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Coronavirus disease 2019 vaccine effectiveness among a population-based cohort of people living with HIV

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Objective: People with HIV were underrepresented in coronavirus disease 2019 (COVID-19) vaccine clinical trials. We estimated vaccine effectiveness (VE) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection for the BNT162b2, mRNA-1273, and ChAdOx1 vaccines among a population-based cohort of people with HIV in Ontario, Canada.

Design: Test-negative design

Methods: We identified people with HIV aged ≥19 years who were tested for SARS-CoV-2 by RT-PCR between December 14, 2020 (first availability of COVID-19 vaccines) and November 21, 2021 (pre-Omicron circulation). Outcomes included any infection, symptomatic infection, and COVID-19-related hospitalization/death. We compared the odds of vaccination between test-positive cases and test-negative controls using multivariable logistic regression with adjustment for age, sex, region, calendar time, SARS-CoV-2 test histories, influenza vaccination, comorbidities, and neighborhood-level socio-economic status. VE was derived as (1 − adjusted odds ratio) × 100%.

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Results: Among 21 023 adults living with HIV, there were 801 (8.3%) test-positive cases and 8,879 (91.7%) test-negative controls. 20.1% cases and 47.8% of controls received ≥1 COVID-19 vaccine dose; among two-dose recipients, 93.4% received ≥1 mRNA dose. Two-dose VE ≥7 days before specimen collection was 82% (95% confidence interval [CI] = 74–87%) against any infection, 94% (95% CI = 82–98%) against symptomatic infection, and 97% (95% CI = 85–100%) against hospitalization/death. Against any infection, VE declined from 86% (95% CI = 77–92%) within 7–59 days after the second dose to 66% (95% CI = −15–90%) after ≥180 days; we did not observe evidence of waning protection for other outcomes.

Conclusion: Two doses of COVID-19 vaccine offered substantial protection against symptomatic illness and hospitalization/death in people with HIV prior to the emergence of the Omicron variant. Our findings do not support a broad conclusion that COVID-19 VE is lower among people with HIV in populations that, for the most part, are attending HIV care, taking antiretroviral medication, and are virally suppressed.

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Introduction

People with HIV may be at higher risk for coronavirus disease 2019 (COVID-19), particularly those who have advanced or untreated HIV infections [1]. HIV-associated immune suppression may increase the risk of COVID-19-related hospitalization compared with the general population [2,3], but its effect on incident disease and mortality is less clear [2–6]. Moreover, many people with HIV face multiple intersecting vulnerabilities, such as belonging to low socio-economic or racialized groups, which may increase their risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure. They may also have other risk factors, such as older biological age and chronic comorbidities [3].

Although people with HIV who participated in early immunological studies do appear to mount a sufficient antibody response to COVID-19 vaccines [7,8], this population was underrepresented in pre-licensure clinical trials of vaccine efficacy, which showed conflicting results [9–13]. The small number of participants with HIV in these trials represented <1–6% of the primary efficacy population; furthermore, the few who were included had normal absolute $CD4^+$ T-cell numbers (>500 cells/mm^3) and few comorbidities [9,10,12]. Observational studies of vaccinated cohorts suggest that people with HIV may be at higher risk of breakthrough infections compared with their non-HIV infected counterparts [14,15].

Prior studies of COVID-19 vaccine effectiveness (VE) in the general population using administrative data in Ontario, Canada, suggest that two doses of mRNA vaccines are highly effective at preventing symptomatic infection and severe COVID-19 outcomes, with VE estimates ranging from 91% to 98% during the initial waves of the pandemic [16]. The extent to which these findings apply to people with HIV is unclear. Our primary objective was to estimate COVID-19 VE against RT-PCR-confirmed SARS-CoV-2 infection for the BNT162b2, mRNA-1273, and ChAdOx1 vaccines during the pre-Omicron period among a population-based cohort of people with HIV in Ontario, Canada. A secondary objective was to estimate VE against COVID-19-related severe outcomes, including hospitalization and death.

