International Journal of Infectious Diseases 127 (2023) 162–170

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Effectiveness of COVID-19 vaccines in people living with HIV in British Columbia and comparisons with a matched HIV-negative cohort: a test-negative design

Adeleke Fowokan[a,#], Hasina Samji[a,b,#,*], Joseph H. Puyat[a,c,d], Naveed Z. Janjua[a,c], James Wilton[a], Jason Wong[a,c], Troy Grennan[a,c], Catharine Chambers[e], Abigail Kroch[f], Cecilia T. Costiniuk[g], Curtis L. Cooper[h], Ann N. Burchell[e,i,j], Aslam Anis[c,d], COVAXHIV study team

[a] British Columbia Centre for Disease Control, Vancouver, Canada
[b] Faculty of Health Sciences, Simon Fraser University, Burnaby, Canada
[c] School of Population and Public Health, University of British Columbia, Vancouver, Canada
[d] Centre for Health Evaluation and Outcome Sciences, St Paul's Hospital, Vancouver, Canada
[e] Dalla Lana School of Public Health, University of Toronto, Toronto, Canada
[f] The Ontario HIV Treatment Network, Toronto, Canada
[g] Department of Medicine, Division of Infectious Diseases and Chronic Viral Illness Service, McGill University Health Centre, Montreal, Quebec, Canada
[h] Department of Medicine, University of Ottawa, Ottawa, Canada
[i] Department of Family and Community Medicine, Faculty of Medicine, University of Toronto, Toronto, Canada
[j] MAP Centre for Urban Health Solutions, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Unity Health, Toronto, Canada

ARTICLE INFO

Article history:
Received 18 August 2022
Revised 24 October 2022
Accepted 25 November 2022

Keywords:
COVID-19
SARS-CoV-2
HIV
Vaccine effectiveness
Canada

ABSTRACT

Objectives: We estimated the effectiveness of COVID-19 vaccines against laboratory-confirmed SARS-CoV-2 infection among people living with HIV (PLWH) and compared the estimates with a matched HIV-negative cohort.

Methods: We used the British Columbia COVID-19 Cohort, a population-based data platform, which integrates COVID-19 data on SARS-CoV-2 tests, laboratory-confirmed cases, and immunizations with provincial health services data. The vaccine effectiveness (VE) was estimated with a test-negative design using the multivariable logistic regression.

Results: The adjusted VE against SARS-CoV-2 infection was 71.1% (39.7, 86.1%) 7-59 days after two doses, rising to 89.3% (72.2, 95.9%) between 60 and 89 days. VE was preserved 4-6 months after the receipt of two doses, after which noticeable waning was observed (51.3% [4.8, 75.0%]). In the matched HIV-negative cohort (n = 375,043), VE peaked at 91.4% (90.9, 91.8%) 7-59 days after two doses and was sustained for up to 4 months, after which evidence of waning was observed, dropping to 84.2% (83.4, 85.0%) between 4 and 6 months.

Conclusion: The receipt of two COVID-19 vaccine doses was effective against SARS-CoV-2 infection among PLWH pre-Omicron. VE estimates appeared to peak later in PLWH than in the matched HIV-negative cohort and the degree of waning was relatively quicker in PLWH; however, peak estimates were comparable in both populations.

Introduction

People living with HIV (PLWH) appear to be at a higher risk for severe COVID-19 [1–5]. Several studies have now shown that those with low clusters of differentiation (CD4) count (<200 cells/mm^3) or CD4 nadir, even with virologic suppression, are at a higher risk for worse outcomes, including severe COVID-19 and death [6–8].

* Corresponding author at: Hasina Samji, Senior Scientist British Columbia Centre for Disease Control, Provincial Health Services Authority, Assistant Professor | Faculty of Health Sciences, Simon Fraser University, 655 West 12th Avenue, Vancouver British Columbia, V5Z 4R4.
E-mail address: Hasina.Samji@bccdc.ca (H. Samji).
Joint first authors

https://doi.org/10.1016/j.ijid.2022.11.035

Yet, the evidence regarding the effectiveness of COVID-19 vaccines in this high-risk group remains sparse because PLWH have been largely under-represented in vaccine trials [9]. Given the paucity of research in this area and the ongoing pandemic despite mass vaccination roll-out, it is important to evaluate COVID-19 vaccine effectiveness (VE) to inform COVID-19 vaccine strategies for PLWH.

In British Columbia (BC), Canada, there were an estimated 10,682 PLWH in 2022, over 90% of whom are currently linked to HIV care [10] and can be identified within population-level provincial health services databases. The integration of provincial COVID-19 immunization records and COVID-19 outcome data enables assessment of VE at a population level, including for previously understudied population subgroups, such as PLWH. One such approach is the test-negative design (TND), which has been widely used to assess the VE for influenza [11] and, more recently, COVID-19 [12,13]. The TND is a modified case-control design, where vaccination status is compared between test-positive cases and test-negative controls [14]. However, the TND has been shown to be less prone to the selection and misclassification biases that commonly plague case-control studies via selecting cases and controls among those who present for testing [15–17]. Findings from Canadian studies using the TND to estimate VE against infection in the general population have reported estimates ≥90% [12,13,18] yet it remains unclear to what extent these estimates apply to PLWH.

Our best knowledge of COVID-19 vaccines in PLWH come from immunogenicity studies, which have shown that immune responses in PLWH with CD4 count ≥250 cells/mm^3 appear comparable to those in the larger population [19,20]. However, these studies provide us with limited insight into the real-world impact of COVID-19 vaccines in PLWH. Consequently, population-based studies provide us with the best available opportunity to evaluate the real-world impact of COVID-19 vaccines in understudied groups, such as PLWH. We estimated the VE of COVID-19 vaccines against laboratory-confirmed infection and compared the VE estimates with a matched HIV-negative cohort in the pre-Omicron era.

Methods

Study population, data sources, and design

This was a TND study using the BC COVID-19 Cohort (BCC19C) to estimate VE among PLWH in BC. The BCC19C was established as a collaboration among the BC Centre for Disease Control, the Data Analytics, Reporting and Evaluation, the Provincial Health Services Authority, and the BC Ministry of Health to support the COVID-19 pandemic response. The BCC19C includes population-level province-wide COVID-19 datasets, including SARS-CoV-2 testing, COVID-19 case surveillance, hospitalizations, and vaccinations, which are integrated with data from other provincial administrative data holdings and registries, including (i) Medical Services Plan (MSP), (ii) Chronic Disease Registry, (iii) Death Records (Vital Stats), (iv) Client Roster; (v) Discharge Abstract Database (DAD), and (vi) National Ambulatory Care Reporting System and Vital Statistics. Detailed information related to the datasets is included in Supplemental File 1.

