BMJ Open

Adverse events and overall health and well-being after COVID-19 vaccination: interim results from the VAC4COVID cohort safety study

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To cite: Rogers A, Rooke E, Morant S, *et al*. Adverse events and overall health and well-being after COVID-19 vaccination: interim results from the VAC4COVID cohort safety study. *BMJ Open* 2022;**12**:e060583. doi:10.1136/bmjopen-2021-060583

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-060583).

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Received 05 January 2022
Accepted 16 May 2022

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ABSTRACT

Objectives To describe the incidence of adverse events (AEs), reactogenicity symptoms, menstrual changes and overall self-rated improvement in health and well-being after COVID-19 vaccination.

Design VAC4COVID is an ongoing prospective, active observational, post-authorisation cohort safety study (PASS) of UK-approved vaccines for COVID-19 disease.

Setting The study is conducted through a secure website (www.vac4covid.com) by MEMO Research, University of Dundee, UK.

Participants 16 265 adult (18 years or older) UK residents with a valid email address and internet access.

Interventions Any UK-authorised COVID-19 vaccination.

Main outcome measures The outcomes reported in this interim analysis include AEs, reactogenicity-type AEs (headache, fatigue, muscle or joint pain, fever, nausea, dizziness or local vaccine reaction), menstrual changes and reported improvement in overall health and well-being.

Results 11 475 consented participants (mean age 54.8 years) provided follow-up data between 2 February and 5 October 2021 (mean follow-up duration 184 days), by which date 89.2% of participants had received two vaccine doses. 89.8% of 5222 participants who completed a follow-up questionnaire in the 7 days after any COVID-19 vaccination reported no AEs. The risk of experiencing any event (not necessarily vaccine-related) requiring hospitalisation was less than 0.2%. 43.7% of post-vaccination follow-up records reported improvement in health and well-being. Reactogenicity-type reactions were more common in the week after the first dose of ChAdOx1 than BNT162b2 (7.8% vs 1.6%), but this relationship was reversed after the second dose (1.3% vs 3.1%). 0.3% of women reported menstrual symptoms after vaccination; no differences between vaccine type or dose order were detected.

Conclusions The study provides reassuring data on low rates of AEs after COVID-19 vaccination. Differences in reactogenicity-type AE profiles between ChAdOx1 and BNT162b2 and between first and second doses of these vaccines were observed.

Trial registration number ISRCTN95881792; Pre-results.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Comprehensive comparison of post-vaccination adverse medical events of commonly used UK COVID-19 vaccines, including first and subsequent doses.
⇒ Events were assessed using open questions and participant reporting using a bespoke entry system based on the MedDRA (Medical Dictionary for Regulatory Activities) coding dictionary.
⇒ Positive affirmation of absence of adverse health events.
⇒ Voluntary online study susceptible to selection and reporting bias.

INTRODUCTION

Vaccination is a cornerstone of worldwide efforts to tackle the COVID-19 pandemic, and over 53.2% of the global population has now received at least one dose of vaccination against SARS-CoV-2.[1] Because vaccines are used to prevent potential future disease, a higher standard of safety is expected than for treatments for active disease, for example, antibiotics.

Three vaccines have been used in the UK COVID-19 vaccine programme to date: Vaxzevria (ChAdOx1, previously COVID-19 vaccine AstraZeneca), Pfizer-BioNTech (BNT162b2) and Spikevax (mRNA-1273, formerly COVID-19 Vaccine Moderna), which was approved later and has been deployed less widely. A fourth, Janssen (Ad26.COV2.S), has been approved but is not yet in routine use.

Monitoring of adverse effects is a significant part of any pre-licensing vaccine research. Clinical trials systematically solicit reports of reactogenicity (expected physical manifestations of the immune response to vaccination), anaphylactic reactions, autoimmune events and any new diagnoses

after vaccination. Clinical trials of all four UK-approved COVID-19 vaccines have found them acceptably safe in terms of serious adverse events (SAEs). However, all have reported non-serious short-term adverse events (AEs), such as local injection site symptoms and systemic symptoms like headache, myalgia, fever and chills, occurring in more than 1 in 10 vaccine recipients.[2–4]

Reactogenicity-related symptoms can impact individual and community behaviours and attitudes towards future vaccination despite not presenting a safety concern.[5] Any reduction in population vaccine coverage threatens the effectiveness of vaccination programmes. Therefore, it is necessary to understand which vaccine recipients are most at risk of reactogenicity symptoms and whether the available vaccines differ in their side effect profiles. Improved understanding of post-vaccine symptoms will allow better-informed planning of future vaccination programmes. Furthermore, by providing accurate information to the public about potential side effects to expect after vaccination, we might also minimise any impact of unexpected symptoms on future vaccine acceptance.

While UK vaccine recipients are encouraged to report side effects to their vaccine provider or directly to the Medicines and Healthcare Regulatory Authority (MHRA) via the Yellow card system,[6] many side effects are likely to be under-reported. Active surveillance studies, proactively eliciting participant-reported symptoms and diagnoses, are necessary to understand better the adverse health events experienced, especially self-limited symptoms managed by self-care alone. The post-vaccination menstrual irregularities that have been reported widely in the media[7–9] are an excellent example of potential vaccine adverse effects that may be best assessed using an active surveillance method.

