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Safety of AZD1222 COVID-19 vaccine and low Incidence of SARS-CoV-2 infection in Botswana following ChAdOx1(AZD1222) vaccination: A single-arm open-label interventional study – final study results

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ABSTRACT

Objectives: We report the final analysis of the single-arm open-label study evaluating the safety and COVID-19 incidence after AZD1222 vaccination in Botswana conducted between September 2021 and August 2022.
Methods: The study included three groups of adults (>18 years), homologous AZD1222 primary series and booster (AZ2), heterologous primary series with one dose AZD1222, and AZD1222 booster (HPS), and primary series other than AZD1222 and AZD1222 booster (OPS). We compared the incidence of AEs in participants with and without prior COVID-19 infection using an exact test for rate ratios.
Results: Among 10,894 participants, 9192 (84.4%) were enrolled at first vaccine dose, 521 (4.8%) at second vaccine, and 1181 (10.8%) at the booster vaccine. Of 10,855 included in the full analysis set, 1700 received one dose of AZD1222; 5377 received two doses; 98 received a heterologous series including one AZD1222 and a booster; 30 in the HPS group; 1058 in the OPS group; and 2592 in the AZ2 group. No laboratory-confirmed COVID-19 hospitalizations or deaths were reported. The incidence of laboratory-confirmed symptomatic COVID infection for the AZ2 group was 6.22 (95% confidence interval: 2.51-12.78) per 1000 participant-years (1000-PY) and 3.5 (95% confidence interval: 0.42-12.57) per 1000-PY for AZ2+booster group. Most adverse events were mild, with higher incidence in participants with prior COVID-19 infection. Individuals with prior COVID-19 exposure exhibited higher binding antibody responses. No differences in outcomes were observed by HIV status.
Conclusion: AZD1222 is safe, effective, and immunogenic for people living with and without HIV.

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Background

COVID-19 is an unprecedented pandemic caused by the SARS-CoV-2 virus, first reported in December 2019. This led to rapid global research, yielding various COVID-19 vaccines with different efficacy and safety levels. Previously referred to as ChAdOx1 nCoV-19, the early development of AZD1222 was performed by the University of Oxford, United Kingdom (UK), with subsequent transfer of development activities to AstraZeneca [1,2]. AZD1222 is a recombinant adenovirus vaccine expressing the SARS-CoV-2 S surface glycoprotein, which demonstrated robust immunogenicity after a single dose and favorable safety profiles [1].

Botswana has the third highest HIV prevalence in the world, with more than one in five adults aged between 15-49 years living with the virus [3]. The country however has HIV treatment success with over 95% of all adults living with HIV currently receiving antiretroviral therapy (ART) [4]. The impact of HIV, ART, and interaction with AZD1222, has not been fully determined. The study is the first clinical trial to determine the safety of the AZD1222 vaccine in the Botswana population; despite the vaccine having been the first COVID-19 vaccine rolled out in the country and other countries within the region. As different variants of COVID-19 continue to emerge and vaccine hesitancy particularly for booster doses is increasing [5], it is important to determine the safety and relative effectiveness of the AZD1222 vaccine.

In the interim results [6] we presented a brief report on AZD vaccine safety and incidence of laboratory-confirmed SARS-CoV-2 infection, including individuals who received up to two vaccine doses [6]. In this final analysis, we include Homologous AZD1222 primary series and booster (AZ2), heterologous primary series with AZD1222 and booster (HPS), and primary series without AZD1222 and booster (OPS), as well as a subset of participants enrolled in the immunogenicity sub-cohort.

Methods

Study design

This was a single-arm, open-label interventional multi-site study (D8111C00013 / ESR-21-21311) conducted in Botswana (ClinicalTrials.gov registration NCT05715944). Participants received COVID-19 AZD1222 vaccinations either homologously (two doses as primary series and one booster) or as part of a heterologous series (with at least one dose of AZD1222 among three vaccine doses). The dosing interval was 8-12 weeks. Participants were followed up by telephone for the first 28 days post-vaccination to monitor adverse events (AEs). Beyond 28 days, follow-up was conducted on an unsolicited basis to identify any other AEs or potential symptomatic COVID-19 infections until one-year post-enrollment, voluntary study withdrawal, death, or the last visit. Symptomatic COVID-19 cases were identified based on protocol-defined qualifying symptoms and duration. Enrollment occurred at five sites across Botswana, encompassing urban and semi-urban areas in line with the COVID-19 disease burden. Additionally, a convenient sample of a subset of participants was co-enrolled in an immunogenicity sub-study, which entailed more frequent in-person visits including blood specimens and nasopharyngeal swab collection.

Participants

The initial study protocol age eligibility was forty (40) years and above. After 2 months of enrollment, the protocol was amended to enroll adult participants ≥18 years of age who were not already vaccinated for COVID-19. About 9 months later, the protocol was further amended to allow for enrollment onto the heterologous COVID-19 vaccine series.

Participants were generally in good health. All chronic and pre-existing conditions were required to be well-controlled for participation in the study. The study excluded people who were pregnant or planning to be pregnant within 3 months after their AZD1222 COVID-19 vaccination. Furthermore, study participants of reproductive potential were required to use appropriate contraception, consistent with the in-country standard of care.

Data collection

Data was gathered directly from participants and/or their medical records through the electronic data capture (EDC) system, compliant with 21 CFR part 11. Rigorous data reviews, queries, and validation were conducted post-collection to ensure data quality. Study personnel were trained in the study protocol, Human Subjects Protection, and Good Clinical Practice. The study, initiated in September 2021, commenced participant vaccination/enrollment sequentially across locations (Gaborone, Francistown, Maun, Selebi Phikwe, and Serowe).

Safety monitoring

Participants were followed up for AEs as part of safety monitoring in the study. After each AZD1222 COVID-19 vaccination, participants were observed in the study clinic for at least 15 minutes for possible hypersensitivity/anaphylaxis and immediate AEs. Following this, participants were provided with an AEs memory tool which they took home to record any events as experienced in real-time. Participants were initially followed up telephonically on days 7, 14 and 28 post-receipts of each AZD1222 vaccine dose, the follow-up schedule was amended to day 28 post-receipt of the study product. The telephonic study visits collected details of AEs, symptom onset, management, and resolution. Clinical staff graded the AEs according to Common Terminology Criteria for Adverse Events CTCAE version 5.0 grading tables.

