the eluates were transferred to 1.5 mL Sarstedt tubes. All samples were tested using Bio-Rad BioPlex SARS-CoV-2 IgG assay (Bio-Rad Laboratories, Inc., Hercules, CA) to determine IgG antibodies against spike, RBD, and nucleocapsid targets. Antibody concentrations were reported in binding antibody units (BAU) per mL using the first World Health Organization standard [24] with an experimentally-determined conversion factor applied to the DBS sample results to provide BAU/mL values equivalent to plasma concentrations. Lower limits of detection, in BAU/mL, were 25.03 for RBD, 41.94 for spike, and 8.44 for nucleocapsid.

2.3. Definitions

The primary outcome, SARS-CoV-2 infection (symptomatic or asymptomatic) occurring during the study period, was defined as a PCR or RAT that was positive for SARS-CoV-2. Illness reports were excluded from these analyses if a positive test was reported within the previous 60 days [25] or if a positive RAT result was followed by a negative PCR test result within 24 hours.

Participants were considered immunized 14 days after vaccination. Receipt of a primary series of vaccines was defined as receipt of both of any two-dose vaccine or one of any single-dose vaccine. Receipt of a primary series of vaccine(s) was coded as two vaccines for ease of reporting additional/booster doses (i.e., three doses were equivalent to a primary series plus one).

Previous infections were those reported in the baseline questionnaire that occurred prior to study enrolment or when the DBS sample obtained at enrolment had detectable levels of anti-nucleocapsid IgG titres and at least one of anti-spike or anti-RBD. Previous infections occurring during participation were defined as illness reports with positive PCR or RAT results or positive blood samples that occurred prior to the infection under consideration. Positive blood samples without a matching illness report were assumed to have occurred midway between the previous negative sample and the date of collection (or midway between enrolment and blood collection, if there was no previous sample).

Anti-RBD IgG titres (in BAU/mL) were categorized into quintiles since they were not normally distributed and could not be normalized by transformation. The base quintile included results below threshold of detection while other quintiles were 10-759, 760-2289, 2290-5849, and ≥5850 BAU/mL.

Covariates collected on the baseline questionnaires included personal (age, gender, previous positive tests for SARS-CoV-2, chronic health conditions, the use of eye glasses and refillable drink containers, self-reported health status, smoking status, hand-to-face habits, education level, occupation), household (household size), and workplace (school size, closeness of contact with

 doi:10.20944/preprints202504.1572.v1

students, closeness of contact with coworkers, hours of work per week) factors (see Table 1 for variable categories).

Table 1. Demographic description of participants in the COVID-19 Cohort Study of Teachers and Other Education Workers, 18 February 2021 to 22 December 2023 by analysis; Number (percent) unless otherwise stated.

Demographic Variable	Risk Factor Analysis (N=3155)	Serological Analysis (N=2977)
Age, median years (IQR)	46 (40, 52)	46 (40, 52)
Gender/sex		
Female	2688 (85.2)	2534 (85.1)
Male	458 (14.5)	435 (14.6)
Other	9 (0.3)	8 (0.3)
Household size, median (IQR)	3 (2, 4)	3 (2, 4)
Caucasian (vs other)	2963 (94.0)	2805 (94.2)
Health status		
Fair or poor	140 (4.4)	140 (4.7)
Good	795 (25.2)	741 (24.9)
Very good	1494 (47.3)	1409 (47.3)
Excellent	726 (23.0)	687 (23.1)
At least one chronic health condition	803 (25.6)	753 (25.3)
Immune compromising condition/medication[1]	86 (2.7)	80 (2.7)
Eye glasses		
No	754 (23.9)	711 (23.9)
Reading and distance	1326 (42.0)	1236 (41.6)
Reading or distance	837 (26.5)	796 (26.8)
Contacts	238 (7.5)	227 (7.6)
Use refillable drink container		
Never	118 (3.7)	104 (3.5)
< Once/month	69 (2.2)	64 (2.2)
Several times/month	106 (3.4)	96 (3.2)
Several times/week	241 (7.6)	229 (7.7)
Most days	2621 (83.1)	2475 (83.4)
Hands to face frequency		
Never	379 (12.0)	353 (11.9)
1-2/day	1345 (42.6)	1289 (43.4)
3-5/day	720 (22.8)	670 (22.5)
>5/day	711 (22.5)	661 (22.2)
Tobacco smoking		
Never	2406 (76.3)	2270 (76.3)
Former	612 (19.4)	588 (19.7)
Current	137 (4.3)	119 (4.0)
Public school board (vs private)	3026 (95.9)	2861 (96.2)
Education level		
Secondary or less	44 (1.4)	43 (1.4)
College diploma	227 (7.2)	210 (7.1)
Bachelor's degree	421 (13.3)	396 (13.3)
Teaching certificate	1735 (55.0)	1645 (55.3)
Master's degree	680 (21.5)	637 (21.4)
Doctoral degree	48(1.5)	46 (1.5)
Occupation		

