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Test negative case–control study of COVID-19 vaccine effectiveness for symptomatic SARS-CoV-2 infection among healthcare workers: Zambia, 2021–2022

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ABSTRACT

Objectives The study aim was to evaluate vaccine effectiveness (VE) of COVID-19 vaccines in preventing symptomatic COVID-19 among healthcare workers (HCWs) in Zambia. We sought to answer the question, 'What is the vaccine effectiveness of a complete schedule of the SARS-CoV-2 vaccine in preventing symptomatic COVID-19 among HCWs in Zambia?'

Design/setting We conducted a test-negative case–control study among HCWs across different levels of health facilities in Zambia offering point of care testing for COVID-19 from May 2021 to March 2022.

Participants 1767 participants entered the study and completed it. Cases were HCWs with laboratory-confirmed SARS-CoV-2 and controls were HCWs who tested SARS-CoV-2 negative. Consented HCWs with documented history of vaccination for COVID-19 (vaccinated HCWs only) were included in the study. HCWs with unknown test results and unknown vaccination status, were excluded.

Primary and secondary outcome measures The primary outcome was VE among symptomatic HCWs. Secondary outcomes were VE by: SARS-CoV-2 variant strains based on the predominant variant circulating in Zambia (Delta during May 2021 to November 2021 and Omicron during December 2021 to March 2022), duration since vaccination and vaccine product.

Results We recruited 1145 symptomatic HCWs. The median age was 30 years (IQR: 26–38) and 789 (68.9%) were women. Two hundred and eighty-two (24.6%) were fully vaccinated. The median time to full vaccination was 102 days (IQR: 56–144). VE against symptomatic SARS-CoV-2 infection was 72.7% (95% CI: 61.9% to 80.7%) for fully vaccinated participants. VE was 79.4% (95% CI: 58.2% to 90.7%) during the Delta period and 37.5% (95% CI: −7.0% to 63.3%) during the Omicron period.

Conclusions COVID-19 vaccines were effective in reducing symptomatic SARS-CoV-2 among Zambian HCWs when the Delta variant was circulating but not when Omicron was circulating. This could be related to immune evasive characteristics and/or waning immunity. These findings support accelerating COVID-19 booster dosing with bivalent vaccines as part of the vaccination programme to reduce COVID-19 in Zambia.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study design used in this study has been well described in influenza vaccine evaluation, and it can be used in post-introduction vaccine evaluation for SARS-CoV-2.
⇒ All health facilities, private and public, in Zambia were eligible for participation in the study hence there was no selection bias to easily accessible public health facilities.
⇒ Healthcare worker of any job classification in any department were eligible for enrolment, regardless of exposure to patients or vaccination status (as long as status was known).
⇒ No genomic sequencing was done to determine lineage, hence we could only associate vaccine effectiveness to the predominant variant in the country at the time of the study.
⇒ Additionally, self-reported vaccination status could have resulted in misclassification of the exposure because of social desirability bias for being vaccinated; however, we encouraged participants to report data from their vaccination card and verified vaccination status of some participants in the national COVID-19 vaccine registry in Zambia.

INTRODUCTION

COVID-19 vaccines have demonstrated good real-world effectiveness at reducing SARS-CoV-2 infections and preventing hospitalisations, and mortality in the western world.[1 2] However, variants continue to emerge with immune evading capabilities; for example, the Omicron variants can escape neutralisation

with vaccine-induced antibodies.[3] However, little evidence of vaccine effectiveness (VE) has been reported from countries in Africa, where SARS-CoV-2 epidemiology has varied compared with other regions of the world.[1 2]

A limited number of studies have been done on COVID-19 vaccines in countries in Africa. The Ad26.COV2.S vaccine was associated with lower hospitalisations and mortality during the Beta and Delta variant waves in South Africa,[4] and additional evidence demonstrated effectiveness of this vaccine against COVID-19 hospitalisations during the Omicron variant wave.[5] In Zambia, full receipt of a primary COVID-19 vaccine was associated with lower SARS-CoV-2 infections and symptomatic illness during an outbreak in a prison when Omicron was the dominant variant,[6] and receipt of ≥1 vaccine dose was associated with lower progression to in-hospital mortality.[7]

