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Predictors of severity of SARS-CoV-2 infections in Brazil: Post hoc analyses of a randomised controlled trial

Kerry Conlin [a,1], Daniel Jenkin [b,1], Philip de Whalley [a,*,1], Lily Yin Weckx [c], Pedro M. Folegatti [b], Sagida Bibi [a], Teresa Lambe [a,d], Parvinder K. Aley [a], Andrew J. Pollard [a,2], Merryn Voysey [a,2], Sue Ann Costa Clemens [a,e,2], COV003 Study Group [3]

[a] Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, UK
[b] Jenner Institute, Nuffield Department of Medicine, University of Oxford, Oxford, UK
[c] Department of Pediatrics, Universidade Federal de São Paulo, São Paulo, Brazil
[d] Chinese Academy of Medical Sciences Oxford Institute, University of Oxford, Oxford, UK
[e] Institute of Global Health, University of Siena, Siena, Brazil

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ABSTRACT

Objectives: To identify demographic, clinical and immunological factors associated with adverse COVID-19 outcomes.
Methods: A large randomised controlled trial of ChAdOx1 nCoV-19 was undertaken in Brazil. Participants were randomised 1:1 either to receive ChAdOx1 nCov-19 or to a control group. COVID-19 infections were confirmed by nucleic acid amplification test (NAAT) and classified using the WHO clinical progression scale. Anti-spike antibody responses and serum neutralising activity were measured 28 days after second vaccination in some participants. Exploratory analyses were conducted into factors associated with COVID-19 infection severity and hospitalisation, using logistic regression models adjusted for demographic and clinical factors.
Results: 10,416 participants were enrolled; 1790 had NAAT-positive COVID-19 infection; 63 cases required hospitalisation. More severe infection was associated with greater body-mass index (BMI) (odds ratio [OR] = 1.06 [95 %CI: 1.01–1.10], $p = 0.01$) and diabetes (OR = 3.67 [1.59–8.07], $p = 0.003$). Hospitalisation risk increased with greater age (OR = 1.06 [1.03–1.08], $p < 0.001$) and BMI (OR = 1.10 [1.05–1.16], $p < 0.001$). More severe infection and hospitalisation risks increased >180 days after last vaccination. In the fully vaccinated subgroup ($n = 841$), only greater age predicted hospitalisation (OR = 1.07 [1.03–1.12], $p < 0.001$). Serological responses to two vaccine doses diminished with age.
Conclusions: Unvaccinated individuals with high BMI and diabetes risked more severe COVID-19 outcomes. Vaccination mitigated this risk.
Clinical Trial Registration Number: NCT04536051

1. Introduction

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), spread quickly, resulting in substantial morbidity and mortality worldwide [1]. Overall global excess deaths due to the COVID-19 pandemic between January 2020 and December 2021 have been estimated at over 18 million [2]. The roll-out of vaccines to protect populations from COVID-19 began at the end of 2020, and several highly effective vaccines are now available [3–5].

The ChAdOx1 nCoV-19 vaccine (AZD1222) was developed at Oxford

* Corresponding author at: Oxford Vaccine Group, CCVTM, Old Road, Headington, Oxford OX3 7LE, UK.
E-mail addresses: kerry.conlin@yale.edu (K. Conlin), daniel.jenkin@ndm.ox.ac.uk (D. Jenkin), philip.dewhalley@paediatrics.ox.ac.uk (P. de Whalley), lily.crie@huhsp.org.br (L.Y. Weckx), pedro.folegatti@ndm.ox.ac.uk (P.M. Folegatti), sagida.bibi@paediatrics.ox.ac.uk (S. Bibi), teresa.lambe@paediatrics.ox.ac.uk (T. Lambe), parvinder.aley@paediatrics.ox.ac.uk (P.K. Aley), andrew.pollard@paediatrics.ox.ac.uk (A.J. Pollard), merryn.voysey@paediatrics.ox.ac.uk (M. Voysey), sue.costaclemens@paediatrics.ox.ac.uk (S.A. Costa Clemens).
[1] Contributed equally to drafting the report.
[2] Joint senior authors.
[3] Members of the COV003 Study group are listed in the Supplement.

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University in collaboration with AstraZeneca and consists of a replication-deficient chimpanzee adenoviral vector ChAdOx1, encoding the SARS-CoV-2 spike protein antigen gene [6]. An initial phase 1 single-blind, randomised controlled trial was conducted in the UK (COV001); this was followed by a phase 2/3 trial in the UK (COV002), a phase 3 trial in Brazil (COV003) and a phase 1/2 trial in South Africa (COV005). Results from these trials have been reported previously [7–11]. They showed the vaccine to have an acceptable safety profile and to be immunogenic across all ages; two doses achieved stronger serological responses than one dose [6–8]. A recent meta-regression analysis, using data from seven publications, showed ChAdOx1 nCoV-19 provided ≥80 % protection against COVID-19 hospitalisation for ~43 weeks post second dose, with some waning [12]. The vaccine's effectiveness is lower in vulnerable populations, such as those with multiple co-morbidities and the immunosuppressed [13].

Observational studies have provided insight into the risk factors for severe COVID-19 infection, prompting an initial vaccine roll-out, and subsequent booster vaccinations, to prioritise older adults and people with certain underlying health conditions [14]. While vaccination continues to provide very high levels of protection against hospitalisation and death from COVID-19, emergence of variants capable of evading vaccine-induced immunity in the upper respiratory tract has resulted in widespread transmission of the virus [15].

In this study, we used prospectively collected clinical and immunological data from a large randomised controlled trial conducted in Brazil between 2020 and 2022 to analyse predictors of breakthrough infection, hospitalisation and poor immune response.