This study design also provides an ideal opportunity to capture positive reporting of an absence of AEs after vaccination, allowing a more accurate estimation of event rates.

VAC4COVID (SARS-CoV-2 Vaccination for COVID-19 Disease Safety Study) is an independent academic UK-wide web-based study designed to collect patient-reported adverse medical events before and after vaccination. The study design also allows clinical validation of any serious or non-serious adverse events of special interest (AESIs).[10] We present an interim analysis of AR data collected between 2 February 2021 and 5 October 2021 in the VAC4COVID study.

OBJECTIVES

The primary objective of the VAC4COVID study is to examine the safety of COVID-19 vaccinations by collecting participant-reported event data and routinely collected hospitalisation and mortality data before and after vaccination. In this interim analysis, we report selected participant-reported secondary outcomes from data collected between 2 February 2021 and 5 October 2021: incidence of AEs, reactogenicity-type symptoms and menstrual changes, and participant self-assessed changes in overall health and well-being.

METHODS

Design

VAC4COVID is a prospective, active observational, post-authorisation cohort safety study (PASS) of UK-approved vaccines for COVID-19 disease.

Setting

VAC4COVID is an online study[10] developed and coordinated by MEMO Research, University of Dundee, UK. Participants included in this analysis were recruited from the UK adult population, between 2 February 2021 and 5 October 2021, by general advertisement, including print media and radio.

Participants

Participants are aged 18 years or over at study entry and can enter the study before or after COVID-19 vaccination. All participants are required to be registered with a UK general practitioner (GP) and have a valid email address and the ability to access the study website. Participants must also supply at least one alternative contact who can be contacted if the participant does not respond to repeated requests for information.

Patient and public involvement

The study team collaborated with their research unit's public involvement group during the design of the VAC4COVID study and website. This group's involvement was critical in developing online questionnaires and participant information documentation. In addition, the study team consulted a local COVID-specific public involvement group regarding the preferred wording of baseline and follow-up questionnaire items about previous SARS-CoV-2 infection and persisting symptoms. Two members of the research unit's public involvement group act as lay members on the study advisory committee.

Variables

After completing the online study registration and informed consent processes, participants are invited to report the following information: demographic (age, sex, ethnicity, size of household, education, occupation, height and weight), medical history (including hospitalisations in the 2 years before consenting to join the study, previous reactions to vaccines or medicines, and all regularly taken medications), lifestyle (smoking history, alcohol consumption), COVID-19-related information (UK government advised shielding status (as a proxy for clinical vulnerability); previous SARS-CoV-2 exposure, illness and testing), and, as applicable, pregnancy (parity, pregnancy history (including any serious adverse pregnancy outcomes), last menstrual period, expected delivery date, breast feeding).

Two additional baseline variables are derived as follows. First, self-reported height and weight are used to

automatically calculate body mass index (BMI) using a participant-facing interface to reduce data-entry errors. Second, comorbidity burden is reported as a count of the number of items selected from a list of significant chronic or prior health conditions.

Participants can enter follow-up information spontaneously at any time. However, they are also prompted by email to provide a scheduled follow-up entry: monthly before vaccination, every week for 4 weeks after any COVID-19 vaccination, and monthly for at least 11 months after the latest COVID-19 vaccine. Each time follow-up information is entered on the website, a new follow-up record is created. At each follow-up contact, participants are asked to report if they have suffered any adverse medical events since their last study contact using the following question: 'Have there been any significant changes in your health and well-being for any reason (including any that you think may have been due to COVID-19 vaccination)? By 'significant', we mean that it was disruptive of usual activities, caused loss of work or education days, or led to hospitalisation.' Any participant answering 'yes' to this question is considered to have experienced an adverse medical event.

Participants are invited to record each adverse medical event using a custom look-up field. The VAC4COVID event participant-facing look-up system uses MedDRA, the Medical Dictionary for Regulatory Activities terminology database. MedDRA is the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Participants are asked to enter the date of onset, if they were hospitalised, and subjective estimation of severity for each AE reported using the MedDRA-based look-up. Severity assessment permits three levels of severity (mild, moderate, severe) with no additional guidance on criteria for severity selection. Participants are also asked to report any improvement or worsening in any long-term conditions reported at baseline. Finally, participants are asked, 'Do you feel your health or well-being have improved since being vaccinated for COVID-19?'. Participants who indicate that their health or well-being has improved are then asked whether this is due to physical and/or mental well-being improvement.

Exposure

At each follow-up contact, participants are asked to report any SARS-CoV-2 symptoms or exposures, vaccinations (date, type, batch number) and tests (date, type, result), and any other non-COVID vaccinations given within 28 days of a COVID-19 vaccine. Participants vaccinated before study entry are invited to supply details of vaccine type(s), batch number(s) and date(s) of administration at baseline data entry. For this analysis, exposure is defined as any reported SARS-CoV-2 vaccination.

Outcomes

The outcomes reported in this interim analysis are as follows: AEs (including hospitalisations), any reactogenicity-type AE (defined as headache, fatigue, muscle or joint pain, fever, nausea, dizziness or local vaccine reaction), changes in menstrual symptoms and reported improvement in overall health or well-being. Reasons for hospitalisation were not assessed in this analysis.