 doi:10.20944/preprints202504.1572.v1

Teacher	2565 (81.3)	2428 (81.6)
Educational assistant	181 (5.7)	161 (5.4)
Early childhood educator	70 (2.2)	69 (2.3)
Principal/vice principal	117 (3.7)	105 (3.6)
Administrative/support[2]	113 (3.6)	110 (3.7)
Professional[3]	109 (3.4)	103 (3.5)
Students in school		
<100	94 (3.0)	90 (3.0)
100-399	1031 (32.7)	997 (33.5)
400-699	926 (29.3)	896 (30.1)
700+	887 (28.1)	874 (29.4)
Not applicable (e.g., board office)	217 (6.9)	116 (3.9)
Level of contact with students		
No close contact	328 (10.4)	208 (7.0)
In same room but >2 metres distance	422 (13.4)	318 (10.7)
In same room and <2 metres distance	1685 (53.4)	1688 (56.7)
Physical contact	720 (22.8)	762 (25.6)
Level of contact with coworkers		
No close contact	344 (10.9)	345 (11.6)
In same room but >2 metres distance	1355 (43.0)	1316 (44.2)
In same room and <2 metres distance	1340 (42.5)	1203 (40.4)
Physical contact	116 (3.7)	113 (3.8)
Region of residence in Ontario[4]		
East	559 (17.7)	550 (18.5)
Central	1084 (34.5)	1028 (34.5)
Toronto	626 (19.8)	565 (19.0)
Southwest	729 (23.1)	690 (23.2)
North	157 (5.0)	144 (4.8)

Close contact with a person with SARS-CoV-2 was defined as being within two metres for two minutes or longer in the two weeks before an illness report or monitoring questionnaire. The SARS-CoV-2 Alpha variant-dominated period started 2 February 2021, Delta on 27 June 2021, Omicron BA.1 on 12 December 2021, BA.2 on 27 March 2022, BA.4/BA.5 on 26 June 2022, BQ on 20 November 2022, XBB on 19 February 2023, and EG.5 on 17 September 2023 using data from the National Microbiology Laboratory [26].

Daily estimates of force of infection with COVID-19 (i.e., risk of COVID-19 exposure in the community) was approximated by using daily mortality rates attributed to COVID-19 in the Ontario population [27]. These values were offset by 14 days to account for the lag between infection and death. This proxy measure was used because testing data were not reliable for the full study period due, largely, to changes in the type of tests used to diagnose SARS-CoV-2 (PCR to RAT) and changes in reporting of positive tests associated with that change [28].

2.4. Data Structuring and Analysis

For the analysis of factors associated with infection, including vaccine effectiveness, survival analysis used an extension of the Cox model (i.e., Prentice-Williams-Peterson gap time [29]) with robust variance estimates to account for repeat infections in the same participant [30]. Start times were either the participant's date of enrolment or 14 days after receipt of a dose of COVID-19 vaccine or a positive test. Stop times were 13 days after the date of a positive test or receipt of a vaccine, or the last day of active study participation. Data from questionnaires and reports were matched to observation periods.

Purposeful selection of covariates was performed, as per Hosmer and Lemeshow [31]. In short, all variables in Table 1 were included in the saturated model if their association with infection, on

 doi:10.20944/preprints202504.1572.v1

bivariable modelling, was p≤0.20 or they were of clinical importance (e.g., vaccination status, previous infection). Multivariable models were adjusted for possible differences in the baseline hazards for the number of infections per participant and the number of days between the outcome and the more recent of vaccination or infection (categorized), by using Stata's *strata* option [32]. Covariates were removed sequentially from the saturated model starting with those with the highest *p*-value. If removal of a variable caused a change of ≥20% in any other variable's coefficient, it was retained as a potentially confounding variable. All variables excluded prior to model fitting were added back into the reduced model, one at a time, to assess their level of association and their impact on the other estimates. If the removal or addition of any variable changed the estimates of other variables by >20%, they were retained. Models were assessed for potential effect measure modification for biologically plausible pairings (e.g., age and health status). All models were assessed for proportionality using the test of Schoenfeld residuals and log-log plots of survival adjusted for covariates. If the models were non-proportional, time-varying covariates (i.e., COVID-19-associated mortality rates for the province) were evaluated and used, as required.

