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# Adverse events after first and second doses of COVID-19 vaccination in England: a national vaccine surveillance platform self-controlled case series study

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## Abstract

**Objectives:** To estimate the incidence of adverse events of interest (AEIs) after receiving their first and second doses of coronavirus disease 2019 (COVID-19) vaccinations, and to report the safety profile differences between the different COVID-19 vaccines.

**Design:** We used a self-controlled case series design to estimate the relative incidence (RI) of AEIs reported to the Oxford-Royal College of General Practitioners national sentinel network. We compared the AEIs that occurred seven days before and after receiving the COVID-19 vaccinations to background levels between 1 October 2020 and 12 September 2021.

**Setting:** England, UK.

**Participants:** Individuals experiencing AEIs after receiving first and second doses of COVID-19 vaccines.

**Main outcome measures:** AEIs determined based on events reported in clinical trials and in primary care during post-license surveillance.

**Results:** A total of 7,952,861 individuals were vaccinated with COVID-19 vaccines within the study period. Among them, 781,200 individuals (9.82%) presented to general practice with 1,482,273 AEIs. Within the first seven days post-vaccination, 4.85% of all the AEIs were reported. There was a 3–7% decrease in the overall RI of AEIs in the seven days after receiving both doses of Pfizer-BioNTech BNT162b2 (RI = 0.93; 95% CI: 0.91–0.94) and 0.96; 95% CI: 0.94–0.98), respectively) and Oxford-AstraZeneca ChAdOx1 (RI = 0.97; 95% CI: 0.95–0.98) for both doses), but a 20% increase after receiving the first dose of Moderna mRNA-1273 (RI = 1.20; 95% CI: 1.00–1.44)).

**Conclusions:** COVID-19 vaccines are associated with a small decrease in the incidence of medically attended AEIs. Sentinel networks could routinely report common AEI rates, which could contribute to reporting vaccine safety.

## Keywords

Epidemiology, public health, vaccination programmes

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## Introduction

The coronavirus disease 2019 (COVID-19) immunisation programme in the United Kingdom (UK) began in December 2020, with the UK's Joint Committee on Vaccination and Immunisation (JCVI) initially recommending COVID-19 vaccination for all adults aged 18 years and over, and prioritising older adults, care home residents and staff, health and social care workers, and individuals in clinical risk groups. This was later expanded to include children and young people aged 12 years and over with underlying chronic conditions that put them at risk of serious COVID-19 disease in July 2021, all 16- to 17-year-olds in August 2021, and

all 12- to 15-year-olds (first dose only) in September 2021. The COVID-19 booster programme also commenced in September 2021. The vaccines currently being used in the UK are the Pfizer-BioNTech BNT162b2 mRNA, the Oxford-AstraZeneca ChAdOx1 nCoV-19 and the Moderna mRNA-1273, hereafter referred to as BNT162b2, ChAdOx1 and mRNA-1273, respectively. Studies have shown that these vaccines are highly effective at reducing severe COVID-19 disease.[1,2]

The safety of COVID-19 vaccines was rigorously assessed through clinical trials before they received emergency use authorisation, and these trials showed that serious adverse events were rare. However, to detect rarer adverse events of interest (AEIs) after COVID-19 immunisation, follow-up is needed post-licensure in larger general populations. Examples include reporting of extremely rare adverse event of concurrent thrombosis and thrombocytopenia ('thrombotic thrombocytopenia syndrome' (TTS)) after vaccination with the first dose of ChAdOx1, and myocarditis and acute pericarditis after BNT162b2 or mRNA-1273 vaccination. The former was only detected after the national immunisation programme was rolled out, which then led the JCVI to advise in May 2021 that all adults aged under 40 years should be offered an alternative to ChAdOx1.[3] A summary of safety signals associated with COVID-19 vaccines that were detected post-licensure is presented in Box 1.

Post-authorisation surveillance is required to continually assess vaccine safety in the real world and to maintain public confidence in vaccines.[10] While such surveillance platforms are well established for influenza vaccination,[11,12] no such systems have been established for COVID-19 vaccination.