Methods

Setting

In Canada, COVID-19 vaccines first became available on December 14, 2020, with four formulations authorized by the end of 2021: Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273), AstraZeneca (ChAdOx1), and Janssen (AD26.COV2.S). mRNA vaccines (BNT162b2 or mRNA-1273) comprised the majority of distributed product, either as mixed or homologous schedules, with <1% receiving the AD26.COV2.S vaccine. Vaccines were initially prioritized for residents and staff of senior living facilities, older adults aged ≥70 years, healthcare workers, and people in Indigenous communities, with gradual roll out to younger ages and communities with higher COVID-19 incidence. People with HIV were not initially prioritized for the two-dose primary series, but those with advanced or untreated HIV infection were prioritized to receive a third dose starting in September 2021. Publicly-funded testing was available for individuals who were symptomatic, had close contact with a

confirmed case, were part of an outbreak investigation, were hospitalized, or were considered at greater risk due to their health condition or employment. Rapid or point-of-care antigen tests were not widely available during the study period.

Study population and design

We conducted a retrospective, population-based study among people with HIV using linked administrative health datasets available at ICES (formerly known as the Institute for Clinical Evaluative Sciences). As of 2020, an estimated 23 380 people were living with HIV in Ontario (range = 20 000–26 500), more than one-third of people with HIV in Canada [17]. The majority (88%) were accessing HIV care and 85% were on antiretroviral therapy, of whom 97% were virally suppressed [18].

We identified adults living with HIV as of December 14, 2020, using a validated case-finding algorithm based on three physician billing claims with an HIV diagnosis (three-digit ICD-9 codes) over a 3-year period [19]. This algorithm has 96.2% sensitivity and 99.6% specificity against medical charts [19]. Additional inclusion criteria were: aged ≥19 years; residing in Ontario; eligible for provincial health insurance; and tested for SARS-CoV-2 by RT-PCR between December 14, 2020 (first availability of COVID-19 vaccines in Ontario) and November 21, 2021 (before first detection of Omicron variant). We excluded individuals who were residents of long-term care facilities, tested positive for SARS-CoV-2 before December 14, 2020, received ≥1 dose of the AD26.COV2.S vaccine or a vaccine not authorized by Health Canada, or received ≥1 dose out of province. Due to the small number of three-dose recipients, we also excluded individuals who received ≥3 doses. Datasets were linked using unique encoded identifiers and analyzed at ICES.

To estimate VE, we used a test-negative design, which is a modified case-control study whereby vaccination status is compared between SARS-CoV-2 test-positive 'cases' and test-negative 'controls' [20]. It adjusts for bias arising from differences in access to healthcare between cases and controls by its restriction to those who present for testing [21,22]. For cases, we selected the first positive SARS-CoV-2 test episode. For controls, we randomly selected a negative test episode stratified by pandemic wave (wave 2: December 14, 2020 to March 6, 2021; wave 3: March 7, 2021 to June 26, 2021; wave 4: June 27, 2021 to November 21, 2021) to control for changes in access to testing and vaccine eligibility; individuals who had multiple test-negative episodes could contribute up to three controls (one per wave).

Outcomes

Outcomes included: any RT-PCR-confirmed SARS-CoV-2 infection, RT-PCR-confirmed SARS-CoV-2 infection associated with symptomatic illness, and COVID-19-related hospitalizations and/or death [23]. For symptomatic infections, we restricted the analysis to individuals who had ≥1 symptom indicated on their laboratory requisition form. We defined a COVID-19-related hospitalization as any all-cause hospital admission associated with a RT-PCR-confirmed SARS-CoV-2 infection occurring within 14 days before or 3 days after admission recorded in the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) or any hospitalization associated with a reported COVID-19 case recorded in the COVID-19 reportable disease database (Case and Contact Management Solution [CCM]). We defined a COVID-19-related death as any all-cause death associated with a RT-PCR-confirmed SARS-CoV-2 infection occurring within 30 days before death or 7 days postmortem recorded in the provincial health insurance registry or any death associated with a reported COVID-19 case recorded in CCM. For severe outcomes (hospitalization and/or death), we restricted test-negative controls to symptomatic testers (Figure S1, Supplemental Digital Content, http://links.lww.com/QAD/C657). We used specimen collection date as the index date for all outcomes.

Coronavirus disease 2019 vaccination

We obtained data on vaccination status from the provincial COVID-19 vaccine registry, including number of doses, date(s) of administration, and vaccine product type(s). For the one-dose analysis, we considered participants as vaccinated if they received one dose ≥14 days before their index date; those who were vaccinated within 14 days or received two doses were excluded. For the two-dose analysis, we considered participants as vaccinated if they received two doses ≥7 days before their index date; those who were vaccinated within 7 days or received one dose were excluded. Participants without a vaccination recorded were considered unvaccinated for all analyses.

