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Half dose ChAdOx1 nCoV-19 vaccine was equivalent to full doses to reduce moderate and severe COVID-19 cases

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ABSTRACT

Objectives: Previously, we presented the effectiveness of ChAdOx1 nCoV-19 half-dose (HD) immunization for preventing new COVID-19 cases. Here, we evaluated the administration of an HD of ChAdOx1 nCoV-19 in the primary immunization protocol (up to two doses) in reducing moderate and severe cases, hospitalizations, and deaths when compared to the administration of full doses (FD) after a long-term follow-up.
Methods: We evaluated data from 29,469 participants between January 2021 and November 2022 who received an HD or FD vaccine and crossed this information with their medical records to identify those who developed moderate or severe cases. All participants were classified into four groups according to their immunization status and followed 500 days after the last vaccine administration.
Results: The propensity-score matching analysis indicates that the administration of the two HDs of ChAdOx1 nCoV-19 was equivalent to the use of two FDs to reduce moderate and severe COVID-19 cases. The relative risk of being infected and developing moderate or severe conditions after the administration of at least one HD or FD was similar 150 or 500 days after the administration of the immunizers.
Conclusion: Administering two HDs can be used safely as a cost-effective alternative to the primary immunization protocol.

Introduction

Since its emergency or regular approval by regulatory agencies worldwide to face the COVID-19 pandemic, different vaccination strategies have become the primary way to combat the development of moderate or severe COVID-19, often resulting in thousands of deaths. Despite the massive sub-notification in several counties during the pandemic, the cumulative data compiling data from January 2020 to the present indicate the occurrence of 767.36 million cases worldwide (high-income countries: 422.32 million; upper-middle income: 243.92 million; low/lower-middle income: 97.6 million), resulting in 6.94 million deaths (high-income countries: 2.88 million; upper-middle income: 2.66 million; low/lower-middle income: 1.34 million). Since their approval for general use (outside a clinical trial), over 13.39 billion doses

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of vaccines were administered worldwide (high-income countries: 2.82 billion; upper-middle income: 5.42 billion; low/lower-middle income: 4.86 billion) [1].

Undoubtedly, the large-scale vaccination process was responsible for the reduction of hospitalizations and for avoiding millions of COVID-19-related deaths [2–5]. According to recent estimates based on computational modeling studies, only the COVID-19 vaccination program in the U.S. prevented more than 110 million new COVID-19 cases, 18.5 million hospitalizations, and 3.2 million related deaths. In addition, it saved US$ 1.15 trillion in medical expenses from December 2020 through November 2022 after granting the general population access to at least one dose of any available COVID-19 vaccines [6,7].

In Brazil, despite the success of COVID-19 vaccination, the delay in starting the massive immunization campaigns and the "herd immunity" belief resulted in new cases and preventable deaths. For instance, until February 2023, the official reports registered over 36 million cases and 698,000 COVID-19-related deaths, while Espírito Santo (a state located in the southeast region with an estimated population of 4.1 million inhabitants) registered over 1.3 million cases and 15 thousand COVID-19-related deaths [8,9].

A recent study by Ferreira and colleagues estimated that more than 165,000 elderly patients (60+ years) were not hospitalized after the first 7 months of vaccination campaigns. Other 104,000 hospitalizations could have been avoided if the vaccination had been started a few months earlier. In addition, 58,000 COVID-19-related deaths among the elderly were prevented between January and August 2021, and an additional 47,000 lives could have been saved if the vaccination campaigns had been strongly encouraged since the beginning [10]. These findings corroborate our data that indicates that COVID-19 vaccination significantly reduced the hospitalization and death of elderly patients after administering at least one dose [5].

Although they induce immunity using different technologies, all vaccines approved for use in Brazil (BNT162b2 - Pfizer/BioNTech; CoronaVac - Sinovac Biotech; ChAdOx1 nCoV-19 - Oxford/AstraZeneca; and Ad26.COV2.S - Jassen) and the adoption of the mix-and-match strategy during the massive immunization process were proved as an efficient approach to induce a protective immune response, to prevent the development of moderate and severe COVID-19 cases and to reduce the lethal outcomes after infection [11–18]. According to the Brazilian Ministry of Health, over 500 million doses were administered from January 2021 to February 2023, 152 million were Oxford/AstraZeneca doses, 208 million from Pfizer/BioNTech, 112 million from CoronaVac, and 29 million from Janssen [19].