The Ministry of Health in Zambia used a nine-pronged approach to control and prevent the outbreak of COVID-19 from spreading further. This was after inclusion of the COVID-19 vaccination strategy. The strategies included: (1) surveillance and case finding; (2) case management; (3) infection prevention and control; (4) risk communication and community engagement; (5) laboratory diagnosis; (6) logistics and supply chain management; (7) appropriate, competent and adequate workforce; (8) routine essential health services; and (9) COVID-19 vaccination.[8] The COVID-19 vaccination programme was approved in Zambia on the 24 March 2021. The vaccines were administered cautiously and in a phased-up manner and on a pilot and voluntary basis. Healthcare workers (HCWs) were prioritised to receive vaccines expeditiously; the police, security, teachers, traditional leaders, clergy and immigration 0fficers as well, as these are essential to maintaining core societal functions. Others included marketers, traders, including bus and truck drivers involved in cross border business, in view of the environment they work in. Those older than 65 years old including those with chronic illnesses were also prioritised as they were at greatest risk of severe illness and death. There was no mandatory vaccination.[8]

Vaccines first became available in Zambia in mid-April 2021 and over 8.2 million (75.6%) of eligible persons have been fully vaccinated through 31 October 2022.[9] ChAdOx1-S COVID-19 vaccine was the first vaccine product available in Zambia and by late 2021, Ad26.COV2.S, mRNA-127, BNT162b2 and Sinopharm BBIBP-CorV were available in the country. An additional vaccine dose (ie, 'booster') after completing a primary vaccine series became available in Zambia in January 2022.

HCWs are at elevated risk of contracting SARS-CoV-2 during their interactions with patients with potential SARS-CoV-2 infection.[10] A key component of controlling the pandemic and protecting the Zambian HCW is deployment of a safe and effective COVID-19 vaccine. However, vaccination rates among HCWs in countries in Africa have been low; for instance, through November 2021, the WHO estimated only 1.3 million (27%) of HCWs in Africa had been fully vaccinated.[11] In Zambia, administrative data estimated much higher coverage, with 237 318 (99%) HCWs having been fully vaccinated through August 2022. Among a convenience sample of HCWs in Zambia, estimated coverage was 90%.[12] Understanding VE from countries in Africa is important since most studies have been conducted in other regions of the world. We sought to measure VE among HCWs in Zambia.

METHODS

We conducted a test-negative case–control COVID-19 VE study among HCWs from May 2021 to March 2022 in Zambia. HCW participants were identified through review of routine SARS-CoV-2 testing data in Zambia from May 2021 through March 2022. Data on relative variant genome frequency by region from GISAID (Global Initiative on Sharing Avian Influenza Data) were used to define the SARS-CoV-2 variant that was circulating during each wave.[13]

District health officers provided line lists to the study team of HCWs in their districts who were recently symptomatic and tested for COVID-19-like illness. Additionally, the study team members inspected national testing data for HCWs who tested for SARS-CoV-2 by PCR or rapid antigen tests. Trained data collectors contacted HCWs by phone or in-person at health facilities to invite them to complete the study questionnaire. Potential HCW participants were contacted up to six times. Data collectors administered a standardised questionnaire that included information on demographics, medical history (including COVID-19 vaccination status and self-reported prior SARS-CoV-2 infection) and COVID-19 preventive measures (like mask use and hand hygiene). COVID-19 vaccination status was collected from self-report, with review of written documentation (ie, vaccine cards) when available. Additionally, a subset of participants' vaccination status was verified in the national register if key variables (vaccine type, dose dates) were not available during the interview. All participants provided informed consent. This study was approved by the Zambia National Health Research Authority (see protocol- online supplemental file 2). The activity was reviewed by US Centers for Disease Control and Prevention (CDC) and was conducted consistent with applicable federal law and CDC policy. (See eg, 45 C.F.R. part 46.102(l),[2] 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C.3501 et seq.)

HCWs included all paid and unpaid persons serving in healthcare settings who had the potential for direct or indirect exposure to patients or infectious materials. HCW roles/cadres in this study included: nurses (nurse practitioners, general nurses, mid-wives, registered nurses), allied health staff (HCWs distinct from optometry, dentistry, nursing, medicine, clinical psychology and pharmacy, eg, anaesthesiologist assistant, perfusionist, radiographers), clinicians (HCWs in clinical practice of optometry, dentistry, medicine, ie, resident physicians, medical licentiates, clinical officers, clinical students),

administrative staff (managers and administrators, clerks, office orderlies, human resource personnel, accounts staff, secretaries), non-clinical workers (cleaners, chaplain, food handlers/cafeteria staff) and other (any classification outside the mentioned categories, eg, community health workers, health science students). Cases were HCWs with symptomatic laboratory-confirmed SARS-CoV-2 infection; controls were HCWs with COVID-19-like illness (CLI) who tested SARS-CoV-2 negative. (CLI was defined as any acute illness characterised by fever, chills, cough, dyspnoea, myalgia, chills, rigours, headache, anosmia, ageusia, sore throat, coryza/rhinorrhoea, congestion, fatigue, general weakness, anorexia, nausea, vomiting, diarrhoea or altered mental status).[14 15]

Patient and public involvement

Patients (HCWs) were not involved in the setting of research priorities, defining research questions and outcome measures, providing input into study design and conduct, dissemination of results and evaluation of studies.