AEs were further categorized into serious AEs (SAE), and/or AEs of special interest (AESI). SAEs and AESIs were recorded throughout the study participation period, and non-serious AEs were solicited in the first 28 days post-vaccination. All AEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. SAEs were submitted to AstraZeneca within 1 day of awareness and reviewed by appropriately qualified medical personnel. AE causal relationship determination to investigational product (IP) included temporal association, consistency with known drug profile and absence of alternate etiology. SAEs and AESIs were reviewed and discussed by the Protocol Safety Review Team (PSRT) at fortnightly meetings. The PSRT comprised of principal investigators, medical specialists, statisticians, and data management team representatives.

Laboratory procedures

Participants were asked about their HIV status and those with unknown/HIV-negative status were offered HIV rapid testing, after providing consent. Serial HIV rapid testing was conducted as per standard of care using Determine HIV 1/2 test (Abbott Diagnostic Division, Hoofddorp, The Netherlands) and Unigold (Trinity Biotech Plc, Bray, Ireland). Combined Nasopharyngeal and Oropharyngeal samples were used for the SARS-CoV-2 testing using real-time polymerase chain reaction (RT-PCR) using the 2019-nCoV RNA (PCR-Fluorescence Probing) Assay (Sun Yat-sen University, Da An Gene Co., Ltd, China) according to the manufacturer's instructions.

Participants with the protocol-defined COVID-19 qualifying symptoms and their specified duration had COVID-19 PCR testing conducted. Fever, shortness of breath and difficulty breathing had no minimum symptoms duration requirement. Other symptoms including cough, chills, fatigue, headache, loss of taste, loss of smell, muscle aches and sore throat had to be present for at least 2 days.

Measurement of anti-SARS-CoV-2 antibodies

We tested for immunoglobulin G (IgG) levels against the receptor-binding domain of the spike protein (Anti-S) and against the nucle-

ocapsid protein (Anti-N) of SARS-CoV-2 by electrochemiluminescence method using the Cobas e411 analyzer (Roche Diagnostics, Basel, Switzerland). Samples with values ≥0.8 U/ml were considered positive (reactive) for Anti-S. Anti-N total antibody values were calculated in the form of a cut-off index (COI), with COI values ≥1.0 as positive (reactive) for anti-SARS-CoV-2 N antibodies.

Statistical analysis

The study data was analyzed according to the following predefined analysis sets. The Full Analysis set (FAS) includes all enrolled patients (i.e., all patients who received at least one dose of AZD1222). The Homologous AZD1222 primary series and AZD1222 booster (AZ2) include all enrolled participants who received AZD1222 as their first and second dose and an AZD1222 booster. The heterologous primary series including one dose of AZD1222 and AZD1222 booster (HPS) includes all enrolled participants who received AZD1222 as at least one of their doses in a two-dose primary series and an AZD1222 booster. The primary series other than AZD1222 and AZD1222 booster (OPS) includes all enrolled participants and an AZD1222 booster or two doses of other COVID-19 vaccines (not AZD1222) as their primary series and an AZD1222 booster. Immunogenicity cohort (IC) is a convenience sample with the sample of participants who receive at least one dose of AZD1222 and were recruited sequentially.

Incidence rates were calculated by the number of events of interest divided by the total participant-years (PY) in which participants were at risk for the event of interest. The risk period post-second dose was defined as 15 days after receipt of the second dose until whichever occurs first between laboratory-confirmed symptomatic COVID-19 disease, study withdrawal, booster dose, or 12 months post-first vaccination. The risk period post-booster dose was defined as 15 days after receipt of the booster dose until whichever occurs first between laboratory-confirmed symptomatic COVID-19 disease, study withdrawal, or 12 months post-first vaccination. The 95% confidence interval (CI) for incidence rates was computed using the exact method for a Poisson distribution [7]. Although we did not reach the initial target sample, we were able to estimate the incidence and make comparisons with less precision than if we had reached our sample size.

As an ad hoc exploratory analysis, we compared the incidence of AEs in participants with and without prior COVID-19 infection using an exact test for rate ratios [8]. Geometric mean concentrations (GMCs) and 95% confidence intervals were used to describe immunological endpoints. GMCs were calculated as exponentiating the mean of the log values and the 95% confidence interval, which was calculated assuming a t-distribution for the log values. All analyses were performed using R Statistical Software, a Language and Environment for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographic characteristics

Of the enrolled participants (Table 1), 53.7 % were male and most were Black African (99.9%). The median participant age was 30 years (interquartile range: 23-42 years). Most of the enrolled participants had never smoked (69.7%), with 21.2% current smokers. Forty percent of participants had never drunk alcohol whilst 30.8% were current drinkers. Over half of all enrolled participants had at least completed secondary education (Table 1). A total of 106 pregnancies were recorded in the analysis period after receiving at least one AZD1222 vaccine dose. Of the participants enrolled 21.8 % were living with HIV, 65.9% were HIV uninfected and 12.3% were of unknown HIV status. Amongst people living with HIV (PLWH), 96.8% were on ART. Other pre-existing conditions included hypertension 452 (4.2%) diabetes 191 (1.8%); and obesity 1759 (16.2%) participants with BMI >30. Prior COVID-19 infection was reported by 855 (7.9%) of the participants.

Between September 2021 and August 2022, 11,235 participants were screened for eligibility to participate in the AZD1222 COVID-19 vaccine study, and 10,894 participants were enrolled and vaccinated across the five enrolling sites in Botswana; 9192 (84.4%) were enrolled at first vaccine dose, 521 (4.8%) at second vaccine dose and 1181 (10.8%) at booster vaccine dose.

Of the 10,855 participants included in the FAS, 1700 received only one dose of AZD1222; 5377 received two doses of AZD1222; 98 received a heterologous primary series including one dose of AZD1222 and a booster; 30 were included in the HPS group; 1058 were included in the OPS group; and 2592 were included in the AZ2 group. In total, 435 were co-enrolled in the immunogenicity cohort. Figure 1 (consort diagram).

