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Short communication

Prior COVID-19 infection is associated with increased Adverse Events (AEs) after the first, but not the second, dose of the BNT162b2/Pfizer vaccine



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ABSTRACT

The BNT162b2/Pfizer SARS-CoV-2 vaccine has been widely used in the UK, particularly amongst healthcare workers (HCWs). To establish whether previous COVID-19 influenced vaccine-associated Adverse Events (AEs), we conducted a survey-based study of HCWs in Northeast England. Out of 1238 HCWs, 32% self-reported prior positive PCR and/or antibody test for SARS-CoV-2. Post-dose AEs were worse in those with prior COVID-19 after the first, but not the second dose of vaccine. Second dose AEs were greater in frequency/severity, regardless of COVID-19 history, and they were more systemic in nature. Women and younger HCW were more likely to report AEs after both doses, while dosing interval had no effect on AEs. Ongoing Symptomatic COVID-19 was associated with greater frequency/severity of AEs after dose 2, but not dose one. Overall, AEs were self-limiting and short-lived (i.e., <48 h) in nature. These findings have implications for vaccine hesitancy and informing guidelines for recommended dosing protocols.

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1. Introduction

The BNT162b2/Pfizer[1] and mRNA-1273/Moderna[2] mRNA vaccines were rapidly approved for use in the UK, with the former widely used amongst priority groups, including healthcare workers (HCWs). Phase three trials established general safety, however these vaccines can cause various adverse events (AE)[3].

Three studies found that systemic AEs after mRNA vaccination in seropositive individuals, were greater than in those with no prior COVID-19[4–6]; another reported that 532 out of 2002 participants with previous infection had increased AEs after either a mRNA or vector-based (AZD1222/AstraZeneca) vaccine[7]. Finally, a study we conducted, showed that prior COVID-19 was associated with increased AEs following first doses of BNT162b2/Pfizer vaccination[8].

Increased AEs in those with prior COVID-19 are likely driven by ‘immune priming’[9]. This notion fits with studies reporting increased antibodies to SARS-CoV-2 spike protein in previously-

infected individuals, versus those who were COVID-19 naïve[4–6,9–11]. Specifically, antibodies after one dose of mRNA vaccine in those without prior COVID-19 have been found equivalent to levels in people with previous natural infection, before receiving any vaccination[6,11]. Furthermore, studies comparing first and second dose antibody responses showed that those without prior COVID-19 required a booster to reach antibody levels equivalent to those seen in people with a history of COVID-19, after only one dose[4–6].

Vaccine-associated AEs reflect changes in antibody levels, whereby AEs increase in frequency and severity between doses one and two, as immune response builds. This happens regardless of COVID-19 history[5,6]. What is still unclear, however, is whether factors such as gender and the presence of ongoing COVID-19 symptoms (OCS)[12] influences reactivity between doses. For example, women and younger people tend to mount a greater immune response to vaccination[11], which may explain the heightened AEs in these groups[8,13]. Also, it is unknown whether a delayed administration of the second dose, as has occurred in the UK (delivered 3 months after the first dose), has any impact on AEs [14].

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To clarify these uncertainties, we conducted a study with HCWs to explore severity and duration of AEs after first and second doses of BNT162b2/Pfizer vaccination. The impact of age, gender, OCS, and dosage timing on AEs, was also considered.

2. Method

HCWs completed an electronic survey of self-reported COVID-19 symptoms, PCR/antibody results, and AEs following first and second doses of the BNT162b2/Pfizer vaccine. HCWs were recruited from three Northeast England NHS hospitals. Participants were approached via email, including clinical and non-clinical staff, between February–July 2021. Adverse Events were captured using a modified version of the FDA Toxicity Grading Scale[15] allowing participants to self-report symptom number, severity (mild/moderate/severe/very severe) and duration (≤ 24 hrs/ > 24 hrs). COVID-19 status was determined using the following criteria; (i) laboratory data confirmed positive-PCR AND/OR antibody-positive COVID-19 history, (ii) laboratory data confirmed negative-PCR AND/OR antibody-negative COVID-19 history, and (iii) COVID-19 history could not be confirmed with laboratory data, as the data was unavailable. Overall AE-related morbidity was measured with a composite score for total symptom number and severity (equal to the sum of number by duration scores), as previously published[8]. Individual and composite scores were compared between doses, for those with and without prior history of COVID-19, and between doses. Effects of age, gender, the presence of OCS, defined as ‘symptoms persisting > 4 weeks post-onset’[16], and the number of days between doses were also considered.