2. Methods

2.1. Study population

Data were analysed from the COV003 study (NCT04536051), a single-blind phase 3 randomised controlled trial conducted across six sites in Brazil. Recruitment targeted those at high risk of viral exposure, including health care workers. Participants were aged 18 years or more, and individuals with stable pre-existing health conditions were eligible. Full eligibility criteria are listed in the study protocol (see Reference 9, supplementary appendix 2, pages 343–441). Participants were enrolled between 23rd June 2020 and 1st December 2020 and followed up until 22nd September 2022.

2.2. Study design

Participants were randomised 1:1 either to receive ChAdOx1 nCoV-19 or to a control group (receiving a meningococcal vaccine (Men-ACWY) first dose, then saline second dose). Participants in the ChAdOx1 nCoV-19 group received up to 3 doses of the vaccine at a dose of 3·5–6·5 $\times 10^{10}$ viral particles. The first two doses were given 4–12 weeks apart, and the third dose given up to 13 months after the second. Participants in the control group initially were offered the ChAdOx1 nCoV-19 vaccine upon unblinding, which occurred following an interim analysis showing efficacy of the vaccine, on the recommendation of the trial Data Safety Monitoring Committee. COVID-19 vaccines were available in the community, and some participants received them outside the trial; these doses were recorded in the study database.

Episodes of symptomatic COVID-19 in the study were confirmed by nucleic acid amplification test (NAAT). Throughout the trial follow-up period, participants were asked to report symptoms of new fever (≥37.8 °C), cough, shortness of breath or anosmia/ageusia, which triggered a clinical assessment and NAAT. If the initial NAAT was negative, it was repeated 3–5 days after symptom onset. Data from participants with NAAT-positive swabs (including those tested outside the trial) were assessed by an independent endpoint review committee. Two blinded assessors independently reviewed available case report form and diary data, determined the start date and relevant symptoms for each event, and graded its severity according to the WHO Clinical Progression Scale (or classified it as asymptomatic). In the WHO Clinical Progression Scale, scores of 1–3 represent ambulatory mild disease, 4–5 represent hospitalised moderate disease, 6–9 represent hospitalised severe disease, and 10 represents death [16].

For some participants (not randomly selected), blood samples obtained at baseline and 28 days after the second dose of vaccine were analysed for anti-spike antibody responses and serum neutralising activity.

2.3. Statistical analysis

Post hoc exploratory analyses were undertaken to describe predictors of COVID-19 infection severity. The software used was R-4.0.4. Analyses were based on treatment received (vaccine doses given both within and outside the study) rather than randomised treatment allocation. WHO scores were categorised into four groups (1, 2–3, 4–5, and 6+), as there were limited case numbers at higher severities. An ordinal logistic regression model was applied with the WHO score categories as the response variable to obtain odds ratios for factors associated with more severe COVID-19 infection. This model was run on all participants with NAAT-positive infection, regardless of vaccination status. The analysis was adjusted for number of vaccine doses received before COVID-19 infection, trial site, sex, age, ethnicity, healthcare worker status, smoking status, BMI, and history of cardiovascular disease, respiratory disease, diabetes and renal disease. Supplementary analyses adjusted for time interval between COVID-19 infection and most recent vaccine dose before infection (regardless of whether this was received as part of the study); this interval was categorised as no vaccination pre-infection, or vaccination <90 days, 90 to <180 days or ≥180 days pre-infection.

To assess the predictors of hospitalisation with a COVID-19 infection as a binary outcome, the severity of each case was categorised as hospitalised (WHO score ≥4) or non-hospitalised (WHO score < 4) and a logistic regression model applied to obtain the odds ratios of being hospitalised given the selected predictors. This model was run in a subgroup containing those with NAAT-positive COVID-19 infection, regardless of vaccination status. This analysis was adjusted for the same factors as noted above for the severity predictor model.

Analyses were undertaken to investigate whether levels of vaccine-induced neutralising antibody and anti-spike Immunoglobulin G (IgG) differed between those who were hospitalised, those with mild COVID-19, and those who were uninfected. Blood was drawn for antibody analysis 28 days after the second vaccine dose. Only those who had received two doses of vaccine in the study, had not received any external vaccine doses before COVID-19 infection, and had not had a COVID-19 infection before the 28 day post-second dose timepoint were included.

Logistic regression was applied to predict non-response of neutralising antibody to vaccination, defined as antibody measured at the lower limit of detection of the assay with a titre value <40. The Monogram Biosciences neutralisation antibody assay was used, which measures the half maximal inhibitory concentration (IC50), or 50 % inhibitory dose of antibody needed to block 50 % of pseudovirus activity. A Kruskal-Wallis test was performed to assess differences in neutralising antibody IC50 at 28 days after the second ChAdOx1 nCoV-19 dose across COVID-19 infection severity groups – categorised as hospitalised, mild, or no COVID-19.

Logistic regression was applied to predict low SARS-CoV-2 anti-spike IgG response. This was defined as those with log-transformed IgG values in the lowest 10th percentile (1st decile) of available measurements. The PPD ELISA SARS-CoV-2 (spike) IgG assay was used. A Kruskal-Wallis test was performed to assess differences in levels of anti-spike IgG at 28 days after the second ChAdOx1 nCoV-19 dose across COVID-19 severity groups – categorised as hospitalised, mild, or no COVID-19.

The neutralising antibody and anti-spike IgG models were adjusted for site, sex, age, ethnicity, healthcare worker status, smoking status,

BMI, and history of cardiovascular disease, diabetes, respiratory disease, and renal disease.

All models were run only on participants with complete data in the relevant variables. Missing data were minimal, with fewer than 10 participants missing data for any of the relevant variables.

