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Estimation of the odds ratio in vaccinated individuals and determination of vaccine efficacy against SARS-CoV-2 infection in Angola – Part I

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ABSTRACT

Introduction: Studies conducted in real-life scenarios on vaccine protection against COVID-19 constitute an important global priority, but one that is currently mostly neglected in low- and middle-income countries such as Angola. Here, we analyze for the first-time vaccine protection against COVID-19 in a real-life scenario after 6 months of implementing a multi-vaccination plan in Angola, providing estimation of odds ratios in vaccinated individuals and vaccine efficacy against infection by SARS-CoV-2 in a period that coincided with the identification of the Omicron variant in the country. **Methods**: We used a negative test case-control design to assess the effectiveness of vaccination against confirmed SARS-CoV-2 infection. A total of 4.232 vaccinated and unvaccinated individuals with the result of a rapid antigen diagnostic test against SARS-CoV-2 performed from December 27 to 28, 2021 were included in the study. Data were extracted from the Digital Vaccination Record Platform (Rediv) of the Ministry of Health of Angola. All ethical procedures related to the authorization necessary to carry out the study were followed. Statistical analyzes were performed using version 7.5.2.0 of CDC's Epi Info. Frequency distributions and measures of central tendency were used to characterize the study universe. The general and sex-adjusted and age-adjusted odds ratios, were evaluated by comparing the chances of vaccination between cases and controls, and their associated 95% CI, which were calculated using the Mantel-Haenszel stratification method. The risk classification of Axel Kroeger, Piscoya and Alarcon was used to interpret the odds ratio. The Breslow-Day statistic was used to assess the homogeneity of the odds ratios. Vaccine efficacy was calculated using the odds ratio applying the accepted statistical vaccine efficacy formula:$(1 - \text{odds ratio}) \times 100$. For all estimates, a P value < 0.05 was considered statistically significant. **Results:** The population consisted of 63.63% male and 36.37% female. The mean age was 36 years with a standard deviation of 13. 83. Regarding vaccination status, 83.27% of individuals were vaccinated and 16.73% were unvaccinated, with 21.81% positive and 78.19% negative for SARS -CoV-2. The odds of SARS-CoV-2 infection were 0.85 (95% CI 0.70 – 1.03) times lower in vaccinated compared to unvaccinated individuals, with P=0.09. The overall vaccine efficacy (VE) was 15% (95% CI -3 – 30). **Conclusion:** There was no statistically significant decrease in the chances of SARS-CoV-2 infection in vaccinated versus unvaccinated individuals. However, the overall vaccine efficacy was 15%.

KEY WORDS: Odds ratio, vaccine efficacy, SARS-CoV-2, Angola

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LIST OF SYMBOLS, ABBREVIATIONS, ABBREVIATIONS

% -Percentage
VE -Vaccine efficacy
CI– Confidence interval
OR -Odds ratio
WHO- World Health Organization
P– Probability
RT-PCR -Reverse transcription polymerase chain reaction
RAD - Rapid Antigen Diagnostic

SUMMARY

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1. INTRODUCTION

On March 2, 2021, Angola began vaccinating the first people against COVID-19 upon receipt of the first batch of 624.000 doses of the AstraZeneca vaccine, recombinant ChAdOx1-S from the University of Oxford, an adenovirus vector vaccine, donated by COVAX initiative (RTP, 2021). The first published results on the efficacy of this vaccine against COVID-19, based on phase 3 trials, showed an efficacy of 72% (95% CI: 63-79%) against symptomatic SARS-CoV-2 infection, with Its immediate use is strongly recommended by the World Health Organization (WHO) with the aim of protecting against serious conditions and death, especially in low- and middle-income countries such as Angola, which may have a limited supply of vaccines (World Health Organization, 2021c). The largest mass vaccination campaign in the country was then started on March 6, 2021 (Notícias de Angola, 2021), almost a year after the notification of the first cases of COVID-19 in the country and at a time when the epidemic it was in a phase of deceleration and a cumulative total of 21.055 confirmed cases, 903 active cases and 512 deaths were recorded throughout the country, with a daily incidence rate of 0.05/100.000 inhabitants and a daily fatality rate of 6.25% (World Health Organization , 2021b). The first phase of the National Vaccination Plan against COVID-19 provided for the vaccination of 95% of people ≥40 years of age based on priority groups. almost a year after the notification of the first cases of COVID-19 in the country and at a time when the epidemic was in a deceleration phase and a cumulative total of 21.055 confirmed cases, 903 active cases and 512 deaths with a daily incidence rate of 0.05/100.000 population and a daily fatality rate of 6.25% (World Health Organization, 2021b).

On March 13, 2021, the first 40.000 doses of the Russian Sputnik V vaccine (Jornal de Angola, 2021b) arrived in the country, a recombinant heterologous vaccine based on adenovirus vectors (rAd) developed by the Research Center for Epidemiology and Microbiology – Gamaleya (Gamaleya, 2021). The primary results reported based on phase 3 clinical trials on the efficacy of Sputnik V were 91.6% (95% CI 85.6–95.2) (Logunov et al., 2021) much higher than Oxford/ AstraZeneca with similar technology.

On March 25, 2021, with the country towards the “second wave” and with the massive vaccination campaign launched 19 days ago, with the AstraZeneca and Sputnik V vaccines being administered to the target population of the National Vaccination Program, with demonstrated efficacy above 70% and approved by the WHO emergency plan (World Health Organization, 2021e), joins

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another 200.000 doses of the People's Republic of China vaccine, Sinopharm, produced by the Beijing Bio-Institute of Biological Products Co Ltd, a subsidiary of the China National Biotec Group (CNBG), being an inactivated virus vaccine (World Health Organization, 2021a). This vaccine has been reported to be effective in individuals with symptomatic disease and hospitalized in all age groups combined from 79% according to WHO (World Health Organization, 2021e).