Statistical analysis was conducted using JASPv0.14.1.0. Scores were compared using 2-way ANCOVA. Multivariable logistic regressions were applied, to identify the relationship between COVID-19 status and moderate-to-severe AEs, and the Bonferroni correction applied to the resulting significance/confidence intervals. Correlational analysis explored associations between AEs and age/gender. Frequencies of categorical variables were examined using the chi-square test. Data from a subset who consented to their laboratory data (SARS-CoV-2 PCR/antibody) being accessed, was used to conduct a sensitivity analysis. The study was approved by Cambridge East Research Ethics Committee.

3. Results

Table 1 shows demographics and a breakdown of the sample. Eight-hundred-and-eighteen HCWs responded to both questionnaires, 138 to the first only, and 372 to the second only. Hence there were 2146 responses providing complete data after receiving dose-one or dose-two of the BNT162b/Pfizer vaccine. A proportion of participants only provided dose-two data, because some of these respondents had already completed a survey after dose-one in an earlier study[8]. The participants in the present study therefore included (i) people who had already given dose-one data and were happy to later provide dose-two data, and (ii) newly recruited participants providing dose-one and dose-two data, not previously published elsewhere. Age and sex did not differ significantly between these groups.

Table 1

Participant Demographics: Participant demographics including number/percentage of participants by COVID-19 status and gender, as well as average age, number of symptoms and severity composite score.

Dose	COVID-19 Status	n (%)	M:F (%F)	Mean (SD) age (yrs), range	Mean (SD) no. symptoms	Mean (SD) severity score
Dose 1 (n = 956)	Covid +	260 (27%)	41:219 (84% F)	48.8 (9.8), 20.0 – 65.0	1.65 (2.09)	2.86 (3.89)
	Covid -	696 (73%)	139:557 (80% F)	47.0 (10.7), 19.0 – 72.0	0.90 (1.38)	1.51 (2.42)
Dose 2 (n = 1190)	Covid +	418 (35%)	67:351 (84% F)	48.4 (11.5), 16.0 – 72.0	1.72(2.03)	2.88 (3.54)
	Covid -	772 (65%)	147:625 (81 %F)	47.2 (11.1), 19.0 – 74.0	1.59 (2.03)	2.69 (3.68)

The proportion of participants reporting at least one moderate-to-severe symptom was higher in the previous COVID-19 group (56% vs 47%, OR 1.5 [95%-CI, 1.1–2.0]) after dose-one, but not dose-two (57% vs 53%, OR 1.2 [95%-C.I. 0.9–1.5]); and after dose-two, compared to dose-one (54% vs 49%, OR 1.2 [95%-C.I. 1.00–1.4]).

For both doses, there were small but significant negative correlations between age, number of symptoms (dose-one, $r = -0.20$, $p < 0.001$; dose-two, $r = -0.14$, $p < 0.001$) and severity-duration composite score (dose-one, $r = -0.19$, $p < 0.001$; dose-two, $r = -0.13$, $p < 0.001$), which could be estimated at approximately 2 symptoms/4.5 symptom-days, for an average 20-year-old, falling to 1 symptom/2 symptom-days, for a 60-year-old. Females reported significantly higher number of symptoms (dose-one, 1.24 [1.66] vs 0.84 [1.46] symptoms, $d = 0.25$ [0.08–0.41], $p = 0.002$; dose-two, 1.78 [2.10] vs 0.99 [1.62] $d = 0.39$ [0.24–0.54], $p < 0.001$). Severity score was also higher in women (dose-1, 2.10 [3.00] vs 1.39 [2.54], $d = 0.40$ [0.24–0.57], $p = 0.001$; dosetwo, 2.98 [3.76] vs 1.71 [2.94], $d = 0.35$ [0.20–0.50], $p < 0.001$). All subsequent analyses include age and gender as covariates.

