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Letter to the Editor

Safety and incidence of COVID-19 following ChAdOx1(AZD1222) COVID-19 vaccination in Botswana

Dear editor,

A recent publication in this journal by Nisar *et al.*[1] assessed the effectiveness of various COVID-19 vaccines in Pakistan using a test-negative case-control design. They report moderate effectiveness of various vaccines and higher effectiveness mRNA vaccines compared with inactivated vaccines. Although they assessed the impact of concurrent medical conditions, they were only a few cases of immunosuppression contributing to < 3% of the study population and approximately 87% of the participants received Sinopharm and Sinovac, and 1% received the Oxford/AstraZeneca vaccine. AstraZeneca (AZD1222), formerly called ChAdOx1, previously demonstrated robust immunogenicity after a single dose with favorable safety profiles.[2,3] Despite Botswana's high HIV prevalence, treatment has been hugely successful with over 90% of all adults living with HIV currently receiving antiretroviral therapy (ART).[4] There are no data on the safety and effectiveness of AZD1222 in this high HIV prevalence setting.

We conducted a single-arm, open-label interventional multi-site study (D8111C00013/ESR-21–21311) to monitor vaccine safety and the occurrence of symptomatic COVID-19 infections, hospitalizations and deaths among individuals vaccinated with AZD1222 between September 15, 2021, and May 18, 2022, at five sites in Botswana. The study was approved by the Health and Research Development Committee (HRDC#00936). All participants provided written informed consent.

We screened 9419 and enrolled 9140 participants (Fig. 1). Of the participants included in this study, 9124 (99.8%) were receiving at least one dose of AZD1222 and remaining in the study 22 days after the first dose without having a SARS-CoV-2 RT-PCR positive confirmed COVID-19 infection, Vaccinated Set (VS); 2275 of these participants were included in the Single Dose Set (SDS) (did not receive

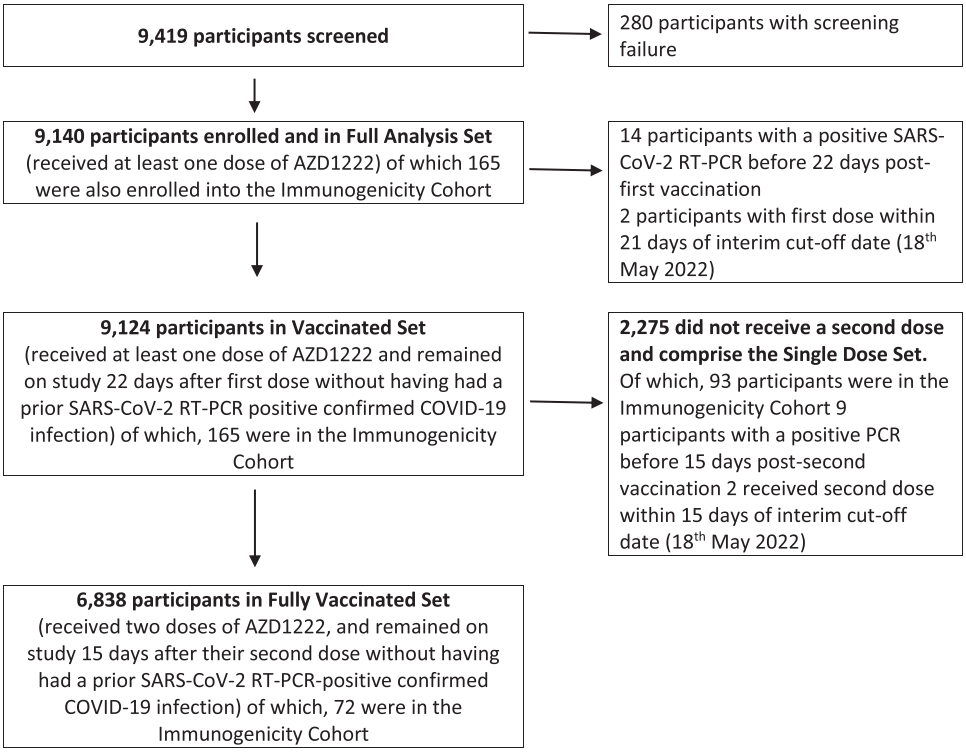

Fig. 1. Overall diagram on study population.