On July 1, 2021, the country received 100.620 doses of the first vaccine produced with mRNA technology, BNT162b2 from Pfizer–BioNTech (Embassy of the Republic of Angola in Portugal, 2021). This vaccine reached 91% efficacy (95% CI 89-93%) in phase 3 studies, 7 days after administration of the 2nd dose against symptomatic SARS-CoV-2 infection with the ancestral strain in people aged 16 years or longer, based on an average follow-up of two months (World Health Organization, 2022).

On 8 August 2021, in the phase that marked the deceleration of the "second wave" and the entry of the "third wave" of the epidemic in Angola, with 1.690.719 doses of the 4 vaccines in force in the country having already been administered, Oxford/AstraZeneca , Sputnik V, Sinopharm and Pfizer, adds to these 165.000 doses of the first single-dose regimen vaccine from the pharmaceutical company Janssen (Lusa, 2021), the Ad26.COV2.S vaccine against COVID-19 a recombinant, incompetent adenovirus vector for replication, serotype 26 (Ad26) encoding a full-length, stabilized SARS-CoV-2 spike protein (World Health Organization, 2021b).

On October 1, 2021, 209 days (more than 7 months) had elapsed since the start of the mass vaccination campaign against COVID-19, more than 3.000.000 doses of the Oxford/AstraZeneca, Sputnik V vaccines had been administered. , Sinopharm, Pfizer and Jansen in a target population of 15.765.837, with 874.719 doses corresponding to the group of subjects in the two-dose vaccine regimen to be considered immunized and 167.755 doses corresponding to the group of subjects in the single-dose vaccine regimen the only one to be considered immunized, this gave us an "effective" vaccination coverage of 6.60%, very low compared to the world average and still far from 50% to be able to provide general protection to the population and counter the evolution of the epidemic. This is remarkable because at this point, On December 24, 2021, with the country experiencing the "fourth wave" of the epidemic and more aggressive since the beginning of the epidemic, since the end of the first half of December, the country's health authorities confirmed the community circulation of the most transmissible variant of the SARS-CoV-2 virus identified since the beginning of the epidemic, Omicron, identified primarily in South Africa and also attributed to the emergence of a respiratory virus that predominated in the country's capital, characterized

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mainly by sore throat, headache and nasal obstruction in individuals of all age groups (AngoRussia, 2021; Jornal de Angola, 2021a). Vaccination coverage at this time was 24.88% given by the Oxford/AstraZeneca, Sputnik V, Sinopharm, Pfizer and Jansen vaccines.

The emergence of this new variant identified in the country and associated with the high transmissibility that triggered the "fourth wave", led the country's health authorities to carry out a massive testing campaign in various parts of the country's capital in order to assess the epidemiological situation (RFI, 2021) in a period when vaccine coverage was above 29%, but still insufficient to counteract a rapid growth of the epidemic that was marked with one of the highest daily incidence rates achieved since the beginning of the epidemic in the country of 6.06/ 100.000 people.

1.1 justification

A review study on “Evaluation of protection by COVID-19 vaccines after deployment in low- and middle-income countries” published in late December last year identified 58 published studies that included 85 evaluations of the effectiveness of different COVID-19 vaccines in Worldwide. In this study, only three had been carried out in low- and middle-income countries, and no impact studies were identified in these settings (Clemens et al., 2022). Also in March 2021, The World Health Organization (WHO) has issued guidelines for the design and conduct of non-randomized vaccine protection efficacy studies for vaccines used in low- and middle-income countries on the basis that there is a divergence in vaccine protection that can occur when vaccines are deployed in public health practice compared to measurement in individually randomized, designed, phase 3 efficacy trials for licensing, because such trials do not take into account all the pertinent vaccine protection issues encountered in a lifetime public health setting real. Therefore, studies conducted in real-life scenarios on vaccine protection against COVID-19 constitute an important global priority, but one that is currently mostly neglected in low- and middle-income countries such as Angola.

Here, we analyze for the first-time vaccine protection against COVID-19 in a real-life scenario after 6 months of implementing a multi-vaccination plan in Angola, providing estimation of odds ratios and vaccine efficacy in a period that coincided with the identification of the Omicron variant in the country. Assuming that there is no decreased risk of SARS-CoV-2 infections in vaccinated individuals compared to unvaccinated individuals. The results of this study will provide the first scientific evidence on the effectiveness and impact of vaccination against COVID-19 in Angola and will allow the adoption of measures aimed at our reality, which is quite different from the reality of countries where most studies addressing on vaccine protection.

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2. OBJECTIVES

2.1 General:

- To estimate the odds ratio of SARS-CoV-2 infection in vaccinated versus unvaccinated individuals.

2.2 Specifics:

- Characterize the participants according to age group, sex, vaccination status and rapid diagnostic test result;
- To estimate the odds ratio of SARS-CoV-2 infection in vaccinated versus unvaccinated individuals by sex and age group;
- To determine the overall vaccine efficacy (VE) by sex and age groups against SARS-CoV-2 infection.

3. MATERIAL AND METHODS

Study design

We used a negative test case-control design to assess the effectiveness of vaccination against confirmed SARS-CoV-2 infection. This is a widely accepted design to determine vaccine efficacy in a population after a vaccine has been introduced (Vandenbroucke et al., 2020).