The fractional dose is a relevant strategy to increase access to vaccines. The Viana Project (ClinicalTrials.gov; NCT05059106), a non-inferiority non-randomized controlled trial, showed that HD of ChAdOx1 nCoV-19 is as effective, safe, and immunogenic as the full dose (FD) in 29,598 individuals aged 18-49 years. The published results showed the effectiveness of primary vaccination with a HD of ChAdOx1 nCoV-19 for preventing new cases at 90 days of follow-up after the second dose [20].

This study aimed to evaluate the effectiveness of a HD of ChAdOx1 n19 CoV-2 in the primary immunization protocol (with up to two doses) in reducing moderate and severe cases, hospitalizations, and deaths related to COVID-19 when compared to the administration of FDs, after a long-term follow-up. To address this question, we crossed the immunization database with the individual medical records of the "Viana Project" participants between January 2021 and November 2022 to identify potential hospitalizations or deaths related to COVID-19. In addition, we explored the impact of the administration of HD as an alternative in the primary immunization protocol in reducing moderate and severe cases, considering the occurrence of hospitalizations, length of hospitalization, comorbidities, and outcome (discharge or death) after COVID-19 infection.

Materials and methods

Half-dose or full-dose administration and database crossing

All data were from Viana Project Study (ClinicalTrials.gov; NCT05059106) and obtained from the recruitment of 20,723 participants between January 2021 and November 2022 who received at least one HD of ChAdOx1 nCoV-19 (AZD1222) and 8746 participants that received at least one FD of ChAdOx1 nCoV-19 (AZD1222). The end of the follow-up (November 2022) of the patients was delimited to 6 months after the last administration of the second HD (in May 2022) and identification of the outcome after immunization.

The city of Viana/ES was chosen because it meets the ideal conditions to perform the proposed analysis - high urban mobility and occurrence of new cases among young adults; good logistics for correctly accessing immunizers; well-structured vaccination and health care network; and structured hospital support to care for moderate and severe cases.

We analyzed data from 29,469 adults (18-49 years), both sexes, regardless of previous COVID-19 infection and no history of immunization with any available vaccine. This group was chosen because they are not part of the priority groups established in the Brazilian National Immunization Program (PNI), and they did not have a scheduled date for receiving any immunization at the time of the study. Therefore, we excluded the participation of all subjects under 18 or adults over 49 years old; pregnant women; people with a previous severe allergic reaction (anaphylaxis) to any administered vaccine; those who received any dose of a COVID-19 vaccine; those subjects participants in other immunization studies; those belonging to a priority risk group for vaccination, as recommended by PNI rules; those with fever or flu-like symptoms; and those with coagulation disorders, use of anticoagulants or a recent COVID-19 diagnosis with the onset of symptoms 28 days before vaccination.

The primary data generated after immunization with HD or FD was obtained using the Vacina e Confia ES database. It was crossed with the official base of notifications of COVID-19 cases obtained from the Health Surveillance Information System (eSUS-VS) [21,22]. The intersection of these data allowed identifying the occurrence of COVID-19 cases among participants if they needed medical support, including hospitalization in intensive care units (ICUs) or clinical units, and the outcome during the analyzed period.

Considering the seroconversion period required for the effective induction of humoral and cellular immune responses, all subjects were classified into five distinct groups according to their immunization status: those who received only 1 HD more than 14 days before the infection, those who received two HD more than 14 days before the infection; those who received only one FD more than 14 days before the infection; and those who received two FD more than 14 days before the infection.

The Secretary of Health of Espírito Santo (SESA/ES) previously anonymized data, and its analysis was authorized after being publicly available in the repository. In addition, the final dataset "Viana_anonymized_EN.csv" used to perform this study was subjected to peer review to improve the rigor of evaluation and information consistency. The complete anonymized data is available in Zenodo at https://doi.org/10.5281/zenodo.7963928.

Data dictionary, processing of information, and interpretation of results

We analyzed the data using a pipeline using Python 3.7.12 and performed the extraction, transformation, and load (ETL) methodology to ensure quality and well-structured data. Considering the need to integrate three databases ("Projeto Viana", "Vacina e Confia" and "eSUS-VS"), the first step (data curation and extraction) is essential to extract precise information from each to obtain the results. During this process, we excluded patients that do not meet the inclusion criteria, those with an

unconfirmed COVID-19 diagnosis, and those with unknown outcomes (discharge or death) at the end of the analyzed period.

During the transformation process, we double-checked the data to ensure that the data was in a consistent, complete, and clean format, removing missing or invalid values, correcting errors, and standardizing the data to be easily compared and combined. In this step, we label each patient with the number and type of doses received throughout the study, age, gender, comorbidities, the occurrence of COVID-19 after immunization, the need for hospitalization, and the outcome. Only attributes of interest to this study were included in the dataset during this selection, whereas details that could potentially identify individuals were excluded.