We included PLWH residing in BC, aged ≥19 years, accessing health care, and alive on December 15, 2020, who received a laboratory test for SARS-Cov-2 between December 15, 2020 and November 21, 2021. In BC, the testing policies during the study period required individuals to display symptoms consistent with COVID-19 before being tested (with exceptions for travelers). We excluded those who tested positive for SARS-Cov-2 before the start of the study period and those who received ≥3 doses from VE analyses because we will seek to explore three-dose VE in future studies. We specified the study period to coincide with the mainstreaming of vaccines in BC and the time before the first case of Omicron was detected in BC to account for the attenuating impact of the Omicron variant on COVID-19 VE, which has been widely reported in the research literature [18,21].

Ascertainment of PLWH status

We adapted a previously validated case-finding algorithm, which has been previously described elsewhere [22], using the International Classification of Disease (ICD) Ninth (ICD-9) and Tenth (ICD-10) Revision diagnostic codes that have been associated with HIV (see Supplemental File 2 for details on the case-finding algorithm and the full list of diagnostic codes) to create a retrospective cohort of PLWH. Briefly, individuals who had 3 or more physician visits (MSP from 2008 to 2021), 1 or more hospitalization (DAD), or 1 or more emergency department visit for any of the HIV-related codes in Supplemental File 2 were considered HIV cases. Modifications were made to the initial algorithm to include individuals with a positive HIV laboratory test results based on provincial HIV laboratory test interpretation guidelines and those in the HIV/AIDS surveillance system [23].

Study variables

Outcome

Our primary study outcome was SARS-CoV-2 infection defined as a positive laboratory-confirmed test identified using a provincial database of COVID-19 test data. Those who tested positive for SARS-CoV-2 during the study period were considered test-positive "cases", whereas those who tested negative were considered test-negative "controls". For cases with multiple positive tests, the first positive test was selected. We used the first test-positive result only to minimize confounding the VE estimates with natural immunity from previous SARS-CoV-2 infection. For controls with multiple test-negative results, a randomly selected negative test was chosen.

Exposure of interest (COVID-19 vaccination status)

In BC, three vaccine products—BNT162b2 (Pfizer-BioNTech), messenger RNA (mRNA)-1273 (Moderna), and ChAdOx1 (Oxford-AstraZeneca)—have been mostly used in its vaccination program, in addition to a small number of Janssen (Johnson and Johnson) vaccines. Information on the specific vaccine type received (*i.e.,* BNT162b2 [Pfizer-BioNTech], mRNA-1273 [Moderna], or ChAdOx1 [Oxford-AstraZeneca]) and the number of doses were obtained from the BC Provincial Immunization Registry. For this study, individuals with a record of a single dose of any vaccine type were considered for inclusion in the VE analyses. Because vaccination strategies for multiple doses varied between homologous and heterologous vaccine schedules, owing to variations in vaccine supply, any combination of any two of the vaccines were considered vaccinated with two doses. We also included information on vaccine dose timing from the index date, which was defined as the date the test specimen was collected.

Covariates

Demographic variables, such as age (categorized in 10-year intervals), sex, socioeconomic status (using neighborhood income quintiles) based on census data, and health region (*i.e.,* Fraser Health, Interior Health, Northern Health, Vancouver Coastal Health, and Vancouver Island Health) to which the individual belonged to were obtained from the Client Roster. The health authorities delineate important geographic distinctions relating to health care service delivery that might provide insight into disparities, particularly among PLWH (see Supplemental File 3 for detailed information about health regions). Clinical information such as a history

of comorbidities known to be associated with increased risk of adverse COVID-19 outcomes were identified from the National Ambulatory Care Reporting System, Chronic Disease Registry, DAD, and MSP databases using relevant ICD-9 and ICD-10 codes. This information was subsequently used to calculate the Elixhauser comorbidity index, categorizing an individual's history of comorbidities as either 0 (no comorbidity), 1 (history of one comorbidity), 2 (a history of two comorbidities), or three or more comorbidities [24]. Individuals who inject drugs were identified in the BCC19C using a previously validated algorithm [25].

To account for the time variations in COVID-19 cases and vaccine roll-out throughout the length of the study period, we categorized dates of testing into bi-weekly calendar time periods and epidemic waves. Our study period spanned COVID-19 epidemic waves 2-4 (wave 2: December 15, 2020 to February 6, 2021; wave 3: February 7, 2021 to July 3, 2021; and wave 4: July 4, 2021 to November 21, 2021).

Matched HIV-negative cohort

We matched each PLWH included in this study to an HIV-negative individual on the following variables: age (5-year intervals), sex, community health service area, and SARS-CoV-2 outcome status. We defined individuals who are HIV-negative as those who did not meet the PLWH algorithm. To increase the precision of the VE estimates obtained from the matched HIV-negative cohort, we applied a one-to-many coarsened exact matching [26] approach to obtain as many HIV-negative matches from the general population.

Statistical analyses

To describe the baseline characteristics of PLWH and the matched HIV-negative cohort, we used means and standard deviation for continuous variables and frequencies and percentages for categorical variables. Standardized differences (SDs) were then used to compare baseline characteristics of test-positive and test-negative PLWH cases, and test-positive and test-negative HIV-negative cases. SD values of >0.10 were used to determine clinically meaningful differences [27]. Multivariable logistic regression was used to estimate the odds ratio (OR), comparing the odds of COVID-19 vaccination between test-positive cases and test-negative controls.

The adjusted analyses included covariates chosen based on comparable VE studies and literature evidence documenting their correlation with SARS-CoV-2 and HIV infection [12,28]. The following covariates were included in the adjusted models: age (10-year age bands), sex, area-level income, health authority, number of COVID-19 tests 3 months before the study period, Elixhauser comorbidity index, and bi-weekly testing periods. The VE was computed using the formula $(1 - OR) \times 100\%$. We conducted two separate regression models to estimate and indirectly compare the VE for the cohort of PLWH and the matched HIV-negative cohort, respectively. We estimated the VE by time since receipt of vaccine dose (*i.e.,* $\geq$14 days after the first dose; 7-59, 60-89, 90-119, 120-179 days after two doses).

Secondary VE analyses

In addition to the stratified VE analyses described above, we conducted secondary analyses combining both the PLWH and HIV-negative group in a single logistic regression model, specifying an interaction term between the composite vaccination status variable and PLWH status to estimate VE for each population. This was done to account for known baseline and clinical differences between both the PLWH and matched HIV-negative groups that might not have been accounted for in the stratified VE analyses. We adjusted for the same covariates included in the stratified VE analyses.

Data preparation was done using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) and all statistical analyses were conducted using R version 3.6.2 (R Foundation for Statistical Computing). All tests were two-sided, with $P < 0.05$ used as the level of statistical significance.

