ORIGINAL RESEARCH

COVID-19 breakthrough infections in vaccinated participants of the Safety and Efficacy of Preventative COVID Vaccines sub-study

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BACKGROUND: The rate of breakthrough infection in vaccinated Ontarians during the Omicron wave is unknown. **METHODS:** Active participants of the Safety and Efficacy of Preventative COVID Vaccines (STOPCoV) study (892 ≥age 70 years and 369 aged 30–50 years) were invited to participate in a sub-study evaluating breakthrough COVID-19 infection. Self-administered rapid antigen tests (RAT) were reported twice weekly and symptom questionnaires weekly for 6 weeks. The primary outcome was the proportion reporting a positive RAT. **RESULTS:** A total of 806 e-consented, and 727 (90%) completed ≥1 RAT, with total 7,116 RATs completed between January 28 and March 29, 2022. Twenty out of twenty-five participants with a positive RAT had a booster vaccine prior to the positive test. All cases were mild, none requiring hospitalization. Nineteen had positive dried blood spot analysis for IgG antibody to the receptor binding domain (RBD) prior to the positive RAT. The mean normalized IgG ratio to RBD was 1.22 (SD 0.29) for younger and 0.98 (SD 0.44) for older participants, values similar to corresponding ratios for those without positive RATs and those in the main cohort. One hundred and five participants reported one and 96 reported ≥2 possible COVID-19 symptoms despite negative RATs. The false negative RAT was low (4% to 6.6 %) compared with subsequent positive nucleoprotein antibody. **CONCLUSIONS:** Positive RAT for COVID-19 was infrequent (3.4%). We were unable to determine a protective antibody level against breakthrough infection. Our findings can inform public health COVID-19 restrictions guidelines. Our decentralized study provides a model for rapid institution of new questions during a pandemic.

KEYWORDS: COVID-19, geriatric medicine, infectious diseases, participants, rapid antigen test, vaccines

HISTORIQUE : On ne connaît pas le taux d'infections postvaccinales pendant la vague Omicron chez les Ontariens vaccinés. **MÉTHODOLOGIE :** Les participants actifs de l'étude *Safety and Efficacy of Preventative COVID Vaccines* (STOPCoV; 892 de 79 ans ou plus et 369 de 30 à 50 ans) ont été invités à prendre part à une sous-étude évaluant les infections postvaccinales causées par la COVID-19. Les résultats des tests d'antigène rapides (TAR) autoadministrés ont été transmis deux fois par semaine et le questionnaire sur les symptômes, toutes les semaines pendant six semaines. Les résultats primaires correspondaient à la proportion ayant déclaré des TAR positifs. **RÉSULTATS :** Au total, 806 ont consenti par voie électronique et 727 (90 %) ont effectué au moins un TAR, pour un total de 7 116 TAR effectués entre le 28 janvier et le 29 mars 2022. Ainsi, 21 des 25 participants ayant obtenu un résultat positif au TAR avaient reçu une dose de rappel auparavant. Tous les cas étaient légers, et aucun n'a dû être hospitalisé. Dix-neuf ont obtenu une analyse des gouttes de sang séché positives aux anticorps des IgG du domaine de liaison des récepteurs (RBD) avant le résultat positif du TAR. L'écart-type moyen du ratio d'IgG normalisé au RBD était de 1,22 (ÉT = 0,29) pour les participants plus jeunes, et de 0,98 (ÉT = 0,44) chez les participants plus âgés, les valeurs étaient semblables aux ratios correspondants pour ceux dont le TAR n'était pas positif et ceux de la cohorte principale. Au total, 105 participants ont déclaré un symptôme possible de COVID-19 et 96 en ont déclaré au moins deux, malgré des résultats négatifs au TAR. Le taux de TAR faussement négatifs était faible (4 % à 6,6 %) par rapport à l'anticorps nucléoprotéique positif subséquent. **CONCLUSIONS :** Les résultats positifs des TAR à la COVID-19 étaient peu courants (3,4 %). Les chercheurs n'ont pas été en mesure de déterminer le taux d'anticorps protecteurs contre l'infection postvaccinale. Ces résultats peuvent éclairer les directives sur

les restrictions sanitaires liées à la COVID-19. La présente étude décentralisée fournit un modèle pour l'adoption rapide de nouvelles questions pendant une pandémie.