Event validation

We present only unvalidated data in this interim analysis. However, the VAC4COVID study design does allow for clinical validation of potential AESIs. Briefly, this is done as follows: potential AESIs are identified using predetermined MedDRA code searches and manual clinical review of reported events. The study team then obtain additional supporting information (eg, description of events, hospital discharge letter, test results) directly from the participant (where appropriate) and their registered GP. These additional supporting data are reviewed independently by two clinicians to determine whether the event meets existing AESI clinical definitions. Disagreements are resolved by consensus with a third clinician.

Statistical analysis

The follow-up time used in the time-to-event analysis of each outcome was time from the date of vaccination (first or second) to the date of onset of the first event in each participant, with follow-up time censored on the date of the last follow-up record submitted if no event occurred. Kaplan-Meier curves were constructed with their 95% CIs and used to estimate cumulative proportions of participants reporting events at specified times since vaccination.

For menstrual symptoms, a proportional hazards model was also fitted (proportional hazard assumption met, p=0.73), adjusting for the different age profiles of the female participants receiving the BNT162b2 and ChAdOx1 vaccines.

Analyses were conducted using R (V.4.1.1) and packages tidyverse, lubridate, flextable, sqldf, survival, survminer, broom and forestmodel.[11–18]

RESULTS

Enrolment

As of 5 October 2021, 23 442 participants had registered through the study website (https://VAC4COVID.com), 16 265 had consented to participate in the study and 217 had subsequently withdrawn their consent. Among the 16 048 participants still providing consent, 11 475 had provided follow-up data on at least one occasion and were included in the analyses (see online supplemental figure S1).

About 31.5% (3618) of participants included in the analysis joined the study before receiving any doses of COVID-19 vaccination (median 12 days). The largest group of participants (6904, 60.2%) entered the study

after their first vaccination (median 36 days after first dose) but before any subsequent vaccinations. 1.9% and 0.8% of participants joined the study before or after their second doses, respectively. A total of 640 (5.6%) participants remained unvaccinated by 5 October 2021.

Baseline characteristics and vaccinations

The baseline characteristics of participants at study entry are summarised in table 1 (see online supplemental table S1 for additional variables).

Observation time

The study's total observation time is 5784 person-years; 423 person-years before vaccination, 2349 following BNT162b2 vaccinations and 2956 following ChAdOx1 vaccinations. The mean average follow-up time per participant was 184 days. 78547 follow-up records have been submitted, an average of 6.8 per participant. Also, 1648 participants submitted 3049 follow-up records before vaccination.

Follow-up records

About 14.6% of follow-up reports were submitted spontaneously by participants. The proportion of follow-up records completed in response to scheduled requests increased from 72.8% in participants aged 18–39% to 80.3% in those aged 40–64% and 87.2% in those aged 65 years and over. Scheduled follow-up completion was lower in participants who had previously experienced symptoms of COVID-19 (77.8%) than in those who had not (84.3%). Scheduled completion rates were similar before and after vaccination (82.2% vs 83.4%) and in men and women (84.4% vs 81.6%).

Vaccine exposure

The vaccination status of participants in each demographic and lifestyle subgroup is summarised in table 1. Of those participants, 86.4% had received two vaccine doses by 5 October 2021 (47.9% both doses ChAdOx1, 36.9% both doses BNT162b2, other combinations 1.6%). Then, 276 participants reported having a third dose of any vaccine. Participants aged 18–39 were more likely to receive the BNT162b2 vaccine than ChAdOx1 (68% vs 16.7%), whereas those aged 40–64 were more likely to receive ChAdOx1 than BNT162b2 (64.1% vs 26.6%). In those over 65, participants were slightly more likely to have received ChAdOx1 than BNT162b2 (50.6% vs 40.9%). There were no significant associations between vaccine type and any other baseline characteristic.

Adverse events

Of the 5103 participants submitting at least one follow-up report (solicited or spontaneous) within 7 days of vaccination, 89.6% explicitly reported no adverse medical events occurring in the first week after COVID-19 vaccination. Of the 10788 participants who submitted any follow-up reports between 0 and 180 days after vaccination, 77.4% reported no adverse medical events (table 2). Spontaneous follow-up reports were more likely than scheduled to include any AE (8.0% vs 5.6%).

The risk of experiencing an event (not necessarily vaccine-related) that required hospitalisation was less than 0.2% in every time period. The risk of experiencing a severe event but not requiring hospitalisation was less than 1% except in the first 2 weeks after vaccination (1.12% and 1.55%, respectively).

Specific adverse events

Reactogenicity-type AEs

We estimated the percentage of participants reporting reactogenicity-type AEs (headache, fatigue, muscle or joint pain, fever, nausea, dizziness or local vaccine reaction) over time after first and second doses of ChAdOx1 and BNT162b2 using Kaplan-Meier curves (figure 1, see online supplemental file for code list). Of the 4877 participants submitting follow-up information after a first dose of ChAdOx1, 7.8% reported at least one reactogenicity-type AE occurring within 7 days of vaccination. Further, 1.6% of the 3482 BNT162b2 recipients submitting post-first dose information reported any reactogenicity-type event within 7 days of vaccination. Conversely, after second doses, only 1.3% of 5917 ChAdOx1 recipients and 3.1% of 5868 BNT162b2 recipients reported any reactogenicity-type AE occurring within 7 days of vaccination. This ranking of the relative cumulative rates at 7 days was observed for each of the individual reactogenicity-type AEs (figure 2).