Full vaccination was defined as having received the first dose of a one-dose vaccine or second dose of a two-dose vaccine ≥14 days before SARS-CoV-2 testing. Partial vaccination was defined as having received only the first dose of a two-dose vaccine ≥14 days before SARS-CoV-2 testing or receiving the second dose ≤13 days before testing. HCWs were deemed to have an indeterminate vaccination status if they received their first dose 0–13 days before testing and unknown vaccination status if the product type or dose dates of COVID-19 vaccine were unknown.

Categorical demographic characteristics of participants by case/control status were compared using a two-sided Pearson χ^2 test to assess for statistical significance. Age, described as a continuous variable, was compared between cases and controls using Wilcoxon rank-sum test as it was not normally distributed. Mixed-effects logistic regression was used to compare the odds of being partially or fully vaccinated against COVID-19 among symptomatic SARS-CoV-2 cases versus controls, adjusting for sex, age, number of comorbidities and province (random-effects term). VE was calculated as 1 minus the adjusted OR multiplied by 100. VE by vaccination status for participants whose vaccination status was unknown were excluded from the analyses as the sample sizes were inadequate for meaningful analyses. Additionally, we did a stratified analyses based on the predominant strain circulating in Zambia (Delta from May to November 2021, Omicron from December 2021 to March 2022) and vaccine type (only for ChAdOx1-S and Ad26.COV2.S vaccines because other vaccine types had small sample sizes).

We did a sensitivity analysis excluding unvaccinated participants who reported prior SARS-CoV-2 infection to account for potential misclassification of immunity status. Although the study procedures emphasised recruiting only symptomatic HCWs, data collectors relied on data sources that sometimes did not always contain information about clinical course to identify HCWs for recruitment (ie, line lists of HCWs who recently tested for SARS-CoV-2 within a given district and laboratory test results spreadsheets). Thus, some HCWs who were contacted and interviewed reported having asymptomatic SARS-CoV-2 infections only; we therefore conducted a secondary analysis including all HCW participants regardless of symptom status (online supplemental appendix).

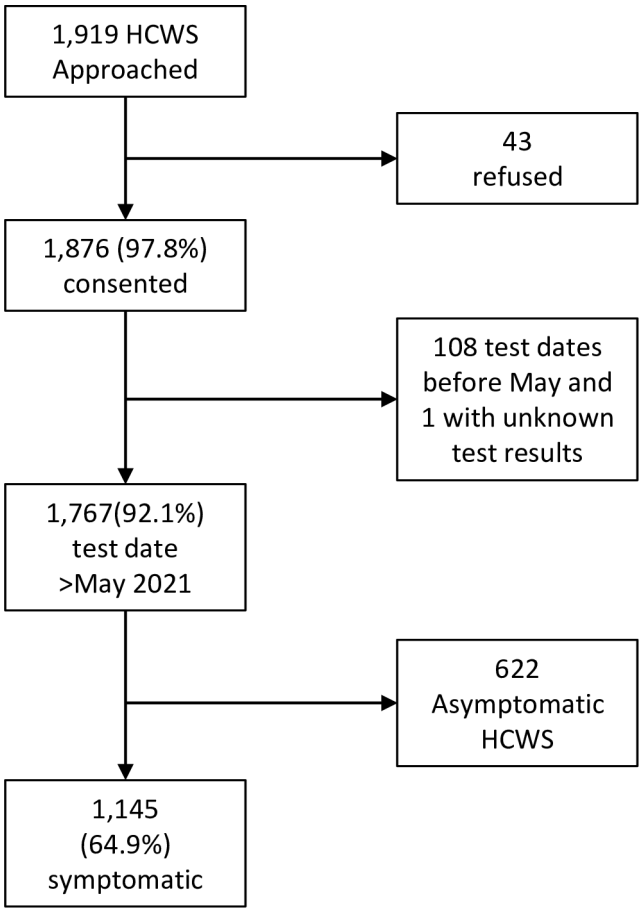

Figure 1 Recruitment flow diagram for the healthcare worker COVID-19 vaccine effectiveness study in Zambia, May 2021 to March 2022. HCWs, healthcare workers.

RESULTS

Between May 2021 and March 2022, 1919 HCWs were approached for study participation, of whom 1767 (92.1%) consented to participate and had test dates since May 2021 (43 refused participation, 1 participant with unknown test result and 108 had test dates before May 2021). Of the total number of HCWs, 1145 (64.8%) had CLI (figure 1).