MOTS-CLÉS: COVID-19, maladies infectieuses, médecine gériatrique, participants, test d'antigène rapide, vaccins

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Clinical trials and population-based studies demonstrate excellent short- term efficacy for mRNA COVID vaccines (1,2). Few people over age 70 were included in the randomized vaccine trials, yet older persons, especially those with comorbidity, have higher risk of mortality from COVID-19 infection (3). Natural antibody appears protective against reinfection (4,5), but we currently do not know if there is an immunity threshold COVID-19 vaccines confer against asymptomatic infection and transmission especially against variant strains (6).

We and others have demonstrated that antibody levels to vaccine wane with time particularly in the elderly (7–10). Despite immunization and booster doses, there are reports of breakthrough COVID-19 infection, especially with the Omicron variant (11) although the severity of illness is generally mild relative to that experienced in the initial COVID-19 wave (12–14). Whether breakthrough infections are more common in an elderly population or following immunization with different vaccine brands or dosing intervals is unknown. Correlation of breakthrough infection with post vaccination antibody levels would provide important information as to whether there is an immunity threshold to guide future vaccine strategies.

The Safety and Efficacy of Preventative COVID Vaccines (STOPCoV) study is an ongoing prospective study designed to longitudinally evaluate the IgG antibody response to COVID-19 vaccination and booster doses in an older relative to a younger cohort (10). We designed this sub-study to evaluate the rate of breakthrough COVID-19 infections and to attempt to correlate with demographics, vaccination history, and antibody levels.

METHODS

Design

The STOPCoV study is a decentralized longitudinal cohort study planned to follow the antibody response of participants with two COVID-19 vaccine doses for 48 weeks and participants with three doses for 96 weeks. The full protocol is available on the study website www.stopcov.ca. Trial registration: ClinicalTrials.gov. NCT05208983. This sub-study was designed to evaluate breakthrough COVID-19 infection through prospective collection of rapid antigen tests.

Recruitment

A data sharing agreement with the Ontario Ministry of Health enabled us to send emails with information on the parent study to persons receiving the COVID-19 vaccine at an Ontario distribution centre who consented to contact for research. A similar email was sent to Ontario Canadian Association of Retired Persons members (www.carp.ca). A total of 1,286 adults (911 older and 375 younger) self-recruited between May 17 and July 31, 2021. Five participants did not meet eligibility criteria and at the time of initiation of this sub-study, 20 had withdrawn consent, leaving 1,261 (98%) continuing in the cohort. These active participants were sent an email describing the sub-study in mid-January 2022.

Electronic consent for the main study and this sub-study were completed on the study website. Both the main and sub-studies and the electronic consent process were approved by the University Health Network Ethics Review Committee. Consented participants used the study website with their personal identification number and password as a portal for communication with study staff, data collection, and results reporting. A schedule for required activities and email reminders are provided.

Questionnaires

For the main study, self-administered electronic questionnaires collected baseline demographic and health data. Electronic diaries collected data on vaccine dates and brand. For the sub-study, participants completed diaries once per week for 6 weeks about possible COVID-19 symptoms and if they tested positive whether they required medical attention or hospitalization.

Normalized antibody ratios

Dried blood spot (DBS) samples for assessment by ELISA for normalized IgG antibody ratios to the receptor binding

domain, nuclear protein and spike protein were collected at intervals as part of the main protocol as previously described (10). Antibody to nuclear protein indicates natural infection.

Rapid antigen tests (RAT)

Participants in the sub-study were provided with Rapid Response COVID-19 antigen rapid test devices (MDSS GmbH, Hannover Germany). Written instructions accompanied the kits and a video on the website guided sample collection. Participants were instructed to complete nasopharyngeal sampling twice per week and to record the results as positive or negative in their portal. With the media advising both cheek, throat, and nasal sampling, the additional sampling sites were permitted.

Statistical analysis

Consenting participants who completed at least one RAT were included in the analysis. Continuous variables are summarized with mean and SD. Categorical variables are summarized with frequency and percent.