This study was conducted to estimate the incidence of a list of prespecified AEIs (Box 2) after the first and second doses of a COVID-19 vaccination compared with background levels using 'real-world' primary care data, and to explore differences in safety profile between vaccine brands. This list is developed through mapping potential adverse events listed in the regulatory approval documents published by the Medicines and Healthcare products Regulatory Agency and the European Medicines Agency (EMA) to Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) (Supplementary Table S1).

**Box 1.** Summary of COVID-19 vaccine safety signals detected in post-licensure surveillance.

| |
|---|
| Thrombotic thrombocytopenia syndrome |
| Thrombotic thrombocytopenia syndrome (TTS), also known as vaccine-induced immune thrombosis and thrombocytopenia (VITT), is a very rare immune condition, in which pathologic antibodies to platelet factor 4 causes blood clots in different parts of the body as well as a low platelet count. A disproportionate number of cases of these rare events have been reported after the first dose of ChAdOx1 vaccination,[4,5] with the signal later being confirmed in population studies.[6,7] During the investigations, a number of countries suspended the use of ChAdOx1, and later restricted their use to certain age groups. |
| Myocarditis and pericarditis |
| Cases of myocarditis and pericarditis have been reported after BNT162b2 and mRNA-1273 vaccination.[7,8] A population-based study in England found increased risks of myocarditis after the first dose of BNT162b2 and ChAdOx1 vaccines, and both doses of the mRNA-1273 vaccine.[9] No increased risk of pericarditis was observed with any of the vaccines. |
| Neurological complications |
| A number of cases of rare neurological adverse events such as Guillain-Barré syndrome (GBS) and Bell's palsy have been reported since large-scale vaccination programmes have commenced around the world. Increased risks of GBS and Bell's palsy after ChAdOx1 vaccination were identified in an English cohort, with the association between ChAdOx1 and GBS replicated in an independent Scottish cohort.[9] |

## Methods

### Data source

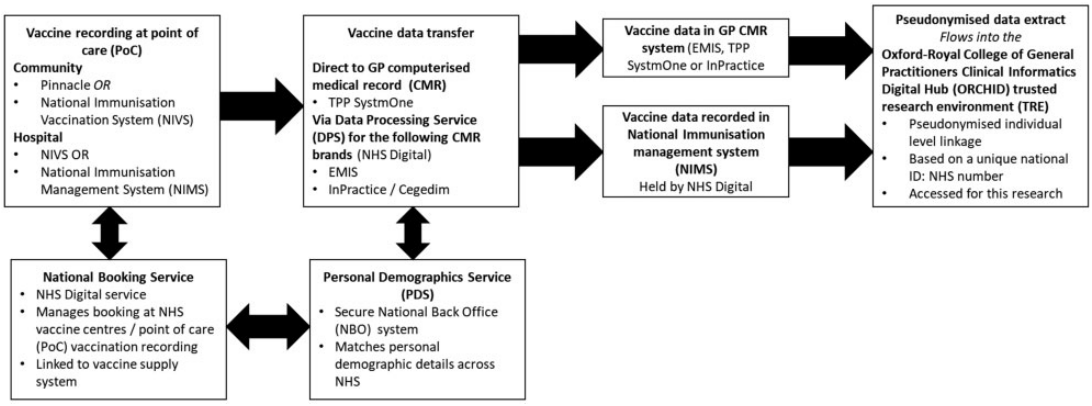
We used data from the Oxford-Royal College of General Practitioners Clinical Informatics Digital Hub (ORCHID),[14] which were derived from pseudonymised extracts of computerised primary care records. The UK has registration-based primary care, where one patient registers with a single general practice, and computerised medical records (CMRs) have been in routine use for over 20 years. This sentinel surveillance database was established in 1957, and has been used for influenza monitoring and assessing influenza vaccine effectiveness since 1967 in influenza vaccine safety surveillance.[15] At the time of this study, the sentinel network cohort included around 8 million ($n = 7{,}952{,}861$) patient records from general practices across England. COVID-19 vaccine data, including vaccine date, type and dose of all individuals vaccinated in England, are automatically transferred into the practice CMR directly or via NHS Digital's Data Processing Service (DPS), see Figure 1. In addition, the ORCHID receives