The median age of symptomatic HCWs was 30 years (IQR: 26–38), and 789 (68.9%) were women (table 1). Most participants (67.4%) were from Lusaka province, in which the capital city is located, and allied HCWs comprised the largest (40.0%) HCW cadre (table 1). The overall prevalence of any chronic comorbidities was 14.7%; hypertension (6.4%) and HIV (3.6%) were the most commonly reported comorbidities. One hundred

Table 1 Demographic characteristics of symptomatic participants by case/control status for the healthcare worker COVID-19 vaccine effectiveness study in Zambia, May 2021 to March 2022

Symptomatic healthcare workers				
Characteristic	Cases (N=509), n (%)	Controls (N=636), n (%)	Overall (N=1145), n (%)	P value†
Age group				0.011
18–29	203 (39.9)	307 (48.3)	510 (44.5)	
30–44	230 (45.2)	236 (37.1)	466 (40.7)	
45+	64 (12.6)	76 (11.9)	140 (12.2)	
Unknown	12 (2.4)	17 (2.7)	29 (2.5)	
Sex				0.183
Female	340 (66.8)	449 (70.6)	789 (68.9)	
Male	168 (33.0)	187 (29.4)	355 (31.0)	
Unknown	1 (0.2)	0 (0.0)	1 (0.1)	
Province,				<0.001
Lusaka	292 (57.4)	480 (75.5)	772 (67.4)	
Eastern	58 (11.4)	31 (4.9)	89 (7.8)	
Luapula	40 (7.9)	41 (6.4)	81 (7.1)	
Copperbelt	37 (7.3)	16 (2.5)	53 (4.6)	
Muchinga	31 (6.1)	39 (6.1)	70 (6.1)	
Central	19 (3.7)	5 (0.8)	24 (2.1)	
Southern	18 (3.5)	22 (3.5)	40 (3.5)	
Western	9 (1.8)	2 (0.3)	11 (1.0)	
Northwestern	5 (1.0)	0 (0.0)	5 (0.4)	
HCW role				<0.001
Nurse	191 (37.5)	210 (33.0)	401 (35.0)	
Allied health	164 (32.2)	294 (46.2)	458 (40.0)	
Clinician	59 (11.6)	41 (6.4)	100 (8.7)	
Administrative	48 (9.4)	34 (5.3)	82 (7.2)	
Non-clinical	40 (7.9)	49 (7.7)	89 (7.8)	
Other	6 (1.2)	8 (1.3)	14 (1.2)	
Unknown	1 (0.2)	0 (0.0)	1 (0.1)	
Prior COVID-19				0.027
Yes	87 (17.1)	80 (12.6)	167 (14.6)	
No	407 (80.0)	542 (85.2)	949 (82.9)	
Unknown	15 (2.9)	14 (2.2)	29 (2.5)	
Comorbidities present*				0.117
Present	84 (16.5)	84 (13.2)	168 (14.7)	
Absent	425 (83.5)	552 (86.8)	977 (85.3)	
Number of comorbidities				0.262
0	425 (83.5)	552 (86.8)	977 (85.3)	
1	73 (14.3)	75 (11.8)	148 (12.9)	
2	11 (2.2)	9 (1.4)	20 (1.7)	
Comorbidities, (top five):				
Hypertension	39 (7.7)	34 (5.3)	73 (6.4)	0.141
HIV	17 (3.3)	24 (3.8)	41 (3.6)	0.816
Diabetes	8 (1.6)	10 (1.6)	18 (1.6)	>0.9

Continued

Table 1 Continued

Symptomatic healthcare workers				
Characteristic	Cases (N=509), n (%)	Controls (N=636), n (%)	Overall (N=1145), n (%)	P value†
Cardiovascular	3 (0.6)	3 (0.5)	6 (0.5)	>0.9
Tuberculosis	2 (0.4)	2 (0.3)	2 (0.2)	0.197
Admitted to a health facility within ±7 days of testing				<0.001
Yes	19 (3.7)	2 (0.3)	21 (1.8)	
No	490 (96.3)	634 (99.7)	1124 (98.2)	
Vaccination status				<0.001
Unvaccinated	366 (71.9)	313 (49.2)	679 (59.3)	
Full	62 (12.2)	220 (34.6)	282 (24.6)	
Partial	65 (12.8)	65 (10.2)	130 (11.4)	
Indeterminate	13 (2.6)	36 (5.7)	49 (4.3)	
Unknown	3 (0.6)	2 (0.3)	5 (0.4)	
Vaccine type				<0.001
ChAdOx1-S	156 (30.6)	163 (25.6)	319 (27.9)	
Ad26.COV2.S	119 (23.4)	274 (43.1)	393 (34.3)	
Sinopharm BBIBP-CorV	0 (0.0)	4 (0.6)	4 (0.3)	
BNT162b2	0 (0.0)	1 (0.2)	1 (0.1)	
unknown	234 (46.0)	194 (30.5)	428 (37.4)	
Past 6 months hospitalisation				<0.001
Yes	14 (2.8)	29 (4.6)	43 (3.8)	
No	491 (96.5)	605 (95.1)	1096 (95.7)	
Unknown	44 (0.8)	2 (0.3)	66 (0.5)	