RESULTS

Of 1,261 active participants of the main STOPCoV study, 588/892 (66%) in the older cohort and 218/369 (59%) of the younger cohort consented to this sub-study. Recruitment took place January 17 to March 9, 2022, and rapid antigen testing continued until March 29, 2022. Of the consented participants, 727 completed at least one RAT and are included in the following analysis.

Table 1 describes the demographics of the sub-study participants which are similar to main study participants who did not join this sub-study. All but 1 participant had at least two doses of a COVID-19 vaccine, and 702 (96.6%) participants had received a booster dose. Most participants received 2–3 doses of BNT162b2 or a combination of BNT162b2 and mRNA 1273. More of the elderly cohort received only BNT162b2 (58% versus 25%) whereas more of the younger cohort received mRNA 1273 or a combination of BNT162b2 and mRNA1273 (59% versus 34.5%).

Table 2 outlines the number of RAT performed for each week of the study period. 509 (70%) participants completed a total of 10–12 RAT and 133 (18%) completed 6–9 RAT.

Table 3 describes the characteristics of the 25 participants reporting at least one positive RAT. Of the positive cases, 16 were women, 10 in the older cohort (≥70 years), 5 reported hypertension, and 13 reported no underlying comorbidity. All but 5 participants had received three vaccine doses; 4 participants received AstraZeneca Vaxzevria® COVID-19 vaccine as the first dose, 16 had received an mRNA (BNT162b2 or mRNA1273) for all three doses. For the 25 participants the mean time between the first two vaccine doses was 9.4 (SD 2.7) weeks and the interval between the second and booster doses was 27.1 (SD 2.1) weeks. Two participants were asymptomatic, 23 were mildly symptomatic (typically for less than 1 week) at the time of the positive RAT, and none required medical attention. The first positive RAT was

Table 1: Demographic and clinical characteristics by inclusion in rapid antigen test analysis

	Not in analysis	In analysis
n[*]	534	727
Age, y, median (IQR)	73 (49–76)	73 (50–76)
Cohort, no. (%)		
30–50 years old	167 (31.3)	202 (27.8)
≥70 years old	367 (68.7)	525 (72.2)
Female or non-binary, no. (%)	281 (60.8)	482 (66.3)
Caucasian, no. (%)	391 (84.6)	656 (90.2)
Diabetes, no. (%)	62 (13.4)	64 (8.8)
Cardiovascular disease, no. (%)	186 (40.3)	241 (33.1)
Chronic obstructive pulmonary disease, no. (%)	7 (1.5)	15 (2.1)
Asthma, no. (%)	51 (11.0)	72 (9.9)
Cancer, no. (%)	60 (13.0)	120 (16.5)
Smoking, no. (%)		
Never	248 (53.7)	421 (57.9)
Not anymore	173 (37.4)	281 (38.7)
Yes	41 (8.9)	25 (3.4)
Body mass index[†], median (IQR)	27.0 (23.6–30.9)	25.8 (23.2–29.1)
No. (%) of vaccine doses		
1	14 (3.0)	1 (0.1)
2	163 (35.3)	24 (3.3)
3	285 (61.7)	702 (96.6)
Vaccine type[‡], no. (%)		
BNT162b2 only	222 (49.6)	353 (48.6)
mRNA1273 only	53 (11.8)	63 (8.7)
BNT162b2 and mRNA1273	136 (30.4)	237 (32.6)
Other or unknown	37 (8.3)	73 (10.1)
Weeks between dose 1 and 2[§], median (IQR)	10.1 (7.9–12.1)	10.4 (8.3–11.7)

** 1189 (94%) of those invited to participate in the sub-study completed the baseline questionnaire*
† Body mass index was missing for 17/1189 (1.4%)
‡ For 1174 participants who received two or three doses
§ 2nd dose date was missing for 5/1174 (0.4%)

Table 2: Number of rapid antigen tests completed by week

	No. (%) of participants *n* = 727
Week 1	
Day 1	706 (97.1)
Day 2	621 (85.4)
Week 2	
Day 1	655 (90.1)
Day 2	546 (75.1)
Week 3	
Day 1	641 (88.2)
Day 2	533 (73.3)
Week 4	
Day 1	630 (86.7)
Day 2	542 (74.6)
Week 5	
Day 1	620 (85.3)
Day 2	519 (71.4)
Week 6	
Day 1	591 (81.3)
Day 2	512 (70.4)

recorded a mean 53 (SD 29) days (range 6–110 d) from the booster vaccine date.