Data source, population and period of analysis

We extracted from the Ministry of Health's *Registo Digital Individual de Vacinação - Rediv* (Individual Digital Vaccination Record) platform a total of 4.232 records of individuals registered with RAD test carried out on December 27th and 28th, 2021. The *Rediv* platform is a dynamic and management platform for the digital pre-registration of users, the digital vaccination record and the management of the logistics chain of vaccination against COVID-19. *Rediv* was designed based on an evolved and innovative architecture, and foresees organic growth in order to meet other needs of the National Health System in the future. Based on this, it was also used to carry out the RAD test registration carried out in community testing campaigns.

Inclusion criteria

All individuals who joined the mass testing campaign against COVID-19 in Luanda on December 27 and 28, 2021 were included.

Exclusion criteria

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Individuals with more than one RAD test result performed in the period of analysis.

Ethical aspects

Study data were made available by the National Directorate of Public Health after approval of the study by the Ethics Committee of the Ministry of Health of Angola.

Statistical analysis

Descriptive statistics (frequency distributions and measures of central tendency) were used to characterize the universe of the study. The overall and adjusted odds ratio was calculated in a contingency table considering the vaccination exposure factor and the result of the RAD test to define cases and controls, adjusting for stratification by sex and age group using the Mantel-Haenszel method. The risk classification of Axel Kroeger, Piscoya and Alarcon was used to interpret the odds ratio, considerable protection (OR 0 - 0.3), moderate protection (OR 0.4 - 0.5), negligible protection (OR 0.6 - 0.8), no effect (OR 0.9 - 1.1), negligible risk (OR 1.2 - 1.6), moderate risk (OR 1.7 - 2.5) and high risk (OR > 2.6). The Breslow-Day statistic was used to assess the homogeneity of the odds ratios. Vaccine efficacy was calculated using the odds ratio result by applying the statistical vaccine efficacy formula:$(1 - \text{odds ratio}) \times 100$. This study interpreted the vaccine protective efficacy point and the respective 95% CI. We included negative estimates such as zero effectiveness. For all estimates, a value of $P< 0.05$ was considered statistically significant. To control for potential for repeat testing bias in RAD TEST Ag-positive individuals seeking to verify infection or repeat testing bias among controls (persons with a higher level of health care seeking behavior who are presumably at lower risk of infection). For each case, we considered the first Ag positive RAD test during the analysis period from December 27, 2021 to December 28, 2021. We considered the first Ag negative RAD test for each control during this period. This generated an independent universe of unique cases and controls. Statistical analyzes were performed using version 7.5.2.0 of the CDC's (Centers for Disease Control and Prevention) Epi Info.

Operational definitions

Case: every individual with confirmed SARS-CoV-2 infection through a positive rapid antigen diagnostic (RAD) test result.

Control: Any individual without SARS-CoV-2 infection confirmed by a negative rapid antigen diagnostic (RAD) test result.

Vaccination status: It was considered as an exposure factor, with individuals who received a vaccine against SARS-CoV-2 were classified as vaccinated (exposed) and those who did not receive any vaccine against SARS-CoV-2 as unvaccinated (unexposed).

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Vaccine efficacy (VE): It represents the proportion of reduction in cases or infections by SARS-CoV-2 among the vaccinated group, compared to the unvaccinated group (Tavares, 2021).

4. RESULTS

Graph nº1 shows the age pyramid of the study population. 63.63% of subjects were male and 36.37% were female. The mean age was 36 years with a standard deviation (SD) of 13.

Graph nº1 - Population age pyramid

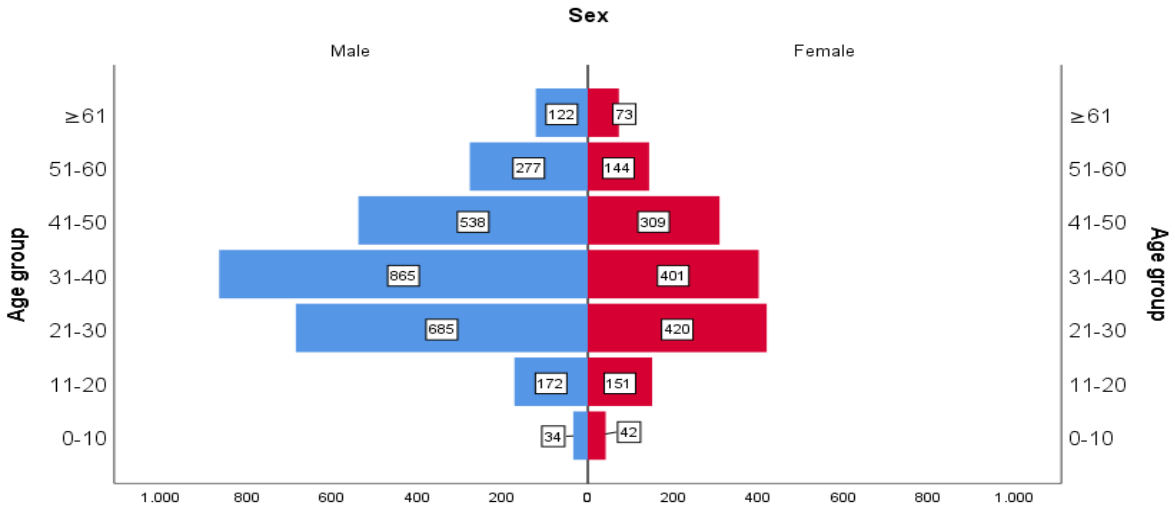

Table nº 1 shows the distribution of individuals according to vaccine status against COVID-19 and the distribution of individuals according to the result of the rapid antigen diagnostic test against COVID-19. The universe consisted of 708 (16.73%) unvaccinated individuals and 3524 (83.27%) vaccinated individuals of which 3309 (78.19%) individuals with a negative result and 923 (21.81%) individuals with a positive result.