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*Comorbidities include asthma, autoimmune or rheumatological disease, cancer, kidney disease, lung disease, diabetes mellitus, heart condition, HIV infection, hypertension, tuberculosis and immunosuppressing condition.
†Pearson's χ^2 test.
HCWs, healthcare workers.

and sixty-seven HCWs (14.6%) reported prior SARS-CoV-2 infections. Twenty-one (1.8%) HCWs had been hospitalised for their illness and none had died.

Of the 1145 symptomatic HCWs, 130 (11.4%) were partially vaccinated while 282 (24.6%) were fully vaccinated. There were two distinct waves of recruitment in this study that corresponded with the periods of Delta variant predominance and Omicron variant predominance in Zambia (figure 2). Full vaccination coverage was highest among allied HCWs (27.9%) and lowest among clinicians (19.0%) (table 2). Vaccine coverage increased with time (figure 3). Only 6 (0.5%) had reported receiving an additional dose (ie, booster) beyond the primary series. The median time since full vaccination was 102 days (IQR: 56–144); this was 46 days (IQR: 25–80) during the Delta predominant period and 111 days (IQR: 69–154) during the Omicron predominant period. Among symptomatic HCWs, there were 509 (44.5%) cases (ie, tested SARS-CoV-2 positive) and 636 (55.5%) controls. Sixty-two (12.2%) HCWs with SARS-CoV-2 (cases) were fully vaccinated, compared with 220 (34.6%) HCWs with CLI but who were SARS-CoV-2 test negative (p=0.001). Few, 21, HCWs were hospitalised but those with COVID-19 (cases) were more likely to be admitted (3.7% vs 0.3%, p<0.01; table 1) than those with a negative SARS-CoV-2 test (controls).

Adjusted VE against symptomatic SARS-CoV-2 was 72.7% (95% CI: 61.9% to 80.7%) for fully vaccinated HCWs and 23.1% (95% CI: −14.7% to 48.5%) for partially vaccinated (table 3). VE during the Delta predominant period was 79.4% (95% CI: 58.2% to 90.7%) and the Omicron predominant period was 37.5% (95% CI: −7.0%