Nineteen out of twenty-five participants had completed a DBS for antibody testing at 24 weeks after the second vaccine dose (as part of the main study) that was also prior to the third vaccine dose and prior to the positive RAT (10,15). The antibody to the receptor binding domain (RBD) is thought to most closely reflect neutralizing activity (16). At this time point, the mean of normalized ratio of IgG antibody to RBD was 1.22 (SD 0.29) for the younger participants reporting a positive RAT and 0.98 (SD 0.44) for the older participants with a positive RAT. For the 702 in the sub-study who did not report a positive RAT, the mean to RBD was 1.10 (SD 0.38); 1.22 (SD 0.39) for the younger, and 1.09 (SD 0.46) for the older participants. The corresponding value for participants in the main study was 1.21 (SD 0.39) for the younger cohort and 1.06 (SD 0.47) for the older cohort.

For 16 participants with a positive RAT, an additional normalized IgG ratio to RBD was available prior to the booster dose (mean 1.06 [SD 0.41] for younger, 0.91 [SD 0.42] for older) and for 9 a normalized IgG RBD ratio was available 2 weeks after the booster dose (mean 1.84 [SD 0.25] for younger; 1.71 [SD 0.05] for older) and was a mean interval of 15.5 (SD 3) days after the booster dose and 53 (SD 29) days before the positive RAT.

Table 4 describes the frequency and types of symptoms from the weekly diaries for participants who did not report a positive RAT. Participants were instructed to report if they had any of the symptoms listed in Table 4 in the previous week. Each weekly symptom diary was completed by a mean 520 participants (range 501–532). Overall, 105 participants reported one symptom in one of the weekly diaries over the 6-week period. 48 participants reported 2 symptoms, 24 reported 3 symptoms, and the remaining 24 reported 4–14 symptoms. Of those with multiple symptoms, 41 reported more than one symptom in the same weekly diary.

The participants continued to be followed as part of the main STOPCoV study. Of the 25 participants with a positive RAT, 22 had a subsequent nucleoprotein (NP) value available. Of these, 14 (64%) had a positive IgG to NP, indicating natural infection at a mean of 62 days (range 19–113 d) following the positive RAT, whereas 8 (36%) had a negative NP at a mean 41.5 days (range 6–109 d) following the positive RAT. Of the 502 participants who did not have a positive RAT during the 6-week study, and did not report any COVID-19-related symptoms in their diary, 196 had an NP measured after their last negative RAT. Of these, 13 (6.6 %) had a positive NP at a mean of 29.5 days (range 0–68 d) after their last RAT, whereas 183/196 (93.4%) had a negative NP at a mean of 29.6 days (range 0–73 d). For the 200 participants who had negative RATs throughout the 6-week sub-study but who reported at least one possible COVID-19 symptom during that time, 165 had subsequent NP measures. Seven out of 165 (4%) had a positive NP on average 32 days (range 0–100 d) after symptom onset.

DISCUSSION

Overall, we found 25/727 (3.4%) symptomatic or asymptomatic COVID-19 infections detected by positive RAT during the study period indicating that breakthrough infection was occurring during the Omicron wave in Ontario, but at low frequency. All cases were mild and none required hospitalization. Eighty percent (20/25) of the cases had received a booster dose of m-RNA COVID-19 vaccine in the 110 days prior to the positive RAT. Our data is consistent with the findings that the population incidence of COVID-19 is decreasing in Ontario and that vaccination appears protective against symptomatic and asymptomatic infection.