Menstrual changes

Overall rates of women aged 18–59 reporting menstrual symptoms in the 12 weeks after vaccination were low (0.3%). Unadjusted percentages of reporting menstrual symptoms, including menstrual cycle alteration or intermenstrual bleeding (12 events), heavy bleeding (11) or painful periods/cramping (5) (see online supplemental file for code list) within 12 weeks of vaccination were higher after BNT162b2 vaccinations (0.6% after first dose, 0.4% after second dose) than after ChAdOx1 (0.2% after first dose, 0.2% after second dose). However, there was no difference between vaccines after adjusting for age in a proportional hazards model (see figure 3), and overall cumulative rates were low (see online supplemental figure S3). Participants reported these events as 25% mild, 54% moderate and 21% severe; none resulted in hospitalisation.

Perceived benefits

Overall, 43.7% of all follow-up records, both spontaneous and solicited, included an agreement that health and well-being had improved after vaccination (95.4% of these specified a mental improvement and 10.5% a physical improvement, not mutually exclusive). Older participants were more likely to report an improvement, particularly after second doses (see online supplemental figure S2).

Table 1 Baseline characteristics and total COVID-19 vaccine exposure (before and during study)

Baseline characteristics, number of participants, n (% of total)*		Total vaccines received by end of follow-up, number of participants, n (% of category)*				
		ChAdOx1		BNT162b2		Other†
		One dose only	Two doses	One dose only	Two doses	Any doses
Overall	11 475 (100)	331 (2.9)	5497 (47.9)	270 (2.4)	4240 (36.9)	1137 (9.9)
Sex						
Male	4609 (40.2)	135 (2.9)	2351 (51.0)	94 (2.0)	1574 (34.2)	455 (9.9)
Female	6855 (59.7)	196 (2.9)	3141 (45.8)	176 (2.6)	2661 (38.8)	681 (9.9)
Age (years)						
18–39	1788 (15.6)	18 (1.0)	280 (15.7)	107 (6.0)	1109 (62.0)	274 (15.3)
4–-64	4661 (40.6)	176 (3.8)	2811 (60.3)	68 (1.5)	1170 (25.1)	436 (9.4)
65+	5023 (43.8)	137 (2.7)	2406 (47.9)	95 (1.9)	1959 (39)	426 (8.5)
BMI (kg/m^2)						
<18.5	163 (1.4)	5 (3.1)	82 (50.3)	<5	61 (37.4)	13 (8.0)
18.5–<25	3780 (32.9)	84 (2.2)	1795 (47.5)	96 (2.5)	1492 (39.5)	313 (8.3)
25–<30	3728 (32.5)	83 (2.2)	1906 (51.1)	71 (1.9)	1352 (36.3)	316 (8.5)
30–<40	2441 (21.3)	75 (3.1)	1155 (47.3)	57 (2.3)	914 (37.4)	240 (9.8)
40+	518 (4.5)	14 (2.7)	260 (50.2)	10 (1.9)	197 (38.0)	37 (7.1)
Ethnicity						
Other	275 (2.4)	13 (4.7)	103 (37.5)	11 (4.0)	120 (43.6)	28 (10.2)
White	11 200 (97.6)	318 (2.8)	5394 (48.2)	259 (2.3)	4120 (36.8)	1109 (9.9)
Occupational status						
Unemployed	524 (4.6)	20 (3.8)	214 (40.8)	18 (3.4)	203 (38.7)	69 (13.2)
Employed	5053 (44.0)	146 (2.9)	2103 (41.6)	159 (3.1)	2038 (40.3)	607 (12.0)
Retired	5898 (51.4)	165 (2.8)	3180 (53.9)	93 (1.6)	1999 (33.9)	461 (7.8)
Currently smoke						
No	10 189 (88.8)	245 (2.4)	4999 (49.1)	223 (2.2)	3844 (37.7)	878 (8.6)
Yes	441 (3.8)	16 (3.6)	199 (45.1)	13 (2.9)	172 (39.0)	41 (9.3)
No. of comorbidities						
None	3548 (30.9)	133 (3.7)	1496 (42.2)	126 (3.6)	1312 (37.0)	481 (13.6)
1	2867 (25.0)	67 (2.3)	1463 (51.0)	56 (2.0)	1057 (36.9)	224 (7.8)
2	2253 (19.6)	58 (2.6)	1109 (49.2)	36 (1.6)	856 (38.0)	194 (8.6)
3+	2807 (24.5)	73 (2.6)	1429 (50.9)	52 (1.9)	1015 (36.2)	238 (8.5)
Advised to shield						
Yes	960 (8.4)	32 (3.3)	506 (52.7)	21 (2.2)	293 (30.5)	108 (11.2)
No	9600 (83.7)	225 (2.3)	4660 (48.5)	213 (2.2)	3702 (38.6)	800 (8.3)
Had COVID before study entry						
Yes	1256 (10.9)	40 (3.2)	544 (43.3)	33 (2.6)	504 (40.1)	135 (10.7)
No	9304 (81.1)	217 (2.3)	4622 (49.7)	201 (2.2)	3491 (37.5)	773 (8.3)

*Subgroups may not sum to the total because unknowns are omitted.
†Includes participants who received both ChAdOx1 and BNT162b2 and any who reported other COVID-19 vaccines alone or in combination with ChAdOx1 or BNT162b2.
BMI, body mass index.