**Box 2.** List of adverse events of interest included in this study.

- General non-specific
  - Asthenia
  - Fatigue
  - Fever
  - Fever with chills
  - Malaise
  - Oedema of face
- Injection site
  - Injection site bruising
  - Injection site burning
  - Injection site erythema
  - Injection site induration
  - Injection site inflammation
  - Injection site irritation
  - Injection site pain
  - Injection site pruritus
  - Injection site rash
  - Injection site swelling
  - Injection site urticaria
- Ear
  - Tinnitus
- Gastrointestinal
  - Abdominal pain
  - Diarrhoea
  - Nausea
  - Vomiting
- Immune
  - Anaphylaxis
  - Hypersensitivity reaction
- Lymphatic
  - Lymphadenopathy
- Metabolic/nutrition
  - Decrease in appetite
- Musculoskeletal
  - Joint pain
  - Myalgia
  - Weakness
- Neurological
  - Bell's palsy
  - Dizziness
  - Drowsiness
  - Guillain-Barre syndrome
  - Headache
  - Lethargy
  - Paraesthesia
  - Peripheral tremor
- Psychiatric
  - Insomnia
- Respiratory
  - Cough
  - Influenza-like illness
  - Sneezing
  - Sore throat
- Skin
  - Angioedema
  - Eruption of skin
  - Hyperhidrosis
- Vascular
  - Capillary leak syndrome
  - Myocarditis
  - Pericarditis

(continued)

**Figure 1.** Flow of data from point-of-care (PoC) vaccination through to the Oxford-RCGP Clinical Informatics Digital Hub (ORCHID). PoC vaccination can be hospital or community. Vaccination bookings and vaccination supplies are managed through a National Booking Service. A Personal Demographic Service (PDS) securely holds all individuals' demographic data to ensure matching across the English NHS, data are linked using NHS number, this is pseudonymised prior to sending into the ORCHID trusted research environment (TRE).




direct feed from the National Immunisation Management System (NIMS). While there were differences between data sources at the start of vaccination from December 2019 to March 2020, the direct DPS transfer route is reliable.

## Prespecified AEIs

Patients were followed up within the pseudonymised data retrospectively for consultations for prespecified AEIs that were determined based on adverse events reported in clinical trials and post-licensure surveillance (see Box 2 for the included conditions). Clinical consultations for adverse events are recorded into primary care CMR systems using SNOMED CT and then curated into variables for research studies. We have excluded thrombotic and haemorrhagic events from this analysis as they have already been investigated in a separate study.[6,16]

## Data extraction

We extracted the following data: date of birth, sex, self-reported ethnicity using an ontology to maximise data capture,[17] socioeconomic status using the 2019 English Index of Multiple Deprivation (IMD) quintile,[18] date of death, dates of registration and deregistration at the general practice, COVID-19 vaccination dates (first and second dose), COVID-19 vaccine brand (first and second dose), AEI date, AEI type. IMD quintile was derived using the postcode of the patient at the individual level at the point of data extraction, after which the postcode is not retained. Where the IMD quintile for the patient was missing, this was imputed using the postcode of the general practice at which they were registered.

## Inclusion/exclusion criteria

We included all individuals aged 16 and over on the study index date (1 October 2020) and who reported at least one consultation for any of the listed AEIs between the study index date and the latest data extract date (12 September 2021). The age cut-off of 16 years was selected based on guidelines at the time of the study.

We excluded AEIs that were recorded for individuals:

- Not registered with a general practice on 1 October 2020;
- Died on or before 1 October 2020;
- With less than 14 days of follow-up after their first dose vaccination due to deregistration or death;
- With their first dose COVID-19 vaccine recorded before 8 December 2020;
- With their first dose ChAdOx1 vaccine recorded before 4 January 2021;
- With their first dose mRNA-1273 vaccine recorded before 13 April 2021;
- Who received their second dose less than 19 days after their first dose;
- Who received different brands of vaccines for their first and second dose; and
- Who did not have a vaccine brand recorded.

Medically attended AEIs recorded after the earliest of extract up-to-date, deregistration date or date of death were also excluded.