Covariates

We identified a participants' age, sex, and public health region as of December 14, 2020, using the provincial health insurance registry. We considered the number of SARS-CoV-2 RT-PCR tests during the 3 months prior to December 14, 2020, as a proxy for routine screening (e.g., healthcare workers who undergo frequent testing and who may be more likely to be vaccinated). We obtained influenza vaccination during the 2019–2020 and/or 2020–2021 seasons as a proxy for health behaviors using physician or pharmacist billing codes in the Ontario Health Insurance Program or the Ontario Drug Benefits databases, respectively [16]. We identified comorbidities associated with an increased risk of COVID-19 and/or severity using validated algorithms and diagnostic codes for chronic diseases, as previously described [16]. We obtained neighborhood-level variables (based on census dissemination area) for the proportion of the working population employed in sales/trades/manufacturing/agriculture (i.e., non-health essential workers), average

number of people per dwelling, proportion of the population who self-identified as a visible minority, and median household income from the 2016 Canadian census.

Analysis

We compared test-positive cases and test-negative controls as well as vaccinated and unvaccinated participants using standardized differences (SDs), which were calculated as the absolute difference in proportions in units of the pooled standard deviation. SDs $\leq$0.1 were taken to indicate negligible differences [24]. We used multivariable logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CIs) comparing the odds of COVID-19 vaccination between test-positive cases and test-negative controls. Models were adjusted for 10-year age group, sex, region, calendar time, SARS-CoV-2 test histories, influenza vaccination histories, number of comorbidities, and neighborhood-level variables for socio-economic status (SES). Calendar time was modeled as a restricted cubic spline with 3 equally-spaced knots based on week of specimen collection. VE was derived as (1 − OR) × 100%. Participants with missing data for $\geq$1 covariate were excluded.

We created separate models for each outcome and number of doses received. Due to supply shortages, Canada's National Advisory Committee on Immunization recommended extending the dosing interval up to 16 weeks to optimize early vaccine distribution starting in March 2021, and allowed for the interchangeability of COVID-19 vaccines for the two-dose primary series starting in June 2021. For this reason, we stratified analyses according to extended dosing intervals and vaccine product. Due to suspected waning over time [25,26], we also analyzed VE by time since last dose. All analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Ethics approval

Research Ethics Board approval was obtained from the University of Toronto (protocol #28456).

Results

Participant characteristics

Among 21 023 adults living with HIV, 7461 unique individuals were tested for SARS-CoV-2 between December 14, 2020, and November 21, 2021, comprising 9962 test episodes. After exclusions (Figure S1, Supplemental Digital Content, http://links.lww.com/QAD/C657), there were 9680 (97.2%) test episodes, including 801 (8.3%) test-positive cases and 8879 (91.7%) test-negative controls (representing 6465 unique individuals). Overall, 131 (16.4%) test-positive cases and 985 (11.1%) test-negative controls (representing 877 unique individuals) had recorded COVID-19 symptoms. Compared to those without symptoms recorded, symptomatic test-negative controls were younger, more likely to be vaccinated, tested during the fourth wave (June 27, 2021 to November 21, 2021), reside in Northern, Peel, or South West regions, have <2 SARS-CoV-2 tests prior to the study period, and reside in lower SES neighborhoods (Table S2, Supplemental Digital Content, http://links.lww.com/QAD/C657); among test-positive cases, only public health region and the SES indicators reached statistical significance.

Compared to test-negative controls, test-positive cases were younger, more likely to be tested during the third wave (March 7, 2021 to June 26, 2021), reside in Toronto or Peel regions, have no SARS-CoV-2 tests prior to the study period, be unvaccinated against influenza, have fewer comorbidities, and reside in lower SES neighborhoods (Table 1); they were also less likely to be vaccinated against COVID-19 (20.1% vs. 47.8%; SD = 0.61). Comparisons between test-positive cases and test-negative controls were similar among the subset of symptomatic testers (Table S1, Supplemental Digital Content, http://links.lww.com/QAD/C657). Among 801 test-positive cases, 101 (12.6%) had a severe outcome, including 99 COVID-19-related hospitalizations and 18 deaths.