Results

There were 8200 PLWH identified in the BCC19C dataset. Between December 15, 2020, when the vaccines became available, and November 21, 2021, a total of 2700 PLWH tested for SARS-CoV-2 and were eligible to be included in this study. Of the eligible cohort, 351 (13.0%) tested positive, whereas 2349 (87.0%) tested negative, constituting our test-positive "cases" and test-negative "controls", respectively (Figure 1). After matching, we included a total of 375,043 (103,049 [27.5%] test-positive cases and 271,994 [72.5%] test-positive "controls") in the matched HIV-negative group who tested for SARS-CoV-2 within the same study period and formed the comparator cohort for this study. The bi-weekly testing patterns across both PLWH and the HIV-negative groups were mostly comparable, except for between March and April 2021 (epidemic wave 3) and September and October 2021 (epidemic wave 4), where noticeable spikes in the proportion of individuals who are HIV-negative and PLWH, who tested negative, respectively, were observed (Figure 2).

PLWH

The baseline and clinical characteristics of the study population by COVID-19 testing status are described in Table 1. The cohort of PLWH identified was predominantly male (71.4%, 1927), which is broadly representative of the PLWH in BC [10]. A total of 2377 (88.4%) participants had received at least one vaccine dose by the end of the study period. Of those vaccinated, 1773 (65.7%) had received two vaccine doses at the study index date. Compared with test-negative controls, test-positive PLWH were younger (mean age: 48.7 [SD = 11.9] years vs 50.6 [SD = 13.2] years), had a higher proportion of females, individuals in the 40-49 age group, individuals who live in the Northern health authority, and individuals who inject drugs. In addition, test-positive PLWH had lower proportions of people who received three vaccine doses, individuals with only one comorbidity, epidemic wave 3 infection (February 7, 2021 to July 3, 2021), individuals who have received any of the three main vaccine types, and individuals who live in the Vancouver Island Health Authority. (Table 1).

VE estimates from unadjusted and adjusted models are presented in Table 2 and Figure 3, respectively. The adjusted VE against laboratory-confirmed infection $\geq$14 days after the first dose was 49.0% (95% confidence interval [CI] = −14.6-77.3%). The VE 7-59 days after the second vaccine dose was 71.1% (95% CI = 39.7-86.1%); this increased to 89.3% (95% CI = 72.2-95.9%) 60-89 days after the second dose and was preserved up to 90-119 days. We found evidence suggestive of the vaccine waning 120-179 days after the second dose (VE = 51.3% [95% CI = 4.8-75.0%]; Figure 3).

Matched HIV-negative cohort

Among the matched cohort of individuals who were HIV-negative by the end of the study period, 330,196 (88.0%) had received at least a single vaccine dose; of those vaccinated, 279,726 (75.4%) had received two vaccine doses at the study index date. Compared with test-negative controls, test-positive participants were younger (mean age: 44.3 [SD = 17.3] years vs 51.2 [SD = 19.1] years), had higher proportions of individuals aged 19-29 and 30-39

Table 1
Demographic and clinical characteristics of study participants by SARS-CoV-2 testing status.

Study characteristics	People living with HIV (n = 2700)		SDs	Matched HIV-negative cohort(n = 375 043)		SDs
n, %[a]	Test-positive case (n = 351)	Test-negative control (n= 2349)		Positive (n = 103,049)	Negative (n = 271,994)	
Mean age (SD)	48.7 (11.9)	50.6 (13.2)	0.15	44.8 (17.3)	51.2 (19.1)	0.35
Age group						
19-29	19 (5.4%)	146 (6.2%)	0.03	23,447 (22.8%)	43,737 (16.1%)	0.17
30-39	68 (19.4%)	393 (16.7%)	0.07	22,557 (21.6%)	44,341 (16.3%)	0.14
40-49	97 (27.6%)	497 (21.2%)	0.15	19,098 (18.5%)	42,814 (15.7%)	0.07
50-59	100 (28.5%)	729 (31.0%)	0.06	16,810 (16.3%)	43,039 (15.8%)	0.01
60-69	51 (14.5%)	414 (17.6%)	0.08	11,642 (11.3%)	42,149 (15.5%)	0.12
70-79	14 (4.0%)	135 (5.8%)	0.08	5924 (5.8%)	36,881 (13.6%)	0.27
≥80	<5	35 (1.5%)	0.09	3871 (3.8%)	19,037 (7.0%)	0.14
Sex						
Female	127 (36.2%)	646 (27.5%)	0.19	51,354 (49.8%)	138,719 (51.0%)	0.02
Neighborhood income (quintiles)						
Lowest	157 (44.7%)	971 (41.3%)	0.07	23,631 (22.9%)	54,962 (20.2%)	0.07
2	60 (17.1%)	461 (19.6%)	0.07	21,143 (20.5%)	51,626 (19.0%)	0.04
3	57 (16.2%)	421 (17.9%)	0.04	20,170 (19.6%)	55,468 (20.4%)	0.02
4	51 (14.5%)	319 (13.6%)	0.03	20,389 (19.8%)	56,614 (20.8%)	0.03
Highest	26 (7.4%)	174 (7.4%)	0	17,522 (17.0%)	52,928 (19.5%)	0.06
Persons who inject drugs						
Yes	176 (50.1%)	922 (39.3%)	0.22	5703 (5.5%)	10,557 (3.9%)	0.08
Number of vaccine doses						
0	75 (21.4%)	248 (10.6%)	0.30	21,153 (20.5%)	23,694 (8.7%)	0.34
1	26 (7.4%)	155 (6.6%)	0.03	6437 (6.3%)	9804 (3.6%)	0.12
2	224 (63.8%)	1549 (65.9%)	0.04	71,217 (69.1%)	208,509 (76.7%)	0.17
3	26 (7.4%)	397 (16.9%)	0.29	4242 (4.1%)	29,987 (11.0%)	0.26
Pandemic wave						
Wave 2: December 15, 2020 to February 6, 2021	74 (21.1%)	467 (19.9%)	0.03	16,886 (16.4%)	47,159 (17.3%)	0.03
Wave 3: February 7, 2021 to July 3, 2021	124 (35.3%)	963 (41.0%)	0.12	45,220 (43.9%)	106,567 (39.2%)	0.10
Wave 4: July 4, 2021 to December 4, 2021	153 (43.6%)	919 (39.1%)	0.09	40,943 (39.7%)	118,268 (43.5%)	0.08
Time since first dose (days)						
0-13	<5	15 (0.64)	0.16	548 (0.53)	671 (0.25)	0.01
≥14	11 (3.13)	54 (2.30)	0.14	1282 (1.24)	2906 (1.07)	0.19
Time since second dose (days)						
0-6	<5	12 (0.51)	0.04	603 (0.59)	2041 (0.75)	0.23
7-59	14 (3.99)	171 (7.28)	0.58	2687 (2.61)	24,652 (9.06)	0.94
60-119	18 (5.13)	255 (10.86)	0.70	3209 (3.11)	41,527 (15.27)	0.86
120-179	22 (6.27)	121 (5.15)	0.23	3581 (3.48)	16,981 (6.24)	0.65
≥180	<5	11 (0.47)	0.02	3452 (3.35)	1766 (0.65)	0.14
Time since third dose						
0-6	<5	10 (0.43)	0.07	110 (0.11)	564 (0.21)	0.15
≥7-29	<5	25 (1.06)	0.36	135 (0.13)	1654 (0.61)	0.32
Elixhauser comorbidity index						
0	39 (11.1%)	268 (11.4%)	0.01	32,433 (31.5%)	64,317 (23.7%)	0.18
1	37 (10.5%)	342 (14.6%)	0.12	25,722 (25.0%)	60,743 (22.3%)	0.06
2	58 (16.5%)	339 (14.4%)	0.06	16,982 (16.5%)	47,039 (17.3%)	0.02
3 or more	217 (61.8%)	1400 (59.6%)	0.05	27,912 (27.1%)	99,895 (36.7%)	0.21
Health authority						
Interior	23 (6.6%)	189 (8.1%)	0.06	19,046 (18.5%)	54,524 (20.1%)	0.04
Fraser	111 (31.6%)	651 (27.7%)	0.09	42,175 (40.9%)	70,581 (26.0%)	0.32
Vancouver Coastal	175 (49.9%)	1218 (51.9%)	0.04	22,764 (22.1%)	63,013 (23.2%)	0.03
Vancouver Island	20 (5.7%)	217 (9.2%)	0.14	8077 (7.8%)	57,540 (21.2%)	0.39
Northern	22 (6.3%)	71 (3.0%)	0.15	10,798 (10.5%)	25,976 (9.6%)	0.03
Vaccine received						
Pfizer	217 (61.8%)	1592 (67.8%)	0.12	57,959 (56.2%)	172,630 (63.5%)	0.15
Moderna	74 (21.1%)	659 (28.1%)	0.16	27,878 (27.1%)	98,048 (36.1%)	0.19
AstraZeneca	20 (5.7%)	222 (9.5%)	0.14	5335 (5.2%)	17,078 (6.3%)	0.05
Other	0	<5	0.04	151 (0.2%)	174 (0.1%)	0.03
Number of tests 3 months before December 15, 2020						
0	255 (72.7%)	1707 (72.7%)	0.00	88,105 (85.5%)	226,567 (83.3%)	0.06
1	70 (19.9%)	455 (19.4%)	0.01	12,826 (12.5%)	38,294 (14.1%)	0.04
2	14 (4.0%)	124 (5.3%)	0.06	1573 (1.5%)	5395 (2.0%)	0.03
3	12 (3.4%)	63 (2.7%)	0.04	545 (0.5%)	1738 (0.6%)	0.01