### Statistical analyses

We computed descriptive statistics to provide an overview of the demographic characteristics of the study sample. For COVID-19 vaccine brand, we undertook a complete case analysis.

For the main analysis, we used the self-controlled case series (SCCS) design.[19,20] The SCCS method is a case-only method, in which the rate of events during pre-defined risk periods are compared with the rate of events during the rest of the observation period (i.e. control period). Each individual is their own control in such an analysis, and potential time-invariant confounding effects of between-person characteristics are thus eliminated. This method is particularly useful for evaluating vaccine safety, as it is often difficult to identify a comparator group since most in the population will receive a vaccine, and those who do not may not be suitable comparators (for instance, they were not vaccinated for medical reasons).

We conducted separate SCCS analysis for the BNT162b2, ChAdOx1 and mRNA-1273 COVID-19 vaccines. The observation period began on the study index date of 1 October 2020 and ended on the earliest of the patient's death, deregistration from their general practice or study end date. For all models, we defined pre-exposure and risk periods relative to the day of vaccination (day 0), with days −7 to −1 as the pre-exposure period and days 0 to 7 as the risk period for both dose 1 and dose 2. The time outside of these defined periods is used as control, and we computed the relative incidence (RI) of medically attended AEIs in the pre-exposure and risk periods compared with control. The duration of seven days was chosen because mild or moderate AEIs tend to have an onset shortly after vaccination. We only included vaccinated individuals in the SCCS.

Model 1 included the vaccine main effect and a calendar month effect to account for variation at different times of the rollout. We have chosen to use a calendar month effect, as while it is expected that some of the prespecified conditions may exhibit a seasonal pattern, it is not expected to show very strong seasonal patterns to require accounting for this by week. Model 2 included an age interaction (with age centred at 50 years) to account for potential effects of the vaccine rollout by calendar age. We chose to centre age at 50 years as this is close to the median age of our vaccinated populations, age 54 years for BNT162b2 and 57 years for ChAdOx1 COVID-19 vaccination. Finally, we performed Model 2 separately for the different categories of AEIs to explore differences between the safety profiles of the three brands of vaccines.

We carried out a sensitivity analysis where we repeated Model 2 but for a 21-day post-vaccine risk period. We compared RI in the control period with the pre-exposure period (seven days before to the day before vaccination) and with three successive risk periods: (1) 0 to 7 days after vaccination (as in the main study); (2) days 8–14 after vaccination; and (3) days 15–21 post vaccination. We hypothesised that the RI of AEIs would decline in successive weeks after the week of vaccination.

All statistical analyses were conducted in R version 4.1.2,[21] using the following packages: *dplyr* (version 1.0.7),[22] *lubridate* (version 1.8.0),[23] *SCCS* (version 1.2)[24] and *tableone* (version 0.12.0).[25] Graphical output was generated using *ggplot2* (version 3.3.5).[26]

### Ethical statement

All potentially identifiable data were pseudonymised as close to the source as possible and not made available to researchers; data were not extracted for patients who opted out of data sharing. All data were stored and processed in the ORCHID Trusted Research Environment. Ethical permission was obtained from the UK's Health Research Authority (REC reference: 21/HRA/2786). Participation in DaCVaP was approved by the RCGP-University of Oxford Joint Research and Surveillance Centre Committee (JRSCC).

## Results

### Frequencies of medically attended AEIs

The ORCHID study consisted of 7,952,861 individuals. Among them, 781,200 (9.82%), our cohort, reported a total of 1,482,273 (1.90 events per person) medically attended AEIs during the study period. Inclusion and exclusion at each step are shown in the flow diagram in Supplementary Figure F1. Only 56,914 (4.85%) of these AEIs were reported within the first seven days after receiving the vaccination. The mean age of the cohort was 51.82 years, with a strong female preponderance (62.36% female) and a large majority were of White ethnicity (74.85%). Around three-quarters of the sample were already double-vaccinated, and close to half of them received the ChAdOx1 vaccine (Table 1). For reference (and completeness), we have also reported medical events that were recorded in the unvaccinated individuals during the study period. The time at which patients received their vaccinations during the study period is presented in Figure 2.