Table nº 1- Vaccination status and rapid antigen diagnostic (RAD) test result

		n	%
Vaccination status	Vaccinate	3524	83.27
	Not vaccinated	708	16.73
	Total	4232	100.00
RAD test result	Positive	923	21.81
	Negative	3309	78.19
	Total	4232	100.00

RAD - Rapid Antigen Diagnostic

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Table nº2 shows the overall, by sex and age group odds ratio (OR) of SARS-CoV-2 infection in individuals vaccinated against COVID-19 versus unvaccinated and vaccine efficacy. The chances of SARS-CoV-2 infection is 0.85 times lower in vaccinated compared to unvaccinated individuals, with (95% CI 0.70 – 1.03) and P value=0.09. The overall vaccine efficacy (VE) was 15% (95% CI -3 – 30).

The chances of SARS-CoV-2 infection is 1.25 times higher in vaccinated females compared to unvaccinated females, with (95% CI 0.90 – 1.75) and P value = 0.18. The resulting VE in this group was -25% (95% CI -75 – 10).

The chances of SARS-CoV-2 infection is 0.68 times lower in male vaccinated individuals compared to unvaccinated males of the same sex, with (95% CI 0.54 – 0.86) and P value = 0.00. The resulting VE in this group was 32% (95% CI 14 – 46).

The chances of SARS-CoV-2 infection in this age group have not been determined because the number of exposed (vaccinated) individuals is zero.

The chances of infection by SARS-CoV-2 are 0.63 times lower in vaccinated individuals aged 11-20 years compared to unvaccinated individuals in the same age group, with (95% CI 0.38 – 1.05) and P value = 0.08. The resulting VE in this age group was 37% (95% CI -5 – 62).

The chances of infection by SARS-CoV-2 are 1.11 times higher in vaccinated individuals aged 21-30 years compared to unvaccinated individuals in the same age group, with (95% CI 0.72 – 1.73) and P value=0.61. The resulting VE in this age group was -10% (95% CI -73 – 28). The chances of infection by SARS-CoV-2 are 1.71 times higher in vaccinated individuals aged 31-40 years compared to unvaccinated individuals in the same age group, with (95% CI 1.05 –2.78) and P value=0.02. The resulting VE in this age group was -71% (95% CI -178 – -5). The chances of infection by SARS-CoV-2 are 0.75 times lower in vaccinated individuals aged 41-50 years compared to unvaccinated individuals in the same age group, with (95% CI 0.43 – 1.31) and P value=0.32. The resulting VE in this age group was 25% (95% CI -31 – 57). The chances of SARS-CoV-2 infection are 1.18 times higher in vaccinated individuals aged 51-60 years compared to unvaccinated individuals in the same age group, with (95% CI 0.54 – 2.55) and P value=0.67. The resulting VE in this age group was -18% (95% CI -155 – 46). The chances of SARS-CoV-2 infection is 0.41 times lower in vaccinated individuals in the age group of≥61 years in relation to unvaccinated individuals in the same age group, with (95% CI 0.18 – 0.91) and P value=0.02. The resulting VE in this age group was 52% (95% CI 9 – 82).

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Table nº 2- Estimate of the odds ratio of SARS-CoV-2 infection in vaccinated individuals and vaccine efficacy, overall, by sex and age group

	Vaccination status	RAD test Result		Total	OR	95% CI for OR		P	VE%	95% CI for VE	
		Positive	Negative			Lower	Higher			Lower	Higher
Overall	Vaccinate	732	2793	3525	0.85	0.70	1.03	0.09	15	-3	30
	Not vaccinated	167	541	708							
	Total	899	3334	4233							
Male	Vaccinate	450	1813	2263	0.68	0.54	0.86	0.00*	32	14	46
	Not vaccinated	115	315	430							
	Total	565	2128	2693							
Female	Vaccinate	565	2128	2693	1.25	0.90	1.75	0.18	25	-75	10
	Not vaccinated	52	226	278							
	Total	334	1206	1540							
0-10	Vaccinate	0	0	0	-	-	-	-	-	-	-
	Not vaccinated	21	64	85							
	Total	21	64	85							
11-20	Vaccinate	33	117	150	0.63	0.38	1.05	0.08	37	-5	62
	Not vaccinated	53	120	173							
	Total	86	237	323							
21-30	Vaccinate	180	764	944	1.11	0.72	1.73	0.61	-10	- 73	28
	Not vaccinated	28	133	61							
	Total	208	897	105							
31-40	Vaccinate	242	873	1115	1.71	1.05	2.78	0.02*	-71	-178	-5
	Not vaccinated	21	130	151							
	Total	263	1003	1266							
41-50	Vaccinate	158	614	772	0.75	0.43	1.31	0.32	25	-31	57
	Not vaccinated	19	56	75							
	Total	177	670	847							
51-60	Vaccinate	90	288	378	1.18	0.54	2.55	0.67	-18	-155	46
	Not vaccinated	9	34	43							
	Total	99	322	421							
≥61	Vaccinate	53	112	165	0.41	0.18	0.91	0.02*	52	9	82
	Not vaccinated	16	14	30							
	Total	69	126	195							

RAD - Rapid Antigen Diagnostic, OR – Odds ratio, CI - Confidence interval, * - Statistically significant for p<0.05, VE -Vaccine efficacy

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Table nº 3 shows the determination of the adjusted odds ratio (OR) stratified by age group and sex with confidence intervals and P value of the risk of infection by SARS-CoV-2 in individuals vaccinated against COVID-19. The chances of infection by SARS-CoV-2 are 0.34 times lower (95% CI 0.18 – 0.91) in male vaccinated individuals aged 41-50 years, with P=0.00 and 8.63 times higher (95% CI 1.15 – 64.62) in vaccinated women of the same age group with P=0.01.