The load step was characterized by integrating the information from each base into a single dataset, preserving their integrity. To avoid bias during the data analysis, we evaluated the period between January 2021 and November 2022, 6 months after all adult (18-49 years) residents in Viana could have received at least one HD or one FD and have a vaccination-associated outcome. Additional analysis using this data can be performed using the deposited database.

Statistical analysis

All data presented in this study were analyzed using GraphPad Prism 9.5.1 software. The statistical analysis was performed using the Kruskal-Wallis test for group comparison and Dunn's test to perform multiple comparisons. The results are shown as the mean ± standard deviation. Comparisons between columns were considered statistically significant when P <0.05 ($^{*}P$ <0.05; $^{**}P$ <0.005; $^{***}P$ <0.001; $^{****}P$ <0.0001). In addition, we performed an exploratory data analysis, for which the graphic libraries "numpy", "pandas", "matplotlib," and "Seaborn" were consolidated in the Python programming language.

Results

Patients immunized with the half dose have the same risk of developing moderate and severe COVID-19 cases when compared to those vaccinated with the full dose

The rationale of the Viana Project Study was to assess whether the administration of HD of ChAdOx1 nCoV-19 (Oxford/AstraZeneca) could be used as a primary immunization protocol (with up to two doses) and would have the same efficacy in reducing moderate and severe cases, hospitalizations and deaths related to COVID-19 as the protocol with the administration of FD. In this sense, we performed the propensity-score matching analysis to evaluate the general features (age, gender, the occurrence of infection between January 2021 and November 2022, hospitalization in clinical or ICU beds, and outcome) among the 20,723 participants who received at least one HD and the 8746 participants who received at least one FD of ChAdOx1 nCoV-19 (AZD1222). The general features of all analyzed groups are presented in Table 1. In addition, our data evidenced no statistically significant difference between the HD and FD groups (P = 0.3795), indicating that both groups are similar in the general features and the risk of hospitalization (regardless of comorbidities). Therefore, the primary protocol of immunization using two HDs had the same effectiveness as administering two FDs in protecting against moderate and severe COVID-19 cases (Figure 1).

Considering the relative risk of being infected and developing moderate or severe conditions after the administration of at least one HD or one FD, it was not possible to observe significant differences between the groups 150 (P = 0.6648) or 500 days (P = 0.3795) after the administration of the respective immunizers, indicating a similar probability to be infected and required medical assistance after immunization between the groups (Figure 2). Similarly, the period after administration of at least one HD or FD and the occurrence of COVID-19 infection was equivalent among the participants with comorbidities (Figure S1).

Table 1
General features of all analyzed groups according to gender, comorbidity, the occurrence of COVID-19 infection, outcome, and the period between the last dose and death.

Vaccinal status (%)	Gender		Comorbidities		Not infected/ asymptomatic cases (%)	Moderate or severe COVID-19 cases		Outcome		Days since the last dose and death
	Male (%)	Female (%)	Yes (%)	No (%)		Clinical units (%)	Intensive care unit (%)	Discharge (%)	Death (%)	
1 HD	2340 (7.94%)	1327 (56.71%)	1013 (43.29%)	35 (1.50%)	2305 (98.50%)	1748 (74.70%)	591 (25.26%)	1 (0.04%)	591 (25.26%)	1 (0.04%)	14
2 HD	18,383 (62.38%)	9643 (52.46%)	8740 (47.54%)	255 (1.39%)	18,128 (98.61%)	12,961 (70.51%)	5417 (29.47%)	5 (0.03%)	5422 (29.49%)	0	N/A
1 FD	1645 (5.58%)	963 (58.54%)	682 (41.46%)	42 (2.55%)	1603 (97.45%)	1320 (80.24%)	325 (19.76%)	0	323 (19.64%)	2 (0.12%)	27
2 FD	7101 (24.10%)	3030 (42.67%)	4071 (57.33%)	409 (5.76%)	6692 (94.24%)	4897 (68.96%)	2197 (30.94%)	7 (0.10%)	2204 (31.04%)	0	N/A
TOTAL	29,469 (100%)	14,963 (50.78%)	14,506 (49.22%)	741 (2.51%)	28,728 (97.49%)	20,926 (71.01%)	8530 (28.95%)	13 (0.04%)	8540 (28.98%)	3 (0.01%)	-

Abbreviations: 1 HD: one half-dose participant; 2 HD: two half-dose participants; 1 FD: one full-dose participant; 2 FD: two full-dose participants.