[a] Unless otherwise specified.SD, standardized difference.SDs of >0.10 are considered clinically relevant.

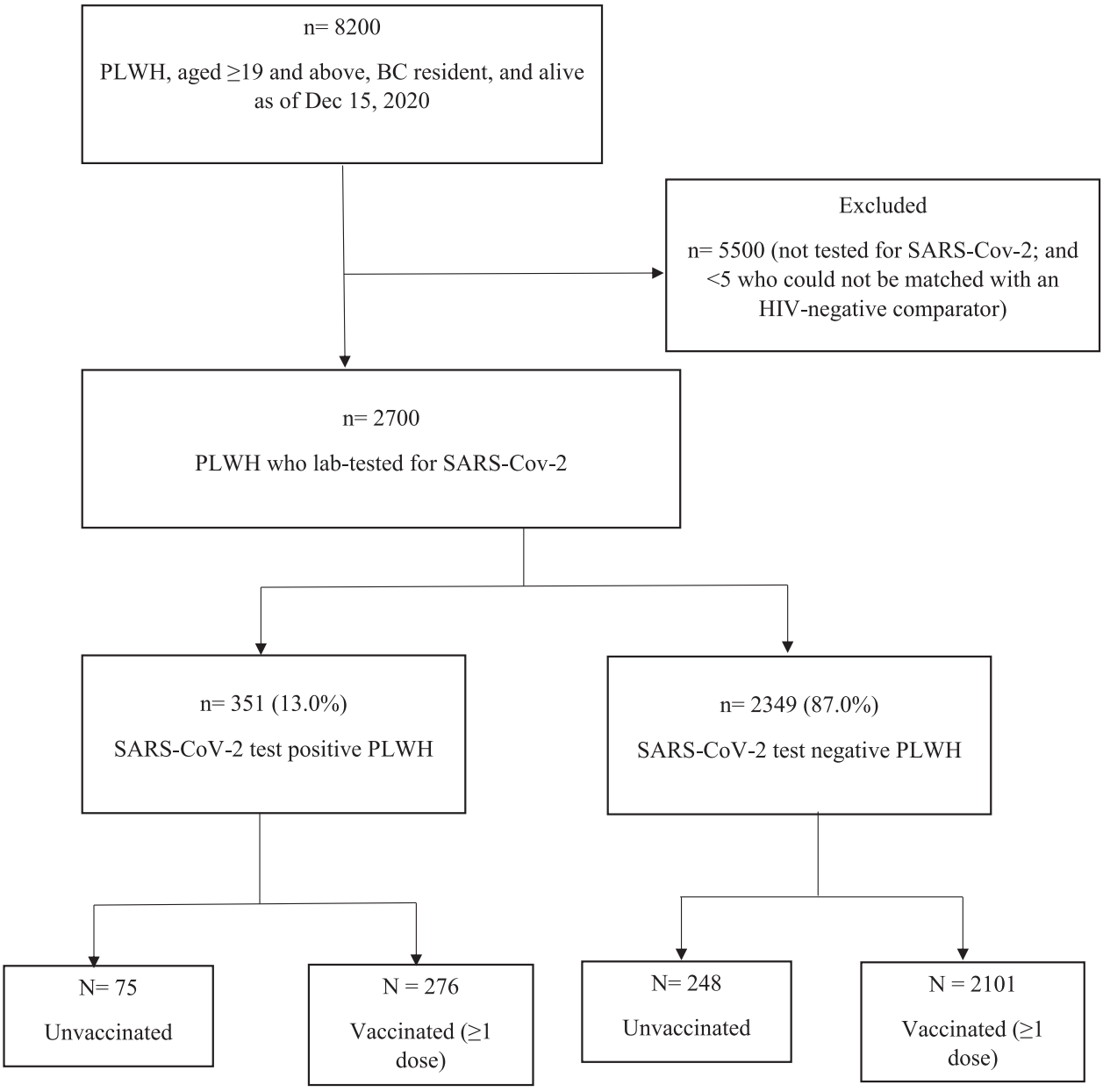

Figure 1. Study flow diagram for PLWH cohort.
BC, British Columbia; PLWH, people living with HIV.

years, with no comorbidities, pandemic wave 3 infections, those residing in the Fraser Health Authority, and individuals who received either no vaccines or one vaccine dose. Conversely, test-positive participants had lower proportions of those in age groups 60-69, 70-79, and ≥80 years, individuals who received two and three vaccine doses, individuals with three or more comorbidities, those who reside in the Vancouver Island Health Authority, and individuals who received a Pfizer or Moderna vaccine dose (Table 1).