Incidence of symptomatic COVID-19 infection

The overall incidence of laboratory-confirmed symptomatic COVID-19 infection after two doses of AZD1222 in the AZ2 group was 6.22 (95% CI: 2.51-12.78) per 1000 PYs (Table 2). The overall incidence of laboratory-confirmed symptomatic COVID-19 infection after two doses of AZD1222 and a booster in the AZ2 group was 3.5 (95% CI: 0.42-12.57) per 1000 PYs (Table 3). Four infections occurred in females (three <40 years of age and one 40-<65 years) and three in males (one <40 years, one 40-<65 years and one ≥65 years of age). One of the participants with a breakthrough infection was living with HIV.

There were no laboratory-confirmed COVID-19 hospitalizations or deaths during the study period. There were 40 symptomatic laboratory-confirmed COVID-19 infections during this study period (Figure 2). Of these, three infections were in participants who received only one dose of AZD1222, 24 infections were in participants who received two doses of AZD1222 and 13 in the AZ2 group. Of the 13 infections in the AZ2 group, one was within 22 days of first vaccination, three were within 5 days of the second vaccination and seven were within 15 days post-booster. Two participants had a symptomatic COVID-19 infection more than 15 days post-booster vaccination in the AZ2 group.

AEs

There were a total of 754 AEs (incidence of 84 per 1000 PYs) from 397 participants (Table 3). Of these, 639 were classified as mild, 79 as moderate, 18 as severe, 14 as life-threatening and 4 AEs from one participant were fatal. The majority of AEs were nervous system disorders (n = 223) and general disorders and administration site conditions (n = 208). A total of 463 were determined to be related to the IP and 291 were not related to IP. The incidence of AEs in HIV-uninfected individuals was 86 per 1000 person-years compared to 82 per 1000 person-years in PLWH (Table 3).

There were eight AESIs reported during the study period (incidence of 0.9 per 1000 person-years), five of which were related to the IP (Supplementary Table S1). The incidence of AESI in HIV-uninfected individuals was 1.0 per 1,000 person-years compared to 1.01 per 1000 person-years in PLWH (Table 3).

Twenty-nine SAEs were reported during the study period (incidence of 3.24 per 1000 person-years), of which 11 were abortions and one maternal complication during pregnancy (Table 3, Supplementary Table S2). Two SAEs were determined related to the IP. The incidence of SAEs in HIV-uninfected individuals was 2.5 per 1000 person-years compared to 6.0 per 1000 person-years in PLWH (Supplementary Table S1). Three SAEs were within 28 days post-first dose, one within 28 days post-second dose and no SAEs occurred within 28 days post-booster dose (Supplementary Table S1).

Overall, reported AEs were mostly mild to moderate. The incidence of AEs was significantly higher in participants with prior COVID-19 infection (incidence rate [IR] = 178.6; 95% CI: 151.2-208.7) compared to those without prior COVID-19 and IR = 76.1; 95% CI: 70.4-82.0), Supplementary Table S3. The incidence of AEs in both naïve and previously

Table 1
Demographic characteristics. All cells display the number of participants.

Variable	Vaccination series			
	FAS[a]	AZ2[b]	HPS[c]	OPS[d]
Total number enrolled[e]	10855	2592	30	1058
Site n[f] (%)				
Gaborone	4200 (38.7)	599 (23.1)	9 (30)	292 (27.6)
Maun	1969 (18.1)	432 (16.7)	7 (23.3)	131 (12.4)
Serowe	1507 (13.9)	474 (18.3)	3 (10)	149 (14.1)
Francistown	1793 (16.5)	579 (22.3)	6 (20)	213 (20.1)
Selibe Phikwe	1386 (12.8)	508 (19.6)	5 (16.7)	273 (25.8)
Gender n (%)				
Female	5028 (46.3)	1061 (40.9)	17 (56.7)	518 (49)
Male	5827 (53.7)	1531 (59.1)	13 (43.3)	540 (51)
Ethnicity n (%)				
Black African	10846 (99.9)	2592 (100)	30 (100)	1058 (100)
Asian	5 (0)	0 (0)	0 (0)	0 (0)
Caucasian	1 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	0 (0)	0 (0)
Missing	3 (0)	0 (0)	0 (0)	0 (0)
Median age, years (IQR)[7]	30 (23-42)	36 (26-44)	32 (26-38)	34 (26-41)
<40	7534 (69.4)	1545 (59.6)	23 (76.7)	743 (70.2)
40-65	3213 (29.6)	1016 (39.2)	7 (23.3)	302 (28.5)
≥65	108 (1)	31 (1.2)	0 (0)	13 (1.2)
Missing	0 (0)	0 (0)	0 (0)	0 (0)
HIV n (%)				
Negative	7152 (65.9)	1645 (63.5)	19 (63.3)	542 (51.2)
Positive	2363 (21.8)	743 (28.7)	6 (20)	247 (23.3)
Unknown	1340 (12.3)	204 (7.9)	5 (16.7)	269 (25.4)
Antiretroviral therapy n (%)	2279 (96.8)	722 (97.3)	6 (100)	242 (98)
Pregnancy n (%)	106 (2.4)	4 (0.5)		
Median body mass index (IQR)[7]	22 (20-27)	22 (19-27)	23 (20-27)	23 (20-27)
<18.5	1607 (14.8)	422 (16.3)	5 (16.7)	128 (12.1)
18.5-<25	5454 (50.2)	1288 (49.7)	12 (40)	547 (51.7)
25-<30	2035 (18.7)	469 (18.1)	9 (30)	224 (21.2)
≥30	1759 (16.2)	413 (15.9)	4 (13.3)	159 (15)
Diabetes n (%)				
No	10661 (98.2)	2540 (98)	30 (100)	1040 (98.3)
Yes	191 (1.8)	52 (2)	0 (0)	15 (1.4)
Missing	3 (0)	0 (0)	0 (0)	3 (0.3)
Hypertension n (%)				
No	10400 (95.8)	2451 (94.6)	27 (90)	1009 (95.4)
Yes	452 (4.2)	141 (5.4)	3 (10)	46 (4.3)
Missing	3 (0)	0 (0)	0 (0)	3 (0.3)
Prior COVID infection n (%)				
No	9997 (92.1)	2415 (93.2)	27 (90)	974 (92.1)
Yes	855 (7.9)	177 (6.8)	3 (10)	81 (7.7)
Missing	3 (0)	0 (0)	0 (0)	3 (0.3)
Smoking status n (%)				
Current	2305 (21.2)	685 (26.4)	7 (23.3)	213 (20.1)
Occasional	398 (3.7)	98 (3.8)	0 (0)	37 (3.5)
Previous	586 (5.4)	176 (6.8)	2 (6.7)	67 (6.3)
Never	7563 (69.7)	1633 (63)	21 (70)	738 (69.8)
Missing	3 (0)	0 (0)	0 (0)	3 (0.3)
Alcohol status n (%)				
Current	3344 (30.8)	840 (32.4)	6 (20)	296 (28)
Occasional	2338 (21.5)	522 (20.1)	10 (33.3)	267 (25.2)
Previous	806 (7.4)	245 (9.5)	2 (6.7)	98 (9.3)
Never	4364 (40.2)	985 (38)	12 (40)	394 (37.2)
Missing	3 (0)	0 (0)	0 (0)	3 (0.3)
Highest education level n (%)				
None	305 (2.8)	107 (4.1)	0 (0)	22 (2.1)
Primary	907 (8.4)	273 (10.5)	4 (13.3)	98 (9.3)
Junior Secondary	3974 (36.6)	1009 (38.9)	14 (46.7)	483 (45.7)
Senior Secondary	3124 (28.8)	713 (27.5)	6 (20)	308 (29.1)
Tertiary	2545 (23.4)	490 (18.9)	6 (20)	147 (13.9)
Employment status n (%)				
Formal-wage employment part time	652 (6)	171 (6.6)	1 (3.3)	111 (10.5)
Formal wage employment-full time)	3266 (30.1)	711 (27.4)	11 (36.7)	361 (34.1)
Self-employed part time)	561 (5.2)	152 (5.9)	2 (6.7)	45 (4.3)
Self-employed full time)	1111 (10.2)	280 (10.8)	3 (10)	53 (5)
Ad hoc work	35 (0.3)	14 (0.5)	0 (0)	1 (0.1)
Seasonal employment	259 (2.4)	82 (3.2)	2 (6.7)	38 (3.6)
Other	4971 (45.8)	1182 (45.6)	11 (36.7)	449 (42.4)
Settlement type n (%)				
Rural	2252 (20.7)	639 (24.7)	5 (16.7)	165 (15.6)
Urban	8603 (79.3)	1953 (75.3)	25 (83.3)	893 (84.4)