3. Results

10,416 participants were enrolled in the study between 23 June 2020 and 1 December 2020 (Table 1). 5206 were randomised to the ChAdOx1 nCoV-19 group and 5210 to the control group. In the ChAdOx1 nCoV-19 group, the first two doses were given 4 to 12 weeks apart (median 35 days, IQR 32–47). Overall, 1790 individuals had a confirmed COVID-19 infection, and infection severity analyses were run in this population; those with complete data in the relevant predictive variables were used in the models ($n = 1788$). Of the participants who contracted a COVID-19 infection, 842/1790 (47.0 %) individuals were considered fully vaccinated, having received at least two doses of COVID-19 vaccine (study or external) at least 14 days before COVID-19 infection.

From the full trial population, 63/10,416 (0.6 %) participants were hospitalised with a COVID-19 infection; of these, 37/63 (58.7 %) had received no vaccine dose before infection, 4/63 (6.3 %) had received one dose, and 22/63 (34.9 %) had received at least 2 doses. 1727 participants had a mild, non-hospitalised infection; of these, 661/1727 (38.3 %) had received no vaccine dose before infection, 246/1727 (14.2 %) had received one dose, and 820/1727 (47.5 %) had received at least 2 doses. Study or external COVID-19 vaccine doses received at least 14 days before COVID-19 infection were included in the dose tallies. Details of vaccinations received externally to the study before cases of confirmed COVID-19 infection are shown in Supplementary Table 1. 8626 participants did not record a qualifying COVID-19 infection. The overall trial population ($n = 10,416$) was 54 % female and 69 % white, with a median age of 38 years (IQR: 30–50) and a median BMI of 26 kg/m^2 (IQR: 23.3–29.4); 4.3 % had a history of diabetes. The hospitalised group ($n = 63$) was 40 % female and 76 % white, with a median age of 50 years and a median BMI of 29.4 kg/m^2; 19 % had a history of diabetes. All hospitalised cases had low oxygen saturations and/or chest X-ray or CT evidence of consolidation.

Compared with those with a mild infection, those hospitalised with COVID-19 were more likely to be male ($p = 0.016$), older ($p \leq 0.001$), have higher BMI ($p \leq 0.001$), cardiovascular disease ($p \leq 0.001$), and diabetes ($p \leq 0.001$), based on univariate analyses. Hospitalised cases were also less likely to be healthcare workers ($p = 0.034$), and less likely to be vaccinated ($p = 0.004$).

Compared with those with no COVID-19 infection, those hospitalised with COVID-19 were more likely to be male ($p = 0.02$), older ($p \leq 0.001$), have a higher BMI ($p \leq 0.001$), cardiovascular disease ($p \leq 0.001$), and diabetes ($p \leq 0.001$), based on univariate analyses.

3.1. Predictors of COVID-19 infection severity

Receiving one or more doses of any COVID-19 vaccine decreased the odds of more severe COVID-19 infection compared with unvaccinated participants (one dose OR: 0.34, 95 % CI [0.18, 0.66]; two or more doses OR: 0.51 [0.32, 0.79]) (Table 2). For each one kg/m^2 increase in BMI, odds of severe infection increased (OR = 1.06 [1.01, 1.10]). A history of diabetes increased the odds of more severe infection relative to non-diabetic participants (OR = 3.46 [1.50, 7.61]).

Participants who had received only one COVID-19 vaccine dose trended towards lower odds of a more-severe infection than those who had received two or more doses. This is likely to be because there was

Table 1
Characteristics of participants.

Characteristic	Enrolled, N = 10,416[1]	COVID with WHO Score, N = 1,790[1]	Hospitalised with COVID, N = 63[1]	Hosp. vs. Mild		Hosp. vs. No COVID	
				Mild COVID, N = 1,727[1]	p-value[2]	No COVID, N = 8,567[1]	p-value[2]
WHO Score							
1		41 (2.3 %)	0 (0 %)	41 (2.4 %)			
2		1165 (65 %)	0 (0 %)	1165 (67 %)			
3		521 (29 %)	0 (0 %)	521 (30 %)			
4		16 (0.9 %)	16 (25 %)	0 (0 %)			
5		29 (1.6 %)	29 (46 %)	0 (0 %)			
6		10 (0.6 %)	10 (16 %)	0 (0 %)			
7		1 (<0.1 %)	1 (1.6 %)	0 (0 %)			
8		2 (0.1 %)	2 (3.2 %)	0 (0 %)			
9		1 (<0.1 %)	1 (1.6 %)	0 (0 %)			
10		4 (0.2 %)	4 (6.3 %)	0 (0 %)			
Doses pre COVID					**0.004**		
0 Doses		698 (39 %)	37 (59 %)	661 (38 %)			
1 Dose		250 (14 %)	4 (6.3 %)	246 (14 %)			
2+ Doses		842 (47 %)	22 (35 %)	820 (47 %)			
Sex					**0.016**		**0.020**
Male	4753 (46 %)	814 (45 %)	38 (60 %)	776 (45 %)		3914 (46 %)	
Female	5663 (54 %)	976 (55 %)	25 (40 %)	951 (55 %)		4653 (54 %)	
Age (Years)	38 (30, 50)	37 (29, 46)	50 (40, 59)	36 (29, 46)	**<0.001**	39 (30, 51)	**<0.001**
Ethnic Origin					0.7		0.8
White	7198 (69 %)	1238 (69 %)	48 (76 %)	1190 (69 %)		5914 (69 %)	
Black	927 (8.9 %)	154 (8.6 %)	6 (9.5 %)	148 (8.6 %)		767 (9.0 %)	
Asian	240 (2.3 %)	25 (1.4 %)	1 (1.6 %)	24 (1.4 %)		215 (2.5 %)	
Mixed	866 (8.3 %)	153 (8.6 %)	4 (6.3 %)	149 (8.6 %)		711 (8.3 %)	
Other	1158 (11 %)	211 (12 %)	4 (6.3 %)	207 (12 %)		942 (11 %)	
Prefer Not to Give	26 (0.2 %)	8 (0.4 %)	0 (0 %)	8 (0.5 %)		18 (0.2 %)	
Healthcare Worker	6723 (65 %)	1214 (68 %)	35 (56 %)	1179 (68 %)	**0.034**	5465 (64 %)	0.2
BMI (kg/m^2)	26.0 (23.3, 29.4)	26.5 (23.6, 30.0)	29.4 (26.8, 33.4)	26.4 (23.5, 29.8)	**<0.001**	25.9 (23.2, 29.3)	**<0.001**
Cardiovascular Disease	1722 (17 %)	260 (15 %)	25 (40 %)	235 (14 %)	**<0.001**	1452 (17 %)	**<0.001**
Diabetes	450 (4.3 %)	61 (3.4 %)	12 (19 %)	49 (2.8 %)	**<0.001**	388 (4.5 %)	**<0.001**