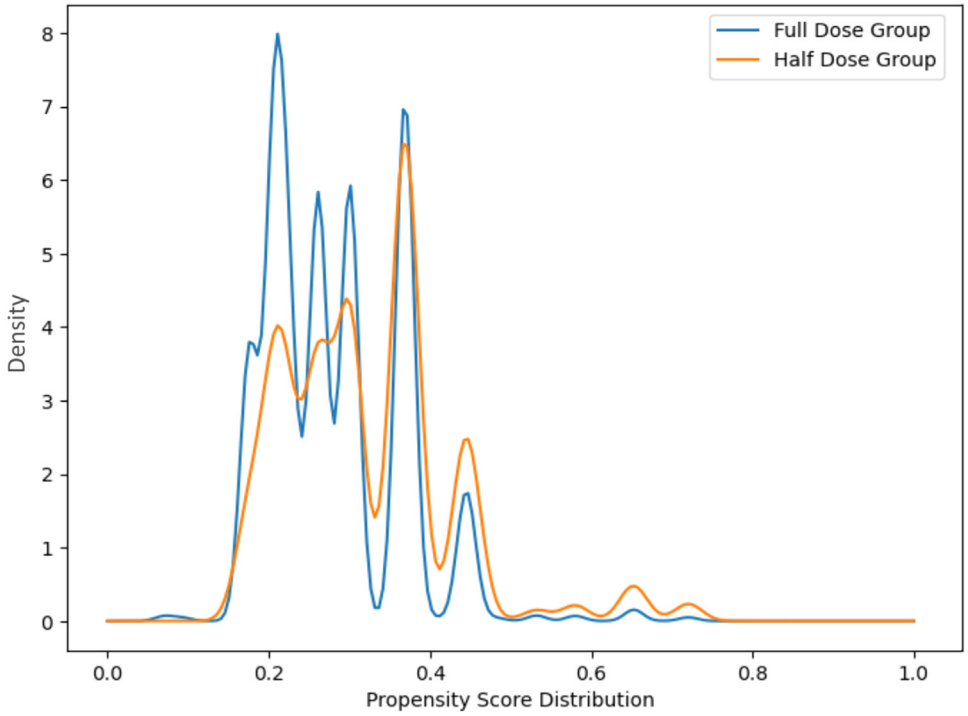

Figure 1. The half-dose immunization protocol is similar to the full-dose protocol in protecting against moderate or severe COVID-19. According to the propensity-score matching analysis, administering ChAdOx1 nCoV-19 (AZD1222) half-dose protocol reduces hospitalization and deaths compared to full dose protocol after COVID-19 infection.

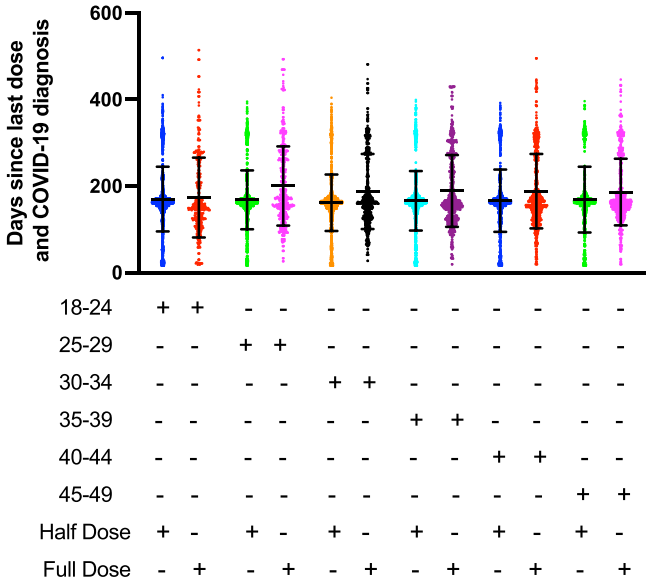

Figure 2. Days since the last half dose or full dose and the development of COVID-19 infection grouped by age. Considering the relative risk of being infected and developing moderate or severe COVID-19 cases, patients who received half dose or full dose have a similar probability of being infected and requiring medical assistance after immunization.

In addition, we evaluated the occurrence of moderate or severe cases considering the total of immunized patients in the respective groups. As a result, the ratio of cases/participant in the one HD group (one case/3.95 participants) was lower than that observed in the one FD group (one case/5.06 participants), indicating that one HD participant developed more moderate or severe cases than those who received one FD. Also, one HD participants have fewer cases than patients who received two HDs (one case/3.39 participants), while two HD participants require less hospitalization than those who received two FDs (one case/3.22 participants).