Increased number of AEs was significantly associated with dose-two, rather than dose-one (1.49 [1.97] vs 1.13 [2.56] symptoms, $d = 0.15$ [0.06–0.23] $p < 0.001$), and with COVID-19 history (1.51 [2.16] v 1.12 [2.08] symptoms, $d = 0.17$ [0.08–0.27], $p < 0.001$). There was a significant interaction between dose and COVID-19 history ($p = 0.03$; Fig. 1A). Simple effects analysis confirmed that the difference in symptom number was significant for dose-one($p < 0.001$) but not dose-two ($p = 0.09$).

For the severity-duration composite score, a similar pattern was found, whereby scores were higher following dose-two (2.51 [3.52] vs 1.93 [4.62] symptom days, $d = 0.13$ [0.04–0.22] $p < 0.001$) and for those with prior COVID-19 (2.56 [3.76] vs 1.88 [3.90] symptom-days, $d = 0.17$ [0.08–0.27] $p < 0.001$), with a significant dose by COVID-19 history interaction ($p = 0.02$). Consequent simple effects analysis revealed that the difference was significant for dose-one ($p < 0.001$) but not dose-two ($p = 0.16$; Fig. 1B). These patterns of results were also observed when analysis was repeated on the subset of 818 participants who reported AEs after both vaccine doses, suggesting this was not due to response bias.

Logistic regressions (Table 1; Fig. 2A), showed that two systemic symptoms were significantly associated with previous COVID-19: myalgia and arthralgia. Pain at the injection site was more likely after dose-one, and in those with prior COVID-19. Fever, nausea and vomiting, headache, fatigue, arthralgia, myalgia and lymphadenopathy were significantly associated with dose-two, whilst the association of fever with previous COVID-19 status was on the border of significance.

For dose-two, time interval from dose-one was available for 867 participants (range 13–147 days; median 58). Dosage interval was not related to number of symptoms ($r = 0.02$, $p = 0.67$), nor severity-duration composite scores ($r = 0.007$, $p = 0.83$). Logistic regressions (controlling for age, sex and COVID-19 history) showed that dose interval did not significantly predict any of the 11 symptoms ($p > 0.1$).