Among the matched cohort, the adjusted VE against infection ≥14 days after the first dose was 54.5% (95% CI = 51.0-57.7%). This increased 7-59 days after second vaccine dose, peaking at 91.4% (95% CI = 90.9-91.8%). The VE was preserved 60-89 days after the second dose (VE = 89.6% [95% CI = 89.1-90.1%]) and up to 90-119 days after the second dose (VE = 87.5% [95% CI = 86.9-88.1%]). The VE 120-179 days after the second dose was 84.2% (95% CI = 83.4-85.0%; Figure 3).

Secondary analyses comparing VE by HIV status

The adjusted VE estimates from the secondary VE analyses are presented in Table 3. Overall, the findings from the secondary VE analyses appear comparable to those from the stratified analyses presented above. For example, the VE peaked earlier in the matched cohort 7-59 days after the receipt of the second dose at 91.3% (95% CI = 90.9-91.8%) compared with 78.1% (95% CI = 59.4-88.1%). Similar to the findings from the stratified analyses, waning was observed 120-179 days after the receipt of the second dose for both cohorts; however, the degree of waning was more pronounced in PLWH (VE = 58.2% [95% CI = 28.7-75.5%] compared with 84.2% [95% CI = 83.4-85.0%] in the matched cohort). The findings from the interaction term analyses show that the differences in the VE for PLWH and participants who are HIV-negative 7-59 days (P-value = 0.003) and 120-179 days (P-value <0.001) after

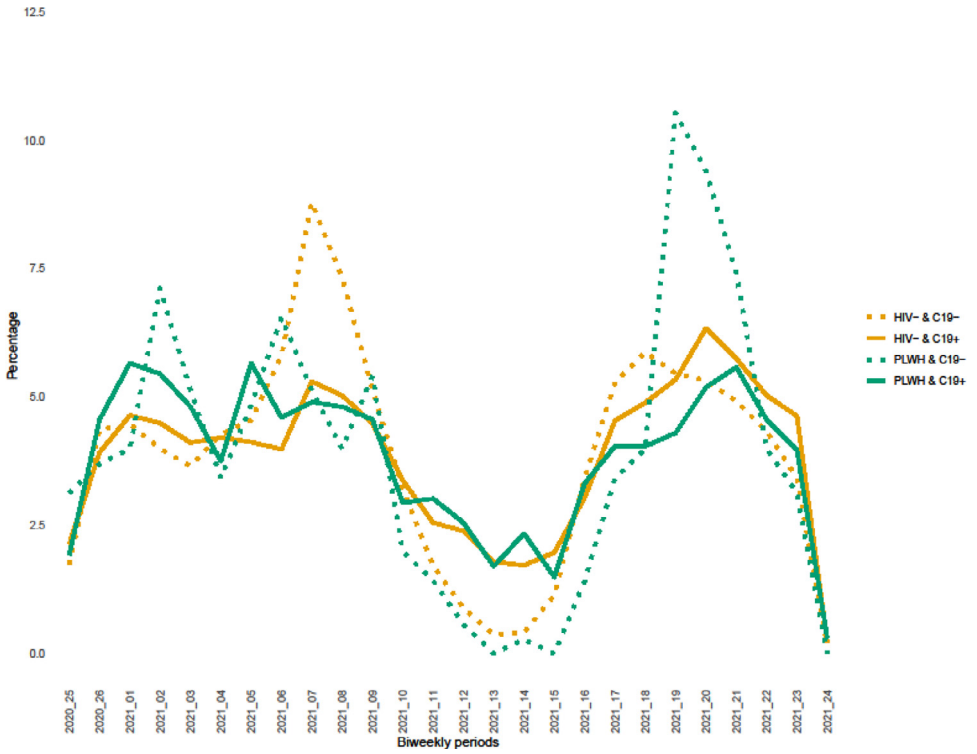

Figure 2. Proportion of PLWH and matched HIV-negative cohort who tested positive and negative for SARS-CoV-2 by bi-weekly period
C19+, test-positive (cases); C19-, test-negative (controls); PLWH, people living with HIV.

Table 2
Unadjusted VE estimates of COVID-19 vaccines against laboratory-confirmed infection during the study period, by time since vaccine dose.

	People living with HIV (n = 2700)			Matched HIV-negative cohort (n = 375,043)		
	VE (%)	Lower CI (%)	Upper CI (%)	VE (%)	Lower CI (%)	Upper CI (%)
1st dose (≥14 days)	32.6	-35.4	66.5	50.6	47.1	53.8
2nd dose (7 to 59 days)	72.9	50.5	85.2	87.8	87.2	88.3
2nd dose (60 to 89 days)	83.0	59.9	92.8	82.7	81.9	83.4
2nd dose (90 to 119 days)	71.2	45.3	84.9	80.7	79.9	81.5
2nd dose (120 to 179 days)	39.9	-1.4	64.3	77.2	76.3	78.1

CI, confidence interval; VE, vaccine effectiveness.

Table 3
Combined test-negative design estimate of VE against laboratory-confirmed infection.

	People living with HIV (n = 2700)			Matched HIV-negative cohort (n = 375,043)		
	VE (%)	Lower CI (%)	Upper CI (%)	VE (%)	Lower CI (%)	Upper CI (%)
1st dose (≥14 days)	41.0	-21.4	71.4	54.5	51.0	57.7
2nd dose (7 to 59 days)	78.1	59.4	88.1	91.3	90.9	91.8
2nd dose (60 to 89 days)	89.5	74.9	95.6	89.6	89.1	90.1
2nd dose (90 to 119 days)	81.4	64.2	90.3	87.5	86.9	88.1
2nd dose (120 to 179 days)	58.2	28.7	75.5	84.2	83.4	85.0

CI, confidence interval; VE, vaccine effectiveness.
Estimates were adjusted for baseline differences between people living with HIV and the matched HIV-negative cohort on the following variables: age, sex, area-level income, health authority, number of COVID-19 tests 3 months prior to study period, Elixhauser comorbidity index, and bi-weekly testing periods.

the receipt of the second dose were statistically significant (Supplemental File 4).

Discussion

Applying the TND to a retrospective cohort of 2700 PLWH and over 375,000 matched non-PLWH in BC from December 15, 2020 to November 21, 2021, we found that two doses of COVID-19 vaccines offered considerable protection against laboratory-confirmed infection among both PLWH and individuals who were HIV-negative during the pre-Omicron period. Among PLWH, VE estimates 1 week to 2 months after the receipt of two vaccine doses were 71.1% (39.7 to 86.1%), rising to 89.3% (72.2, 95.9%) up to 3 months after the receipt of the vaccine doses, and were relatively sustained for up to 4 months. We found evidence of vaccine waning 4-6 months after the receipt of two COVID-19 vaccine doses, with the VE against infection declining to 51.3%.