The analysis of the association between anti-RBD IgG levels (in quintiles) and rates of subsequent infection also used the Prentice-Williams-Peterson gap time model. Start times for survival analyses were the dates of blood collection; stop times were the date prior to the following sample or the last day of active participation, as applicable. Data from questionnaires and reports were matched to observation periods. Multivariable models were adjusted for possible differences in the baseline hazards for the number of infections per participant and the number of days between the date of blood collection and the more recent of vaccination or infection (categorized). Estimates were adjusted for age, gender, health status, number of doses of vaccine, and whether they had previously tested positive for SARS-CoV-2. All models were assessed for proportionality, as noted above, using Stata SE v18 [33] and were adjusted for the potential time-varying covariate (i.e., previous SARS-CoV-2 positive test). No imputation of missing data was performed.

3. Results

3.1. Cohort Characteristics

Of the 3818 education workers who consented to participate, 3155 (82.6%) were eligible for inclusion in the risk factor analysis and 2977 for the serological analysis. The median (IQR) duration of participation was 740 days (361, 971) days (24.3 months). During the 34 months of study follow-up, 1909 SARS-CoV-2 infections were reported by participants (0.93 per 1,000 participant-days). Most 1582 (82.9%) were single infections while 302 (15.8%) were second, 23 were third, and 2 were fourth infections. Most infections (1866 or 97.8%) were symptomatic.

Incidence rates were 0.04 and 0.03 per 1,000 participant days during the Alpha- and Delta-dominated periods, respectively. Rates were higher during the Omicron subvariant periods with rates of 1.45 during BA.1, 2.01 through BA.2, 1.61 during BA.4/5, 1.03 throughout BQ, 0.60 during XBB, and 1.71 during the period dominated by EG.5 (see Supplementary Figure S1). The incidence of SARS-CoV-2 was lower when masks were required to be worn within schools than after the mandate was discontinued on 21 March 2022 (0.42 vs 1.30 per 1,000 participant days; p<0.001).

Overall, 540 of 3155 (17.1%) participants had received at least one dose of a COVID-19 vaccine before enrolment and the median (IQR) number of doses of COVID-19 vaccine received was 3 (2, 4). Prior to leaving the study, 2912 (92.3%) participants had received at least two doses of vaccine of which 61.1% were BNT162b2, 17.4% mRNA-1273, 21.3% ChAdOx1-S, and 0.1% others; none were single dose vaccines. As such, the term 'two doses' was used to define receipt of the primary series of vaccine.

As shown in Table 1, 85% of participants were female, 81% were teachers, the median household size was 3 (including the participant), and the median age was 46 years. Most participants worked at schools with 100 or more students while about 7% worked at school boards offices or were

 doi:10.20944/preprints202504.1572.v1

professional support staff. There were no statistically significant differences in the demographic characteristics of participants included in the risk factor and serological analyses.

IQR: interquartile range;

(1) HIV/AIDS or other immune suppressing disease or immunosuppressive medication for >7 consecutive days including prednisone (>20 mg/day), methotrexate, cyclosporine, imuran, azathioprine tacrolimus, or other

(2) office and clerical staff, superintendent, human resources, finance, planner, audio-visual or computer technicians, bus driver, building maintenance/custodial, cafeteria/lunchroom staff

(3) psychologist, social worker, therapist, school nurse

(4) as defined by the first character of the postal code

3.2. Risk Factors for SARS-CoV-2 Infections

Data were available for 3155 education workers who reported 1909 positive tests for SARS-CoV-2 spanning 2,044,008 days of follow-up. Overall vaccine effectiveness estimates (1 - adjusted hazard ratio (aHR)) for second through fifth doses ranged from 76% (95% CI 50, 89) to 86% (95% CI 70, 94) after adjusting for previous SARS-CoV-2 infection (Table 2). As noted in the table, vaccine effectiveness estimates were substantially higher for participants without, compared to those with, a previous SARS-CoV-2 infection.

Table 2. Factors associated with SARS-CoV-2 infections, COVID-19 Cohort Study of Teachers and Other Education Workers, 18 February 2021 to 22 December 2023; Cox proportional hazards estimates.