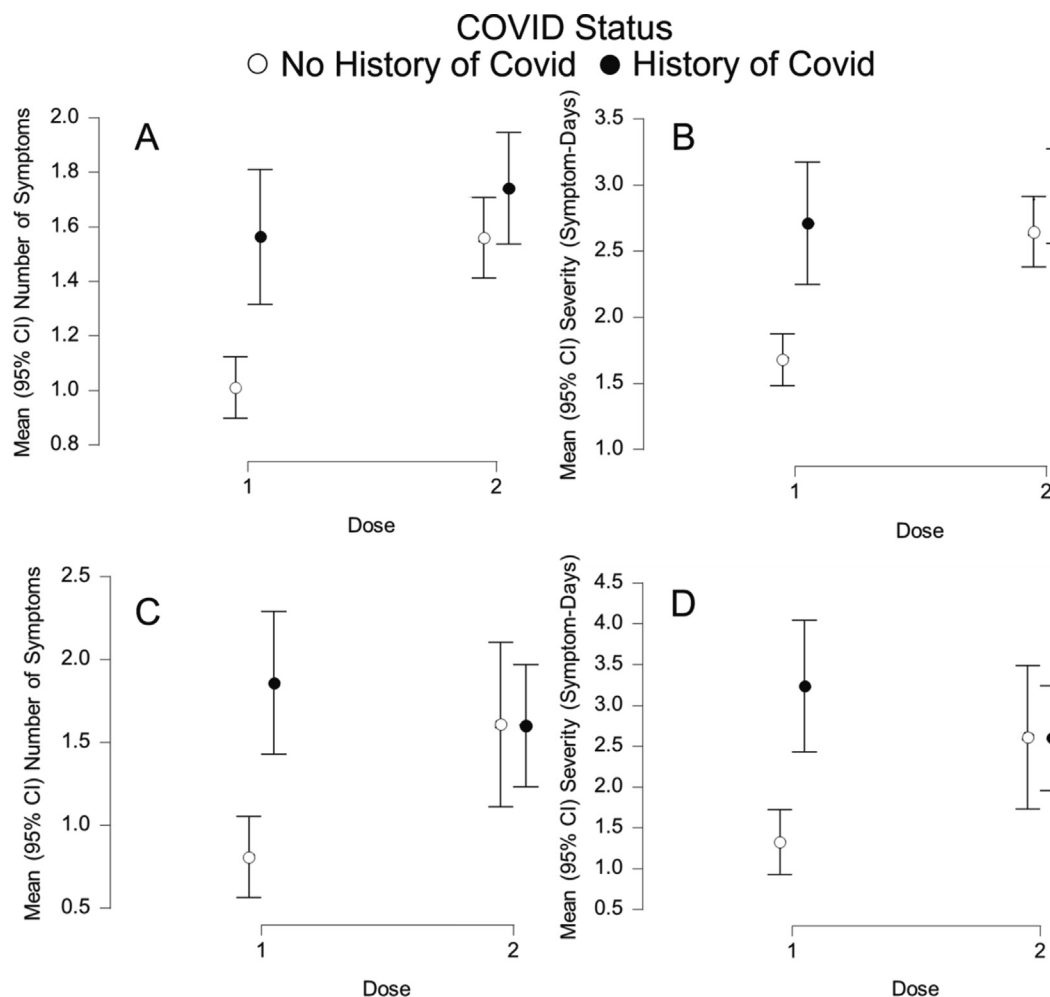


Fig. 1. Frequency and Duration of AEs by Prior COVID-19 Status: Symptom number (A & C) and duration (B & D), according to previous COVID-19 status, for the complete population (A & B), and the sensitivity analysis subset (C & D; i.e. where previous positive PCR and/or antibody results was confirmed from laboratory data).

The presence of OCS was defined with reference to NICE guidance[16]. Participants reporting OCS when vaccinated would have been at least 4 weeks post-onset to qualify for vaccination, and hence these participants formed the OCS group. Of those with prior COVID-19, 30 (83 %F, mean-age 48.8) complained of OCS at dose-1, and 44 (89 %F, mean-age 57.5) at dose-two. Symptom number and duration was not significantly higher in those with OCS, compared to those whose symptoms had resolved, at dose-one. At dose-two, however, self-reported OCS was associated with increased reporting of one or more symptoms (80% vs 54% OR 3.35 [95%-C.I. 1.6–7.2]), with a higher mean symptom number (2.39 [2.07] vs 1.38 [2.62] symptoms, $d = 0.39$ [0.07–0.72], $p = 0.002$) and severity (4.21 [3.71] vs 2.30 [4.59] symptom days, $d = 0.42$ [0.10–0.74], $p = 0.001$). Fatigue (OR 2.81 [1.15–6.84], myalgia (OR 3.01 [1.24–7.29]) and arthralgia (OR 2.71 [1.07–6.84]) were significantly associated with OCS after dose-two, after controlling for age and sex.