DISCUSSION

We have demonstrated that most people in a UK population cohort receiving ChAdOx1 and BNT162b2 vaccines reported no AEs after vaccination. Indeed, reactogenicity-type symptoms are comparable to those associated with seasonal influenza vaccination.[19] Furthermore, 43.7% of follow-up records submitted reported improved overall health and well-being after vaccination.

Table 2 Proportion of participants explicitly reporting no adverse event and the maximum self-assessed severity of adverse events in participants who did report them

Post-vaccination period	Participants submitting follow-up reports during time period	Participants reporting at least one event (% of participants)					
		Maximum self-assessed severity of any event					
		None*	Mild	Moderate	Severe	Hospitalised	Unknown†
Week							
1	5103	89.61	1.23	4.59	1.12	0.08	3.37
2	2714	91.6	0.59	3.54	1.55	0.15	2.58
3	6374	92.63	0.2	0.5	0.2	0.03	6.43
4	6798	94.67	0.19	0.4	0.15	0.03	4.56
Month							
2	8479	93.25	0.47	1.24	0.66	0.19	4.19
3	7199	94.37	0.26	0.58	0.53	0.07	4.18
4	7734	95.51	0.13	0.43	0.32	0.04	3.57
5	6898	95.07	0.35	1.09	0.75	0.19	2.55
6	4909	95.25	0.29	0.51	0.33	0.12	3.5
0–180 days, or last follow up if earlier							
Overall	10 788	77.38	1.21	4.15	1.37	0.18	15.71

*Answered 'No' to the question, 'Have there been any significant changes in your health and wellbeing for any reason (including any that you think may have been due to COVID-19 vaccination)?' on every occasion in the period.
†Answered 'Yes' but did not record any symptoms.

We were aware of media coverage of vaccine anxiety and concerns about vaccine hesitancy when designing our study. Most vaccine safety studies rightly concentrate on detecting adverse symptoms or side effects. However, there was concern expressed among peers and public involvement group members that a study asking only about negative consequences of vaccination could adversely impact vaccination rates. Our improved health and well-being finding is reassuring but should not be considered without acknowledging some limitations in our approach.

Participants were encouraged to join the study before receiving their first COVID-19 vaccination, but due to a fast UK vaccine roll-out and delays to study launch, many did not join until after their first vaccine. As a result, our findings may be subject to recall bias and the possibility that persons may have entered the study only to report an event that had already occurred.

By defining an AE as a significant change in health and well-being in the online questionnaire (eg, disruptive of usual activities), all events included in this analysis would likely be at least moderate according to severity grading scales commonly used in clinical research. In addition, the open question format did not prompt specific symptoms, which may reduce reporting of events that individual participants did not consider important or relevant. Therefore, we expect the rate of AEs reported by our participants as mild to be lower than those reported in studies that did not use the same question format. For example, a Dutch web-based cohort study reporting data up to 13 days after vaccination asked participants to indicate if they had experienced specific common vaccine adverse reactions.[20] The Dutch study reported a far higher 62.9% overall rate of reactogenicity AEs, similar to phase III vaccine trial findings.

We have reported only data provided by participants who have submitted at least one study follow-up record. Therefore, we may have overestimated actual rates of moderate to severe events as participants who have experienced a change in health may be more likely to respond to email requests for follow-up entry than those who have not.

Although the study is designed to collect data on all UK-approved COVID-19 vaccines, the relatively small numbers of reported mRNA-1273 vaccinations limit a meaningful comparison of this vaccine against ChAdOx1 and BNT162b2. Previous research has documented reactogenicity-associated AEs in people receiving BNT162b2 and ChAdOx1 vaccines.[21]

Several factors are known to affect the likelihood of vaccine reactogenicity-related symptoms. Active vaccine components and adjuvants can both influence symptoms, and aspects of administration such as storage temperature and injection technique are known to have an effect.[5] In trials, adverse effects of ChAdOx1 were reported as milder and less frequent after second doses than first doses.[2 22] Conversely, in UK and US prospective cohort studies, researchers found systemic symptoms to be more common after second doses of BNT162b2 and mRNA-1273 than first doses, suggesting a potential