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a second dose), and 6838 participants were included in the Full vaccinated set (FVS) (2 doses of AZD1222, at least 15 days after their second dose without a PCR-confirmed COVID-19 infection).

Most participants were male (54.1%) and Black African (99.9%) with a median age of 30 years (IQR: 23–42 years), Table 1. Of the participants enrolled, 21.4% were people with HIV (PWH). Amongst PWH, 96.5% were on ART. There were no laboratory-confirmed COVID-19 hospitalizations or deaths during the study reporting period. There were 27 laboratory-confirmed symptomatic COVID-19 infections post-vaccination; 14 were within 22 days of the first vaccination. Of the 13 post-22 days after the first vaccination, 9 were within 14 days post-Dose 2 (Supplementary Fig. 1). The overall incidence of laboratory-confirmed symptomatic COVID-19 infection in the study, after two doses of AZD1222 in the FVS, was 1.67 (95% CI: 0.34–4.86) per 1000 participant years (1000-PY) (Supplementary Tables 1, 2). The three infections that occurred > 15 days post-second vaccination (18, 20, and 22 days) were from HIV-uninfected individuals (female 40- < 65 years, male 40- < 65 years and one male < 40 years of age). All infections occurred when Omicron was the dominant circulating variant.[5] The overall incidence of laboratory-confirmed symptomatic COVID-19 infection after one dose of AZD1222 in the VS was 3.46 (95% CI: 1.84–5.90) per 1000-PY. This incidence was significantly higher at 8.07 (95% CI: 3.25–16.64) in PWH compared to 2.34 (95% CI: 0.86–5.09) in HIV-uninfected participants. In contrast, the overall incidence of symptomatic COVID-19 infection in FVS was 1.67 (95% CI: 0.34–4.87) per 1000-PY. There were no differences by HIV status in the FVS (Supplementary Table 2). Point estimates of incidence in participants with at least one dose were higher in PWH (8.07; 95% CI: 3.25–16.57) compared with HIV-uninfected individuals (2.34; 95% CI: 0.86–5.09), although the difference was not statistically significant.

There was a total of 673 adverse events (AEs) incidence of 158 per 1000-PY; (Supplementary Table 3). Three-hundred and fifty-six participants (3.9%) experienced at least one AE (Supplementary Table 5). The distribution of the number of AEs experienced per participant was comparable between HIV-uninfected and PWH (Supplementary Table 5). The 456 reported AEs deemed related to study product were generally mild to moderate in severity, headache (114) (26.7 per 1000-PY), fatigue (51) (12 per 1000-PY); pyrexia (33) (7.7 per 1000-PY, and dizziness (29) (0.32 per 1000-PY). Participants with prior COVID-19 infection had a significantly higher incidence of AEs compared to those who were COVID-19-naive, with 321 AEs occurring per 1000-PY versus 144 per 1000-PY in COVID-naive individuals (p-value < 0.0001; Supplementary Table 4). Furthermore, the incidence of AEs was higher in both COVID-19-naive and previously infected participants after the first vaccination, as compared to after the second vaccination. The incidence of AEs in HIV-uninfected individuals and PWH was 160 per 1000-PY and 153 per 1000-PY, respectively. Seventeen SAEs from 15 participants were reported during the study period (incidence of 4 per 1000-PY), of which five SAEs were abortions (Supplementary Tables 1 and 3). Overall, there were 15 localized AEs and 658 systemic AEs (Supplementary Tables 8–10).

The incidence of AESI in HIV-uninfected individuals was 1.72 per 1000 participant-years compared to 2.05 in PWH. Three SAEs were within 28 days post-first dose and no SAEs occurred after second dose (Supplementary Table 3). This study confirms that AZD1222 is equally efficacious in preventing severe infections and is consistent with findings from other populations.[3,6–9] The overall incidence of laboratory-confirmed symptomatic COVID-19 infection after two doses of AZD1222 in the FVS was 1.67 (95% CI: 0.34–4.86) per 1000-

Table 1
AZD 1222 study participants baseline characteristics by vaccination sets.