The mean age among the two HD patients who developed moderate or severe cases is lower compared to the two FD group

Analyzing the age of individuals vaccinated with HD or FD who required hospitalization (moderate or severe cases) and were discharged (n = 8540; 28.98% of total), the mean age was similar between the groups without comorbidities who received one HD compared to one FD and one HD compared to two HD. In addition, it was significantly lower in the two HD groups without comorbidities than in the two FD groups without comorbidities (Figure 3a). Considering the individuals with comorbidities, the mean age was similar between the groups one HD without comorbidity compared to one HD with comorbidity, one HD with comorbidity when compared to two HD with comorbidity, and one HD comorbidity when compared to one FD with comorbidity.

However, the mean age was significantly different between the groups, two without comorbidity vs two HDs with comorbidity; and two HDs with comorbidity vs two FDs with comorbidity. These data indicate that patients without comorbidities (97.49% of study participants) who received only one HD and developed moderate or severe cases have the same mean age as those who received one FD, while those who received two HDs and needed some type of medical support because of COVID-19 has a mean age lower than those who received two FDs, regardless of the existence of comorbidities. Similar findings were obtained when we analyzed the data from discharged patients hospitalized in clinical beds (n = 8530; 28.95% of the total; Figure 3b). However, considering the few cases of discharged patients admitted to the ICU (n = 13; 0.04%) and the occurrence of only three deaths among the study participants, it was not possible to compare these groups to assess the impact of the use of HD on these individuals.

Discussion

Undoubtedly, the massive advancement of vaccination campaigns using different immunizers was responsible for controlling the viral spread and the occurrence of deaths related to COVID-19 worldwide. However, especially considering the Brazilian scenario where the initial slowness in the acquisition of immunizers, mass campaigns, and the frequent dissemination of anti-vax messages meant that thousands of