(*continued on next page*)

Table 1 (*continued*)

Variable	Vaccination series			
	FAS[a]	AZ2[b]	HPS[c]	OPS[d]
Marital status n (%)				
Single	8249 (76)	1896 (73.1)	20 (66.7)	819 (77.4)
Cohabiting	1477 (13.6)	381 (14.7)	7 (23.3)	137 (12.9)
Married	950 (8.8)	262 (10.1)	3 (10)	79 (7.5)
Divorced	71 (0.7)	24 (0.9)	0 (0)	6 (0.6)
Widowed	105 (1)	28 (1.1)	0 (0)	17 (1.6)
Other	3 (0)	1 (0)	0 (0)	0 (0)
Running water n (%)				
No	685 (6.3)	155 (6)	1 (3.3)	62 (5.9)
Yes	10170 (93.7)	2437 (94)	29 (96.7)	996 (94.1)

FAS, full analysis set; IQR, interquartile range.

[a] The FAS will include all enrolled patients (i.e., all patients who received at least one dose of AZD1222). Demographic and other baseline characteristics will be analyzed for the FAS.

[b] The Homologous AZD1222 primary series and AZD1222 booster (AZ2) includes all enrolled participants who received AZD1222 as their first and second dose and an AZD1222 booster.

[c] The heterologous primary series including one dose of AZD1222 and AZD1222 booster (HPS) includes all enrolled participants who received AZD1222 as at least one of their doses in a two-dose primary series and an AZD1222 booster.

[d] The primary series other than AZD1222 and AZD1222 booster (OPS) includes all enrolled participants who received one dose of J&J and an AZD1222 booster or two doses of other COVID-19 vaccines (not AZD1222) as their primary series and an AZD1222 booster.

[e] Five participants from the total enrolled participants were excluded because of inconsistency in the data

[f] n is the number of participants.

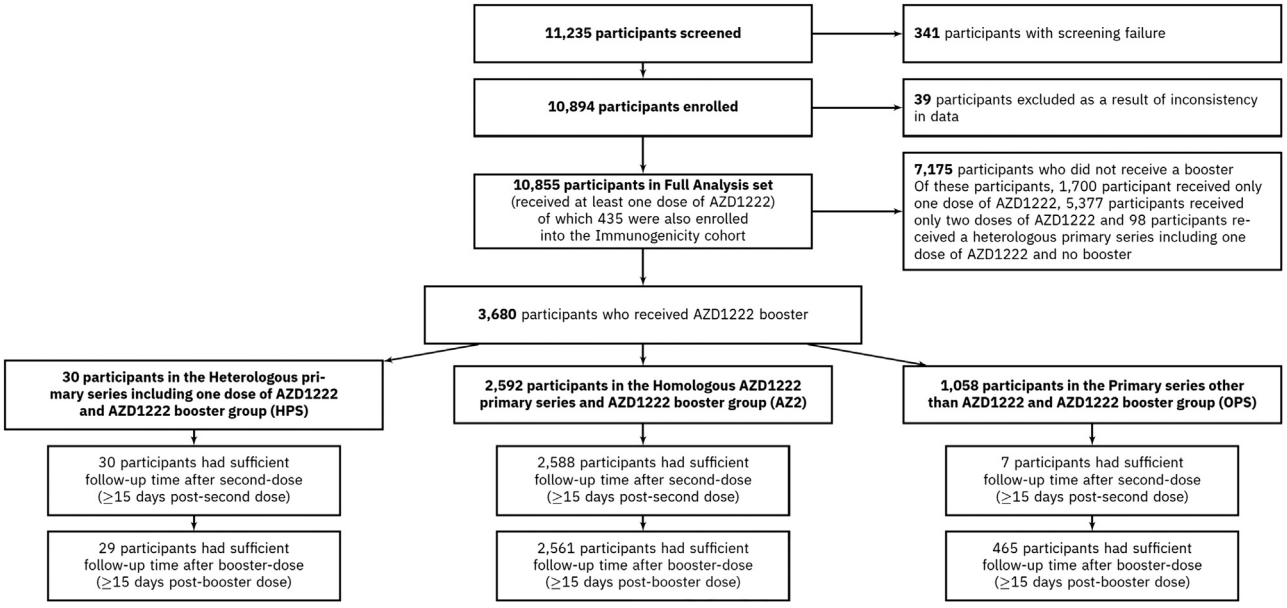


Figure 1. Consortium diagram for participant enrollment and vaccination series.