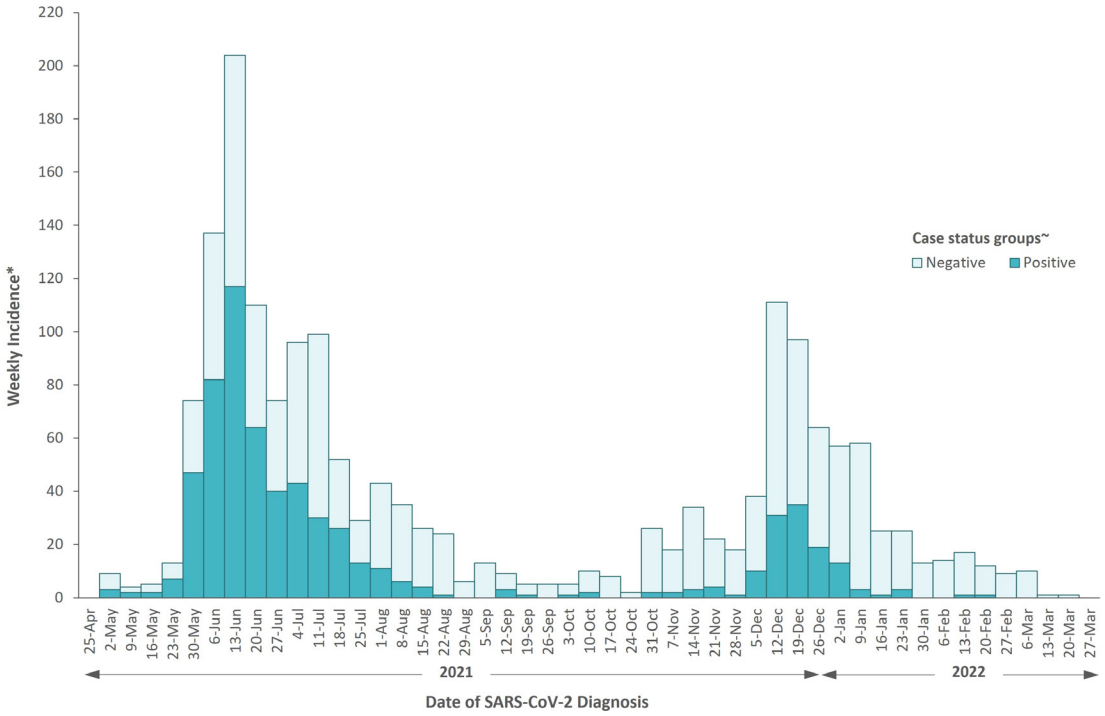

Figure 2 Weekly number of cases (positive) and controls (negative) among healthcare workers in Zambia, May 2021 to March 2022. *Incidence of SARS-CoV-2 testing by PCR and Rapid Antigen tests. ~Positive: refers to a positives SARS-Cov-2 test result by PCR or Rapid Antigen test; Negative: refers to a negative SARS-Cov-2 test result by PCR or Rapid Antigen test.

to 63.3%) for fully vaccinated HCWs. VE for ChAdOx1-S vaccine was 87.0% (95% CI: 74.4% to 93.7%) and for Ad26.COV2.S vaccine was 68.2% (95% CI: 48.0% to 80.8%) for fully vaccinated HCWs. A similar pattern of VE was observed when the outcome variable was any SARS-CoV-2 infection (online supplemental appendix table 1). After excluding unvaccinated HCWs who reported a prior SARS-CoV-2 infection, VE against symptomatic SARS-CoV-2 was 69.9% (95% CI: 57.5% to 78.9%) for fully vaccinated participants over the complete study period (online supplemental appendix table 2). Among 19 persons with COVID-19 (ie, cases) who were hospitalised, none (0.0%) were fully vaccinated, 2 (10.5%) were partially vaccinated, 1 (5.3%) had an indeterminate vaccination status and 16 (84.2%) were unvaccinated.

DISCUSSION

COVID-19 vaccines were effective at preventing symptomatic SARS-CoV-2 among HCWs in Zambia during the period when the Delta variant was dominant in the country. The VE estimate decreased when the Omicron variant became predominant, which could be related to waning immunity and/or immune evasive mutations in the virus.[16–18] In a US-based study, VE after receipt of both two and three doses was lower during the Omicron-predominant than

Table 2 Vaccination coverage among symptomatic healthcare workers in the healthcare worker COVID-19 vaccine effectiveness study in Zambia, May 2021 to March 2022

Vaccination status	Administrative	Allied health	Clinician	Non-clinical	Nurse	Other
Unvaccinated	54 (65.9)	258 (56.3)	62 (62.0)	56 (62.9)	241 (60.1)	7 (50.0)
Full	16 (19.5)	128 (27.9)	19 (19.0)	20 (22.5)	94 (23.4)	5 (35.7)
Partial	10 (12.2)	52 (11.4)	14 (14.0)	7 (7.9)	45 (11.2)	2 (14.3)
Indeterminate	2 (2.4)	20 (4.4)	3 (3.0)	5 (5.6)	19 (4.7)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	2 (2.0)	1 (1.1)	2 (0.5)	0 (0.0)

HCWs included all paid and unpaid persons serving in healthcare settings who had the potential for direct or indirect exposure to patients or infectious materials. HCW roles/cadres in this study included: nurses (nurse practitioners, general nurses, mid-wives, registered nurses), allied health (HCWs distinct from optometry, dentistry, nursing, medicine, clinical psychology and pharmacy, eg, anaesthesiologist assistant, perfusionist, radiographers), clinicians (HCWs in clinical practice of optometry, dentistry, medicine, ie, resident physicians, medical licentiates, clinical officers, clinical students), administrative (managers and administrators, clerks, office orderlies, human resource personnel, accounts staff, secretaries), non-clinical (cleaners, chaplain, food handlers/cafeteria staff), other (any classification outside the mentioned categories, eg, community health workers, health science students).
HCWs, healthcare workers.