[1] n (%); Median (IQR).
[2] Fisher's exact test; Pearson's Chi-squared test; Wilcoxon rank sum test.

Table 2
Ordinal logistic regression of WHO clinical progression scores (categorised as 1, 2–3, 4–5, 6+) showing factors associated with more severe COVID-19 infections in participants with NAAT-positive COVID-19 infection. Full model and sensitivity analysis.

Characteristic	Full Model				Sensitivity Analysis			
	N	OR[1]	95 % CI[1]	*p*-value	N	OR[1]	95 % CI[1]	p-value
Doses of vaccine received pre COVID-19 infection*								
0 Doses	698	–	–		698	–	–	
1 Dose	249	0.34	0.18, 0.66	**0.002**	235	0.35	0.17, 0.69	**0.003**
2+ Doses	841	0.51	0.32, 0.79	**0.003**	282	0.35	0.18, 0.65	**0.001**
Sex								
Male	814	–	–		567	–	–	
Female	974	1.03	0.67, 1.57	0.9	648	1.15	0.69, 1.91	0.6
Age (Years)	1788	1.02	1.00, 1.04	0.063	1215	1.01	0.99, 1.04	0.3
Ethnicity								
White	1237	–	–		851	–	–	
Black	154	1.03	0.50, 2.10	>0.9	97	1.17	0.49, 2.66	0.7
Asian	25	1.14	0.21, 4.82	0.9	17	1.88	0.23, 9.52	0.5
Mixed	153	0.48	0.23, 1.01	0.052	108	0.56	0.23, 1.33	0.2
Other	211	0.54	0.27, 1.10	0.091	134	0.38	0.16, 0.88	**0.024**
Prefer not to give	8	0.70	0.05, 9.86	0.8	8	0.72	0.05, 11.1	0.8
Healthcare worker								
0	575	–	–		404	–	–	
1	1213	0.74	0.45, 1.22	0.2	811	0.67	0.37, 1.20	0.2
Current smoker								
Non-smoker	1704	–	–		1152	–	–	
Smoker	84	0.59	0.23, 1.54	0.3	63	0.76	0.26, 2.26	0.6
BMI (kg/m^2)	1788	1.06	1.01, 1.10	**0.010**	1215	1.08	1.03, 1.13	**0.002**
Cardiovascular disease								
0	1528	–	–		1026	–	–	
1	260	1.73	0.94, 3.17	0.077	189	1.47	0.70, 3.06	0.3
Diabetes								
0	1727	–	–		1173	–	–	
1	61	3.46	1.50, 7.61	**0.003**	42	3.43	1.19, 9.17	**0.017**
Respiratory disease								
0	1617	–	–		1094	–	–	
1	171	0.78	0.39, 1.55	0.5	121	0.90	0.40, 1.96	0.8
Renal disease								
0	1739	–	–		1180	–	–	
1	49	0.69	0.21, 2.28	0.6	35	0.43	0.12, 1.77	0.2

Full model includes all participants with NAAT-positive COVID-19 infection (n = 1788). **Sensitivity analysis** includes all unvaccinated participants with NAAT-positive COVID-19 infection plus vaccinated participants who developed NAAT-positive infection <102 days after most recent vaccination (n = 1215). Ordinal logistic regression model applied to WHO clinical progression scores (categorised as 1, 2–3, 4–5, 6+), adjusted for trial site.

[1] OR = Odds Ratio, CI = Confidence Interval.

* Doses of vaccine received prior to infection may have been administered as part of the study or in the community. Data were censored at the time of infection so vaccinations occurring after infection do not contribute to analyses.

only a short period after the first dose in which an infection could occur before a second dose was received. Those infected after only one vaccine dose were infected a median of 44 days after vaccination; this interval was >180 days in only 2.4 %. Those infected after two or more vaccine doses were infected a median of 145 days after their most recent dose; the interval was >180 days in 37 % (Supplementary Table 2).

For the participants whose COVID-19 infection occurred after only one dose of vaccine, the 95th percentile for time between COVID-19 infection and vaccination was calculated to be 101.8 days. This interval was used as a cut-off for a sensitivity analysis to determine the impact of timing of vaccination on severity of infection (Table 2). Participants were only included if their infection occurred less than 102 days after their most recent vaccine dose. This excluded 14 participants infected after only one vaccination and 559 participants infected after two or more vaccinations, leaving a total of 1215 included in the sensitivity analysis. In this analysis, the characteristics that significantly predicted more severe infection were largely the same as in the full population analysis. For each one kg/m^2 increase in BMI, odds of severe infection increased (OR = 1.08 [1.03, 1.13]). A history of diabetes increased the odds of more severe infection relative to participants without diabetes (OR = 3.43 [1.19, 9.17]). The sensitivity analysis suggested that time since most recent vaccine dose might be a more important predictor of severity than number of doses before infection, as the odds ratio for more severe infection was the same whether one or more than one dose of vaccine had been received (1 dose OR = 0.35 [0.17, 0.69]; 2 or more doses OR = 0.35 [0.18, 0.65]). The analysis was repeated with "time between COVID-19 and most recent dose before infection" as the predictive variable instead of "number of doses pre COVID-19" (Supplementary Table 3). In this analysis, a COVID-19 vaccine dose received <180 days before infection decreased the odds of more severe COVID-19 infection compared with unvaccinated participants (<90 days OR = 0.33, 95 % CI [0.19, 0.57]; 90 to <180 days OR = 0.48 [0.26, 0.88]). Each additional one kg/m^2 BMI increased odds of severe infection (OR = 1.06, 95 % CI [1.01, 1.10]). Compared with participants without diabetes, those with diabetes had increased odds of more severe infection (OR = 3.67 [1.59, 8.07]).