Covariate	All Participants (n=1909 Positive) aHR (95% CI)	No Previous Infection(s) (n=1525 Positive) aHR (95% CI)	SARS-CoV-2 Previously (n=384 Positive) aHR (95% CI)
Doses of vaccine: <2	Referent	Referent	Referent
2	1.15 (0.55, 2.44)	0.84 (0.49, 1.44)	0.50 (0.16, 1.55)
3	0.24 (0.11, 0.50)‡	0.08 (0.04, 0.14)‡	0.43 (0.15, 1.27)
4	0.14 (0.07, 0.30)‡	0.03 (0.02, 0.06)‡	0.29 (0.10, 0.87)*
≥5	0.14 (0.06, 0.30)‡	0.02 (0.01, 0.05)‡	0.32 (0.10, 0.97)*
SARS-CoV-2 previously[1]	0.05 (0.04, 0.07)‡	NA	NA
Not infected	Referent		
Age group: 20-29	Referent	Referent	Referent
30-39	0.64 (0.47, 0.88)†	0.57 (0.39, 0.83)†	1.10 (0.46, 2.64)
40-49	0.61 (0.45, 0.83)†	0.59 (0.41, 0.86)†	0.94 (0.40, 2.19)
50-59	0.58 (0.43, 0.79)‡	0.55 (0.38, 0.79)†	1.02 (0.44, 2.40)
≥60	0.61 (0.43, 0.85)†	0.53 (0.35, 0.81)†	1.11 (0.46, 2.91)
Caucasian ancestry	0.82 (0.71, 0.96)†	0.87 (0.73, 1.02)	0.68 (0.46, 1.00)*
Other	Referent	Referent	Referent
No close contact[2]	Referent	Referent	Referent
Household member	1.53 (1.38, 1.70)‡	1.34 (1.17, 1.53)‡	2.20 (1.65, 2.94)‡
Coworker or student	1.21 (1.04, 1.41)*	1.10 (0.95, 1.29)	1.67 (1.31, 2.13)‡
Other person[3]	0.94 (0.55, 1.62)	1.25 (0.70, 2.24)	0.29 (0.03, 2.46)
More than one of the above	1.45 (1.29, 1.63)‡	1.29 (1.12, 1.49)‡	2.16 (1.62, 2.89)‡
Mortality rate, in province[4]	1.31 (1.28, 1.35)‡	1.36 (1.32, 1.40)‡	1.66 (1.41, 1.96)‡

* p<0.05; † p≤0.01; ‡ p≤0.001; aHR: adjusted hazard ratio; CI: confidence interval; NA: not applicable.

In the overall model, and the model restricted to participants without a previous infection, older participants had significantly lower rates of infection than education workers 20-29 years of age. Also,

 doi:10.20944/preprints202504.1572.v1

participants who reported that their cultural/racial background was Caucasian/European had lower rates of infection than others (aHR 0.82; 95% CI 0.71, 0.96).

Compared with participants who did not report close contact (≤2 metres for ≥2 minutes) with someone with SARS-CoV-2, those in close contact with a member of their household (aHR 1.53; 95% CI 1.38, 1.70), their workplace/school (aHR 1.21; 95% CI 1.04, 1.41), or people from different venues (1.45; 95% CI 1.29, 1.63) had higher rates of infection with SARS-CoV-2 within the following 14 days. The results were similar for the models based on previous infection status. In a post-hoc analysis, higher rates of infection were detected after workplace/school exposures when the close contact was with an infected coworker (aHR 1.27; 95% CI 1.08, 1.50) than an infected student (aHR 0.91; 95% CI 0.48, 1.56).

Cox proportional hazard using Prentice, Williams, and Peterson extension; clustered on user; stratified by number of events and days since most recent vaccination or infection; includes, as time varying covariate: whether they were previously positive with SARS-CoV-2

(5) Positive by respiratory swab (self-reported) or DBS sample (anti-nucleocapsid and anti-RBD and/or anti-spike IgG levels above threshold of detection); n=9/384 or 2.3% of participants with previous positive results were detected by serology alone
(6) Close contact (≤2 metres for >2 minutes) with someone with SARS-CoV-2 in previous 14 days
(7) Close contact not listed above (e.g., extended family member, friend, or other)
(8) Deaths attributed to COVID-19 in province, with 14-day lag, used as a proxy for force of infection

3.3. RBD Levels as Correlates of Protection

Data were available for 2977 education workers who reported 1508 positive tests for SARS-CoV-2 and submitted 15,991 blood samples that were tested for IgG antibody levels against SARS-CoV-2; the median number of blood samples submitted was 4 (IQR 2, 6). Supplementary Table S1 demonstrates that anti-RBD IgG titres increased after each dose of vaccine and that participants with a previous SARS-CoV-2 infection had higher antibody levels, on average, than those without (p<0.001). As demonstrated in Supplementary Table S2, maximal RBD values were observed in blood samples taken 10-59 days after vaccination for all participants.

Estimates from adjusted Cox multivariable models indicated that the rates of a subsequent SARS-CoV-2 infection (n=1505 infections) were significantly lower (aHR 0.40; 95% CI 0.23, 0.72; p=0.002) when IgG anti-RBD levels were ≥5850 BAU/mL (i.e., the highest quintile) compared to when levels were below the threshold of detection (see Table 3). Similarly, the rates of subsequent infection (n=1328 infections) were significantly lower (aHR 0.39; 95% CI 0.21, 0.73; p=0.003) for participants with no previous infection. However, no association between anti-RBD levels and infection were detected in samples from participants with previous infections. A post-hoc analysis (not shown) using deciles of RBD levels (rather than quintiles) did not detect a level that was associated with a lower rate of infection in this small sample (n=177 infections).