We compare this to observations during the main study protocol (10). In the main protocol, prior to the second vaccine dose, 29 (3%) participants had positive anti-nucleoprotein (NP) antibodies indicating possible prior natural infection. Of these, 10 reported a prior symptomatic COVID-19 infection. An additional eight participants (0.7%) had a positive anti-NP 2 weeks after their second dose, six more participants (0.5%) 12 weeks after the second dose, and two (0.16%) additional

Table 3: Characteristics of participants with a positive rapid antigen test

			Vaccine brand			Days from				
Age	Gender	Underlying comorbidity	1st dose	2nd dose	3rd dose	1st to 2nd dose	2nd to 3rd dose	Last dose* to positive RAT	Symptoms	RBD prior to 3rd dose
33	F	None	BNT162b2	mRNA1273	mRNA1273	42	190	25	Yes	1.73
33	M	None	mRNA1273	mRNA1273	N/A	28	N/A	204	Yes	N/A
36	F	Transplant	BNT162b2	mRNA1273	mRNA1273	63	190	33	Yes	1.44
38	M	Asthma	BNT162b2	BNT162b2	N/A	77	N/A	213	Yes	N/A
43	F	Asthma, chronic neurologic disease	AstraZeneca	mRNA1273	mRNA1273	66	186	50	Yes	1.08
44	F	None	mRNA1273	mRNA1273	mRNA1273	65	180	46	Yes	1.19
44	F	Asthma	BNT162b2	BNT162b2	mRNA1273	60	192	85	Yes	0.77
44	M	Asthma	BNT162b2	BNT162b2	N/A	50	N/A	277	Yes	1.05
45	F	None	BNT162b2	BNT162b2	mRNA1273	35	201	45	Yes	N/A
45	F	None	AstraZeneca	mRNA1273	mRNA1273	61	183	57	Yes	0.95
45	F	None	BNT162b2	BNT162b2	N/A	52	N/A	273	Yes	N/A
46	F	None	BNT162b2	BNT162b2	BNT162b2	83	215	18	Yes	1.12
47	M	None	AstraZeneca	mRNA1273	mRNA1273	61	183	55	Yes	1.56
48	M	None	AstraZeneca	AstraZeneca	BNT162b2	57	170	100	Yes	N/A
49	F	Hypertension	BNT162b2	mRNA1273	N/A	40	N/A	199	Yes	1.29
71	F	Diabetes	BNT162b2	BNT162b2	mRNA1273	96	163	48	Yes	N/A
73	F	None	BNT162b2	BNT162b2	BNT162b2	83	213	27	N/A	0.62
73	F	None	BNT162b2	BNT162b2	BNT162b2	73	179	75	Yes	0.49
73	F	None	BNT162b2	BNT162b2	BNT162b2	90	176	110	Yes	1.75
75	M	Hypertension	BNT162b2	BNT162b2	BNT162b2	80	217	6	Yes	0.79
76	M	Hypertension, stroke	BNT162b2	mRNA1273	BNT162b2	89	197	26	No	1.31
76	M	Hypertension, asthma, cancer	BNT162b2	mRNA1273	mRNA1273	88	182	68	Yes	0.49
76	F	None	BNT162b2	BNT162b2	mRNA1273	73	187	91	Yes	1.15
80	M	Diabetes, hypertension, myocardial infarction	BNT162b2	BNT162b2	BNT162b2	83	187	73	Yes	0.81
83	F	Hypertension	BNT162b2	mRNA1273	mRNA1273	49	203	25	No	1.36

* *The 3rd dose if available or the 2nd dose if a participant did not receive a 3rd dose*
M = Male; F= Female; RAT = Rapid antigen test; RBD = Normalized ratio of IgG antibody to the receptor binding domain

cases 24 weeks after the second dose; three of these participants reported a COVID-19 diagnosis. It is unclear whether the breakthrough infections we detected in the sub-study are a consequence of incomplete vaccine coverage against the variants (17) or from waning immunity with time after vaccination. Our data would infer that vaccination provided greater protection against the original COVID-19 strain and the delta variant than the Omicron variant as shown by others (18).