Extending this model by including a continuous variable representing calendar month of infection (Supplementary Table 4), showed that infections occurring later in the study were more likely to be severe (OR = 1.12, 95 % CI [1.03, 1.21]). In this model, vaccinated participants had lower odds of more severe COVID-19 infection than unvaccinated participants; infection was less likely to be severe with shorter intervals between vaccination and infection (<90 days OR = 0.24 [0.13, 0.44]; 90 to <180 days OR = 0.28 [0.14, 0.58]; 180+ days OR = 0.31 [0.13, 0.73]). For each one kg/m^2 increase in BMI, odds of severe infection increased (OR = 1.06, [1.01, 1.10]). Diabetic participants had higher odds of more severe infection than participants without diabetes (OR = 3.86 [1.67, 8.48]).

Analysis of the full study population was repeated with hospitalisation as the outcome (Table 3). Vaccinated participants were less likely

Table 3
Predictors of hospitalisation for COVID-19 (WHO score ≥ 4) in participants with NAAT-positive COVID-19 infection. Full model and sensitivity analysis.

Characteristic	Full Model				Sensitivity Analysis			
	N	OR[1]	95 % CI[1]	*p*-value	N	OR[1]	95 % CI[1]	p-value
Doses of vaccine received pre COVID-19 infection*								
0 Doses	698	Ref	–		698	Ref	–	
1 Dose	249	0.23	0.07, 0.62	**0.008**	235	0.22	0.06, 0.61	**0.008**
2+ Doses	841	0.34	0.18, 0.61	**<0.001**	282	0.14	0.04, 0.42	**0.001**
Sex								
Male	814	Ref	–		567	Ref	–	
Female	974	0.78	0.44, 1.38	0.4	648	1.04	0.52, 2.08	>0.9
Age (Years)	1788	1.06	1.03, 1.08	**<0.001**	1215	1.05	1.02, 1.08	**<0.001**
Ethnicity								
White	1237	Ref	–		851	Ref	–	
Black	154	0.75	0.26, 1.87	0.6	97	0.81	0.24, 2.28	0.7
Asian	25	0.71	0.04, 3.94	0.7	17	1.31	0.06, 8.65	0.8
Mixed	153	0.58	0.17, 1.54	0.3	108	0.63	0.14, 1.97	0.5
Other	211	0.37	0.10, 1.03	0.083	134	0.23	0.03, 0.88	0.062
Prefer not to give	8	0.00		>0.9	8	0.00		>0.9
Healthcare worker								
0	575	Ref	–		404	Ref	–	
1	1213	0.98	0.53, 1.83	>0.9	811	0.69	0.32, 1.46	0.3
Current smoker								
Non-smoker	1704	Ref	–		1152	Ref	–	
Smoker	84	0.26	0.01, 1.30	0.2	63	0.34	0.02, 1.83	0.3
BMI (kg/m^2)	1788	1.10	1.05, 1.16	**<0.001**	1215	1.13	1.07, 1.20	**<0.001**
Cardiovascular disease								
0	1528	Ref	–		1026	Ref	–	
1	260	1.33	0.68, 2.57	0.4	189	1.34	0.58, 3.00	0.5
Diabetes								
0	1727	Ref	–		1173	Ref	–	
1	61	2.34	0.96, 5.42	0.052	42	2.43	0.77, 7.26	0.12
Respiratory disease								
0	1617	Ref	–		1094	Ref	–	
1	171	0.70	0.22, 1.75	0.5	121	0.73	0.20, 2.06	0.6
Renal disease								
0	1739	Ref	–		1180	Ref	–	
1	49	0.48	0.03, 2.46	0.5	35	0.00	0.00, 2.58×10^{11}	>0.9

Full model includes all participants with NAAT-positive COVID-19 infection (n = 1788). **Sensitivity analysis** includes all unvaccinated participants with NAAT-positive COVID-19 infection plus vaccinated participants who developed NAAT-positive infection <102 days after most recent vaccination (n = 1215). Logistic regression model of hospitalisation, adjusted for trial site.

[1] OR = Odds Ratio, CI = Confidence Interval.

* Doses of vaccine received prior to infection may have been administered as part of the study or in the community. Data were censored at the time of infection, so vaccinations occurring after infection do not contribute to analyses.

to be hospitalised than the unvaccinated (one dose OR = 0.23, [0.07, 0.62]; two or more doses OR = 0.34 [0.18, 0.61]). Odds of hospitalisation were increased for each one-year increase in age (OR (1 year) = 1.06, [1.03, 1.08], OR (10 years) = 1.73 [1.37, 2.20]) and for each one kg/m^2 increase in BMI (OR = 1.10 [1.05, 1.16]). A sensitivity analysis with hospitalisation as the outcome, including only participants with <102 days between their most recent vaccine dose and COVID-19 infection, gave similar results to the full population analysis.