For the ‘sensitivity analysis’, PCR/antibody results were verified for 391 participants, of whom 171 (44%) were PCR and/or antibody negative (93 %F, mean-(SD)-age 47.6 [11.3]), and 220 (56%) were PCR and/or antibody positive (89 %F, mean-(SD)-age 47.7 [10.6]). The effect of previous COVID-19 was broadly replicated in this subgroup. Although previous COVID-19 was not significantly associated with the presence of one or more symptoms (59% v 52% OR 1.35 [95%-C.I. 0.90–2.05]), individuals with prior COVID-19 reported a higher mean number of symptoms (1.65 [2.24] vs 1.06

[2.25] symptoms, $d = 0.28$ [0.09–0.50], $p = 0.003$) of greater severity (2.76 [3.99] vs 1.59 [4.02] symptom-days $d = 0.30$ [0.11–0.53], $p = 0.003$); and the significant dose-history interaction was retained (Fig. 1C-1D; number symptoms $p = 0.008$, severity $p = 0.007$). Overall symptom reporting was maintained (Fig. 2B). Previous COVID-19 significantly predicted arthralgia in this subgroup once multiple comparisons were accounted for (Table 2), but was also significantly associated with fever in the positive cohort. Due to small numbers, a meaningful analysis of OCS and dosage interval was not possible in this subset.

4. Discussion

This study of HCWs found that AEs following BNT162b2/Pfizer vaccination were worse in those with a prior history of COVID-19 after the first, but not the second, dose of vaccine. By contrast, AEs were greater in frequency and duration for all participants after the second dose, regardless of COVID-19 history. The nature of AEs also differed between doses. Dose-one AEs typically related to pain at the injection site, whereas systemic symptoms including myalgia, arthralgia, headaches, fever, and lymphadenopathy were all more common after dose-two.

Recent similar work that has compared AEs between doses of mRNA vaccine, also found that symptoms were worse after dose-two[5,6]. Nevertheless, these studies did not consider the impact