Table 3. Association between IgG anti-RBD levels and subsequent SARS-CoV-2 infections, COVID-19 Cohort Study of Teachers and Other Education Workers, 18 February 2021 to 22 December 2023; adjusted[1] Cox proportional hazards.

Anti-RBD Level (in BAU/mL)	All Participants[1] (n=15991 Samples) aHR (95% CI)	No Previous Infection(s)[2] (n=11584 Samples) aHR (95% CI)	SARS-CoV-2 Previously[2] (n=4407 Samples) aHR (95% CI)
Below threshold of detection	Referent	Referent	Referent
10-759	0.88 (0.51, 1.52)	0.80 (0.44, 1.46)	1.98 (0.44, 8.97)
760-2289	0.78 (0.45, 1.36)	0.72 (0.40, 1.32)	1.14 (0.24, 5.37)
2290-5849	0.66 (0.38, 1.15)	0.63 (0.34, 1.16)	0.74 (0.16, 3.48)
≥5850	0.40 (0.23, 0.72)†	0.39 (0.21, 0.73)†	0.51 (0.11, 2.42)

 doi:10.20944/preprints202504.1572.v1

*p<0.05; †p≤0.01; ‡p≤0.001; aHR: adjusted hazard ratio; CI: confidence interval; NA: not applicable; IgG: immunoglobulin G; RBD: receptor binding domain of the spike protein; BAU: binding antibody units; mL: millilitres; SARS-CoV-2: severe acute respiratory syndrome-coronavirus 2.

(1) Cox proportional hazard model using Prentice-William-Peterson extension; adjusted for age, gender, health status, number of doses of COVID-19 vaccines, and whether they had tested positive for SARS-CoV-2 prior to the blood sample; stratified by time since vaccination or SARS-CoV-2 infection, and using previous SARS-CoV-2 history as a time-varying covariate
(2) Adjusted as above less a) whether they had tested positive for SARS-CoV-2 prior to the blood sample as a covariate and b) history of SARS-CoV-2 infection as a time-varying covariate

4. Discussion

This 34-month long prospective cohort study of teachers and other education workers supported existing research findings that vaccination against COVID-19 vaccines was protective against SARS-CoV-2 to December 2023. It also revealed that exposure to people with COVID-19 occurred in many venues including households and workplaces/schools with exposure to infected coworkers having a greater impact on the rate of infection than exposure to infected students.

Adjusted vaccine effectiveness estimates in this cohort of education workers ranged from 76% to 86% over the study period (18 February 2021 to 22 December 2023), depending on the number of vaccines they had received. These estimates were similar to pooled estimates reported in systematic reviews for vaccine effectiveness in the general public. Tsang et al. [8] and Zeng et al. [34] reported pooled vaccine effectiveness estimates of 71-90%, with higher effectiveness during the Alpha through Delta than the Omicron-dominated periods. Also, Nealon et al. [35] reported pooled vaccine effectiveness estimates of 48-62% and 47-48% after third and fourth doses of vaccine, respectively. Song et al. [36] reported an estimate of 53.5% effectiveness after receipt of a bivalent booster dose. These data indicate that the use of COVID-19 vaccines reduced the likelihood of infection that, in turn, reduced transmission, lost work days, and the possibility of severe complications.

In this study, rates of infection among teachers and others working in the education system were elevated after close contact with a household member or a coworker who were ill with COVID-19. Higher rates of infection were reported after exposure to infected household members compared with other persons in several school-based studies and in studies of health care workers [13,16,37,38]. Cordery et al. [39], Bark et al. [40], and Choi and Lavoie [41] conducted contact tracing of cases in which transmission was determined to be more prevalent within households than in schools. A retrospective chart review of school staff cases in a study by Campeau et al. [42] reported the same conclusion: that few cases appeared to be in-school transmission. Although the rates of infection were somewhat higher, in our study, for infection following close contact with a household member than a coworker or student, the confidence bands overlapped. This apparent discrepancy may be because the other studies were all conducted during the 2020/2021 school year, prior to the repeal of the mask mandate in schools. In a post-hoc analysis, we found that the incidence of SARS-CoV-2 was significantly higher following the repeal of the mask mandate compared to the period when the mandate was in effect. However, we were not able to conduct a subgroup analysis to estimate the impact of masking on rates of infection by source of exposure due to small numbers of infections during the masks-required period. As evidenced by a companion analysis from this study cohort [13], the consistent use of masks while at work dropped from 73% to 19% following the repeal of the mask mandate, with significant accompanying declines in hand hygiene and staying home when ill. Cowger et al. [43] and DeJonge et al. [44] also reported higher rates of SARS-CoV-2 infection in educators working in school districts in the United States without mask mandates compared to those in districts with mandates in the same state. Similarly, Peng et al. [45] determined that community mask mandates in Ontario were effective in reducing transmission by 31-76%, depending on the model. The use of protective strategies including vaccination and non-pharmaceutical interventions

 doi:10.20944/preprints202504.1572.v1

such as wearing masks, hand and cough hygiene, and isolating when ill, are necessary to reduce the incidence of respiratory diseases within households, workplaces, and beyond.