infected participants was higher post-first vaccination compared to post-second vaccination. However, individuals with prior COVID-19 infection had a statistically significantly higher incidence of AEs than those without prior COVID-19-infection (Supplementary Table S1) in post-first vaccination (IR ratio [IRR] = 2.4; 95% CI: 1.93-2.84) and post-second vaccination (IRR = 2.38; 95% CI: 1.87-2.99). Overall, the systemic AEs were higher than any other category in both participants with prior COVID-19 infection (IR = 174.4 [95% CI: 147.33-204.23] and those without prior COVID-19 infection [IR = 74.23; 95% CI: 68.66-80.11]). Systemic AEs were statistically significantly higher in participants with prior COVID-19 infection than those without (IRR = 2.35 [95% CI: 1.92-2.85]), and with only significant differences observed during the post-first vaccination.

Antibody responses following vaccination with AZD1222

A total of 521 participants were included in the analysis of total antibody responses. Participants were mostly male (55.7%) with median age 28 (Q_1, Q_3: 22-37), and 19% were PLWH at the time of enrollment (Supplementary Table S4). We observed a significant increase in median Anti-S responses from baseline to days 7 and 28 (after first vaccination), followed by a significant decline between day 28 and day 70 (Supplementary Figure S1), but still significantly higher than baseline ($p<0.001$). Anti-S responses picked up again between day 70 and day 98 following the second dose. At baseline several participants were already exposed to SARS-CoV-2 as shown by a high proportion of detectable Anti-N responses, 93.1% (95% CI: 86.4-96.6), even though only 12.1% (95% CI: 9.4-15.2) reported prior SARS-CoV-2 infection (Supplementary Table S5). Consistent with the Ant-N results, at baseline 59.4% (95% CI: 49.9-68.3) of participants had Anti-S responses, suggesting prior exposure to natural infection (Supplementary Table S6, Supplementary Figure S1). These responses increased with vaccination from 73.9% by day 7 and 96.3% by the time of the second dose and 100% post-second-dose and at booster doses (Supplementary Table S6). However, the baseline Anti-S responses (before vaccination) were the lowest, with GMC 1.9 (95% CI :1.2-2.9) and increased 4-fold in 7 days (GMC = 8.0, 95% CI:

Table 2
Incidence (per 1000 participant-years) of laboratory-confirmed symptomatic COVID-19 disease in Homologous AZD1222 primary series and AZD1222 booster (AZ2) includes all enrolled participants who received AZD1222 as their first and second dose and an AZD1222 booster, by age, gender and HIV status.

subgroup	n[a]/N[b]								
	IR[c] (95% CI)[d]								
	All participants	Female				Male			
		<40	*40-< 65*	≥65	*Overall*	<40	*40-< 65*	≥65	Overall
Post-second dose[e]									
Overall	7/1125; 6.22 (2.51-12.78)	3/253; 11.86 (2.45-34.26)	1/231; 4.33 (0.11-23.88)	0/6; 0 (0-459.26)	4/490; 8.16 (2.23-20.77)	1/370; 2.7 (0.07-14.97)	1/257; 3.89 (0.1-21.49)	1/9; 111.11 (2.81-482.5)	3/635; 4.72 (0.98-13.74)
People living with HIV	1/337; 2.97 (0.08-16.42)	1/61; 16.39 (0.41-87.99)	0/125; 0 (0-29.08)	0/1; 0 (0-975)	1/187; 5.35 (0.14-29.43)	0/37; 0 (0-94.89)	0/111; 0 (0-32.69)	0/2; 0 (0-841.89)	0/150; 0 (0-24.29)
HIV-uninfected	6/684; 8.77 (3.23-18.99)	2/166; 12.05 (1.46-42.84)	1/92; 10.87 (0.28-59.08)	0/5; 0 (0-521.82)	3/263; 11.41 (2.36-32.97)	1/293; 3.41 (0.09-18.87)	1/122; 8.2 (0.21-44.82)	1/6; 166.67 (4.21-641.23)	3/421; 7.13 (1.47-20.68)
Within 3 months of second dose	2/548; 3.65 (0.44-13.12)	1/125; 8 (0.2-43.77)	0/97; 0 (0-37.32)	0/3; 0 (0-707.6)	1/224; 4.46 (0.11-24.62)	1/202; 4.95 (0.13-27.27)	0/118; 0 (0-30.78)	0/4; 0 (0-602.36)	1/324; 3.09 (0.08-17.08)
3-6 months post-second dose	5/470; 10.64 (3.46-24.65)	2/104; 19.23 (2.34-67.74)	1/101; 9.9 (0.25-53.93)	0/3; 0 (0-707.6)	3/208; 14.42 (2.98-41.57)	0/146; 0 (0-24.95)	1/112; 8.93 (0.23-48.74)	1/4; 250 (6.31-805.88)	2/262; 7.63 (0.93-27.3)
Post-booster dose[f]									
Overall	2/572; 3.5 (0.42-12.57)	0/128; 0 (0-28.41)	0/95; 0 (0-38.09)	0/2; 0 (0-841.89)	0/225; 0 (0-16.26)	0/214; 0 (0-17.09)	2/128; 15.62 (1.9-55.3)	0/4; 0 (0-602.36)	2/347; 5.76 (0.7-20.66)
People living with HIV	0/165; 0 (0-22.11)	0/34; 0 (0-102.82)	0/51; 0 (0-69.78)	0/0; NC NC	0/86; 0 (0-41.99)	0/22; 0 (0-154.37)	0/56; 0 (0-63.75)	0/1; 0 (0-975)	0/79; 0 (0-45.62)
HIV-uninfected	1/364; 2.75 (0.07-15.21)	0/82; 0 (0-43.99)	0/38; 0 (0-92.51)	0/2; 0 (0-841.89)	0/122; 0 (0-29.78)	0/175; 0 (0-20.86)	1/64; 15.62 (0.4-84.01)	0/3; 0 (0-707.6)	1/242; 4.13 (0.1-22.81)
Within 3 months of second dose	2/486; 4.12 (0.5-14.79)	0/111; 0 (0-32.69)	0/81; 0 (0-44.52)	0/2; 0 (0-841.89)	0/194; 0 (0-18.84)	0/183; 0 (0-19.96)	2/105; 19.05 (2.32-67.12)	0/3; 0 (0-707.6)	2/292; 6.85 (0.83-24.52)
3-6 months post-second dose	0/86; 0 (0-41.99)	0/16; 0 (0-205.91)	0/14; 0 (0-231.64)	0/0; NC NC	0/31; 0 (0-112.19)	0/31; 0 (0-112.19)	0/23; 0 (0-148.19)	0/1; 0 (0-975)	0/55; 0 (0-64.87)