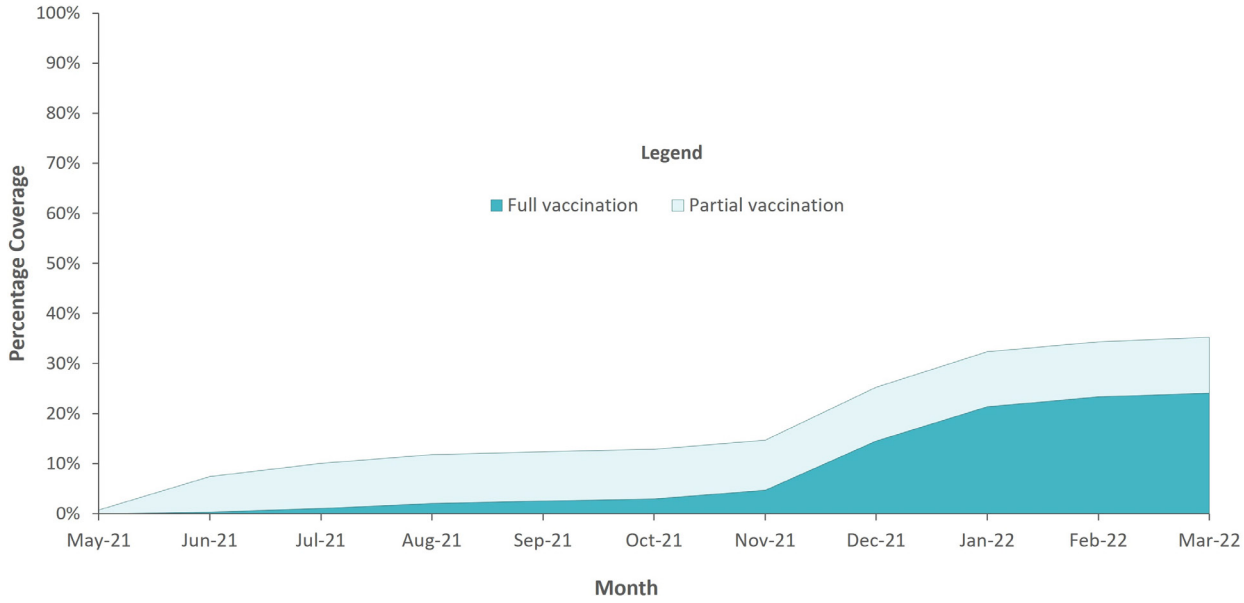

Figure 3 Vaccine coverage by month for the healthcare worker COVID-19 vaccine effectiveness study in Zambia, May 2021 to March 2022.

during the Delta-predominant period at all time points evaluated. During both periods, VE after receipt of a third dose was higher than that after a second dose; however, VE waned with increasing time since vaccination.[17] These findings of increasing VE following additional vaccine doses have been evidenced in other studies done in the western world.[16 19] That most vaccinated HCWs in this study had only received the complete primary vaccine series could point to the need to increase booster vaccination coverage in Zambia, as an additional vaccine dose has been shown to strengthen immunity against SARS-CoV-2 variants.[19] Moreover, most HCWs in this study had not been vaccinated at all (although recent progress in Zambia points to improving coverage). Perceptions about vaccine safety and efficacy were the strongest predictors of vaccine acceptance for adult COVID-19 vaccination[20]; bad perceptions potentially explaining the low vaccination rates. Perception of COVID-19 disease severity as well were especially strong predictors of vaccine uptake,[20] and bad perceptions likely leading to poor uptake. Although many people in Zambia have likely had SARS-CoV-2 infection (potentially offering some immunity), vaccination offers additional protection after natural infection.[21–24] The findings in this study provide important evidence

Table 3 SARS-CoV-2 vaccine effectiveness estimates for symptomatic SARS-CoV-2 infection in the healthcare worker COVID-19 vaccine effectiveness study in Zambia, May 2021 to March 2022

Characteristic	SARS-CoV-2 infection, (%)	Vaccine effectiveness, % (95% CI)	
		Crude VE	Adjusted VE§
Vaccination status*			
Full (n=282)	62 (22.0)	75.9 (66.8 to 82.5)	72.7 (61.9 to 80.7)
Partial (n=130)	65 (50.0)	14.5 (–24.5 to 41.3)	23.1 (–14.7 to 48.5)
Indeterminate (n=49)	13 (26.5)	69.1 (40.7 to 83.9)	68.7 (39.3 to 84.8)
Time period (predominant variant)†			
May to November 2021 (Delta) (n=43)	10 (23.3)	78.7 (57.6 to 90.2)	79.4 (58.2 to 90.7)
December 2021 to March 2022 (Omicron) (n=239)	52 (21.8)	30.0 (–18.1 to 58.1)	37.5 (–7.0 to 63.3)‡
Vaccine type†			
ChAdOx1-S (n=97)	27 (27.8)	86.2 (73.3 to 93.1)	87.0 (74.4 to 93.7)
Ad26.COV2.S (n=183)	35 (19.1)	70.1 (52.3 to 81.6)	68.2 (48.0 to 80.8)

*Full vaccination defined as receiving the first dose of a one-dose vaccine or second dose of a two-dose vaccine ≥14 days prior to COVID-19.
†Estimate for full vaccination series adjusted for sex, age, comorbidity and province.
‡All healthcare workers for Omicron predominant phase were from Lusaka; adjusted for sex, age and number of comorbidities.
§Mixed-effects model for sex, age, number of comorbidities and province (random-effects term).
VE, vaccine effectiveness.

about VE in Africa. Few countries in Africa have reported on COVID-19 VE, which is an important question considering the sizeable financial and human resources going toward increasing vaccine coverage on the continent.