In this study, results of DBS IgG antibody tests indicated that higher titres of RBD antibodies were associated with lower rates of subsequent SARS-CoV-2 infection. In a systematic review, Rahmani et al. [46] determined that protection against infection was higher with anti-RBD titres of ≥1341.5 BAU/mL. Although these data agree with our results, there are several issues to consider when attempting to use SARS-CoV-2 antibody levels as correlates of protection: comparisons of the absolute values are fraught due to differences in testing platforms and collection methods; antibody levels wane over time, but at different rates depending on vaccination(s) and/or previous infection(s); and the specificity of antibodies may be different to new variants. Given these limitations, anti-RBD titres may be useful for the licensure processes for COVID-19 vaccines and for estimating levels of protection at the population or sub-population level, if updated antigen-specific titres can be assessed.

4.1. Strengths and Limitations

One of the greatest strengths of our study is its duration; there were 34 months of follow-up that included eight waves of SARS-CoV-2 variant transmission. Although the study did not commence until 21 February 2021, it started prior to the availability of vaccines for most adults in Canada and after most educators were once again working directly with students thus allowing the estimation of rates of infection relative to a variety of workplace-related factors. However, the length of the study likely caused participants to withdraw, introducing the possibility of selection bias in which those who remained differed from those who withdrew. Another strength is the use of infections, per se, rather than restricting the assessment to severe outcomes (i.e., based on hospital admission or mortality data). Also, estimates of vaccine effectiveness may have been biased by the depletion of susceptible participants (i.e., unvaccinated participants who were eventually vaccinated or were immunized through infection). Of note, we accounted for previous infections to reduce the impact of this bias. Respiratory sample testing shifted from PCR to RAT during the study, with RATs becoming the primary detection tool in early 2022 [28]. This may have resulted in higher rates of false negative results due to their lower sensitivity and thus had an impact on estimates of effect. All data were self-reported making it possible that infections and/or vaccinations were not reported, which could bias the results albeit in either direction for vaccine effectiveness estimates. Participants were generally representative of the educators in the province given their age, gender, and district. However, this study was conducted in a single jurisdiction and may not be generalizable to other jurisdictions.

4.2. Conclusions

Vaccine effectiveness estimates indicate that COVID-19 vaccines continued to provide protection against infection with SARS-CoV-2 through December 2023 in this cohort of education workers. Infection following close contact with people infected with SARS-CoV-2 occurred in a variety of venues including the household and workplace. This indicates the need to practice multiple intervention strategies (e.g., vaccination and non-pharmaceutical) when the potential for transmission is high.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Authors' Contributions: Conceptualization, B.L.C. and A.M.; methods, B.L.C.; validation, B.L.C.; formal analysis, B.L.C.; investigation, B.L.C. and K.F.; resources, B.L.C.; data curation, B.L.C., K.F., K., and V.Z.; writing—original draft preparation B.L.C.; writing—review and editing, B.L.C., S.B., I.G., A.M., V.Z., K., and K.F.; supervision, B.L.C.; project administration, B.L.C.; funding acquisition, B.L.C., A.M., S.S., and S.B.

 doi:10.20944/preprints202504.1572.v1

Funding: This research was funded by the Public Health Agency of Canada (#2021-HQ-000149) and the Canadian Institutes of Health Research (#181116).

Data Sharing: The dataset is available from https://www.maelstrom-research.org/study/ccs-2 or upon reasonable request from the corresponding author.

Ethics Statement: This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Research Ethics Board of Sinai Health (# 20-0343-A; 26 January 2021).

Acknowledgements: The investigators thank their staff, who worked tirelessly throughout the study and the participants, who gave freely of their time throughout the early years of the COVID-19 pandemic. Likewise, we thank the staff of the National Laboratory for HIV Reference Services for prompt testing of thousands of DBS samples for this study. We also thank the staff of the associations, federations, and unions of educators who provided feedback on the study protocol and also promoted the study among their members.