Compared with the matched HIV-negative cohort, we observed different patterns in the VE estimates. For example, the VE peaked

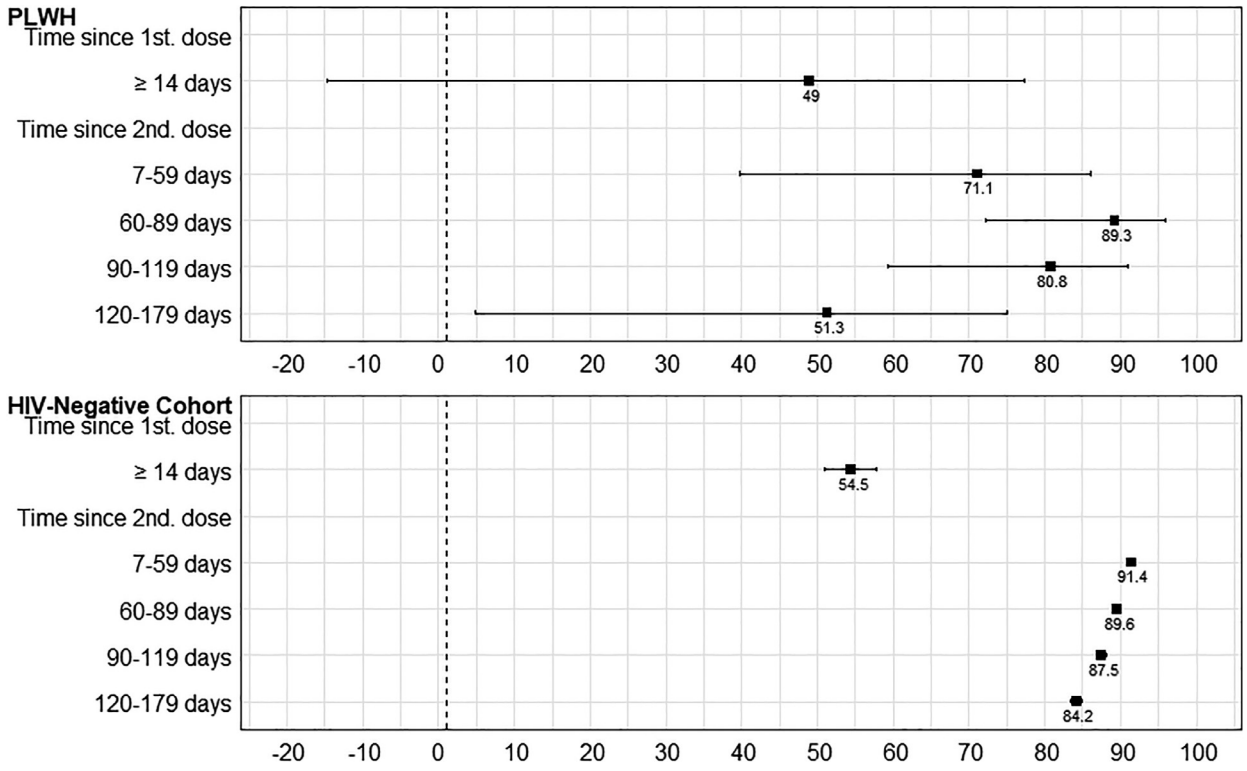

Figure 3. Adjusted vaccine effectiveness estimates of COVID-19 vaccines against laboratory-confirmed infection during the study period, by time since vaccine dose. PLWH, people living with HIV.

earlier in the matched HIV-negative cohort at 91.4% 7-59 days after the second dose; whereas in PLWH, the VE peak was observed later 60-89 days after the second dose. Similarly, the differences in the pattern of waning between the two populations were evident. After reaching their individual peaks, VE was relatively sustained in the matched HIV-negative cohort up to 3 months after the second dose, with waning observed after the 4-month mark, with a VE of 84.2%. Although similar patterns of waning were observed in the PLWH cohort at the 4-month mark, the degree to which waning occurred was higher in PLWH with a VE estimate of 51.3% 4 months after the receipt of two doses. These findings compared with our VE estimates in PLWH affirm our findings that although COVID-19 vaccines are effective in PLWH, a longer period might be required to achieve effectiveness levels noticed earlier in the larger non-HIV population, and that waning might occur earlier in PLWH than in otherwise healthier cohorts. However, these results appear in contrast to findings from immunological studies that show similar antibody responses in PLWH with high CD4 counts compared with healthy controls [19,20,29]. It is possible that the VE patterns we observed for PLWH relative to the HIV-negative cohort might be explained by the CD4 count distribution, as was reported in a study of VE of the Sputnik vaccines in PLWH [30], but CD4 count data were unavailable for PLWH in this cohort. The VE against infection for those with CD4 count <350 cells/μl was 73% compared with 79% in those with CD4 ≥350 cells/μl [30]. Consequently, understanding the role that HIV clinical parameters play in impacting VE will be integral to fully informing COVID-19 strategies in PLWH.

Our VE estimates among the HIV-negative cohort are in line with other studies estimating the real-world VE of COVID-19 vaccines in the general population during pre-Omicron periods. Although the study periods we report were different, in Ontario, Canada, Chung *et al.* [12] reported a VE of 91% against symptomatic infection 7 days after the receipt of two doses. Likewise in a cohort of BC and Quebec participants, the two-dose mRNA VE against symptomatic infection was sustained at 90% through the third month, with slight declines noted, but were sustained at ≥80% up until the 6-7 months [12,13]. It should be noted that the period specified in these studies were also before the spread of the Omicron variant.

To the best of our knowledge, there are no known studies estimating the real-world effectiveness of the included vaccines solely among PLWH, thus limiting our ability to contextualize our VE findings within the broader PLWH context. However, mixed patterns were observed in other immunocompromised populations. In a meta-analysis estimating the pooled, short-term, two-dose VE of COVID-19 vaccines against symptomatic infection in immunocompromised individuals (n = 42,821, including recipients of hematopoietic cell or solid organs transplant; patients with inflammatory disorders; PLWH; patients under immunosuppressive therapy; asplenia; and chronic renal failure: advanced kidney disease, dialysis, or nephrotic syndrome, *etc.*), the VE was 70.4% (95% CI = 18.9-89.2%) [31]. Individual study estimates from the included studies, however, ranged from 63% to 80%. One of the studies [32] included in the meta-analysis enrolled a merged immunocompromised cohort that contained a population of PLWH; yet, the sampling approach adopted precluded us from making direct HIV-related VE comparisons. Another review comparing VE in immunocompromised populations to the general population by vaccine type found that the Pfizer-BioNTech (BNT162b2) had the highest VE in immunocompromised populations (90% in immunocompromised population to 93% in the general population). The lowest VE reported in an immunocompromised cohort was for the Ad26.COV2.S (Janssen vaccine; 64% VE in the immunocompromised cohort to 79% in the general population) [33]. Taken together, these findings suggest that although the VE in the immunocompromised population might be lower relative to the broader population, the vaccine type and health conditions are relevant factors to consider. Future studies, where possible, should refrain from sampling ap-

proaches that treat individuals considered to be immunocompromised as a homogenous cohort.