Given the small number of positive RAT we observed we were unable to determine if there was any correlation to age,

Table 4: Number of participants with negative rapid antigen test who reported the following symptoms over the study period

Symptom	Frequency
Fever	9
New onset of cough	23
Worsening cough	7
Shortness of breath	17
Difficulty breathing	5
Sore throat	45
Decreased or loss of sense of taste or smell	3
Chills	22
Unexplained headaches	51
Unexplained fatigue, malaise, muscle aches	48
Nausea/vomiting/diarrhea/stomach pain	32
Eye pain/pink eye/conjunctivitis	14
Runny nose or stuffy nose without known cause	86
Night sweats	37

vaccine brand, dose intervals, boosters, or antibody levels. Eighty percent of participants with positive RAT had received the booster vaccine dose, with the mean time between booster and the first positive RAT of 53 days (range 6–110 d). A larger proportion of the younger cohort in the sub-study reported a positive RAT than the older cohort, but the significance of this is unclear as the impact of other confounders such as exposure history is unavailable. The IgG antibody levels to RBD at 24 weeks after the second vaccine dose were similar to those who did not report a positive RAT and to those of the main cohort.

Although the number with positive RAT was low during the study period, 201 participants reported at least one symptom that could be related to COVID-19, although the majority listed only one symptom on a single weekly diary. As PCR testing had been eliminated by the province, we were unable to confirm whether these were false negative RAT or unrelated symptoms. When the participants complete their next DBS in the main study, we will be able to better understand this as the development of antibody to NP represents natural infection. False negative and false positive RAT have been reported (19). False negatives could occur when the viral burden is low such as early or late in the disease course, or with inadequate sampling. Prior vaccination and booster doses could also decrease viral burden with infection. Our weekly RAT would have been anticipated to decrease the rate of false negatives.

For our participants with a positive RAT, we were able to confirm natural infection by the presence of NP antibody in their subsequent DBS analysis in 64%. The 36% with negative NP on the subsequent DBS could reflect too early sampling before antibody could be detected, a false positive RAT, too high a cut-off value set by the laboratory, or sufficient prior antibody to vaccine that they were unable to mount an NP response. Given the majority of these had multiple symptoms suggestive of COVID-19, we believe a false positive RAT is less likely. The proportion of participants with a negative RAT who subsequently had a positive NP was low and did not differ whether they had reported possible COVID-19 symptoms or not. We conclude that the false negative rate was low in our population.

Breakthrough infections with the Omicron variant have been increasingly reported since November 2021. The reasons for the breakthrough are unclear and could be a consequence of decreased neutralizing activity of vaccine induced immunity versus the variant strains (17) or waning immunity from vaccination with time. The impact of vaccine brand or dose intervals or underlying demographic characteristics are unclear. Most studies indicate the breakthrough infections are milder than cases seen early in the pandemic, suggesting some degree (but not complete) immunity, especially with booster doses (20).

The first reported cases of vaccine breakthrough infections with the Omicron variant were a group of seven visitors to Cape Town in late November 2021 (21). Breakthrough infections were mild to moderate and occurred 22–59 days after the booster dose, five had received BNT162b2 for all doses.

Since that time, country-wide surveillance programs have reported breakthrough infections with the variant and have assessed the impact of booster doses and vaccine brand. Booster doses appear to provide protection relative to two doses. In Denmark, 7.1% of 785 SARS-CoV-2 Omicron variant cases were identified in booster-vaccinated individuals compared with 76% in double-vaccinated persons (22). The majority were symptomatic but few required hospitalization. In a test negative case control analysis in the United States, receipt of three mRNA vaccine doses was reported for 18.6% (2441) Omicron cases compared with 55.3% (7245) in those with two mRNA doses.

The mRNA vaccines also appear to provide greater protection, and mRNA1273 may be better than BNT162b2. In England, using a test negative case control design, primary immunization with two doses of ChAdOx1 or BNT162b2 vaccine provided limited protection against symptomatic Omicron infection. An mRNA booster increased vaccine effectiveness to 74% at 2–4 weeks but fell to 64% at 5–9 weeks (13). In Qatar, for those receiving BNT162b2 the cumulative incidence of Omicron was 2.4% in the booster cohort and

4.5% in the non- booster cohort after 35 days of follow-up, whereas comparable figures for those receiving mRNA1273 was 1.0% and 1.9% respectively (12).