Note: NC denotes not calculable
CI, confidence interval; IR, incidence rate.
[a] n is the number of participants with COVID disease.
[b] N is the total follow-up time.
[c] IR is the incidence rate calculated by the number of participants who experienced laboratory-confirmed symptomatic COVID disease 15 days after receipt of second dose divided by the total participant years during the defined risk period multiplied by 1000. After the first vaccination dose.
[d] The 95% CI will be computed using an exact method for a Poisson distribution.
[e] The risk period is defined as 15 days after receipt of the second dose until whichever occurs first between laboratory-confirmed symptomatic COVID disease, study withdrawal, booster dose, or 12 months post first-vaccination.
[f] The risk period is defined as 15 days after receipt of the post-second dose until whichever occurs first between laboratory-confirmed symptomatic COVID disease, study withdrawal, or 12 months post-first vaccination.

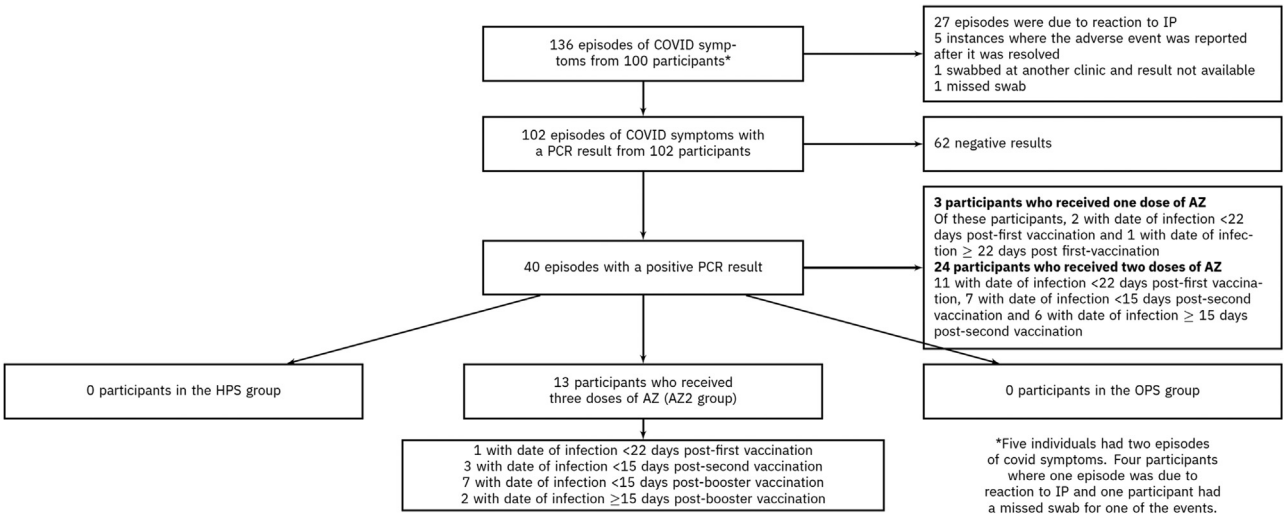


Figure 2. Consort diagram for laboratory-confirmed symptomatic COVID. IP, investigational product; PCR, polymerase chain reaction.

4.4-14.5) following vaccination and up to 6-fold between day 14 and 28 following vaccination, GMC 13.3 (95% CI: 7.8-22.5) and GMC 29.4 (95% CI: 19.9-43.6), respectively (Supplementary Table S6, Supplementary Figure S1).

We observed higher binding antibody responses among participants with prior COVID-19 exposure after 28 days from baseline and a trend towards significance up to day 70, and no differences thereafter. There were no differences by HIV status across all time points. We overserved a 6-fold increase in SARS-CoV-2 Anti-S responses from baseline, followed by a decline after 28 days, whose highest peak was restored by the second dose and maintained by the booster doses. History of natural infection SARS-CoV-2 infec-

Table 3
Incidence (per 1000 participant-years) of AE, AESIs, and SAEs and number of participants with at least one AE, AESI, and SAE by maximum CTCAE grade.