Variable	FAS	SDS	VS	FVS
Total number enrolled	9140	2275	9124	6838
Site n(%)				
Gaborone	3759 (41.1)	851 (37.4)	3745 (41)	2888 (42.2)
Maun	1751 (19.2)	612 (26.9)	1751 (19.2)	1138 (16.6)
Serowe	1269 (13.9)	257 (11.3)	1269 (13.9)	1011 (14.8)
Francistown	1454 (15.9)	324 (14.2)	1454 (15.9)	1130 (16.5)
Selebi Phikwe	907 (9.9)	231 (10.2)	905 (9.9)	671 (9.8)
Gender n(%)				
Female	4192 (45.9)	932 (41)	4184 (45.9)	3245 (47.5)
Male	4948 (54.1)	1343 (59)	4940 (54.1)	3593 (52.5)
Ethnicity n(%)				
Black African	9130 (99.9)	2272 (99.9)	9114 (99.9)	6831 (99.9)
Asian	5 (0.1)	3 (0.1)	5 (0.1)	2 (0)
Caucasian	1 (0)	0 (0)	1 (0)	1 (0)
Other	0 (0)	0 (0)	0 (0)	0 (0)
Missing	4 (0)	0 (0)	4 (0)	4 (0.1)
Median age in years (IQR)	30 (23–42)	26 (21–33)	30 (23–42)	32 (23–43)
< 40	6329 (69.2)	1976 (86.9)	6315 (69.2)	4334 (63.4)
40–65	2719 (29.7)	287 (12.6)	2717 (29.8)	2424 (35.4)
≥65	92 (1)	12 (0.5)	92 (1)	80 (1.2)
HIV n(%)				
Negative	6283 (68.7)	1600 (70.3)	6274 (68.8)	4671 (68.3)
Positive	1960 (21.4)	346 (15.2)	1959 (21.5)	1606 (23.5)
Unknown	897 (9.8)	329 (14.5)	891 (9.8)	561 (8.2)
ART n(%)	1884 (96.5)	331 (95.7)	1883 (96.5)	1545 (96.7)
Pregnancy n (%)	72 (1.9)	68 (7.7)	72 (2)	4 (0.1)
Median BMI (IQR) tnote2	22 (20–27)	21 (19–26)	22 (20–27)	23 (20–28)
< 18.5	1415 (15.5)	398 (17.5)	1412 (15.5)	1012 (14.8)
18.5- < 25	4563 (49.9)	1269 (55.8)	4557 (49.9)	3284 (48)
25- < 30	1673 (18.3)	344 (15.1)	1671 (18.3)	1324 (19.4)
≥30	1489 (16.3)	264 (11.6)	1484 (16.3)	1218 (17.8)
Diabetes n (%)				
No	8970 (98.1)	2247 (98.8)	8954 (98.1)	6696 (97.9)
Yes	169 (1.8)	28 (1.2)	169 (1.9)	141 (2.1)
Missing	1 (0)	0 (0)	1 (0)	1 (0)
Hypertension n (%)				
No	8770 (96)	2242 (98.5)	8756 (96)	6503 (95.1)
Yes	369 (4)	33 (1.5)	367 (4)	334 (4.9)
Missing	1 (0)	0 (0)	1 (0)	1 (0)
Prior COVID infection n (%)				
No	8414 (92.1)	2131 (93.7)	8398 (92)	6258 (91.5)
Yes	725 (7.9)	144 (6.3)	725 (7.9)	579 (8.5)
Missing	1 (0)	0 (0)	1 (0)	1 (0)
Smoking status n (%)				
Current	1958 (21.4)	568 (25)	1957 (21.4)	1387 (20.3)
Occasional	337 (3.7)	106 (4.7)	336 (3.7)	229 (3.3)
Previous	489 (5.4)	117 (5.1)	489 (5.4)	371 (5.4)
Never	6355 (69.5)	1484 (65.2)	6341 (69.5)	4850 (70.9)
Missing	1 (0)	0 (0)	1 (0)	1 (0)
Alcohol status n (%)				
Current	2854 (31.2)	825 (36.3)	2851 (31.2)	2023 (29.6)
Occasional	1942 (21.2)	482 (21.2)	1940 (21.3)	1454 (21.3)
Previous	651 (7.1)	158 (6.9)	650 (7.1)	492 (7.2)
Never	3692 (40.4)	810 (35.6)	3682 (40.4)	2868 (41.9)
Missing	1 (0)	0 (0)	1 (0)	1 (0)
Highest education level n (%)				
None	267 (2.9)	47 (2.1)	267 (2.9)	218 (3.2)
Primary	740 (8.1)	135 (5.9)	740 (8.1)	605 (8.8)
Junior Secondary	3229 (35.3)	821 (36.1)	3226 (35.4)	2400 (35.1)