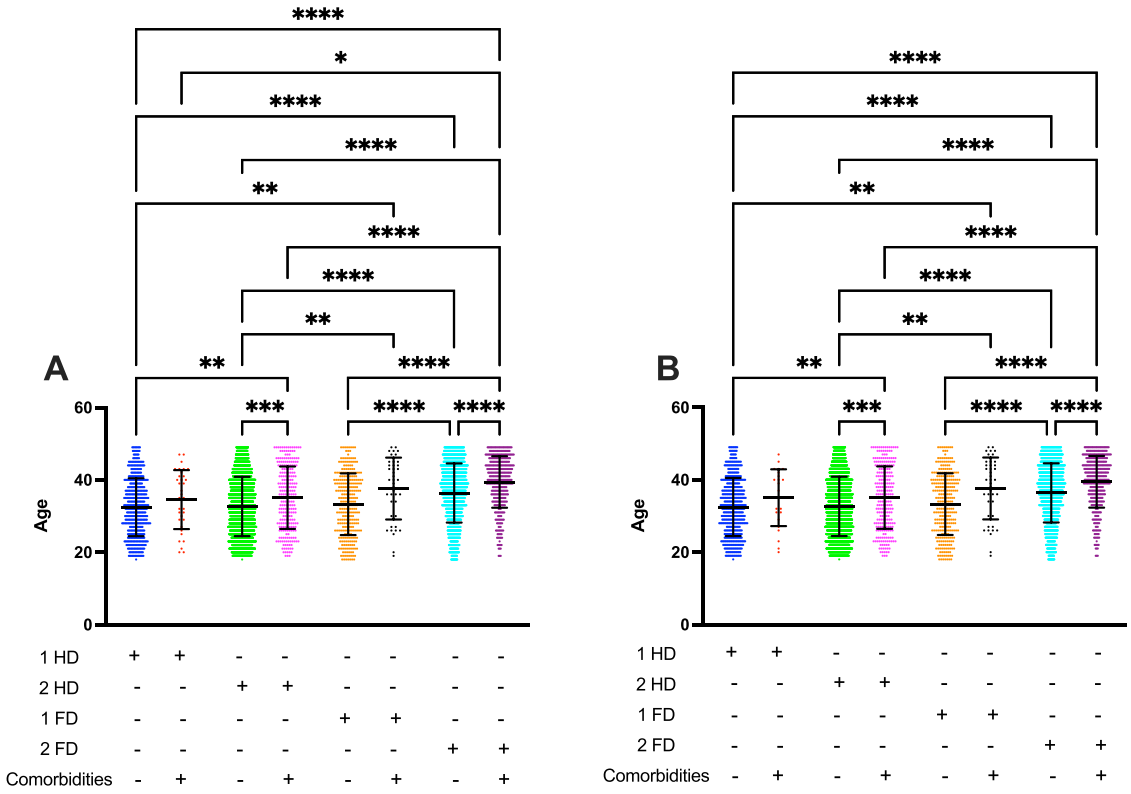

Figure 3. The mean age among patients who received HD or FD is similar, regardless of the existence of comorbidities. Among the individuals vaccinated with HD or FD who required hospitalization (moderate or severe cases) in general (a) or specifically in clinical beds (b) and were discharged, we observe that the mean age was similar between the groups without comorbidities who received one HD compared to one FD and one HD compared to two HD. Considering the individuals with comorbidities, the mean age was similar between the groups one HD without comorbidity compared to one HD with comorbidity, one HD with comorbidity when compared to two HD with comorbidity, and one HD comorbidity when compared to one FD with comorbidity. Comparisons between columns were considered statistically significant when P <0.05 (*P <0.05; **P <0.005; ***P <0.001; ****P <0.0001).
FD, full dose; HD, half dose.

patients were infected and died even when the rest of the world already had access to safe and effective ways to control the disease. As a result, several fronts to combat COVID-19 were established, from strategies to contain the flow of people in the busiest places (lockdown), to hospital actions to reduce the number of deaths from the most severe cases. As a result, the first successful vaccines, an essential phase for disease control, were approved for general use in early 2021, starting with vaccinating health professionals and vulnerable groups and establishing priority groups for access to immunizations because of the high vaccine demand worldwide.

In this sense, using a HD of the ChAdOx1 nCoV-19 (AZD1222) vaccine was an important strategy to accelerate the population's immunization process. We previously showed 44.4 new cases per 1000 person-year for the HD, close to the incidence in the FD group of 49.8 cases per 1000 person-year in short-term follow-up [20]. Recently, Fadlyana and colleagues indicated that administering HDs of ChAdOx1-S as a booster was safe and capable of inducing immunity after priming with CoronaVac in a controlled trial in Indonesia [23]. Thus, our results obtained along the Viana Project Study corroborates these findings and add new evidence on the long-term effectiveness of primary vaccination protocol using the HD of ChAdOx1 nCoV-19 (AZD1222) for protecting moderate or severe COVID-19.

The option to evaluate the effectiveness of vaccination in adults aged 18 to 49 years who are not part of the priority group considered the increase in the proportion of cases of COVID-19 in young adults and who, at that moment, did not have enough two doses to complete the primary vaccination schedule in such a large age group. In this sense, despite the occurrence of comorbidities being part of the exclusion criteria in the Viana Project Study, during the database crossing, we identified participants (n = 741; 2.51% of total) with other comorbidities than those included in the priority groups of the Ministry of Health (Table 1). Interestingly, the period between the administration of the last HD or FD and the COVID-19 diagnosis was similar between the groups, regardless of the type of comorbidity (Figure S1).

Throughout the study, we analyzed data from 20,723 patients who received at least one HD and 8746 patients who received at least one FD. This database is slightly different from the one presented in our previous publication because we included those patients who received the half or FD in this period and removed those who did not meet the inclusion criteria [20]. The complete database used for this study is available on Zenodo.

Considering all participant data, some individuals were infected during the pandemic and developed moderate or severe cases. From all participants who received at least one HD, 6014 developed moderate or severe cases, and only one death was observed. In contrast, among the participants who received at least one FD, 2529 developed moderate or severe cases, resulting in two deaths in this period. In addition, 20,926 participants (71.01%) did not report infection or were asymptomatic during the study period, meeting the primary objective of large-scale immunization – to prevent the development of conditions requiring hospitalization or COVID-19-related deaths. As the study's main limitations, it was impossible to assess the influence of immunization protocols on the length of hospital stay or the severity associated with the condition because these data were unavailable in the consulted databases. Additionally, the absence of data from infected patients who developed moderate or severe cases before the immunization period would bring new information about the impact of HD in reducing hospitalizations and deaths.

Considering the results obtained during the propensity-score matching analysis, we observed that patients immunized with the HD have the same risk of developing moderate and severe COVID-19 cases when compared to those vaccinated with the FD and the relative risk of being infected and developing moderate or severe conditions after the administration of at least one HD or one FD was similar 150 or 500 days after the administration of the respective immunizers, suggesting an equivalent performance to avoid hospitalizations and deaths after COVID-19 infection. Furthermore, the ratio of cases/participants indicated that the administration of only one HD predisposes the individual to develop moderate or severe cases in a more significant proportion than those who received only one FD. Interestingly, this proportion increases compared to patients who received two HD or two FD, respectively.