Lastly, although we provide findings highlighting the real-world effectiveness of COVID-19 vaccines against SARS-CoV-2 infection, low hospitalizations and death counts impeded our ability to estimate the VE against hospitalizations and deaths in PLWH. Future studies are needed to examine severe outcomes to provide a complete outlook on the impact of COVID-19 vaccines in PLWH. This will help provide the totality of real-world evidence to inform vaccine strategies in this priority population.

Study limitations and strengths

Low event counts prevented us from generating more precise estimates and inhibited our ability to estimate VE against hospitalizations and death. In addition, the absence of HIV clinical characteristics impeded our ability to provide information on the HIV profile of the cohort. This prevents the identification of subpopulations of PLWH who may be more likely to experience lower VE (*e.g.*, individuals not on antiretroviral treatment, worse immune status, *etc.*). Available estimates, however, suggest that among the diagnosed PLWH in BC, about 92% are on antiretrovirals, whereas about 95% have suppressed viral loads [34]. Although the use of the algorithms enabled PLWH case identification within administrative holdings, the imprecise sensitivity of the adapted algorithm at 88% means some PLWH might have been missed, potentially impacting study findings. Although the modifications [23] made to the algorithm helped to address some of this, validation information on the modifications might be needed to better inform its use in PLWH case identification. We were also limited in our ability to stratify findings by the dominant variants during our study period. However, data from other studies showing comparable VE rates during similar time periods may suggest that stratification by the dominant strains within our specified period might not be as important. In addition, the use of specimen collection date as a proxy of SARS-CoV-2 symptom onset restricted our ability to limit the VE analysis to individuals who were tested within a specific time since the onset of symptoms, potentially resulting in outcome misclassification. The study strengths include the novel nature of this research and the methodological approach adopted, which allowed us to estimate the real-world VE in this population and provide us with critical insight into the impact of COVID-19 in this population.

Conclusion

Our study demonstrates that the effectiveness of two doses of COVID-19 vaccines among PLWH is broadly similar to the VE in the general population against confirmed SARS-CoV-2 infection up until November 2021, representing the period before Omicron circulation in Canada. Future work will evaluate the impact of Omicron and other variants on VE among PLWH, test whether the observed trends in earlier waning are confirmed, and evaluate the VE against hospitalizations and deaths among PLWH.

Declaration of competing interest

The authors have no competing interests to declare.

Funding

This project is supported by funding from the Public Health Agency of Canada, through the Vaccine Surveillance Reference group and the COVID-19 Immunity Task Force, and the Canadian Institutes for Health Research Canadian HIV Trials Network. Joseph Puyat is supported by the Michael Smith Foundation for Health Research (Scholar Awards). Ann N. Burchell is a Canada Research Chair in Sexually Transmitted Infection Prevention; she is also a recipient of a Non-Clinician Scientist Award from the Department of Family and Community Medicine, Faculty of Medicine, University of Toronto.

Ethical approval

This study was reviewed and approved by the University of BC Research Ethics Board (research ethics board #: H20-02097).

Acknowledgments

The authors acknowledge the assistance of the Provincial Health Services Authority, BC Centre for Disease Control, BC Ministry of Health, and the Regional Health Authority staff involved in data access, procurement, and management. The authors gratefully acknowledge the population of PLWH in BC whose data have been used in this manuscript. The BCC19C was established and is maintained through operational support from Data Analytics, Reporting, and Evaluation and BC Centre for Disease Control at the Provincial Health Services Authority. The authors would also like to acknowledge the contribution of their community partners, Darren Lauscher and Monte Strong, who provided valuable insight that helped inform data analysis and writing.

Author contributions

HS, NJ, AB, and AA conceptualized the study, secured research funding, contributed to study design, and reviewed the manuscript. AF drafted the initial manuscript, contributed to the analysis, and revised the manuscript. JP conducted data analysis and reviewed the manuscript. AK, CC, CTC, CLC, JW, and TG provided methodological and analytical input and reviewed the manuscript. All authors approved the manuscript.

Disclaimer

All inferences, opinions, and conclusion drawn in this manuscript are those of the authors and do not reflect the opinions or policies of the data steward(s).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.11.035.

References

[1] Ge E, Li Y, Wu S, Candido E, Wei X. Association of pre-existing comorbidities with mortality and disease severity among 167,500 individuals with COVID-19 in Canada: a population-based cohort study. *PLoS One* 2021;**16**:e0258154. doi:10.1371/journal.pone.0258154.

[2] Nomah DK, Reyes-Urueña J, Díaz Y, Moreno S, Aceiton J, Bruguera A, et al. Sociodemographic, clinical, and immunological factors associated with SARS-CoV-2 diagnosis and severe COVID-19 outcomes in people living with HIV: a retrospective cohort study. *Lancet HIV* 2021;**8**:e701–10. doi:10.1016/s2352-3018(21)00240-x.

[3] Ssentongo P, Heilbrunn ES, Ssentongo AE, Advani S, Chinchilli VM, Nunez JJ, Du P. Epidemiology and outcomes of COVID-19 in HIV-infected individuals: a systematic review and meta-analysis. *Sci Rep* 2021;**11**:6283. doi:10.1038/s41598-021-85359-3.

[4] Yang X, Sun J, Patel RC, Zhang J, Guo S, Zheng Q, et al. Associations between HIV infection and clinical spectrum of COVID-19: a population level analysis based on US National COVID Cohort Collaborative (N3C) data. *Lancet HIV* 2021;**8**:e690–700. doi:10.1016/s2352-3018(21)00239-3.

[5] Western Cape Department of Health in collaboration with the National Institute for Communicable Diseases, South AfricaRisk factors for coronavirus disease 2019 (COVID-19) death in a population cohort study from the Western Cape Province, South Africa. *Clin Infect Dis* 2021;**73**:e2005 –15-e2015.

[6] Bhaskaran K, Rentsch CT, MacKenna B, Schultze A, Mehrkar A, Bates CJ, et al. HIV infection and COVID-19 death: a population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform. *Lancet HIV* 2021;**8**:e24–32. doi:10.1016/s2352-3018(20)30305-2.

[7] Dandachi D, Geiger G, Montgomery MW, Karmen-Tuohy S, Golzy M, Antar AAR, et al. Characteristics, comorbidities, and outcomes in a multicenter registry of patients with human immunodeficiency virus and coronavirus disease 2019. *Clin Infect Dis* 2021;**73**:e1964–72. doi:10.1093/cid/ciaa1339.

[8] Liu Y, Xiao Y, Wu S, Marley G, Ming F, Wang X, et al. People living with HIV easily lose their immune response to SARS-CoV-2: result from a cohort of COVID-19 cases in Wuhan, China. *BMC Infect Dis* 2021;**21**:1029. doi:10.1186/s12879-021-06723-2.

[9] Ong S, Bryce E, British Broadcasting Corporation. How effective are Covid-19 vaccines for people with HIV?, https://www.bbc.com/future/article/20220419-how-effective-are-covid-19-vaccines-for-people-with-hiv; 2022 [accessed 10 August 2022].