The hospitalisation outcome model was also run with "time between COVID-19 and most recent dose before infection" as the predictive variable instead of "number of vaccine doses pre COVID-19" (Supplementary Table 5). Vaccination <180 days before COVID-19 infection decreased the odds of hospitalisation compared with unvaccinated participants (<90 days OR = 0.21 [0.08, 0.46]; 90 to <180 days OR = 0.25 [0.10, 0.59]). Odds of hospitalisation were increased by one year increase in age (OR = 1.06 [1.03, 1.08]), one kg/m^2 increase in BMI (OR = 1.11 [1.05, 1.17]) and were greater in diabetics than non-diabetics (OR = 2.52 [1.03, 5.89]). This analysis was also run in a fully vaccinated subgroup of participants who had received at least two doses of a COVID-19 vaccine, with the most recent dose at least 15 days prior to COVID-19 infection. In this vaccinated subgroup, time since most recent dose, BMI, and diabetes no longer significantly predicted hospitalisation; only a one-year increase in age increased the odds of hospitalisation (OR = 1.07 [1.03, 1.12]).

3.2. Predictors of low antibody response to vaccination

617 participants who had relevant results recorded for pseudovirus neutralisation antibody (nAb) were included in the analysis of predictors of having nAb below the lower limit of the assay 28 days after the second dose of ChAdOx1 nCov-19 (Table 4). The full model adjusted for all variables of interest, and the reduced model contained only statistically significant variables. A one-year increase in age increased the odds of neutralising antibody non-response (fully adjusted OR = 1.03 [1.01, 1.05]). Participants with diabetes had increased odds of neutralising antibody non-response relative to non-diabetics (OR = 2.48 [1.07, 5.67]). Fig. 1(A) shows the relationship between COVID-19 infection severity and IC50 of neutralising antibody. Eight of the eleven hospitalised cases showed no neutralising antibody response to two doses of vaccine. A Kruskal-Wallis test across the three groups showed a significant difference between all three groups ($p < 0.001$).

897 participants who had relevant results recorded for anti-spike IgG were included in the analysis of predictors of having IgG in the lowest 10th percentile 28 days after the second dose of ChAdOx1 nCov-19 (Table 5). The full model adjusted for all variables of interest, and the reduced model contained only statistically significant variables. Females were less likely than males to have a low anti-spike IgG response (fully adjusted OR = 0.48 [0.29, 0.77]). A one-year increase in age increased the odds of low IgG response (fully adjusted OR = 1.03 [1.01, 1.05]). Fig. 1(B) shows the relationship between COVID-19 infection severity and anti-spike IgG level. A Kruskal-Wallis test across the three groups

Table 4
Predictors of pseudovirus neutralisation antibody (nAb) being below the lower limit of the assay, 28 days after second dose of COVID-19 vaccine ($n = 617$).

Characteristic	Full Model				Reduced Model			
	N	OR[1]	95 % CI[1]	*p*-value	N	OR[1]	95 % CI[1]	p-value
Sex								
Male	274	Ref	–					
Female	343	1.06	0.68, 1.66	0.8				
Age (Years)	617	1.03	1.01, 1.05	**0.001**	617	1.03	1.01, 1.04	**0.001**
Ethnicity								
White	394	Ref	–					
Black	74	0.82	0.39, 1.64	0.6				
Asian	15	0.28	0.04, 1.18	0.13				
Mixed	50	0.61	0.24, 1.38	0.3				
Other	83	0.85	0.40, 1.72	0.7				
Prefer not to give	1	0.00		>0.9				
Healthcare worker								
0	149	Ref	–					
1	468	0.68	0.39, 1.20	0.2				
Current smoker								
Non-smoker	593	Ref	–					
Smoker	24	1.06	0.33, 2.82	>0.9				
BMI (kg/m^2)	617	0.98	0.94, 1.03	0.4				
Cardiovascular disease								
0	515	Ref	–					
1	102	0.64	0.34, 1.17	0.2				
Diabetes								
0	583	Ref	–		583	–	–	
1	34	2.48	1.07, 5.67	**0.032**	34	1.89	0.86, 4.06	0.10
Respiratory disease								
0	548	Ref	–					
1	69	0.60	0.26, 1.22	0.2				
Renal disease								
0	607	Ref	–					
1	10	2.88	0.67, 11.3	0.13				

Full model adjusts for all variables of interest. **Reduced model** contains only significant variables. Logistic regression model with non-response of neutralising antibody to vaccination as the response variable, adjusted for site.
[1] **OR = Odds Ratio, CI = Confidence Interval.**

showed a significant difference between them ($p = 0.011$).

4. Discussion

Although the COVID-19 pandemic is no longer classified by WHO as a public health emergency of international concern, infection with the SARS-CoV-2 virus continues to increase the risk of hospitalisation among the frail and those with underlying comorbidities. Understanding risk factors for adverse COVID-19 outcomes helps to target public health interventions to those who would gain the most benefit. Here we report exploratory multivariate analyses evaluating associations between adverse COVID-19 outcomes and several health-related and demographic factors, using prospectively collected data from a large phase 3 clinical trial undertaken in Brazil. Multivariate analysis showed that increased COVID-19 infection severity scores, as defined by the WHO ordinal severity scale, were associated with being unvaccinated, having a greater BMI, and a history of diabetes. COVID-19 infection requiring hospitalisation was associated with being unvaccinated, having a greater BMI, and increased age.

Our findings broadly accord with the existing literature. Obesity was identified early in the pandemic as an important risk factor for adverse COVID-19 outcomes [17–19]. One very large study found a linear increase in risk of COVID-19 hospitalisation (adjusted hazard ratio [HR] 1.05 per kg/m^2) and death (HR 1.04 per kg/m^2) with increasing BMI above 23 kg/m^2 [20]. Diabetes mellitus was also rapidly recognised to be a significant risk factor for adverse COVID-19 outcomes [21–23]. We found the increased risks conferred by raised BMI and diabetes mellitus to be similar in magnitude to those reported elsewhere. Cardiovascular, respiratory or renal comorbidities have also been identified as risk factors for severe COVID-19 outcomes [24–26]. However, we did not find significant associations between these comorbidities and adverse COVID-19 outcomes. This could be in part because cardiovascular and respiratory comorbidities are less strongly associated with severe COVID-19 outcomes than is diabetes mellitus. Also, the categories of "cardiovascular disease" and "respiratory disease" are broad, including many different diagnoses, whilst "diabetes" is a more focussed category. It might be harder to demonstrate significant associations in the broader disease categories, particularly in studies (such as ours) not including individuals with severe or uncontrolled comorbidities, who might be expected to be most at risk of adverse outcomes. Our study included relatively few individuals with renal disease.