Subgroup		Maximum CTCAE grade					
		Total n (np); IR (95% CI)	Mild n (np); IR (95% CI)	Moderate n (np); IR (95% CI)	Severe n (np); IR (95% CI)	Life-threatening n (np); IR (95% CI)	Fatal n (np); IR (95% CI)
AE	**Overall**	**754; 84.26 (78.58-90.2)**	**639; 71.41 (66.16-76.94)**	**79; 8.83 (7-10.99)**	**18; 2.01 (1.19-3.18)**	**14; 1.56 (0.86-2.62)**	**4; 0.45 (0.12-1.14)**
	Related to IP	463; 51.74 (47.24-56.53)	410; 45.82 (41.58-50.35)	44; 4.92 (3.57-6.6)	7; 0.78 (0.31-1.61)	1; 0.11 (0-0.62)	1; 0.11 (0-0.62)
	Not related to IP	291; 32.52 (28.94-36.4)	229; 25.59 (22.42-29.08)	35; 3.91 (2.73-5.44)	11; 1.23 (0.61-2.2)	13; 1.45 (0.77-2.48)	3; 0.34 (0.07-0.98)
	HIV-uninfected	516; 85.67 (78.72-93.03)	440; 73.05 (66.61-79.92)	55; 9.13 (6.89-11.87)	14; 2.32 (1.27-3.9)	7; 1.16 (0.47-2.39)	0; 0 (0-0.61)
	People living with HIV	162; 81.6 (69.94-94.53)	127; 63.97 (53.61-75.65)	22; 11.08 (6.96-16.73)	4; 2.01 (0.55-5.15)	5; 2.52 (0.82-5.87)	4; 2.01 (0.55-5.15)
	No prior covid	626; 76.05 (70.42-81.99)	530; 64.39 (59.18-69.91)	62; 7.53 (5.78-9.65)	16; 1.94 (1.11-3.15)	14; 1.7 (0.93-2.85)	4; 0.49 (0.13-1.24)
	Prior covid	128; 178.61 (151.24-208.66)	109; 152.1 (126.58-180.52)	17; 23.72 (13.88-37.71)	2; 2.79 (0.34-10.04)	0; 0 (0-5.13)	0; 0 (0-5.13)
AESI	**Overall**	**8; 0.89 (0.39-1.76)**	**1; 0.11 (0-0.62)**	**6; 0.67 (0.25-1.46)**	**1; 0.11 (0-0.62)**	**0; 0 (0-0.41)**	**0; 0 (0-0.41)**
	Related to IP	5; 0.56 (0.18-1.3)	1; 0.11 (0-0.62)	4; 0.45 (0.12-1.14)	0; 0 (0-0.41)	0; 0 (0-0.41)	0; 0 (0-0.41)
	Not related to IP	3; 0.34 (0.07-0.98)	0; 0 (0-0.41)	2; 0.22 (0.03-0.81)	1; 0.11 (0-0.62)	0; 0 (0-0.41)	0; 0 (0-0.41)
	HIV-uninfected	6; 1 (0.37-2.17)	1; 0.17 (0-0.92)	5; 0.83 (0.27-1.94)	0; 0 (0-0.61)	0; 0 (0-0.61)	0; 0 (0-0.61)
	People living with HIV	2; 1.01 (0.12-3.63)	0; 0 (0-1.86)	1; 0.5 (0.01-2.8)	1; 0.5 (0.01-2.8)	0; 0 (0-1.86)	0; 0 (0-1.86)
	No prior covid	7; 0.85 (0.34-1.75)	1; 0.12 (0-0.68)	5; 0.61 (0.2-1.42)	1; 0.12 (0-0.68)	0; 0 (0-0.45)	0; 0 (0-0.45)
	Prior covid	1; 1.4 (0.04-7.75)	0; 0 (0-5.13)	1; 1.4 (0.04-7.75)	0; 0 (0-5.13)	0; 0 (0-5.13)	0; 0 (0-5.13)
SAE	**Overall**	**29; 3.24 (2.17-4.65)**	**1; 0.11 (0-0.62)**	**3; 0.34 (0.07-0.98)**	**10; 1.12 (0.54-2.05)**	**13; 1.45 (0.77-2.48)**	**2; 0.22 (0.03-0.81)**
	Related to IP	2; 0.22 (0.03-0.81)	0; 0 (0-0.41)	0; 0 (0-0.41)	1; 0.11 (0-0.62)	0; 0 (0-0.41)	1; 0.11 (0-0.62)
	HIV-uninfected	15; 2.49 (1.39-4.1)	1; 0.17 (0-0.92)	2; 0.33 (0.04-1.2)	6; 1 (0.37-2.17)	6; 1 (0.37-2.17)	0; 0 (0-0.61)
	People living with HIV	12; 6.04 (3.13-10.54)	0; 0 (0-1.86)	1; 0.5 (0.01-2.8)	4; 2.01 (0.55-5.15)	5; 2.52 (0.82-5.87)	2; 1.01 (0.12-3.63)
	No prior covid	27; 3.28 (2.16-4.77)	1; 0.12 (0-0.68)	2; 0.24 (0.03-0.88)	9; 1.09 (0.5-2.07)	13; 1.58 (0.84-2.7)	2; 0.24 (0.03-0.88)
	Prior covid	2; 2.79 (0.34-10.04)	0; 0 (0-5.13)	1; 1.4 (0.04-7.75)	1; 1.4 (0.04-7.75)	0; 0 (0-5.13)	0; 0 (0-5.13)

AE, adverse event; AESI, AEs of special interest; CI: Confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; n, number of events; np, number of participants with at least one event; IP, investigational product; IR, incidence rate; SAE, serious AE.

tion was associated with higher levels of Anti-S responses following vaccination.

Discussion

This was the first study to evaluate the safety and incidence of severe COVID-19 infections following vaccination with ChAdOx1 (AZD1222) in the Botswana population. Despite the large sample size, there were no cases of COVID-19-related hospitalizations or deaths reported in the study. The safety profile was consistent with interim analysis [6], with no additional concerns observed. This final analysis includes the Homologous and heterologous AZD1222 primary series and booster, the primary series without AZD1222 and booster, and a subset of participants from the immunogenicity sub-cohort.

We observed a low incidence of laboratory-confirmed symptomatic COVID-19 infection in this study, after two doses of AZD1222 which is lower than in the placebo group of a similar study conducted by Voysey et al. [1] in Brazil, UK, and South Africa. The current study was implemented when Omicron variant was the most dominant circulating COVID-19 variant within the Botswana population (Supplementary Figure S2). The Omicron variant of COVID-19 is known to be highly transmissible resulting in extensive population immunity to COVID-19 [9]. The low symptomatic COVID-19 in our study may also potentially be attributed to this Omicron phenomenon. At the time of these infections, the circulating variant, effectiveness reports and guidance on COVID-19 vaccines were limited to the prevention of severe infections. There is generally a paucity of data on the effectiveness of the AZD1222 vaccine and other COVID-19 vaccines in the prevention of symptomatic COVID-19 infections in persons living with HIV [10]. Past research has suggested that PLWH may have compromised immune responses following vaccination for COVID-19 [10,11], thus potentially making them more prone to reduced protection from COVID-19 vaccines. Among the seven breakthrough infections in our study after two doses of AZD1222, only one participant was living with HIV. The incidence of symptomatic COVID-19 infection after two doses of AZD1222 did not differ by HIV status, both post-second dose and post-booster dose (Table 2).