Table nº 3 - Stratification by age group and sex of vaccine efficacy (VE) and estimate of the odds ratio (OR) of SARS-CoV-2 infection in vaccinated individuals

Age group	Sex	OR	95% CI for OR		P	VE (%)	95% CI for VE	
			Lower	Higher			Lower	Higher
0-10	Male	-	-	-	-	-	-	-
	Female	-	-	-	-	-	-	-
11-20	Male	0.60	0.30	1.20	0.15	40	-20	70
	Female	0.71	0.34	1.50	0.37	29	-50	66
21-30	Male	0.89	0.52	1.51	0.66	11	-51	48
	Female	1.46	0.66	3.22	0.35	- 46	-222	34
31-40	Male	1.49	0.84	2.65	0.17	- 49	-165	16
	Female	2.10	0.86	5.10	0.10	- 110	-410	14
41-50	Male	0.34	0.18	0.63	0.00*	66	37	82
	Female	8.63	1.15	64.62	0.01*	- 763	-6362	-15
51-60	Male	0.87	0.36	2.15	0.77	13	-115	64
	Female	2.02	0.42	9.66	0.37	- 102	-866	58
≥61	Male	0.27	0.10	0.75	0.01*	73	25	90
	Female	0.66	0.18	2.41	0.53	34	-141	82

RAD - Rapid Antigen Diagnostic, OR – Odds ratio, CI - Confidence interval, * - Statistically significant for p<0.05, VE -Vaccine efficacy

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5. DISCUSSION

For the first time, we present results that allow the assessment of vaccine protection against COVID-19 in a real-life scenario by estimating the odds ratio and overall vaccine efficacy and adjusted for sex and age groups.

The overall odds ratio of SARS-CoV-2 infection estimated at 4.232 individuals who took part in this analysis was 0.85 (95% CI 0.70 – 1.03). According to the Axel and CDC odds ratio risk classification, this means that there is a protective effect of the vaccine, although this protection is negligible and therefore not statistically significant if we look at the confidence interval values for the odds ratio and for the value of P=0.09. The estimated overall vaccine efficacy (VE) was 15%. Remember here that the minimum efficacy recommended by the WHO for an anti-SARS-CoV-2 vaccine is 50% in phase 3 clinical trials (UOL, 2021). All vaccines used in the COVID-19 Vaccination Program in Angola had reported efficacy in phase 3 clinical trials superior to that recommended by the WHO (Logunov et al., 2021; World Health Organization, 2021a, 2021b, 2021c, 2022). The difference found in the general VE of our study with those published previously may be due to the fact that the phase 3 clinical trials in which the VE used in Angola were determined do not consider relevant factors present in the real world, such as the expansion of the range recipients of vaccines beyond those eligible for testing initially, administration of vaccine with incomplete or mixed regimens, variation of dosing intervals, possibility of storage and incorrect administration of vaccines, concomitant administration with other drugs by vaccinates that are not permitted for participants in phase 3 trial, the decline in vaccine immunity over time and the emergence of new genetic variants of SARS-CoV-2 with protein targets not initially considered in the manufacture of currently available vaccines such as Omicron (Clemens et al., 2022). This last question seems to us to be the most relevant. The latest UK Health Safety Agency report on “SARS-CoV-2 variants of concern and variants under investigation in England” found an EV similar to that found in our study in vaccinated individuals of 13.0 % (95% CI 11-15) where it evaluated the effectiveness of vaccination by comparing symptomatic individuals > 18 years old infected with the Omicron and Delta variant in the period from November 27, 2021 to January 6, 2022 (UKHSA/Andrews et al, 2022). Also, Jara et al.,

in contrast, several studies (Bernal et al., 2021; Dickerman et al., 2022; Eyre et al., 2022; Young-Xu et al., 2021) conducted in a real-life setting reported a higher VE than that found in our study. It is also necessary to emphasize here the need for some consideration in the comparison of these results with ours, since in this analysis we did not consider several issues such as VE by type of vaccine, by clinical status (asymptomatic vs symptomatic), by dominant variants, by number of doses taken and time elapsed since taking the 1st or 2nd dose that were considered in some of the cited studies.

As for the stratified analysis of the odds ratio by sex, we found that there is a significant difference between the sexes. The odds of SARS-CoV-2 infection in male vaccinated individuals was 0.68 (95% CI 0.54 – 0.86) times lower compared to unvaccinated male individuals. According to Axel's odds ratio risk rating, this means that there is a “negligible” protective effect of vaccination in men and this protection is statistically significant (P=0.00). The same was not seen in women where the odds of SARS-CoV-2 infection in vaccinated were 1.25 (95% CI 0.90 – 1.75) times higher than in unvaccinated. According to Axel's odds ratio risk rating, this means that there is a “negligible” risk of vaccination in women although this is not statistically significant (P=0.18). Thus, the VE in men was 32% (95% CI 14 – 46) and -25% in women (95% CI -75 – 10). In the published and unpublished literature, we did not find findings similar to ours and no reason to explain the difference in VE between the sexes. We postulate that, other non-biological factors such as poor adherence to individual protection measures such as mask use and greater exposure to the virus in places of large population areas such as informal markets frequented mostly by women may explain the greater risk found in vaccinated women compared to men whose work activity is more focused on institutional environments where compliance with individual protection measures is mandatory, which is a synergistic measure for higher levels of vaccine protection seen in men. However, other host-related biological factors such as the post-vaccination antibody production response, duration and type of vaccine and vaccine type as well as factors related to the viral agent such as the presence of genetic variants more transmissible to predominant in one sex should be considered in further studies that are justified to clarify this difference found.