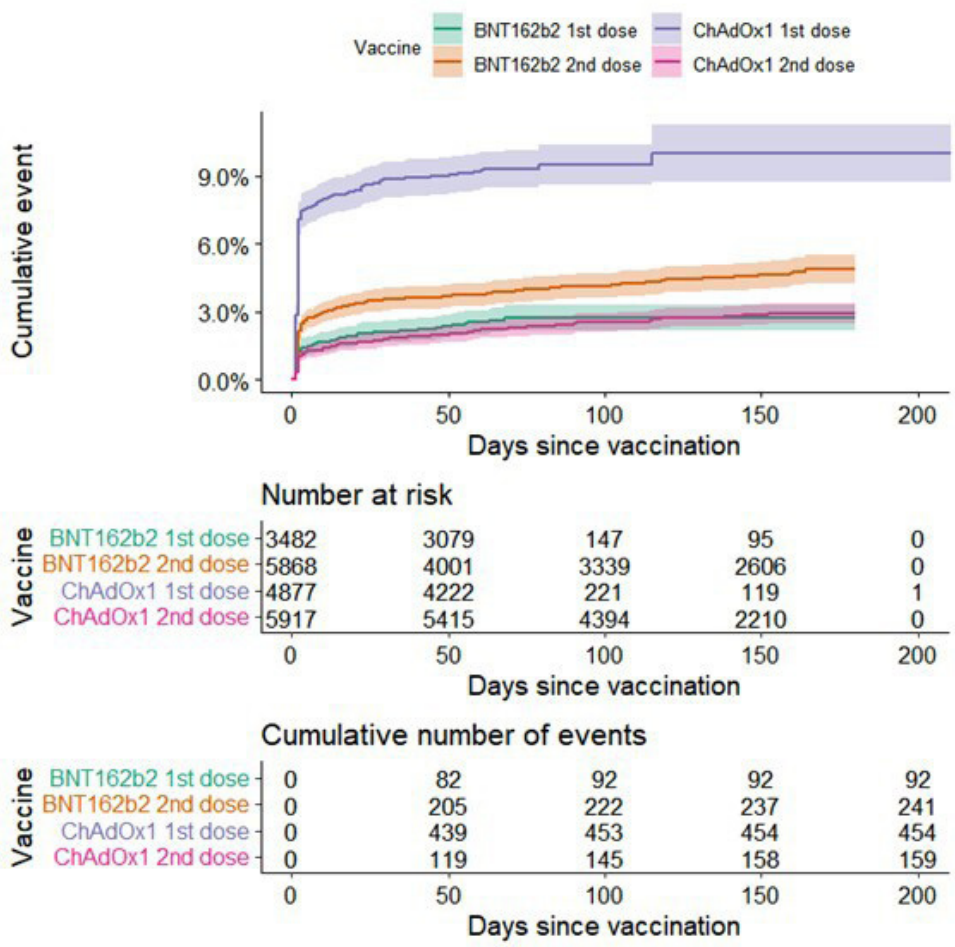

Figure 1 Kaplan-Meier curves for any reactogenicity-related symptom. Individuals considered 'at risk' from date of vaccination until last submitted follow-up.

difference between conventional and mRNA vaccines.[21 23] Additionally, vaccine-recipient factors such as age, sex, ethnicity, BMI and previous infection exposure are likely to play a role.[5] Clinical trials and previous observational research suggest that younger COVID-19 vaccine recipients are more likely to report adverse effects after vaccination than older recipients.[4 21] People with previous SARS-CoV-2 infection are more likely to report experiencing systemic symptoms after vaccination than people not known to have had a prior SARS-CoV2 infection.[21]

The VAC4COVID results support previous findings and provide additional detail on symptoms after second dose administration. Reactogenicity-type symptoms lessen with repeated dosing of the ChAdOx1 vaccine compared with the BNT162b2 vaccine, where second doses were associated with higher symptom reporting. Evolving UK vaccine deployment policies have resulted in differences in the characteristics of participants receiving each vaccine type (including age and comorbidity); this may introduce confounding. For example, health and social care workers are likely to have different vaccination and COVID-19 exposure patterns than the general population.

As reported in the media, COVID-19 vaccination may be associated with menstrual changes in a small proportion of women under 65 years. However, unlike reactogenicity-type symptoms, we detected no difference in menstrual changes between vaccines.

These results demonstrate the viability of assessing the adverse health event burden of vaccinations using an online platform. A patient-friendly medical terminology entry system allows participants to report symptoms freely; this minimises the risk of missing adverse effects not expected by questionnaire designers. For example, VAC4COVID participants reported menstrual irregularities before widespread public awareness that these may be associated with vaccination.

Conversely, participant-reported events may be more susceptible to missing data and misclassification. With the assumption that missing data would be more likely in participants who had not experienced an AE, given that participants were encouraged to record events at any time during the study, we mitigated the potential impact of missing data by using a time-to-event rather than cross-sectional approach. However, there will likely be a degree of missingness in AE data, leading to underestimating true event rates and possible bias. As demonstrated by the event severity assessment in this study, the wording of any accompanying question text or guidance will affect what