Post AZD1222 vaccination, participants mostly reported mild AEs, with more systemic AEs compared to local AEs. More AEs were reported after the first vaccine dose, when compared to the second vaccine dose or booster dose. A similar study conducted in the United States, Chile, and Peru by Falsey et al. [12] showed a similar trend with local symptoms occurring in 74.1% whilst systemic symptoms occurred in 71.6 % of the participants with AEs. Other studies from other continents have reported similar AEs as noted in our study, albeit with differing frequencies. In a study conducted in Saudi Arabia, the most reported systemic AEs were muscle aches (49%), fever (42%) and headache (40%) [13], whilst the study conducted in the United States, Chile and Peru by Falsey et al. [12] had the most reported AEs as headache (50.2%), fatigue (49.7%), muscle pains (41.9%) and malaise (35.0%). According to our study, persons living with HIV are not at increased risk of AEs post-vaccination (Table 3). This is confirmation of the safety of the AZD1222 vaccine in the HIV-infected population. The interaction of HIV, ART, and COVID-19 vaccines and their effect on incident AEs would require further research.

The incidence of AEs post-first vaccination was significantly higher in participants with prior COVID-19 infection compared to those without prior COVID-19 infection (Table 3). Prior COVID-19 infection has been reported to be associated with an increased risk of AEs following

vaccination for COVID-19 [14]. This is consistent with our study which also showed that the incidence of severe systemic AEs was higher in participants with prior COVID-19 infection compared to participants with no prior infection [15]. This is likely to be a result of the immune system's ability to mount a better response to antigens previously encountered.

The decline in vaccine effectiveness over time is influenced by the pattern of immune responses observed after the initial primary dose series of vaccines. We studied immune responses following vaccination in a convenient sample subset of the study participants. AZD122 vaccine was immunogenic as evidenced by increasing titers after first and second dose above the baseline measurements (Supplementary Figure S1). We observed a high background of seroprevalence of SARS-CoV-2 infection at baseline as shown by the 93% of individuals with detectable nucleocapsid responses in this vaccine naïve population (Supplementary Figure S5). This is consistent with findings from West Africa [16] and from South Africa and, that also observed high exposure to SARS-CoV-2 infection during the Omicron wave [17]. Although there was a background of our data confirming the vaccine-elicited immune responses increased from the first dose to 28 days followed by a slight decline and peak was restored with the second dose and booster doses (Supplementary Figure S1). Waning antibody titers after second dose further highlights the need for booster dosing. The persistent measurable antibody response after two doses of AZD1222 has been shown to have a positive impact against severe disease and death [18]. We observed that individuals who had previously been exposed to COVID-19 had higher levels of binding antibodies in their immune response. Some studies have also demonstrated that a combination of natural immunity and vaccination results in significantly higher levels of neutralizing antibodies against SARS-CoV-2 compared to either natural infection or vaccination alone [19]. The study demonstrated that the immune response from vaccination in previously infected individuals may have acted as a booster, further strengthening their protection. Another study in South Africa also demonstrated AZD122 had higher GMC among the SARS-CoV-2 seropositive as compared to SARS-CoV-2 seronegative individuals [20]. Although our data is limited by maximum of 182 days of follow-up, we observed a durable antibody response with GMC titers and trajectories comparable to those seen in other studies following AZD1222 [20,21].

The study had a large sample size and was conducted in different areas of the country making it more generalizable in-country and regionally. The findings of our study should be interpreted in the context of the rapidly evolving COVID-19 global pandemic landscape and access to COVID-19 vaccines which necessitated amendments of the study protocol. The study reduced the eligibility age from 40 years initially to 18 years at two months post-initiation. This was consistent with the in-country COVID-19 vaccination eligibility at that time point thus extending study results to be more generalizable to the adult population. The study further included a booster AZD1222 vaccine dose and a heterologous vaccine series. Thus, findings of our study are more a reflection of real-life scenarios.

Given the low incidence of symptomatic COVID-19 infections in our study we were not able to elucidate the differences of homologous vs heterologous COVID-19 vaccine series. Other studies have shown that heterologous series in particular the heterologous booster vaccine may have some immunological advantages of extending the breadth and longevity of the protection against COVID-19 [22]. Adverse events were mainly reported telephonically, and this could have resulted in under-reporting and potentially misgrading of the AEs, as there was no visual inspection and examination of the participant in some instances. The study however endeavored to collect complete information through the standardized AEs case report forms. Although a single-arm study design is limited in confirming efficacy of an interventional agent, it remains useful for determination of safety.

In conclusion, the Botswana study has demonstrated AZD1222 prevents severe COVID-19 infections in a Black African population. AZD1222 is safe and effective in both PLWH with HIV and HIV-uninfected people. Symptomatic COVID-19 infections following the first vaccine dose of AZD1222 occurred more in HIV-uninfected participants compared to PLWH; further research would be warranted to explicate the mechanism by which this happens. The incidence of AEs post AZD1222 vaccination was significantly higher in participants with prior COVID-19 infection compared to those without prior COVID-19 infection and was higher post-first vaccination compared to post-second vaccination.

Declarations of competing interests

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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Ethical considerations

Study ethical approval for "Open-Label, Single-Arm, Phase 3B Study of the Incidence of Severe COVID-19 and Adverse Events Following AZD1222 COVID-19 Vaccination in Botswana Against SARS-CoV-2, D8111C00013 / ESR-21-21311" was obtained from Health and Research Development Committee in the Botswana Ministry of Health (Protocol HRDC#00936 and Botswana Medicines Regulatory Authority). All participants provided written informed consent before the study procedures. All study procedures were conducted by study personnel, qualified by training and/or had GCP experience.

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Author contributions

Conceptualization JM, SM, ES, TG,ST, PG; Methodology JM,SM, ES, TG, LK, ST,PG, Resources JM,SM, ES, TG,LK, CK, ST ; Validation JM, SM, ES,CK,AW,LC; Formal analysis AI, CK; Investigation JM, SM, ES, TG, LK,CK, TS, NS, TM, CM, TM. TN, TTF, BM, AD, TP, AK, PK, TK, GP, IP, MM, ST, SM, JM; Visualization JM, SM, ES, TG, Writing-original draft preparation ES, AI, JM, SM; Writing-review and editing: All authors Supervision, ES, TG, JM, SM; Funding acquisition JM, TS, SM. All authors have read and agreed to the published version of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2023.11.002.

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