Stratification by age group also revealed differences in the odds ratio in the different groups. The odds of SARS-CoV-2 infection were 0.63 (95% CI 0.38 – 1.05) times lower in vaccinated individuals aged 11-20 years compared to unvaccinated individuals in the same age group,

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although the value of P=0.08 indicates that there is no statistical significance for this “negligible” protection according to the Axel risk classification. The VE in this age group was 37% (CI 95% -5 – 62). On the other hand, the chances of infection by SARS-CoV-2 in the following age group of 21-30 years old showed no difference between vaccinated and unvaccinated since OR=1.11 (95% CI 0.72 – 1.73) although the value of P=0.61 indicates that there is no statistical significance for the “null effect” of the vaccine in this group according to Axel's risk classification. The VE in this age group was -10% (95%CI -73 – 28). The risk of infection by SARS-CoV-2 becomes moderate according to the Axel risk classification in individuals aged 31-40 being 1.71 (95% CI 1.05 –2.78) times higher in vaccinated individuals compared to unvaccinated individuals and statistically significant for P=0.02. The VE in this age group was -71% (95% CI -178 – - 5). In the 41-50 age group, the chances of SARS-CoV-2 infection were 0.75 (95% CI 0.43 – 1.31) times lower in vaccinated individuals compared to unvaccinated individuals of the same age group, however this “negligible” protection according to Axel's risk classification, it was not statistically significant for P=0.32. The VE in this age group was 25% (CI 95% -31 – 57). The odds of SARS-CoV-2 infection were 1.18 (95% CI 0.54 – 2.55) times higher in vaccinated individuals aged 51-60 years compared to unvaccinated individuals in the same age group, however this negligible risk was not statistically significant with P=0.67. The VE in this age group was -18% (95% CI -155 – 46). The last age group showed that there is 0.41 (95% CI 0.18 – 0.91) times less chance of SARS-CoV-2 infection in vaccinated elderly compared to unvaccinated elderly in the same age group, this difference being statistically significant with P value =0.02. According to the Axel risk score, there was moderate protection conferred by vaccination in this age group with an EV of 59% (95% CI 9 – 46). A possible reason for better VE seen in the age group of According to the Axel risk score, there was moderate protection conferred by vaccination in this age group with an EV of 59 % (95% CI 9 – 46). A possible reason for better VE seen in the age group of According to the Axel risk score, there was moderate protection conferred by vaccination in this age group with an EV of 59 % (95% CI 9 – 46). A possible reason for better VE seen in the age group of ≥61 years and not seen in the lower age groups may be because this group has developed lasting immunity as this is a risk group that was prioritized at the beginning of the vaccination campaign, supporting the fact that the protective effect of vaccine-induced immunity also it is supported by long-term components of the humoral response, including memory B cells as is the response to infection.

Adjusting the odds ratio and VE in each age group by sex, we found that men had a lower risk

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and, consequently, a higher VE compared to women in all age groups. A protective effect was seen in all age groups for men except the 31-40 age group where the odds of SARS-CoV-2 infection was 1.49 (95% CI 0.84 – 2.65).

times higher in vaccinated men compared to unvaccinated men. Protective effect was only seen in women aged 11-20 and in women ≥61 years of age, although the negligible protective effect was not statistically significant in both age groups for women. The resulting VE in these age groups was 29% (95% CI -50 - 66) and 34% (95% CI -141– 82) respectively. On the other hand, in men in the range ages 41-50 and ≥61 years old, there was a statistically significant protective effect with VE of 66% (95% CI 37 – 82) and 73% (95% CI 25 – 90) respectively. Protection in these age groups was moderate, different from "negligible" seen in men of other strata. Surprisingly, we cannot fail to point out here that vaccinated women aged 41-50 years had an odds ratio of SARS-CoV-2 infection of 8.63 (95% CI 1.15–64.62) times greater than unvaccinated women of the same age group, this risk according to the Axel classification considered high was statistically significant for P= 0.01. Why did vaccination have a better effect on men than on women in virtually all age groups? For now, the best explanation we can find for such differences, it is limited to non-biological or environmental factors or also socio-cultural factors with possible antagonistic effects on the effectiveness of vaccination seen in women who most frequent places in population clusters such as informal markets where there is greater viral exposure. However, there may be a combination of factors also linked to the viral agent, because in a scenario where 81.94% (1,262) of the women who were part of our universe were vaccinated and despite this it is verified in practically all age groups except the age groups from 11-20 and from ≥61 an increased risk, this leads us to think that this risk in women may be an epidemiological translation of the presence of viral genetic variants with vaccine evasion capacity, as supported by a study recently published by researchers from the University of New South Wales, in Australia who mapped an infection rate of the Omicron variant compared to the old Delta variant, Omicron was 10 times higher in evasion of vaccines against COVID-19 and acquired(Aggarwal et al., 2022).