References

1. **Beale S, et al.** Differential risk of SARS-CoV-2 infection by occupation: evidence from the Virus Watch prospective cohort study in England and Wales. *J Occup Med Toxicol* 2023; **18**: 5.
2. **Silver SR, et al.** Prevalence of COVID-19 and long COVID by industry and occupation: Behavioral Risk Factor Surveillance System 2022. *Am J Ind Med* 2025; **68**: 26-52.
3. **Hume S, Brown SR, Mahtani KR**. School closures during COVID-19: an overview of systematic reviews. *BMJ Evidence-Based Medicine* 2023; **28**: 164.
4. **Pooley N, et al.** Durability of vaccine-induced and natural immunity against COVID-19: a narrative review. *Infect Dis Ther* 2023; **12**: 367-387.
5. **Wei J, et al.** Risk of SARS-CoV-2 reinfection during multiple Omicron variant waves in the UK general population. *Nat Commun* 2024; **15**: 1008.
6. **Bøås H, et al.** Frequency and risk of SARS-CoV-2 reinfections in Norway: a nation-wide study, February 2020 to January 2022. *BMC Public Health* 2024; **24**: 181.
7. **Mostafavi F, et al.** COVID-19 vaccine effectiveness of booster doses against Delta and Omicron variants over follow-up times using longitudinal meta-analysis. *J Res Health Sci* 2024; **24**: e00626.
8. **Tsang TK, et al.** Prior infections and effectiveness of SARS-CoV-2 vaccine in test-negative studies: a systematic review and meta-analysis. *Am J Epidemiol* 2024; **193**: 1868-1881.
9. World Health Organization. Correlates of vaccine-induced protection: methods and implications. Geneva, CH: World Health Organization,; 2013.
10. **Martínez-Barnetche J, et al.** Comparable diagnostic accuracy of SARS-CoV-2 Spike RBD and N-specific IgG tests to determine pre-vaccination nation-wide baseline seroprevalence in Mexico. *Scientific Reports* 2022; **12**: 18014.
11. **Spiteri G, et al.** Protective role of SARS-CoV-2 anti-S IgG against breakthrough infections among European healthcare workers during pre and post-Omicron surge—ORCHESTRA project. *Infection* 2024; **52**: 1347-1356.
12. **Seekircher L, et al.** Anti-spike IgG antibodies as correlates of protection against SARS-CoV-2 infection in the pre-Omicron and Omicron era. *Journal of Medical Virology* 2024; **96**: e29839.
13. Coleman BL, et al. Risk factors for infection with SARS-CoV-2 in a cohort of Canadian healthcare workers: 2020-2023. In, 2025: 30.
14. **Baratto N, et al.** Anti-SARS-CoV-2 IgG antibody response in individuals infected post complete vaccination: a 6-month longitudinal study in healthcare professionals. *Vaccines (Basel)* 2023; **11**.
15. **Erice A, Prieto L, Caballero C**. Long-term analyses of SARS-CoV-2 humoral and T cell responses and breakthrough SARS-CoV-2 infections after two doses of BNT162b2 followed by mRNA-1273 and bivalent Omicron-adapted BNT162b2 vaccines: a prospective study over 2 years in non-immunocompromised individuals. *Vaccines (Basel)* 2023; **11**.