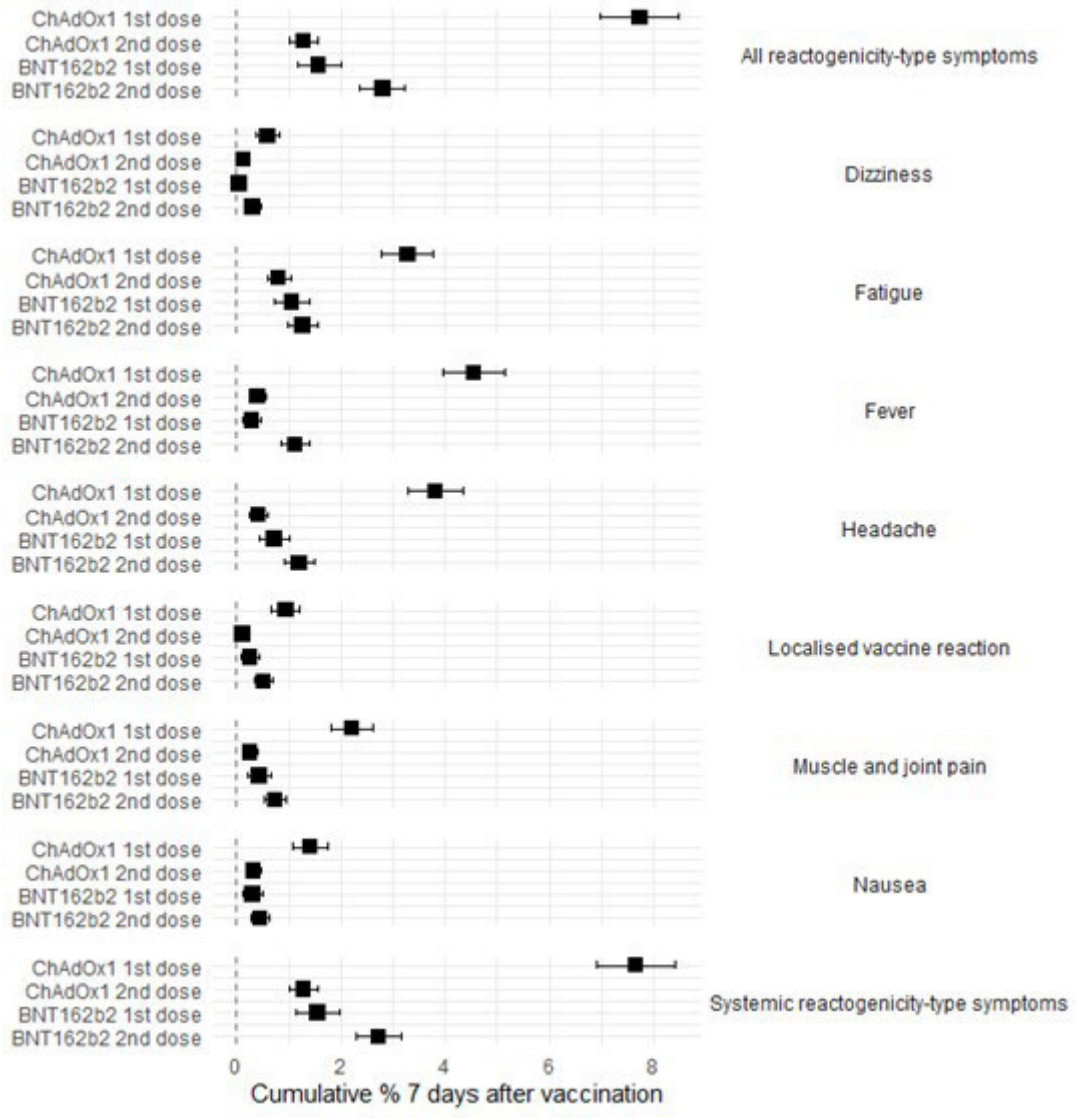

Figure 2 Cumulative percentage of participants reporting individual reactogenicity-related adverse events rates up to 7 days post-vaccination, estimated from Kaplan-Meier curves.

participants choose to report. Clinical event validation and integration of linked hospitalisation and mortality data in the VAC4COVID study should mitigate misclassification and under-reporting. It should also be remembered that observational cohort studies like VAC4COVID are not designed to assess causality.

The reported results are derived from a self-selecting cohort of UK-only residents. The baseline characteristics of the study cohort (eg, relatively high educational status and low numbers of people reporting non-white ethnicity) imply that the results may not be generalisable to the whole UK population. Ongoing efforts are required to encourage more diverse populations to participate in studies like VAC4COVID. Caution is also advised in generalising these results to different countries and vaccine types.

Further analysis will be needed to assess the effect of coadministration of seasonal influenza vaccines (as offered by the NHS in the UK[24]) and additional booster doses as vaccination programmes progress. Other areas for potential further study include the effects of vaccines on children, combining different vaccine types in dosing and booster schedules, and differing prevalent virus (and variant) exposure pre-vaccination, on post-vaccination symptoms.