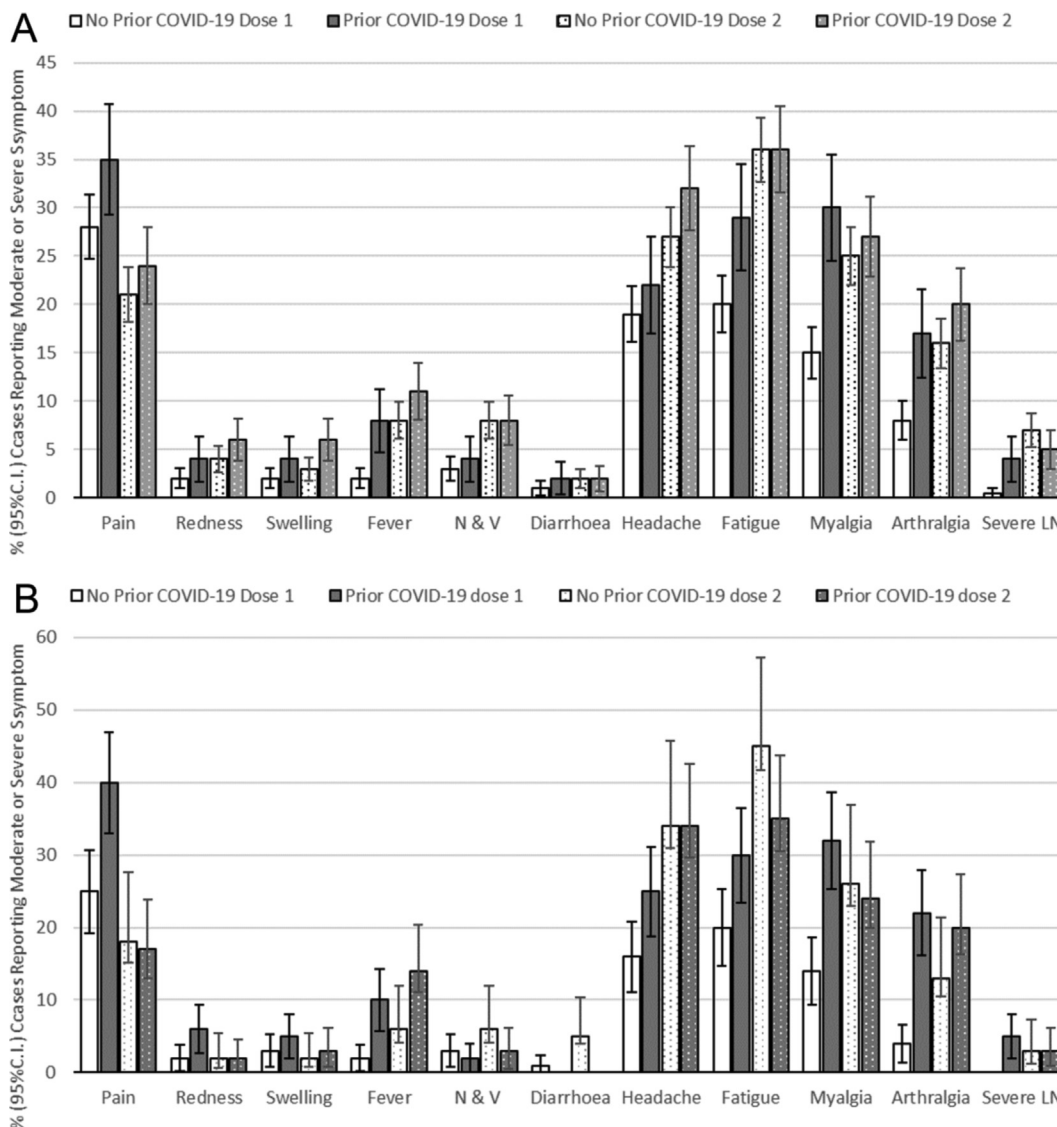


Fig. 2. Nature of AEs by Prior COVID-19 Status and Dose: Frequency of local and systemic AEs according to dose and prior COVID-19 status in the complete population (A) and sensitivity analysis subset (B). LN = lymph nodes (lymphadenopathy). N&V = nausea and vomiting.

of dosing interval on AEs, nor did they explore whether factors such as gender, and OCS, play a role in these reactions. Our present study therefore provides new information. Firstly, we found that dosing interval did not affect the likelihood of AEs. Secondly, we showed AEs were more common in younger and female participants. Finally, after dose-two, but not dose-one, those with OCS reported more vaccine-associated symptoms, specifically fatigue, myalgia, and arthralgia.

These findings have implications for vaccine delivery and uptake. A survey prior to the rollout of COVID-19 vaccines reported that approximately 72% of the UK population were likely to accept vaccination, and safety concerns were important in vaccine acceptance [17]. Furthermore, women and younger individuals showed greater vaccine hesitancy, which could be explained by these groups mounting stronger immune responses to vaccination [11,13], and equally having worse AEs [8]. Clear communication about what to expect from vaccination, and an emphasis on the typically mild and short duration AEs, is critical to reduce hesitancy, especially in those at greater risk of AEs.

Our work also reports new information on the effect of dosage interval on AEs. This may help to inform guidelines on dose delivery. Some studies on vaccine-associated antibody levels, suggest that second doses might not be warranted in those with prior COVID-19, because they already possess some natural immunity [9,14]. However, we found that AEs were worse following the second dose, irrespective of COVID-19 history, and that dosing interval had no effect on AEs. Therefore, our study provides reassurance that extending the time between doses to between 8 and 12 weeks is not associated with more AEs.

Limitations of our study include the likelihood of non-responder bias (more HCWs without previous COVID-19 not responding to the survey), as 32% reported prior positive PCR and/or antibody result. Our sample was also comprised mainly women, and past research has shown that females are more likely to report AEs [8]. Self-reported information on AEs was also subjective in nature, though our findings were broadly replicated when only analysing data from participants with laboratory confirmed PCR/antibody results.

Table 2

Results of Logistic Regressions by Prior COVID-19 Status and Dose: Logistic regressions of effect of first versus second dose, and prior COVID-19 history, controlling for age and gender. An odds ratio of > 1 indicates the outcome is more likely in the presence of vaccine dose two (versus dose one), or a history of COVID-19 (versus no history of COVID-19). LN = lymph nodes (lymphadenopathy). N&V = nausea and vomiting.