Coronavirus disease 2019 vaccination

Among 801 test-positive cases, 161 (20.1%) had received $\geq$1 dose of COVID-19 vaccine, including 63 (9.0%) who received 1 dose $\geq$14 days before specimen collection and 53 (7.6%) who received two doses $\geq$7 days before specimen collection. By comparison, among 8879 test-negative controls, 4244 (47.8%) had received $\geq$1 dose of COVID-19 vaccine, including 1055 (18.5%) who received 1 dose $\geq$14 days before specimen collection and 2706 (36.9%) who received two doses $\geq$7 days before specimen collection. Most vaccinated participants received $\geq$1 mRNA dose, including 80.3% of single-dose recipients and 93.4% of two-dose recipients (of whom, 88.9% received mRNA vaccines for both doses). Compared to unvaccinated participants, vaccinated participants were more likely to be older, test during the third (single-dose recipients) or fourth waves (two-dose recipients), have $\geq$2 SARS-CoV-2 tests prior to the study period (two-dose recipients only), be vaccinated against influenza, and have a higher number of comorbidities (single-dose recipients only) (Table 2).

Vaccine effectiveness

After adjustment for potential confounders, VE for receipt of two doses $\geq$7 days before specimen collection was 82% (95%CI = 74–87%) against any infection, increasing to 94% (95% CI = 82–98%) against symptomatic outcomes, and 97% (95% CI = 85–100%) against severe outcomes (Table 3). VE was lower for receipt of 1 dose $\geq$14 days before specimen collection against all three

Table 1. Participant characteristics by case status among people with HIV tested for SARS-CoV-2 infection between December 14, 2020 and November 21, 2021, Ontario, Canada.

	Test-positive cases		Test-negative controls		
	N	%	*N*	%	SD
Total	801	100.0	8879	100.0	
Number of COVID-19 vaccine doses (at time of test)					
0	640	79.9	4635	52.2	0.61
1	105	13.1	1409	15.9	0.08
2	56	7.0	2835	31.9	0.66
Age group (years)					
19–29	74	9.2	656	7.4	0.07
30–39	193	24.1	1699	19.1	0.12
40–49	206	25.7	2036	22.9	0.07
50–59	217	27.1	2640	29.7	0.06
≥60	111	13.9	1848	20.8	0.18
Sex					
Male	586	73.2	6656	75.0	0.04
Female	215	26.8	2223	25.0	0.04
Year-month of specimen collection					
2020-12	63	7.9	624	7.0	0.03
2021-01	127	15.9	1036	11.7	0.12
2021-02	72	9.0	892	10.0	0.04
2021-03	119	14.9	1097	12.4	0.07
2021-04	196	24.5	966	10.9	0.36
2021-05	108	13.5	789	8.9	0.15
2021-06	23	2.9	568	6.4	0.17
2021-07	10	1.2	577	6.5	0.27
2021-08	28	3.5	633	7.1	0.16
2021-09	21	2.6	643	7.2	0.21
2021-10	22	2.7	650	7.3	0.21
2021-11	12	1.5	404	4.6	0.18
Pandemic wave					
Wave 2: Dec. 14, 2020 to March 6, 2021	284	35.5	2799	31.5	0.08
Wave 3: March 7, 2021 to June 26, 2021	423	52.8	3099	34.9	0.37
Wave 4: June 27, 2021 to November 21, 2021	94	11.7	2981	33.6	0.54
Public health region					
Toronto	446	55.7	4457	50.2	0.11
Central East	7	0.9	295	3.3	0.17
Central West	99	12.4	1190	13.4	0.03
Durham	23	2.9	231	2.6	0.02
Eastern	11	1.4	288	3.2	0.12
Northern	23	2.9	354	4.0	0.06
Ottawa	45	5.6	663	7.5	0.07
Peel	72	9.0	449	5.1	0.15
South West	44	5.5	698	7.9	0.09
York	31	3.9	254	2.9	0.06
Number of tests in 3 months before December 14, 2020					
0	600	74.9	5995	67.5	0.16
1	132	16.5	1697	19.1	0.07
2+	69	8.6	1187	13.4	0.15
Receipt of 2019/20 or 2020/21 flu vaccine					
Neither season	471	58.8	4630	52.1	0.13
Either season	181	22.6	2310	26.0	0.08
Both seasons	149	18.6	1939	21.8	0.08
Number of comorbidities					
0	442	55.2	4191	47.2	0.16
1	221	27.6	2566	28.9	0.03
2+	138	17.2	2122	23.9	0.17
Comorbidities					
Chronic respiratory disease	155	19.4	2338	26.3	0.17
Hypertension	151	18.9	2085	23.5	0.11
Diabetes	103	12.9	1173	13.2	0.01
Frailty/dementia	73	9.1	838	9.4	0.01
Chronic heart disease	53	6.6	780	8.8	0.08
Chronic kidney disease/dialysis	54	6.7	622	7.0	0.01
Advanced liver disease	34	4.2	374	4.2	0.00
Autoimmune disorders	24	3.0	426	4.8	0.09
History of stroke/TIA	13	1.6	162	1.8	0.02
Neighborhood-level essential workers quintile					
1 (0–32.5%)	193	24.1	2921	32.9	0.20
2 (32.5–42.3%)	134	16.7	1586	17.9	0.03