[10] British Columbia Centre for Excellence in HIV/AIDS. HIV monitoring semi-annual report for British Columbia - second quarter 2022, https://stophivaids.ca/qmr/2022-Q2/#/bc; 2022 (accessed 10 August 2022).

[11] Chua H, Feng S, Lewnard JA, Sullivan SG, Blyth CC, Lipsitch M, et al. The use of test-negative controls to monitor vaccine effectiveness: a systematic review of methodology. *Epidemiology* 2020;**31**:43–64. doi:10.1097/ede.0000000000001116.

[12] Chung H, He S, Nasreen S, Sundaram ME, Buchan SA, Wilson SE, et al. Effectiveness of BNT162b2 and mRNA-1273 Covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe Covid-19 outcomes in Ontario, Canada: test negative design study. *BMJ* 2021;**374**:n1943. doi:10.1136/bmj.n1943.

[13] Skowronski DM, Febriani Y, Ouakki M, Setayeshgar S, El Adam S, Zou M, et al. Two-dose SARS-CoV-2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec. *Canada. Clin Infect Dis* 2022:ciac290. doi:10.1093/cid/ciac290.

[14] De Serres G, Skowronski DM, Wu XW, Ambrose CS. The test-negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomised placebo-controlled clinical trials. *Euro Surveill* 2013;**18**:20585. doi:10.2807/1560-7917.es2013.18.37.20585.

[15] Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine* 2013;**31**:2165–8. doi:10.1016/j.vaccine.2013.02.053.

[16] Sullivan SG, Tchetgen Tchetgen EJ, Cowling BJ. Theoretical basis of the test-negative study design for assessment of influenza vaccine effectiveness. *Am J Epidemiol* 2016;**184**:345–53. doi:10.1093/aje/kww064.

[17] Vandenbroucke JP, Brickley EB, Vandenbroucke-Grauls CMJE, Pearce N. A test-negative design with additional population controls can be used to rapidly study causes of the SARS-CoV-2 epidemic. *Epidemiology* 2020;**31**:836–43. doi:10.1097/ede.0000000000001251.

[18] Buchan SA, Chung H, Brown KA, Austin PC, Fell DB, Gubbay JB, et al. Estimated Effectiveness of COVID-19 vaccines against Omicron or Delta symptomatic infection and severe outcomes. *JAMA Netw Open* 2022;**5**:e2232760. doi:10.1001/jamanetworkopen.2022.32760.

[19] Brumme ZL, Mwimanzi F, Lapointe HR, Cheung PK, Sang Y, Duncan MC, et al. Humoral immune responses to COVID-19 vaccination in people living with HIV receiving suppressive antiretroviral therapy. *npj Vaccines* 2022;**7**:28. doi:10.1038/s41541-022-00452-6.

[20] Nault L, Marchitto L, Goyette G, Tremblay-Sher D, Fortin C, Martel-Laferrière V, et al. Covid-19 vaccine immunogenicity in people living with HIV-1. *Vaccine* 2022;**40**:3633–7. doi:10.1016/j.vaccine.2022.04.090.

[21] Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. *N Engl J Med* 2022;**386**:1532–46. doi:10.1056/nejmoa2119451.

[22] Nosyk B, Colley G, Yip B, Chan K, Heath K, Lima VD, et al. Application and validation of case-finding algorithms for identifying individuals with human immunodeficiency virus from administrative data in British Columbia. *Canada. PLoS One* 2013;**8**:e54416. doi:10.1371/journal.pone.0054416.

[23] Janjua NZ, Kuo M, Chong M, Yu A, Alvarez M, Cook D, et al. Assessing hepatitis C burden and treatment effectiveness through the British Columbia hepatitis testers cohort (BC-HTC): design and characteristics of linked and unlinked participants. *PLOS ONE* 2016;**11**:e0150176. doi:10.1371/journal.pone.0150176.

[24] Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998;**36**:8–27. doi:10.1097/00005650-199801000-00004.

[25] Janjua NZ, Islam N, Kuo M, Yu A, Wong S, Butt ZA, et al. Identifying injection drug use and estimating population size of people who inject drugs using healthcare administrative datasets. *Int J Drug Policy* 2018;**55**:31–9. doi:10.1016/j.drugpo.2018.02.001.

[26] Ripollone JE, Huybrechts KF, Rothman KJ, Ferguson RE, Franklin JM. Evaluating the utility of coarsened exact matching for pharmacoepidemiology using real and simulated claims data. *Am J Epidemiol* 2020;**189**:613–22. doi:10.1093/aje/kwz268.

[27] Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput* 2009;**38**:1228–34. doi:10.1080/03610910902859574.

[28] Skowronski DM, Setayeshgar S, Zou M, Prystajecky N, Tyson JR, Galanis E, et al. Single-dose mRNA vaccine effectiveness against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), including alpha and gamma variants: a test-negative design in adults 70 years and older in British Columbia. *Canada. Clin Infect Dis* 2022;**74**:1158–65. doi:10.1093/cid/ciab616.

[29] Levy I, Wieder-Finesod A, Litchevsky V, Biber A, Indenbaum V, Olmer L, Huppert A, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in people living with HIV-1. *Clin Microbiol Infect* 2021;**27**:1851–5. doi:10.1016/j.cmi.2021.07.031.

[30] Gushchin VA, Tsyganova EV, Ogarkova DA, Adgamov RR, Shcheblyakov DV, Glukhoedova NV, et al. Sputnik V protection from COVID-19 in people living with HIV under antiretroviral therapy. *EClinicalmedicine* 2022;**46**:101360. doi:10.1016/j.eclinm.2022.101360.

[31] Marra AR, Kobayashi T, Suzuki H, Alsuhaibani M, Tofaneto BM, Bariani LM, et al. Short-term effectiveness of COVID-19 vaccines in immunocompromised patients: a systematic literature review and meta-analysis. *J Infect* 2022;**84**:297–310. doi:10.1016/j.jinf.2021.12.035.

[32] Tenforde MW, Patel MM, Ginde AA, Douin DJ, Talbot HK, Casey JD, et al. Effectiveness of severe acute respiratory syndrome coronavirus 2 messenger RNA vaccines for preventing coronavirus disease 2019 hospitalizations in the United States. *Clin Infect Dis* 2022;**74**:1515–24. doi:10.1093/cid/ciab687.

[33] Di Fusco M, Lin J, Vaghela S, Lingohr-Smith M, Nguyen JL, Scassellati Sforzolini T, et al. COVID-19 vaccine effectiveness among immunocompromised populations: a targeted literature review of real-world studies. *Expert Rev Vaccines* 2022;**21**:435–51. doi:10.1080/14760584.2022.2035222.

[34] Public Health Agency of Canada. Estimates of HIV incidence, prevalence and Canada's progress on meeting the 90-90-90 HIV targets, https://www.canada.ca/en/public-health/services/publications/diseases-conditions/estimates-hiv-incidence-prevalence-canada-meeting-90-90-90-targets-2020.html#a4.3; 2022 [accessed 19 October 2022].