Omicron variant caused a large wave in December 2021 to February 2022. The findings from our study suggest that vaccination might not have reduced symptomatic infections during this period, although data from Zambia indicate vaccination protected people against severe disease during this wave.[25] Our findings that vaccination was not associated with lower odds of symptomatic COVID-19 during the Omicron period, contrasts with findings from a COVID-19 outbreak in a prison in Zambia in December 2021.[6] In that study, full vaccination was associated with 72.9% effectiveness for symptomatic COVID-19. Timing of vaccine receipt could account for this difference, as the median time since full vaccination was 102 days in this current study compared with much more recent vaccination (ie, <2 months) in the other study (Simwanza *et al*). The longer time since vaccination among HCWs could reflect that this group was prioritised for vaccination at the outset of the national campaign given their elevated risk of exposure to the virus. Beyond waning immunity, the Omicron variant of SARS-CoV-2 has mutations that enable it to evade prior immunity, both vaccine-induced and natural immunity.[26–28] Furthermore, it has been similarly observed in other study findings that Ad26.COV2.S vaccines (majorly administered in the Omicron variant predominant period in our study) have diminished effect against the Omicron variant.[19] Our findings are consistent with current understanding of immunity against SARS-CoV-2.[19 26–28]

HCWs with COVID-19 had a higher proportion of hospitalisation than controls, consistent with relatively greater severity of SARS-CoV-2 infection compared with some other respiratory viruses that can cause CLI. Our findings of more hospitalisation among HCWs with COVID-19 who were not fully vaccinated further emphasises the importance of vaccines in strengthening immunity against severe disease.[25]

Since this study was done, Zambia has made substantial strides in increasing full vaccination coverage among eligible persons (aged ≥12 years). By the end of October 2022, Zambia had fully vaccinated ~76% of persons aged ≥12 years.[9] This is a major achievement considering that just 5% persons were fully vaccinated in October 2021. However, booster vaccine coverage among Zambians remains low (36%), highlighting the need for ongoing COVID-19 vaccination efforts in the country.

Our study had strengths and limitations. The study design used in this study has been well described in influenza vaccine evaluation, and it can be used in post-introduction vaccine evaluation for SARS-CoV-2. All health facilities, private and public, in Zambia were eligible for participation in the study hence there was no selection bias to easily accessible public health facilities. HCW of any job classification in any department were eligible for enrolment, regardless of exposure to patients or vaccination status (as long as status was known). Many participants were partially vaccinated and the sample size for fully vaccinated HCWs was small, resulting in wide CIs for our primary objective of assessing full vaccination. No genomic sequencing was done to determine lineage, hence we could only associate VE to the predominant variant in the country at the time of the study.[3] Additionally, self-reported vaccination status could have resulted in misclassification of the exposure because of social desirability bias for being vaccinated; however, we encouraged participants to report data from their vaccination card and verified vaccination status of some participants in the national COVID-19 vaccine registry in Zambia. Because so few participants had a booster dose, we could not assess VE for this vaccination status.

COVID-19 vaccination protected HCWs from symptomatic SARS-CoV-2 infections in Zambia during the Delta wave. Considering ongoing need for COVID-19 vaccine delivery in Zambia, where possible, COVID-19 vaccination could be integrated into other healthcare services to improve efficiency in under-resourced health systems like in Zambia.[29] Examples of existing platforms include vaccination in HIV care clinics supported by the US President's Emergency Plan for AIDS Relief, routine antenatal care services, for inpatients prior to discharge from the hospital, or into Expanded Programme on Immunisation programmes such as mass measles or polio vaccination campaigns. New SARS-CoV-2 variants are predicted to emerge,[27 30] and thus having an ongoing ability to conduct VE studies in Zambia will be useful. Platforms like severe acute respiratory infection surveillance can provide this information, since studies like this are resource intensive.[31] In addition, there is need to conduct immunological studies to ascertain that COVID-19 vaccines induce appropriate immune responses in Zambia, alongside clinical evaluation of outcomes as was done in this study. These findings support the acceleration of COVID-19 vaccination programmes in Zambia to reach high coverage, especially for booster vaccine doses in people who have finished their primary series months ago.

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