Table 1 (*continued*)

	Test-positive cases		Test-negative controls		
	N	%	*N*	%	SD
3 (42.3–49.8%)	143	17.9	1439	16.2	0.04
4 (50.0–57.5%)	163	20.3	1480	16.7	0.09
5 (57.5–100%)	168	21.0	1453	16.4	0.12
Neighborhood-level average number of persons per dwelling quintile					
1 (0–2.1)	314	39.2	4046	45.6	0.13
2 (2.2–2.4)	119	14.9	1492	16.8	0.05
3 (2.5–2.6)	87	10.9	861	9.7	0.04
4 (2.7–3.0)	133	16.6	1415	15.9	0.02
5 (3.1–5.7)	148	18.5	1065	12.0	0.18
Neighborhood-level proportion of persons self-identifying as visible minority quintile					
1 (0.0–2.2%)	26	3.2	687	7.7	0.20
2 (2.2–7.5%)	49	6.1	849	9.6	0.13
3 (7.5–18.7%)	125	15.6	1532	17.3	0.04
4 (18.7–43.5%)	236	29.5	2886	32.5	0.07
5 (43.5–100%)	365	45.6	2925	32.9	0.26
Neighborhood-level median income quintile					
1 (lowest)	359	44.8	3161	35.6	0.19
2	166	20.7	1885	21.2	0.01
3	123	15.4	1582	17.8	0.07
4	90	11.2	1087	12.2	0.03
5 (highest)	63	7.9	1164	13.1	0.17

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standardized difference.

outcomes. We did not observe waning protection from time since second dose for symptomatic infection or severe outcomes. However, against any infection, VE declined from 86% (95% CI = 77–92%) within 7–59 days after the second dose to 66% (95% CI = −15–90%) ≥180 days after the second dose. VE was slightly lower among participants who received only the ChAdOx1 vaccine (either as a single dose or two doses), but differences were not statistically significant. We did not observe heterogeneity in two-dose VE by age, sex, region, number of comorbidities, or pandemic wave (Table S3, Supplemental Digital Content, http://links.lww.com/QAD/C657).

Discussion

In a population-based study of adults living with HIV in Ontario, Canada, two doses of a COVID-19 vaccine offered significant protection against SARS-CoV-2 infection, symptomatic illness, and severe outcomes when Alpha and Delta variants, along with wild-type viruses, were predominately circulating. Although some previous reports suggest lesser effectiveness in immunocompromised individuals [27,28], our findings do not support a broad conclusion that COVID-19 VE is lower among people with HIV who, for the most part, are attending HIV care, taking antiretroviral medication, and are virally suppressed [18].

Our VE estimates against symptomatic infection and severe outcomes (94–97%) are comparable to those measured in the general population (82–98%) during similar time periods and against non-Omicron variants [16,29]. Consistent with immunological evidence [7,8], these findings provide reassurance that HIV-mediated immune suppression does not meaningfully interfere with real-world protection from (predominantly) mRNA COVID-19 vaccines against clinically-relevant outcomes for populations in which HIV is well managed. Nonetheless, we anticipate that VE will be lower against the Omicron variant and with increasing time since the last dose [30]. We also anticipate lower VE in people with HIV who have AIDS-defining illness, low $CD4^+$ cell count (e.g., <200 cells/μl), or unsuppressed HIV viral loads and in people with other immunocompromised conditions [7,8].

Few observational studies have evaluated the real-world effectiveness of COVID-19 vaccines in people with HIV, and none specifically examined VE for mRNA vaccines. These studies may also be prone to confounding bias due to healthcare seeking behavior. In a retrospective cohort study among people with HIV on antiretroviral therapy in Russia from January to July 2021, VE of the Sputnik V viral vector vaccine was 79% (95% CI = 70–81%) against any COVID-19 infection and 90% (95% CI not reported) against hospitalization [31]. That study found slightly lower VE in participants with low CD4 counts (<350 cells/μl) but differences were not statistically significant [31]. Among healthcare workers living with HIV in South Africa from February to May 2021, VE for a single dose of the AD26.COV2.S viral vector vaccine was 73% (95% CI = 58–85%) against COVID-19-related hospitalization and 65% (95% CI = 13–93%) against death [32]. Among a small, prospective cohort of people seeking HIV care at a hospital in Taiwan between March and September 2021, the incidence rate of SARS-CoV-2 infection was 6.4 per 100 000 person-days in the

Table 2. Participant characteristics by COVID-19 vaccination status among people with HIV tested for SARS-CoV-2 infection between December 14, 2020 and November 21, 2021, Ontario, Canada.