**Table 1.** Demographic characteristics of the cohort included in this study.

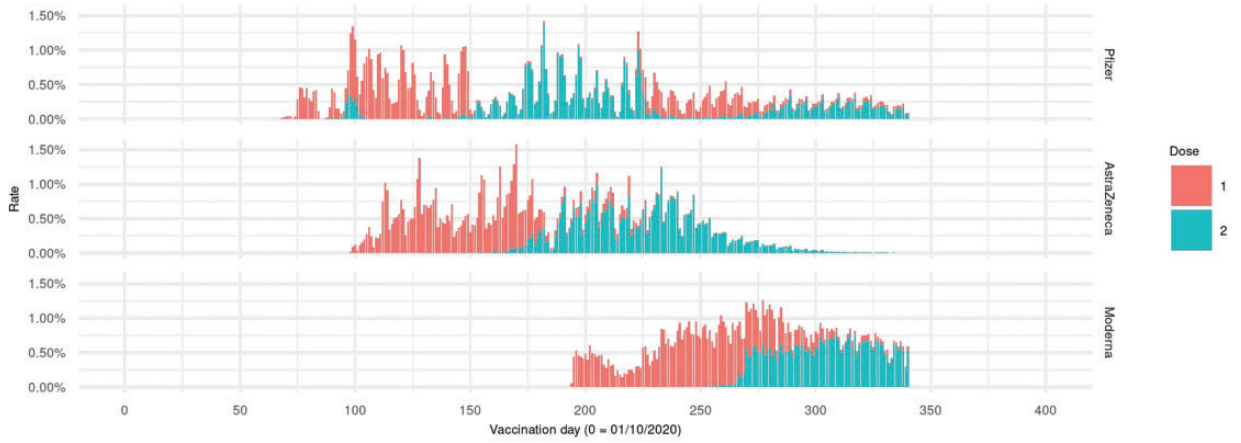
| | BNT162b2 ($n = 300,641$) | ChAdOx1 ($n = 368,898$) | mRNA-1273 ($n = 12,024$) | Unvaccinated ($n = 99,637$) |
|---|---|---|---|---|
| Age at study index date (years), mean (SD) | 52.09 (22.76) | 56.19 (15.95) | 32.39 (9.49) | 37.16 (17.18) |
| Sex, *n* (%) | | | | |
| Female | 192,364 (63.98) | 223,982 (60.72) | 7,386 (61.43) | 63,438 (63.67) |
| Male | 108,277 (36.02) | 144,916 (39.28) | 4,638 (38.57) | 36,199 (36.33) |
| Ethnicity, *n* (%) | | | | |
| White | 226,147 (75.22) | 287,569 (77.95) | 8,384 (69.73) | 62,629 (62.86) |
| Asian | 19,939 (6.63) | 22,354 (6.06) | 792 (6.59) | 7,722 (7.75) |
| Black | 6,190 (2.06) | 8,233 (2.23) | 245 (2.04) | 7,777 (7.81) |
| Mixed | 3,399 (1.13) | 3,400 (0.92) | 220 (1.83) | 2,703 (2.71) |
| Other | 2,802 (0.93) | 2,991 (0.81) | 186 (1.55) | 2,002 (2.01) |
| Missing | 42,164 (14.02) | 44,351 (12.02) | 2,197 (18.27) | 16,804 (16.87) |
| Index of Multiple Deprivation quintile, *n* (%) | | | | |
| 1 – most deprived | 50,606 (16.83) | 64,157 (17.39) | 1,931 (16.06) | 30,872 (30.98) |
| 2 | 55,542 (18.47) | 66,510 (18.03) | 2,391 (19.89) | 23,302 (23.39) |
| 3 | 60,069 (19.98) | 73,129 (19.82) | 2,196 (18.26) | 17,284 (17.35) |
| 4 | 64,612 (21.49) | 79,883 (21.65) | 2,496 (20.76) | 15,004 (15.06) |
| 5 – least deprived | 69,784 (23.21) | 85,188 (23.09) | 3,009 (25.02) | 13,150 (13.20) |
| Missing | 28 (0.01) | 31 (0.01) | 1 (0.01) | 25 (0.03) |
| Number of vaccine doses received, *n* (%) | | | | |
| 0 | 0 (0.00) | 0 (0.00) | (0.00) | 99,637 (100.00) |
| 1 | 41,826 (13.91) | 30,103 (8.16) | 3,426 (28.49) | 0 (0.00) |
| 2 | 258,815 (86.09) | 338,795 (91.84) | 8,598 (71.51) | 0 (0.00) |