In our study, one dose of vaccine reduced risk of severe disease. Time since most recent vaccine dose was a better predictor of severity than number of doses before infection. Risk of hospitalisation from COVID-19 was significantly reduced for at least 180 days after receipt of a vaccine dose. Regarding serological response to two doses of vaccine, our multivariate analysis found that the only significant predictors of pseudoneutralising antibody non-response were greater age and diabetes; low anti-spike IgG response was associated with both increased age and male sex. Older adults are well-recognised to be at higher risk of severe disease from common viral respiratory pathogens, such as influenza, whilst producing a weaker immune response to vaccination than young adults [27]. For influenza, this has led to suggestions that immunogenicity of vaccines given to older adults could be increased by giving higher doses of antigen or using adjuvants [28].

Some studies have shown that SARS-CoV-2 vaccination may be less immunogenic in obese and diabetic populations [29,30], but we did not find increased BMI to be independently associated with reduced immune response to vaccination after adjusting for other factors. Furthermore, in the fully vaccinated subset of our study population, increased BMI and diabetes were not significantly associated with being hospitalised for COVID-19 infection. These findings highlight the value of ensuring that people with high BMI and diabetes are vaccinated against COVID-19.

Previous studies have found that males are at higher risk of

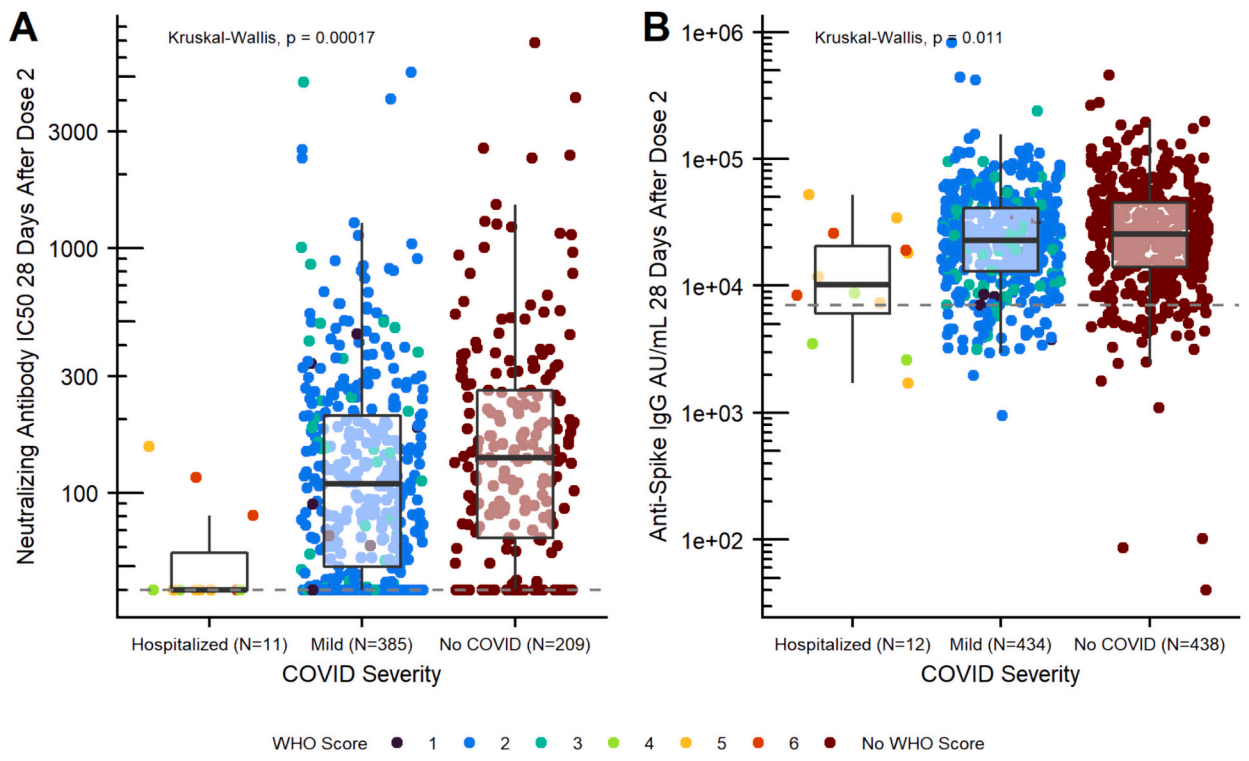

Fig. 1. (A) Pseudovirus neutralising antibody and (B) anti-spike IgG, 28 days after two doses of vaccine, by severity of COVID-19 infections occurring after blood sampling.

The dotted line in plot A represents the lower limit of detection of the pseudovirus neutralising antibody assay (IC50 titre of 40) and in plot B represents the 1st decile of IgG values (Arbitrary Units per millilitre). Hospitalised: WHO score $\geq$ 4. Mild: WHO score $<$ 4. IC50: Half-maximal inhibitory concentration. Boxplots show median, 25th, and 75th percentile with whiskers extending to the last data point within 1.5 x the inter-quartile range.

Table 5

Predictors of anti-spike IgG being in the lowest 10th percentile, 28 days after second dose of COVID-19 vaccine (n = 897).