There are little data on demographic risk factors for breakthrough and whether they are increased in the elderly. In a Veteran's administration study in the pre-Omicron era vaccine effectiveness of three doses of an mRNA vaccine was 85% compared with 82% for two doses (23).

Knowledge gaps and future directions

It will still be important to determine whether or not there is an IgG RBD antibody threshold that will determine protection against COVID-19 and its variants to inform future vaccine strategies and boosters. Our parent STOPCoV study will continue to follow the antibody response to the COVID-19 vaccines and the rate of breakthrough infections with time. Others are exploring the correlation between antibody, neutralizing antibody, cell immunity, and breakthrough infection in different populations. Differentiating the cause of breakthrough infections as loss of immunity with time or inadequate immunity for new variants will need to be ongoing. The rate of and reasons for false negative self-administered rapid antigen tests remain unclear. Our follow-up of the cohort will help us to determine a better understanding of the rate of false negative RAT in the sub-study participants.

Limitations of our study

Given the timing of our study, we may have missed the main peak of the Omicron variant in Ontario which was early January 2022. We cannot be sure of the adequacy of the self-sampling. Participants were provided written and video instructions to guide them. There was concern that nasopharyngeal tests may be inferior to those which also included the oropharynx. Although, there may be a high false negative rate of RAT especially with low viral burden in a vaccinated population, this did not appear to occur in our study when we followed with analysis of their DBS for NP. However, we did appear to have a higher false positive rate, which may have reflected an inability or inadequate time to mount a significant NP response to infection or too high of a cut-off value set by the laboratory. There were 201 persons who reported one or more possible COVID-19 related symptoms during the study period, of these 96 had multiple symptoms suggesting possible infection; however, the frequency of subsequent positive NP was the same as in those with no symptoms. We were unable to collect data on possible COVID-19 exposures, and our older cohort may have had additional behaviours that were protecting them from infection.

CONCLUSIONS

We conclude that breakthrough infection with the Omicron variant was occurring in Ontario in the early part of 2022 despite persons having received a booster mRNA COVID-19 vaccine. In our study this rate was low (3.4%) and infection minor in severity. There were insufficient positive RATs for us to determine if there was a threshold level of protective antibody to RBD from vaccine. The levels of normalized ratio to RBD antibody (reflecting neutralizing antibody) at 24 weeks after the second vaccine in those with positive RAT prior to the booster were not different than those in the sub-study without a positive RAT or in the main study cohort. Overall, our findings imply that further booster doses of vaccine will be required as immunity fades. When followed up with an evaluation of antibody to NP, the RATs had a moderate false positive rate but low false negative rate and, therefore, are useful to help rule out infection.

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ETHICS APPROVAL: The manuscript has been reviewed by the University Health Network ethics review board.

INFORMED CONSENT: N/A

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL: N/A

DATA SHARING STATEMENT: One of the study funders, the COVID-19 Immunology Task Force (CITF), has a data sharing protocol for all funded projects. The authors will transfer relevant anonymized study data as available to the CITF as a part of these standard data sharing requirements. This is submitted together with a data dictionary defining each field in the set. External researchers will be able to submit a request to the CITF to receive access to all CITF data through their data access committee. The CITF will employ a rigorous checklist to ensure that these external requests follow all necessary ethical and privacy protocols.

The data provided to the CITF will be stored on the CITF Database. The data on the CITF Database will be held under the custodianship of McGill University or one of its collaborators and be shared via the cloud, both nationally and internationally. Data in the CITF Database can be used by researchers across Canada and in other countries following Data Access Committee (DAC) approval. These transfers will also be made in compliance with Canadian law and research ethics.

A DAC will be responsible for reviewing applications for access to the data and for approving applications that respect the privacy and access policies of the CITF. The DAC will require that researchers confirm that their intended research activities have received necessary ethics approvals. The data may also be shared with other COVID-19 research databases that follow similar protections and procedures as the CITF Database.

Further, the main study protocol, statistical analysis plan, informed consent form and full protocol are available on the study website www.stopcov.ca.

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PEER REVIEW: This manuscript has been peer reviewed.

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