There were no vaccinated individuals in the 0-10 age group, which is why the odds ratio in this age group was not estimated because Angola, until the date that this analysis was made, had not included this age group in its vaccination program against COVID-19.

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6. CONCLUSIONS

There was no statistically significant decrease in the odds of SARS-CoV-2 infection in vaccinated versus unvaccinated individuals. The sex-adjusted and VE-adjusted risk decreases were statistically significant only in men. The age-adjusted risk revealed a statistically significant decrease in the risk of SARS-CoV-2 infection only in vaccinated individuals aged 61 years and over and who had a VE greater than 50%. In the adjusted risk for age group and sex, there was a statistically significant decrease in the risk of infection by SARS-CoV-2 only in men aged 41-50 and older than or equal to 61 years of age and VE greater than 60%. Vaccinated women aged 41-50 years had a risk of infection with SARS-CoV-2 considered high and VE had no protective effect.

7. LIMITATIONS

This study has some limitations: first, as an observational study, it is subject to confounding. We do not provide estimates of effect (odds ratio) or vaccine efficacy (VE) in vaccinated individuals taking into account the different types of vaccine, number of doses given or the time elapsed since the administration of the vaccine who may also be exerting a residual confounding effect. However, all these aspects will be considered in a complementary analysis

Second, as the selection test for cases and controls used was a rapid antigen diagnostic test and there was no laboratory confirmation of the results by the gold standard test, in this case the RT-PCR, we consider that there may have been a risk of classification bias cases and controls due to the possibility of false positives (considered in the case group) and false negatives (considered in the control group).

Third, at the time of writing this paper, a preprint published by researchers at the University of New South Wales, Australia found that the Omicron variant had 10 times more ability to evade COVID-19 vaccines compared to Delta. Although the national genomic surveillance for SARS-CoV-2 in Angola has reported the circulation of the alpha, gamma, Delta and Omicron variant, we do not have data to estimate their effect on vaccine efficacy because this data is not obtained from the positive results during the performance of the tests routine RT-PCR testing in Angola because there are no resources to perform genotyping in-house and antigen tests do not provide this information.

Fourth, estimates of vaccine efficacy (VE) were obtained under specific epidemiological and vaccine conditions, and therefore we assume here that they can clearly vary over time and across these conditions.

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9. REFERENCES

1. Aggarwal,A., Stella AO, Walker G, Akerman A, Milogiannakis V, Brilot F, Amatayakul-Chantler S, Roth N, Coppola G, Schofield P, Jackson , J., Henry, JY, Mazigi, O., Lu, Y., Forster, C., McAllery, S., Mathivanan, V., Fichter, C., Hoppe, AC, … Building, WW (2022). SARS-CoV-2 Omicron: Evasion of potent humoral responses and resistance to clinical immunotherapeutics relative to viral variants of concern. 16.
2. AngoRussia. (2021, December21). National Director of Public Health warns that outbreak in the flu he can to besignal in Covid 19. *AngoRussia*.https://angorussia.com/noticias/directora-nacional-de-saude-publica-adverte-que-surto-de-gripe-pode-ser-sinal-de-covid-19/
3. Bernal JL, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, Simmons R, Cottrell S, Roberts R, O'Doherty M., Brown, K., Cameron, C., Stockton, D., McMenamin, J., & Ramsay, M. (2021). Effectiveness of the Pfizer- BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: Test negative case-control study. BMJ, 373, n1088. https://doi.org/10.1136/bmj.n1088
4. Clemens, J., Aziz, AB, Tadesse, BT, Kang, S., Marks, F., & Kim, J. (2022). Evaluation of protection by COVID-19 vaccines after deployment in low and lower-middle income countries. *EClinicalMedicine*, *43*. https://doi.org/10.1016/j.eclinm.2021.101253

 doi:10.20944/preprints202208.0014.v1

5. Dickerman, BA, Gerlovin, H., Madenci, AL, Kurgansky, KE, Ferolito, BR, Figueroa Muñiz, MJ, Gagnon, DR, Gaziano, JM, Cho, K., Casas, JP, & Hernán, MA (2022). Comparative Effectiveness of BNT162b2 and mRNA-1273 Vaccines in US Veterans. New England Journal of Medicine, 386(2), 105–115. https://doi.org/10.1056/NEJMoa2115463
6. Embassy of the Republic of Angola in Portugal. (2021, June 1). Embassy of the Republic of Angola in Portugal—ANGOLA RECEIVES MORE THAN 100,000 DOSES OF VACCINES FROM PFIZER. Embassy of the Republic of Angola in Portugal.http://www.embaixadadeangola.pt/angola-recebe-mais-de-100-mil-vaccine-dose-from-pfizer/
7. Eyre DW, Taylor D, Purver M, Chapman D, Fowler T, Pouwels KB, Walker AS & Peto TEA (2022). Effect of Covid-19 Vaccination on Transmission of Alpha and Delta Variants. New England Journal of Medicine. https://doi.org/10.1056/NEJMoa2116597
8. Gamaleya. (2021). НИЦЭМ им. Н. Ф. Гамалеи. https://www.gamaleya.org/
9. Jara A., Undurraga, EA, González, C., Paredes, F., Fontecilla, T., Jara, G., Pizarro, A., Acevedo, J., Leo, K., Leon, F., Sans , C., Leighton, P., Suárez, P., Garcia-Escorza, H., & Araos, R. (2021). Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. New England Journal of Medicine, 385(10), 875–884. https://doi.org/10.1056/NEJMoa2107715
10. Angola newspaper. (2021a). Jornal de Angola—Notícias—Angola already has community circulation of the Omicron variant. Angola newspaper. https://www.Jornaldeangola.ao
11. Angola newspaper. (2021b). Jornal de Angola—News—Sputnik vaccine arrives *to Angola*. Angola newspaper. https://www.Jornaldeangola.ao