 doi:10.20944/preprints202504.1572.v1

16. **Coleman BL, et al.** Study of the epidemiology of COVID-19 in Ontario elementary and secondary school education workers: an interim analysis following the first school year. *Can J Public Health* 2022; **113**: 185-195.
17. **Public Health Ontario**. COVID-19 vaccine uptake in Ontario: December 14, 2020 to April 17, 2021. (https://www.publichealthontario.ca/-/media/Documents/nCoV/Archives/Vaccine-Uptake/2021/04/covid-19-vaccine-uptake-report-2021-04-22.pdf). Accessed 2021-Apr-30.
18. **Public Health Agency of Canada**. COVID-19 vaccination: doses administered. (https://health-infobase.canada.ca/covid-19/vaccine-administration/). Accessed 2024-Sep-12.
19. **Public Health Agency of Canada**. NACI rapid response: recommended use of AstraZeneca COVID-19 vaccine in younger adults. (https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/rapid-response-recommended-use-astrazeneca-covid-19-vaccine-younger-adults.html). Accessed 2021-Apr-01.
20. **Government of Ontario**. Approach to reopening schools for the 2020-2021 school year. (https://www.ontario.ca/page/approach-reopening-schools-2020-2021-school-year#section-5). Accessed 2020-Jun-30.
21. **Akanteva A, et al.** Canadian COVID-19 pandemic public health mitigation measures at the province level. *Scientific Data* 2023; **10**: 882.
22. **Government of Ontario**. Statement from Ontario's Chief Medical Officer of Healt. (https://news.ontario.ca/en/statement/1001732/statement-from-ontarios-chief-medical-officer-of-health). Accessed 2023-04-04.
23. SimpleSurvey. SimpleSurvey Enterprise. In. Montreal, QC, 2021.
24. **World Health Organization**, WHO International Standard. First WHO international standard for anti-SARS-CoV-2 immunoglobulin (human). *World Health Organization,*. 17-Dec-2020.
25. **Hadley E, et al.** Insights from an N3C RECOVER EHR-based cohort study characterizing SARS-CoV-2 reinfections and Long COVID. *Communications Medicine* 2024; **4**: 129.
26. **Public Health Agency of Canada**. National Microbiology Laboratory. (https://www.canada.ca/en/public-health/programs/national-microbiology-laboratory.html). Accessed 2024-07-07.
27. Public Health Ontario. Ontario COVID-19 data tool. In: Public Heatlh Ontario, ed. Toronto, ON, 2021.
28. **Government of Canada**. Interim guidance on the use of rapid antigen detection tests for the identification of SARS-CoV-2 infection. (https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/guidance-documents/use-rapid-antigen-detection-tests.html). Accessed 15 Sept 2024.
29. **Prentice RL, Williams BJ, Peterson AV**. On the regression analysis of multivariate failure time data. *Biometrika* 1981; **68**: 373-379.
30. **Amorim LDAF, Cai J**. Modelling recurrent events: a tutorial for analysis in epidemiology. *International Journal of Epidemiology* 2015; **44**: 324-333.
31. **Hosmer D, Lemeshow S**. *Applied survival analysis. Regression modeling of time to event data*. Toronto, ON: John Wiley & Sons Inc, 1999, pp.
32. StataCorp. Stata survival analysis reference manual. In. College Station, TX: StataCorp LLC, 2023.
33. StataCorp. Stata statistical software: release 18. In. College Station, TX: StataCorp LLC, 2023.
34. **Zeng B, et al.** Effectiveness of COVID-19 vaccines against SARS-CoV-2 variants of concern: a systematic review and meta-analysis. *BMC Med* 2022; **20**: 200.
35. **Nealon J, et al.** Reported effectiveness of COVID-19 monovalent booster vaccines and hybrid immunity against mild and severe Omicron disease in adults: A systematic review and meta-regression analysis. *Vaccine X* 2024; **17**: 100451.
36. **Song S, et al.** A systematic review and meta-analysis on the effectiveness of bivalent mRNA booster vaccines against Omicron variants. *Vaccine* 2024; **42**: 3389-3396.
37. **Alghader MRM, Valvi D, de la Hoz RE**. Transmission and Risk Factors of COVID-19 among Health Care Workers. *Seminars in Respiratory and Critical Care Medicine* 2023; **44**: 340-348.

 doi:10.20944/preprints202504.1572.v1

38. **Elgersma IH, et al.** Transmission of severe acute respiratory coronavirus virus 2 (SARS-CoV-2) between hospital workers and members of their household: Nationwide, registry-based, cohort study from Norway. *Infection Control & Hospital Epidemiology* 2023; **44**: 604-609.
39. **Cordery R, et al.** Transmission of SARS-CoV-2 by children to contacts in schools and households: a prospective cohort and environmental sampling study in London. *Lancet Microbe* 2022; **3**: e814-e823.
40. **Bark D, et al.** SARS-CoV-2 transmission in kindergarten to grade 12 schools in the Vancouver Coastal Health region: a descriptive epidemiologic study. *CMAJ Open* 2021; **9**: E810-e817.
41. **Choi A, et al.** Symptomatic and asymptomatic transmission of SARS-CoV-2 in K-12 schools, British Columbia, Canada April to June 2021. *Microbiol Spectr* 2022; **10**: e0062222.
42. **Campeau L, et al.** Transmission dynamics of SARS-CoV-2 in British Columbia's largest school district during the second half of the 2020-2021 school year. *Can J Public Health* 2022; **113**: 653-664.
43. **Cowger TL, et al.** Lifting universal masking in schools - COVID-19 incidence among students and staff. *N Engl J Med* 2022; **387**: 1935-1946.
44. **DeJonge PM, et al.** School district prevention policies and risk of COVID-19 among in-person K-12 educators, Wisconsin, 2021. *Am J Public Health* 2022; **112**: 1791-1799.
45. **Peng A, et al.** Impact of community mask mandates on SARS-CoV-2 transmission in Ontario after adjustment for differential testing by age and sex. *PNAS Nexus* 2024; **3**: pgae065.
46. **Rahmani A, et al.** Serological correlates of protection induced by COVID-19 vaccination in the working age population: a systematic review and meta-analysis. *Vaccines (Basel)* 2024; **12**.