Characteristic	Full Model				Reduced Model			
	N	OR[1]	95 % CI[1]	p-value	N	OR[1]	95 % CI[1]	p-value
Sex								
Male	394	Ref	–		394	–	–	
Female	503	0.48	0.29, 0.77	**0.003**	503	0.45	0.29, 0.72	**<0.001**
Age (Years)	897	1.03	1.01, 1.05	**0.011**	897	1.04	1.02, 1.06	**<0.001**
Ethnicity								
White	567	Ref	–					
Black	104	0.69	0.29, 1.47	0.4				
Asian	23	1.11	0.24, 3.78	0.9				
Mixed	76	1.17	0.48, 2.56	0.7				
Other	126	1.01	0.47, 2.06	>0.9				
Prefer not to give	1	0.00		>0.9				
Healthcare worker								
0	189	Ref	–					
1	708	1.28	0.69, 2.42	0.4				
Current smoker								
Non-smoker	857	Ref	–					
Smoker	40	1.82	0.69, 4.25	0.2				
BMI (kg/m^2)	897	1.01	0.96, 1.06	0.6				
Cardiovascular disease								
0	767	Ref	–					
1	130	1.49	0.80, 2.71	0.2				
Diabetes								
0	857	Ref	–					
1	40	1.67	0.69, 3.82	0.2				
Respiratory disease								
0	795	Ref	–					
1	102	1.05	0.50, 2.05	0.9				
Renal disease								
0	885	Ref	–					
1	12	1.63	0.23, 6.98	0.6				

Logistic regression model with low SARS-CoV-2 anti-spike IgG response to vaccination as the response variable, adjusted for site.

[1] **OR = Odds Ratio, CI = Confidence Interval.**

developing severe COVID-19 and are more likely to die from the disease than females [31–33]. Male sex is associated with a lower antibody response to several vaccinations [34]. A recent analysis (combining data from the Brazilian COV003 study and the UK COV002 study), reported slightly higher anti-spike IgG titres in females than males, 28 days after a second dose of ChAdOx1 nCoV-19 (adjusted GMR 1.14; 95 % CI 1.04–1.26), but there were no statistically significant differences in other immunological endpoints [35].

In vaccinated individuals, neutralising and binding antibody responses measured 28 days after a second dose of ChAdOx1 nCoV-19 were significantly lower in those with severe COVID-19 infection (Fig. 1). This finding aligns with known antibody correlates of protection for COVID-19 [36]. However, some individuals with a poor antibody response to vaccination subsequently developed only mildly symptomatic COVID-19 infection. This suggests that other factors, probably involving cell-mediated immunity, contribute to protection against severe infection.

The study had several limitations. The study population was relatively young (median age 38, IQR 30–50 years), and individuals with severe or uncontrolled co-morbidities were not enrolled, limiting the generalisability of the findings. The study population included individuals who were randomised to the control group but who later self-reported receiving COVID-19 vaccine doses outside the trial; this provided a less robust dataset than if all vaccines had been administered and recorded under the trial protocol. The analysis was not one of intention to treat based on random allocation. Due to small numbers, it was not possible to distinguish between two and >2 doses of COVID-19 vaccine, of relevance to understanding the effect of additional boosters. COVID-19 variants emerged during the study, but sequencing data were not available to characterise which strain was responsible for every infection. Immunology assays were only performed in a relatively small and non-randomly sampled sub-population of participants, which prevented the inclusion of immunology outcomes in the multivariate models of COVID-19 severity and hospitalisation.

In conclusion, these exploratory analyses of a large, prospectively collected dataset, from a clinical trial during the COVID-19 pandemic, show that in unvaccinated individuals increasing age, high BMI and diabetes are significant predictors of severe COVID-19 outcomes. In fully vaccinated individuals, only increased age was found to be a significant predictor of COVID-19 severity; serological response to vaccination was diminished in older adults. Vaccination was, therefore, particularly beneficial to those with high BMI and diabetes.

Well-conducted vaccine efficacy trials can provide valuable data to identify subgroups of the population who are most at risk of severe outcomes from the disease and to determine whether vaccination benefits these subgroups. However, this can only be achieved if individuals who are likely to be in high-risk categories (such as the very young, the very old, people with co-existing morbidities or pregnant women) are included in the trials. Knowing which subgroups are most at risk, and which are most likely to benefit from vaccination, is most important in the early stages of roll-out of a pandemic vaccine, when supplies and distribution infrastructure are limited. Therefore, in a future pandemic, it would be advantageous to include individuals who are potentially at highest risk from disease in the earliest efficacy trials of candidate vaccines.

Author contributions

AJP conceived the trial and is the chief investigator. AJP, PMF, DJ, MV, and TL contributed to the protocol and design of the study. SACC, LYW, PKA, TL and SB contributed to the implementation of the study and data collection. MV and KC did the statistical analysis. KC, DJ, PdW, MV, AP and SACC prepared the report. All authors critically reviewed and approved the final version.

Data sharing statement

Anonymised participant data will be made available when the trials are complete, upon requests directed to the corresponding author. Proposals will be reviewed and approved by the sponsor, investigator, and collaborators on the basis of scientific merit. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement. All data will be made available for a minimum of 5 years from the end of the trial.

CRediT authorship contribution statement

Kerry Conlin: Writing – original draft, Formal analysis. **Daniel Jenkin:** Writing – original draft, Methodology. **Philip de Whalley:** Writing – original draft. **Lily Yin Weckx:** Supervision, Project administration, Investigation. **Pedro M. Folegatti:** Methodology, Investigation. **Sagida Bibi:** Investigation, Formal analysis, Data curation. **Teresa Lambe:** Supervision, Methodology, Investigation. **Parvinder K. Aley:** Supervision, Project administration. **Andrew J. Pollard:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Merryn Voysey:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation. **Sue Ann Costa Clemens:** Writing – review & editing, Supervision, Project administration, Investigation.

Declaration of competing interest

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Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.126582.

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