(*continued on next page*)

Table 1 (*continued*)

Variable	FAS	SDS	VS	FVS
Senior Secondary	2624 (28.7)	711 (31.3)	2620 (28.7)	1905 (27.9)
Tertiary	2279 (24.9)	561 (24.7)	2270 (24.9)	1709 (25)
Employment status n (%)				
Formal wage employment part-time	481 (5.3)	125 (5.5)	480 (5.3)	355 (5.2)
Formal wage employment fulltime)	2670 (29.2)	537 (23.6)	2669 (29.3)	2127 (31.1)
Self-employed part time)	486 (5.3)	118 (5.2)	486 (5.3)	368 (5.4)
Self-employed full time)	1029 (11.3)	204 (9)	1026 (11.2)	821 (12)
Ad-hoc work	32 (0.4)	5 (0.2)	32 (0.4)	27 (0.4)
Seasonal employment	195 (2.1)	46 (2)	195 (2.1)	148 (2.2)
Other	4246 (46.5)	1240 (54.5)	4235 (46.4)	2991 (43.7)
Marital status n (%)				
Single	1980 (21.7)	460 (20.2)	1980 (21.7)	1518 (22.2)
Cohabiting Married	7159 (78.3)	1815 (79.8)	7143 (78.3)	5319 (77.8)
Divorced	6917 (75.7)	1873 (82.3)	6902 (75.7)	5020 (73.4)
Widowed	1260 (13.8)	307 (13.5)	1260 (13.8)	953 (13.9)
Other	815 (8.9)	79 (3.5)	814 (8.9)	733 (10.7)

FAS-Full analysis set.
FVS-Full vaccinated set (two doses of AZD1222, at least 15 days after their second dose without having a PCR-confirmed COVID-19 infection).
SDS-Single Dose Set (did not receive a second dose).
VS-Vaccinated Set (receiving at least one dose of AZD1222 and remaining in the study 22 days after the first dose without having a SARS-CoV-2 RT-PCR positive confirmed COVID-19 infection).

PY which is lower than in the placebo group of a similar study in Brazil, UK, and South Africa.[3]

Participants with prior COVID-19 infection had a higher incidence of AEs after the first vaccination (Supplementary Table 4). This is consistent with previous reports linking prior infection to increased risk of AEs post-vaccination.[10] We also found a higher incidence of severe systemic AEs in participants with prior COVID-19 infection compared to those without prior infection.

Our results should be interpreted in the context of the changing COVID-19 pandemic landscape and vaccine access. Limitations include telephonic reporting which could have resulted in underreporting and potentially misgrading of AEs partially mitigated by collecting complete information through standardized AEs case report forms.

In conclusion, AZD1222 was effective in preventing severe COVID-19 infections in both PLWH and HIV-uninfected people. No COVID-19-related hospitalizations or deaths were observed.

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Ethical statement

Written consent was obtained from the study participants before their enrollment.

Conflicts of interest

ST and PG are employees of, and hold or may hold stock in, AstraZeneca. AW is an employee of X4 Group contracted to AstraZeneca for this work. LC is an employee of SRG Recruitment contracted to AstraZeneca for this work. All other authors declare that they have no conflict of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2023.02.037.

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