	Unvaccinated		Received one dose ≥14 days before index date			Received two doses ≥7 days before index date		
	N	%	*N*	%	SD	*N*	%	SD
Total	5275	100.0	1118	100.0		2759	100.0	
Lab-confirmed SARS-CoV-2 infection								
Test-positive case	640	12.1	63	5.6	0.23	53	1.9	0.41
Test-negative control	4635	87.9	1055	94.4	0.23	2706	98.1	0.41
Age group (years)								
19–29	449	8.5	64	5.7	0.11	177	6.4	0.08
30–39	1085	20.6	174	15.6	0.13	537	19.5	0.03
40–49	1259	23.9	242	21.6	0.05	620	22.5	0.03
50–59	1540	29.2	340	30.4	0.03	813	29.5	0.01
≥60	942	17.9	298	26.7	0.21	612	22.2	0.11
Sex								
Male	3898	73.9	834	74.6	0.02	2114	76.6	0.06
Female	1377	26.1	284	25.4	0.02	645	23.4	0.06
Year-month of specimen collection								
2020-12	683	12.9	0	0.0	0.55	0	0.0	0.55
2021-01	1099	20.8	14	1.3	0.66	≤5	≤0.2	-
2021-02	871	16.5	23	2.1	0.51	40-44	1.4–1.6	-
2021-03	1000	19.0	52	4.7	0.45	80	2.9	0.53
2021-04	739	14.0	223	19.9	0.16	80	2.9	0.41
2021-05	370	7.0	346	30.9	0.64	72	2.6	0.21
2021-06	117	2.2	269	24.1	0.68	138	5.0	0.15
2021-07	108	2.0	80	7.2	0.25	363	13.2	0.43
2021-08	94	1.8	50	4.5	0.16	503	18.2	0.57
2021-09	84	1.6	25	2.2	0.05	543	19.7	0.61
2021-10	69	1.3	26	2.3	0.08	571	20.7	0.65
2021-11	41	0.8	10	0.9	0.01	363	13.2	0.50
Pandemic wave								
Wave 2: December 14, 2020 to March 6, 2021	2893	54.8	39	3.5	1.37	63	2.3	1.43
Wave 3: March 7, 2021 to June 26, 2021	1979	37.5	861	77.0	0.87	319	11.6	0.63
Wave 4: June 27, 2021 to November 21, 2021	403	7.6	218	19.5	0.35	2377	86.2	2.55
Public Health Region								
Toronto	2645	50.1	551	49.3	0.02	1431	51.9	0.03
Central East	149	2.8	42	3.8	0.05	94	3.4	0.03
Central West	699	13.3	168	15.0	0.05	356	12.9	0.01
Durham	133	2.5	33	3.0	0.03	72	2.6	0.01
Eastern	169	3.2	44	3.9	0.04	70	2.5	0.04
Northern	212	4.0	43	3.8	0.01	95	3.4	0.03
Ottawa	390	7.4	73	6.5	0.03	207	7.5	0.00
Peel	292	5.5	58	5.2	0.02	145	5.3	0.01
South West	427	8.1	79	7.1	0.04	207	7.5	0.02
York	159	3.0	27	2.4	0.04	82	3.0	0.00
Number of tests in 3 months before December 14, 2020								
0	3682	69.8	762	68.2	0.04	1820	66.0	0.08
1	1001	19.0	204	18.2	0.02	516	18.7	0.01
2+	592	11.2	152	13.6	0.07	423	15.3	0.12
Receipt of 2019/20 or 2020/21 flu vaccine								
Neither season	2966	56.2	565	50.5	0.11	1313	47.6	0.17
Either season	1307	24.8	272	24.3	0.01	771	27.9	0.07
Both seasons	1002	19.0	281	25.1	0.15	675	24.5	0.13
Number of comorbidities								
0	2526	48.6	481	43.0	0.11	1334	48.4	0.00
1	1534	29.1	324	29.0	0.00	783	28.4	0.02
2+	1179	22.4	313	28.0	0.13	642	23.3	0.02
Comorbidities								
Chronic respiratory disease	1359	25.8	312	27.9	0.05	684	24.8	0.02
Hypertension	1135	21.5	294	26.3	0.11	688	24.9	0.08
Diabetes	654	12.4	182	16.3	0.11	367	13.3	0.03
Frailty/dementia	530	10.0	133	11.9	0.06	196	7.1	0.11
Chronic heart disease	427	8.1	120	10.7	0.09	228	8.3	0.01
Chronic kidney disease/dialysis	329	6.2	99	8.9	0.10	205	7.4	0.05
Advanced liver disease	223	4.2	65	5.8	0.07	96	3.5	0.04
Autoimmune disorders	232	4.4	54	4.8	0.02	147	5.3	0.04
History of stroke/TIA	87	1.6	31	2.8	0.08	52	1.9	0.02
Neighborhood-level essential workers quintile								
1 (0–32.5%)	1594	30.2	358	32.0	0.04	997	36.1	0.13
2 (32.5–42.3%)	933	17.7	196	17.5	0.00	482	17.5	0.01