The mean age was similar between one HD and one FD without comorbidities groups. However, it was significantly lower in the two HD groups without comorbidities than in the two FD groups without comorbidities. Despite being significant, the clinical application of this finding is uncertain. It may be related to several variables, including lifestyle habits and many new interactions among younger individuals, but which do not influence the ability to protect against moderate or severe cases induced after HD administration.

Conclusion

In summary, the data presented in this paper indicate that administering the HD ChAdOx1 nCoV-19 vaccine was equivalent to using FDs to reduce moderate and severe COVID-19 cases in long-term follow-up. Two HDs can be used safely as a cost-effective alternative to the primary protocol with two FDs of the ChAdOx1 nCoV-19 vaccine. Additionally, we encourage the development of new studies to support the development of new strategies to combat COVID-19, especially in developing countries, maintaining the best health surveillance actions because the emergence of new strains of SARS-COV-2 are not discarded and may generate a re-emergence of vaccination worldwide.

Declarations of competing interest

The authors have no competing interests to declare.

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Ethical approval

The studies involving human participants were reviewed and approved by the National Research Ethics Committee (CONEP, Protocol No. 4.752.775/2021); and the Ethics Review Committee of the Pan American Health Organization (PAHOERC, Protocol No. 0367.02/2021). In addition, the patients/ participants provided their written informed consent to participate in this study.

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Author contributions

LJGL, NFMJ, GSJ, AHFM, MPGG, LFPN, CMASD, ATC, OAMF, VV, and RAMV conceived and designed the study. NFMJ, AHFM, ATC, OAMF, VV, and RAMV were responsible for the founding acquisition. LJGL, NFMJ, GSJ, GJPCS, JPQS, MR, MMS, PAF, and RDS conducted the data acquisition, analysis, and interpretation of the results. LJGL, GSJ, AHFM, GJPCS, JPQS, MR, MMS, PAF, and RDS wrote the manuscript. NFMJ, MPGG, LFPN, CMASD, ATC, OAMF, VV, and RAMV contributed to data analysis and the critical revision of the manuscript. All authors reviewed and approved the final version of the manuscript and its submission.

Data availability statement

The data presented in this study are openly available in Zenodo at https://doi.org/10.5281/zenodo.7963928.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2023.09.007.

References

[1] Mathieu E, Ritchie H, Rodés-Guirao L, Appel C, Giattino C, Hasell J, et al. Coronavirus pandemic (COVID-19). OurWorldInDataOrg, https://ourworldindata.org/explorers/coronavirus-data-explorer?zoomToSelection=true&time=2020-03-01..latest&facet=none&pickerSort=desc&pickerMetric=total_deaths&Metric=Confirmed+deaths&Interval=Cumulative&Relative+to+Population=false&Color+by+test+positivity=false; 2020 [accessed 31 May 2023].

[2] Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021;**384**:1412–23. doi:10.1056/NEJMoa2101765.

[3] Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. *Lancet Infect Dis* 2022;**22**:1293–302. doi:10.1016/S1473-3099(22)00320-6.

[4] Huang YZ, Kuan CC. Vaccination to reduce severe COVID-19 and mortality in COVID-19 patients: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci* 2022;**26**:1770–6. doi:10.26355/eurrev_202203_28248.

[5] Sales-Moioli AIL, Galvão-Lima LJ, Pinto TKB, Cardoso PH, Silva RD, Fernandes F, et al. Effectiveness of COVID-19 vaccination on reduction of hospitalizations and deaths in elderly patients in Rio Grande do Norte, Brazil. *Int J Environ Res Public Health* 2022;**19**:13902. doi:10.3390/ijerph192113902.

[6] Fitzpatrick MC, Moghadas SM, Pandey A, Galvani AP. Two years of U.S. COVID-19 vaccines have prevented millions of hospitalizations and deaths. CommonwealthfundOrg, https://www.commonwealthfund.org/blog/2022/two-years-covid-vaccines-prevented-millions-deaths-hospitalizations; 2022 [accessed 07 February 2023].

[7] Vilches TN, Moghadas SM, Sah P, Fitzpatrick MC, Shoukat A, Pandey A, et al. Estimating COVID-19 infections, hospitalizations, and deaths following the US vaccination campaigns during the pandemic. *JAMA Netw Open* 2022;**5**:e2142725. doi:10.1001/jamanetworkopen.2021.42725.

[8] Ministério da Saúde, Brasil PC. Secretaria de Vigilância à Saúde (SVS): Guia de Vigilância Epidemiológica, https://covid.saude.gov.br; 2023 [accessed 08 February 2023].