		Whole cohort (n = 2146)		Sensitivity Subset (n = 391)	
		Odds Ratio (95% C.I.)	p	Odds Ratio (95% C.I.)	p
Pain	Dose 2 vs 1	0.60 (0.45 – 0.78)	<0.001	0.41 (0.21 – 0.42)	0.012
	Prior COVID-19	1.41 (1.04 – 1.90)	0.02	1.70 (0.34 – 8.58)	0.110
Redness	Dose 2 vs 1	1.99 (0.94 – 4.21)	0.165	0.29 (0.05 – 1.91)	0.935
	Prior COVID-19	1.65 (0.84–3.29)	>0.99	4.89 (0.58– 41.10)	>0.99
Swelling	Dose 2 vs 1	1.23 (0.60 – 2.52)	>0.99	0.43 (0.08–2.38)	>0.99
	Prior COVID-19	1.573 (0.85 – 3.51)	0.436	2.98 (0.48 – 18.58)	>0.99
Fever	Dose 2 vs 1	2.29 (1.32 – 3.93)	<0.001	1.70 (0.60 – 4.80)	>0.99
	Prior COVID-19	1.69 (1.00 – 2.81)	0.050	4.49 (1.18 – 17.16)	0.033
N & V	Dose 2 vs 1	2.62 (1.43 – 4.81)	<0.001	2.22 (0.45 – 10.99)	>0.99
	Prior COVID-19	1.01 (0.44 – 3.81)	>0.99	0.88 (0.18 – 4.17)	>0.99
Diarrhoea	Dose 2 vs 1	2.17 (0.66 – 7.09)	>0.99	4.07 (0.17 – 96.82)	>0.99
	Prior COVID-19	1.32 (0.45 – 3981)	>0.99	0.56 (0.03 – 9.26)	>0.99
Headache	Dose 2 vs 1	1.60 (1.20 – 2.14)	<0.001	2.1 (1.06 – 4.)	0.044
	Prior COVID-19	1.32 (0.98 – 1.78)	0.143	1.75 (0.88 – 3.49)	0.341
Fatigue	Dose 2 vs 1	2.03 (1.55 – 2.67)	<0.001	2.07 (1.11 – 3.86)	0.022
	Prior COVID-19	1.21 (0.92 – 1.61)	0.745	1.39 (0.74 – 2.62)	>0.99
Myalgia	Dose 2 vs 1	1.44 (1.07 – 1.94)	0.010	1.09 (0.56 – 2.14)	>0.99
	Prior COVID-19	1.48 (1.09 – 1.99)	0.006	1.80 (0.90 – 3.62)	0.275
Arthralgia	Dose 2 vs 1	1.75 (1.22 – 2.52)	<0.001	1.24 (0.56 – 2.77)	>0.99
	Prior COVID-19	1.63 (1.15 – 2.32)	0.003	3.78 (1.46 – 9.82)	0.002
Severe LN	Dose 2 vs 1	3.66 (1.69 – 7.92)	<0.001	1.23 (0.23 – 6.55)	>0.99
	Prior COVID-19	1.02 (0.53– 1.95)	>0.99	2.18 (0.34 – 13.88)	>0.99

5. Conclusion

We confirm that AEs following vaccination are greater in those with previous COVID-19 and additionally provide new evidence that dosing interval is unlikely to affect AEs, though symptoms are worse after the second dose of vaccine (especially in the presence of OCS). Women and young people are also more vulnerable to AEs. Importantly, AEs were self-limiting and short-lived in nature. These results have implications for vaccine hesitancy, which is exacerbated by fear of side effects [17–19], and recommendations on dosing.

Contributors

DRC/CK/RKR conceived the study and DRC is chief investigator of CHOIS. RKR acted as site principal investigator. DRC/RKR/CW contributed to the study protocol, design, and data collection. JR/RKR/DRC did the statistical analysis. RKR/JR/DRC prepared the manuscript. All authors critically reviewed and approved the final version.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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