Table 2 (*continued*)

	Unvaccinated		Received one dose ≥14 days before index date			Received two doses ≥7 days before index date		
	N	%	*N*	%	SD	*N*	%	SD
3 (42.3–49.8%)	888	16.8	187	16.7	0.00	421	15.3	0.04
4 (50.0–57.5%)	907	17.2	208	18.6	0.04	431	15.6	0.04
5 (57.5–100%)	953	18.1	169	15.1	0.08	428	15.5	0.07
Neighborhood-level average number of persons per dwelling quintile								
1 (0–2.1)	2335	44.3	513	45.9	0.03	1273	46.1	0.04
2 (2.2–2.4)	905	17.2	192	17.2	0.00	434	15.7	0.04
3 (2.5–2.6)	508	9.6	101	9.0	0.02	293	10.6	0.03
4 (2.7–3.0)	855	16.2	187	16.7	0.01	418	15.2	0.03
5 (3.1–5.7)	672	12.7	125	11.2	0.05	341	12.4	0.01
Neighborhood-level proportion of persons self-identifying as visible minority quintile								
1 (0.0–2.2%)	372	7.1	91	8.1	0.04	210	7.6	0.02
2 (2.2–7.5%)	490	9.3	109	9.7	0.02	247	9.0	0.01
3 (7.5–18.7%)	902	17.1	198	17.7	0.02	468	17.0	0.00
4 (18.7–43.5%)	1660	31.5	376	33.6	0.05	935	33.9	0.05
5 (43.5–100%)	1851	35.1	344	30.8	0.09	899	32.6	0.05
Neighborhood-level median income quintile								
1 (lowest)	1989	37.7	405	36.2	0.03	934	33.9	0.08
2	1152	21.8	219	19.6	0.06	570	20.7	0.03
3	881	16.7	208	18.6	0.05	526	19.1	0.06
4	619	11.7	132	11.8	0.00	360	13.0	0.04
5 (highest)	634	12.0	154	13.8	0.05	369	13.4	0.04

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standardized difference.

unvaccinated group, 2.9 per 100 000 in the partially-vaccinated group, and 0 per 100 000 in the fully-vaccinated group, corresponding to VE of 53% and 100% for partial and full vaccination, respectively [33]. In that study, most participants (>70%) had received the ChAdOx1 vaccine, with less than one-quarter receiving mRNA vaccines [33]. Differences in study design, vaccine products and dosing, healthcare setting, and HIV populations preclude direct comparison of these findings.

To our knowledge, ours is among the first to evaluate the real-world effectiveness of mRNA COVID-19 vaccines

Table 3. Vaccine effectiveness estimates among people with HIV tested for SARS-CoV-2 infection between December 14, 2020 and November 21, 2021, Ontario, Canada.