 doi:10.20944/preprints202208.0014.v1

12. Logunov, DY, Dolzhikova, IV, Shcheblyakov, DV, Tukhvatulin, AI, Zubkova, OV, Dzharullaeva, AS, Kovyrshina, AV, Lubenets, NL, Grousova, DM, Erokhova, AS, Botikov, AG, Izhaeva, FM, Popova, O., Ozharovskaya, TA, Esmagambetov, IB, Favorskaya, IA, Zrelkin, DI, Voronina, DV, Shcherbinin, DN, … Gintsburg, AL (2021). Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: An interim analysis of a randomized controlled phase 3 trial in Russia. The Lancet, 397(10275), 671-681. https://doi.org/10.1016/S0140- 6736(21)00234-8
13. Lusa, A. (2021). Covid-19. Angola received 165,000 doses of Janssen vaccines. Observer. https://observador.pt/2021/08/08/covid-19-angola-recebeu-165-thousand-dose-of-vaccines-janssen/
14. News from Angola. (2021, March 5). Covid-19: Mass vaccination campaign begins in this Saturday. *News in Angola*. https://noticiasdeangola.co.ao/covid-19-campanha-vacinacao-massa-comeca-neste-sabado/
15. RFI. (2021, December 27). Omicron forces mass testing of the Angolan population. RFI. https://www.rfi.fr/pt/angola/20211227-%C3%B3micron-obriga-the-mass-testing-%C3%A0-population%C3%A7%C3%A3o-Angolan
16. RTP, R. and T. de. (2021). Angola opens vaccine warehouse and starts vaccination campaign. Angola opens vaccine warehouse and starts vaccination campaign. https://www.rtp.pt/noticias/mundo/angola-inaugura- vaccine-deposit-and-start-up-with-vaccination-campaign_n1301332

 doi:10.20944/preprints202208.0014.v1

17. Tavares, C. (2021). Understand how the effectiveness of a vaccine is measured—Fiotec. https://www.fiotec.fiocruz.br/noticias/outros/7353-entenda-como-e-medida-a- effectiveness-of-a-vaccine

18. UKHSA/Andrews et al. (2022). SARS-CoV-2 variants of concern and variants under investigation in England: Technical briefing 34. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1050236/technical- briefing-34-14-january-2022.pdf

19. UOL. (2021). Vaccine with 50% effectiveness could be approved, admits chief scientist *gives WHO*. https://www.uol.com.br/vivabem/noticias/redacao/2020/09/21/vacina-com-50- de-efficacy-can-be-approved-admits-who-chief-scientist.htm

20. Vandenbroucke, JP, Brickley, EB, Vandenbroucke-Grauls, CMJE, & Pearce, N. (2020). A Test-Negative Design with Additional Population Controls Can Be Used to Rapidly Study Causes of the SARS-CoV-2 Epidemic. epidemiology *(Cambridge, Mass.)*, *31*(6), 836–843. https://doi.org/10.1097/EDE.0000000000001251

21. World Health Organization. (2021a). Background document on the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm: Background document to the WHO Interim recommendations for use of the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm, 7 May 2021 (WHO/2019-nCoV/vaccines/SAGE_recommendation/BIBP/background/2021.1). World Health Organization. https://apps.who.int/iris/handle/10665/341252

22. World Health Organization. (2021b). Interim recommendations for the use of the *Janssen Ad26.COV2.S (COVID-19) vaccine: Interim guidance, 17 March 2021*

(WHO/2019-nCoV/vaccines/SAGE_recommendation/Ad26.COV2.S/2021.1). World Health Organization. https://apps.who.int/iris/handle/10665/340203

23. World Health Organization. (2021c). Interim recommendations for use of the ChAdOx1-S [recombinant] vaccine against COVID-19 (AstraZeneca COVID-19 vaccine AZD1222 VaxzevriaTM, SII COVISHIELDTM): Interim guidance, first issued 10 February 2021, updated 21 April 2021, last updated 30 July 2021 (WHO/2019-nCoV/vaccines/SAGE_recommendation/AZD1222/2021.3). World Health Organization. https://apps.who.int/iris/handle/10665/343388
24. World Health Organization. (2021d). Weekly epidemiological update—9 March 2021. https://www.who.int/publications/m/item/weekly-epidemiological-update 10-march-2021
25. World Health Organization. (2021e). WHO lists additional COVID-19 vaccine for *emergency use and issues interim policy recommendations*. https://www.who.int/news/item/07-05-2021-who-lists-additional-covid-19-vaccine-for-emergency-use-and-issues-interim-policy-recommendations
26. World Health Organization. (2022). Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under emergency use listing: Interim guidance, first issued 8 January 2021, updated 15 June 2021, updated *19 November 2021, updated 21 January 2022*(WHO/2019-nCoV/vaccines/SAGE_recommendation/BNT162b2/2022.1). World Health Organization. https://apps.who.int/iris/handle/10665/351139
27. Young-Xu, Y., Korves, C., Roberts, J., Powell, EI, Zwain, GM, Smith, J., & Izurieta, HS (2021). Coverage and Estimated Effectiveness of mRNA COVID-19 Vaccines Among US Veterans. JAMA Network Open, 4(10), e2128391. https://doi.org/10.1001/jamanetworkopen.2021.