CONCLUSION

The two most commonly used COVID-19 vaccines in the UK, ChAdOx1 and BNT162b2, are well tolerated. The majority of vaccine recipients in this study reported no adverse health events after vaccination, and most reported events were of mild or moderate severity. Furthermore, a high proportion of participants reported subjective improvements in overall health and well-being after vaccination. These data should be reassuring to people contemplating vaccination. However, there are differences between the reactogenicity-related

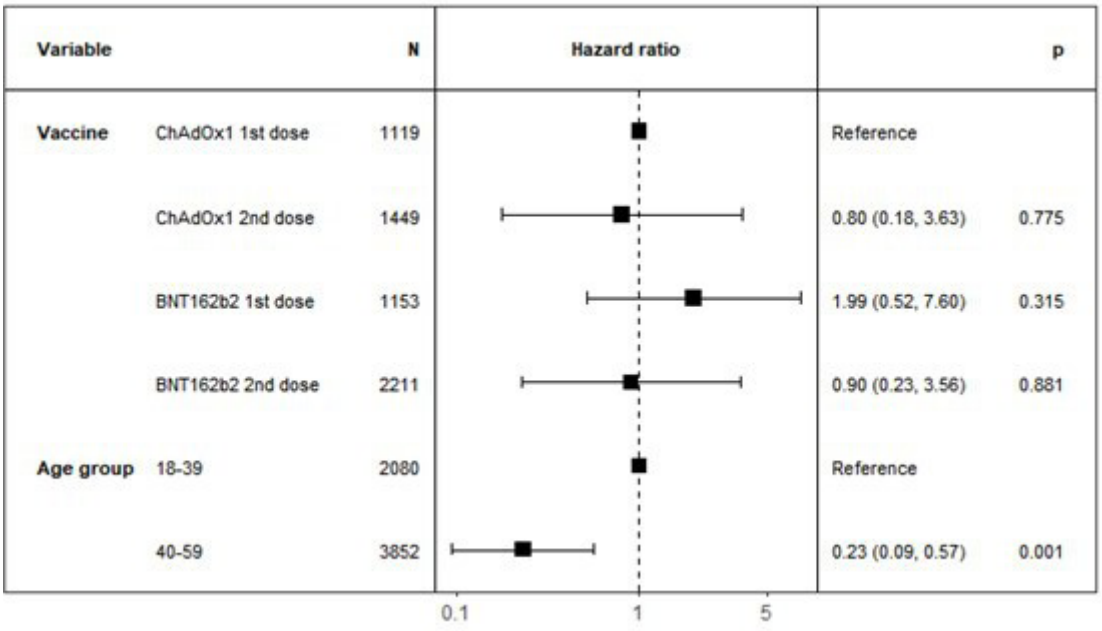

Figure 3 Hazard ratios for menstrual symptoms in different vaccines (adjusted for age) and age groups in a proportional hazards analysis.

symptom profiles of the vaccines that should be considered in planning future vaccination programmes. The ongoing VAC4COVID remote active surveillance system is designed to monitor vaccine safety and effectiveness by combining participant-reported data with linked health and administrative data; the flexible design would allow data collection in any country for which there is a suitable translated MedDRA dictionary. As well as providing comparative COVID-19 vaccine AE data, the system may also be adapted to monitor new non-COVID vaccines and other medications.

Correction notice This article has been corrected since it first published. The acknowledgements statement has been updated.

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Acknowledgements The authors thank all VAC4COVID participants for generously giving their time and attention to the study. Thanks are also due to the non-author members of the VAC4COVID Advisory Committee (Sir Lewis Ritchie, Sheina Bell, Stephen Vincent, Colin Simpson, and Chris Robertson), Public Involvement in MEMO Research Studies (PIMS) group, and to the Tayside Medical Science Centre (TASC) COVID PPI group for their invaluable input. Recruitment to this study was facilitated by SHARE – the Scottish Health Research Register and Biobank. SHARE is supported by NHS Research Scotland, Universities in Scotland and the Chief Scientists Office. In addition, several colleagues have contributed significantly to VAC4COVID, including, but not limited to, Margaret Barton, Gavin Dobson, Caroline Hall, Lewis McConnachie, Daniel Morales, David Rorie, and Wendy Saywood. MedDRA® trademark is registered by ICH.

Contributors TMM initiated the project and is the guarantor responsible for this finished work and the conduct of the study. TMM, IM, ER and AR designed the study. The protocol was developed by TMM, IM, AR, ER, GG, A Doney, SM and RB. KZ, ER and AR developed the VAC4COVID website and software. SM is responsible for statistical analysis. AR, ER and GG drafted the manuscript. AR, ER, SM, A Doney, A Duncan, IM, RB, FP, KZ and TMM reviewed and edited further drafts before all authors approved the final submitted version. AR and ER contributed equally to this work. The corresponding author (AR) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors and was funded by the University of Dundee.

Competing interests TM, IM and A Doney have received consultancy fees to their university from AstraZeneca not relating to this work. IM has received personal consultancy fees from AstraZeneca not pertaining to this work. A Duncan has previously worked as an NHS study physician on COVID-19 vaccine trials sponsored by Oxford University, Valneva, BioNTech and AstraZeneca. The authors declare no other relationships or activities that could appear to have influenced the submitted work.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by South Central - Berkshire B Research Ethics Committee (ref: 21/SC/0015, IRAS project ID: 286051). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The dataset will be stored within a user-access controlled database on the MEMO Research server which is part of the University of Dundee. At the end of the study, it will be archived according to UoD guidelines and accessible on request for the purpose of audit and regulatory inspection only. The analysed data will be part of the publication of the results at the end of the study. Individual-level data will not be made available to ensure that anonymity is maintained.

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