	Any infection		Symptomatic infection		Severe outcomes (hospitalization/death)	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
	VE (95% CI)	VE (95% CI)	VE (95% CI)	VE (95% CI)	VE (95% CI)	VE (95% CI)
Received one dose ≥14 days before index date	57 (43, 67)	64 (52, 74)	51 (5, 75)	55 (1, 80)	38 (−19, 67)	67 (23, 86)
Time since first dose (days)						
14–29	41 (13, 60)	51 (27, 68)	46 (-54, 81)	38 (-105, 81)	NE	NE
30–59	66 (47, 78)	74 (58, 83)	56 (-27, 84)	58 (-36, 87)	NE	NE
≥60	62 (34, 79)	66 (39, 82)	49 (-70, 85)	66 (-33, 91)	NE	NE
Vaccine product type						
ChAdOx1	28 (-16, 55)	39 (-1, 63)	24 (-163, 78)	22 (-228, 81)	NE	NE
BNT162b2 or mRNA-1273(mRNA vaccines)	64 (50, 73)	70 (57, 79)	57 (7, 80)	61 (6, 84)	NE	NE
Received 2 doses ≥7 days before index date	86 (81, 89)	82 (74, 87)	91 (81, 96)	94 (82, 98)	97 (89, 99)	97 (85, 100)
Time since second dose (days)						
7–59	88 (80, 93)	86 (77, 92)	87 (58, 96)	92 (69, 98)	NE	NE
60–119	86 (78, 91)	78 (62, 87)	89 (70, 96)	93 (74, 98)	NE	NE
120–179	84 (72, 91)	77 (53, 89)	96 (69, 99)	98 (73, 100)	NE	NE
≥180	79 (34, 93)	66 (-15, 90)	NE	NE	NE	NE
Vaccine product type						
ChAdOx1 only	84 (56, 94)	77 (34, 92)	NE	NE	NE	NE
≥1 mRNA vaccine dose	86 (81, 90)	82 (74, 88)	90 (79, 95)	93 (80, 98)	97 (88, 99)	97 (83, 100)
mRNA only	86 (81, 90)	82 (74, 88)	89 (77, 95)	93 (79, 98)	97 (87, 99)	97 (80, 99)
Mixed ChAdOx1 and mRNA doses	87 (69, 95)	80 (49, 92)	NE	NE	NE	

NE, not estimated; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE, vaccine effectiveness.
[a]Adjusted for age group, sex, public health region, calendar time (restricted cubic spline for week of specimen collection), number of SARS-CoV-2 test episodes in 3 months prior to December 14, 2020, received influenza vaccine in 2019/20 or 2020/21 seasons, number of comorbidities, and neighborhood-level SES indicators. Severe outcomes models adjusted for 4-level region (Greater Toronto Area, East, West, North); any or symptomatic infection models adjusted for public health region.

in people with HIV using a test-negative design. This study design, via restriction to those who present for SARS-CoV-2 testing, mitigates potential bias arising from differences in access to healthcare. As in the general population, we found lower protection against any infection, with evidence of waning immunity with time since last dose [25,26]. However, this analysis is more prone to bias since it includes asymptomatic testers undergoing routine screening or those in close contact with a suspected case for whom the likelihood of test positivity is lower than that in symptomatic testers [21]. Individuals with recorded symptoms systematically differed from those without symptom information, although this was largely driven by regional variability as not all laboratories had the ability to enter symptom information into the provincial system. As such, symptom information was missing for >85% of test episodes, limiting our sample size for the more conventional test-negative design analysis restricted to symptomatic testers [20]. Nonetheless, we expect that most testers likely had symptoms consistent with COVID-19, as per provincial test guidelines during this period.

There are other limitations. We used specimen collection date as a proxy for date of symptom onset as the latter was inconsistently reported. Some severe outcomes may be misclassified due to delays in capturing hospital discharges in CIHI-DAD and deaths in the provincial insurance registry or incomplete reporting of severe outcomes in CCM. Although we attempted to control for confounding due to healthcare-seeking behavior, neighborhood-level SES and other demographic factors, residual confounding may remain. We used the number of SARS-CoV-2 tests in the 3 months prior to the study period as a proxy for routine screening but we were otherwise unable to standardize the testing indication for SARS-CoV-2 [22]. Data on HIV clinical indicators were unavailable at the time of analysis.

In conclusion, we measured high VE against symptomatic infection and severe illness among adults living with HIV in Ontario prior to the emergence of the Omicron variant. These findings may provide reassurance for people with HIV and their healthcare providers, particularly for those whose HIV is well controlled, and has important implications for COVID-19 vaccination guidelines, including the potential need for booster doses. Further research is required to estimate the effectiveness of COVID-19 vaccines among people with HIV who have moderate to severe immunodeficiencies, and among all people with HIV against Omicron or future variants.

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Conflicts of interest

N.Z.J. declares speaking and advisory board participation for Abbvie. All other authors have no conflicts of interest.

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