[9] IBGE, Demográfico C, Santo E, IBGE, https://cidades.ibge.gov.br/brasil/es/panorama; 2021 [accessed 08 February 2023].

[10] Ferreira LS, Darcie Marquitti FM, Paixão da Silva RL, Borges ME, Ferreira da Costa Gomes M, Cruz OG, et al. Estimating the impact of implementation and timing of the COVID-19 vaccination programme in Brazil: a counterfactual analysis. *Lancet Reg Health Am* 2023;**17**:100397. doi:10.1016/j.lana.2022.100397.

[11] Spencer AJ, McKay PF, Belij-Rammerstorfer S, Ulaszewska M, Bissett CD, Hu K, et al. Heterologous vaccination regimens with self-amplifying RNA and adenoviral COVID vaccines induce robust immune responses in mice. *Nat Commun* 2021;**12**:2893. doi:10.1038/s41467-021-23173-1.

[12] Shaw RH, Stuart A, Greenland M, Liu X, Nguyen Van-Tam JS, Snape MD, et al. Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data. *Lancet* 2021;**397**:2043–6. doi:10.1016/S0140-6736(21)01115-6.

[13] Schmidt T, Klemis V, Schub D, Mihm J, Hielscher F, Marx S, et al. Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination. *Nat Med* 2021;**27**:1530–5. doi:10.1038/s41591-021-01464-w.

[14] Tregoning JS, Flight KE, Higham SL, Wang Z, Pierce BF. Progress of the COVID-19 vaccine effort: viruses, vaccines and variants versus efficacy, effectiveness and escape. *Nat Rev Immunol* 2021;**21**:626–36. doi:10.1038/s41577-021-00592-1.

[15] Cerqueira-Silva T, Katikireddi SV, de Araujo Oliveira V, Flores-Ortiz R, Júnior JB, Paixão ES, et al. Vaccine effectiveness of heterologous CoronaVac plus BNT162b2 in Brazil. *Nat Med* 2022;**28**:838–43. doi:10.1038/s41591-022-01701-w.

[16] Jara A, Undurraga EA, Zubizarreta JR, González C, Pizarro A, Acevedo J, et al. Effectiveness of homologous and heterologous booster doses for an inactivated SARS-CoV-2 vaccine: a large-scale prospective cohort study. *Lancet Glob Health* 2022;**10**:e798–806. doi:10.1016/S2214-109X(22)00112-7.

[17] Duarte-Salles T, Prieto-Alhambra D. Heterologous vaccine regimens against COVID-19. *Lancet* 2021;**398**:94–5. doi:10.1016/S0140-6736(21)01442-2.

[18] Atmar RL, Lyke KE, Deming ME, Jackson LA, Branche AR, El Sahly HM, et al. Homologous and heterologous Covid-19 booster vaccinations. *N Engl J Med* 2022;**386**:1046–57. doi:10.1056/NEJMoa2116414.

[19] Ministério da Saúde *Vacinômetro COVID-19 - Brasil*. Rede nacional de dados de Saúde - RNDS; 2023 *https://infoms.saude.gov.br/extensions/DEMAS_C19_Vacina_v2/DEMAS_C19_Vacina_v2.html* [accessed 16 February 2023].

[20] Valim V, Martins-Filho OA, Gouvea MDPG, Camacho LAB, Villela DAM, de Lima SMB, et al. Effectiveness, safety, and immunogenicity of half dose ChAdOx1 nCoV-19 COVID-19 Vaccine: Viana project. *Front Immunol* 2022;**13**:966416. doi:10.3389/fimmu.2022.966416.

[21] LAIS/UFRN. Plataforma vacina e confia. Secretaria de Saúde do Espírito Santo (SESA/ES), https://vacinaeconfia.es.gov.br/cidadao/; 2021 [accessed 19 February 2023].

[22] Secretaria de saúde do Espírito Santo (SESA/MS). Plataforma ESUS - vigilância em Saúde (ESUS-VS). Secretaria de saúde do Espírito Santo (SESA/MS), https://esusvs.saude.es.gov.br/auth/entrar; 2019 [accessed 19 February 2023].

[23] Fadlyana E, Setiabudi D, Kartasasmita CB, Putri ND, Rezeki Hadinegoro S, Mulholland K, et al. Immunogenicity and safety in healthy adults of full dose versus half doses of COVID-19 vaccine (ChAdOx1-S or BNT162b2) or full-dose CoronaVac administered as a booster dose after priming with CoronaVac: a randomised, observer-masked, controlled trial in Indonesia. *Lancet Infect Dis* 2023;**23**:545–55. doi:10.1016/S1473-3099(22)00800-3.