The frequencies of medically attended AEIs reported within the study period are presented by condition and by vaccine brand in Table 2. There were consultations for almost all AEIs within the study period, with the highest frequencies observed for milder symptoms such as joint pain, abdominal pain, cough and headache. More severe conditions, such as Guillain-Barre syndrome, myocarditis and pericarditis, were relatively rare. For reference (and completeness), we have also reported medical events that were recorded in the unvaccinated individuals during the study period.

### *Incidence of medically attended AEIs in the different periods*

In Model 1, we observed a slightly lower RI of medically attended AEIs in the pre-exposure and risk periods for both BNT162b2 and ChAdOx1 compared with background levels, but a higher incidence

**Figure 2.** Time when individuals received their first and second doses by brand.




of medically attended AEIs in the risk period after the second dose of mRNA-1273 (Table 3).

After accounting for age with an age interaction effect (Model 2), the RI remained lower than background levels in the pre-exposure and risk periods for both BNT162b2 and ChAdOx1, but there was a marginally higher RI after dose 1 of mRNA-1273. The significant age interaction effects indicated that fewer medically attended AEIs were reported as age increased for individuals who received BNT162b2 or ChAdOx1. We ran the models with age centred at 30 and 70 years to illustrate the differences in main effects for the different age groups (Supplementary Table S2 and S3).

### *Incidence of medically attended AEIs by category*

As the frequencies of medically attended AEIs among individuals who received the mRNA-1273 vaccine were too low for many of the categories, we performed the secondary analysis only for BNT162b2 and ChAdOx1.

After the first dose of ChAdOx1, there was an increased presentation with general non-specific, injection site and skin conditions. After both doses of BNT162b2 but just the first dose of ChAdOx1 there was an increased incidence in immune and lymphatic conditions (Table 4).

### *Sensitivity analysis*

Our sensitivity analysis showed that in the third observation period, days 15 to 21 after both doses of BNT162b2 and mRNA-1273, and after the first dose of ChAdOx1, the RI of AEIs was not significantly different from background levels. In days 8 to 14 and days 15 to 21 after the second dose of ChAdOx1, the RI of AEIs was slightly elevated (Supplementary Table S4).

## Discussion

There was a small decrease in medically attended AEIs after COVID-19 vaccination, reported by just under 10% of the registered population. A total of 781,200 individuals sought medical attention for any of the prespecified AEIs, reporting 1,482,273 events with a rate of almost two events per person. Most of these AEIs were not temporally associated with vaccination, and even those that occurred within seven days of vaccination, may not necessarily be causally related to vaccination.

The incidence of medically attended AEIs was low compared with background levels of presentation, but were detectable in the first seven days post-vaccination after both first and second doses for BNT162b2 and ChAdOx1. We found a 3–7% decrease in incidence of medically attended AEIs in the seven days post-vaccination for BNT162b2 and ChAdOx1, but a 20% increase after the first dose of mRNA-1273. Fewer medically attended AEIs were reported as age increased for both BNT162b2 and ChAdOx1 vaccines. We think that the small decrease in AEIs may have been due to vaccines having a higher threshold for attending their practice while they waited for the vaccine to induce an immune response.

The safety profile varied slightly between different vaccine brands. The only notable differences were in the increased incidence of general non-specific, injection site and skin conditions after the first dose of ChAdOx1, as well as the increased incidence of immune and lymphatic conditions after the second

**Table 2.** Frequencies of individuals who experienced AEIs, by condition and vaccine brand.

| | BNT162b2 (1 or 2 doses) ($n = 300,641$) | ChAdOx1 (1 or 2 doses) ($n = 368,898$) | mRNA-1273 (1 or 2 doses) ($n = 12,024$) | Unvaccinated ($n = 99,637$) |
|---|---|---|---|---|
| General non-specific | | | | |
| Asthenia | 1,064 | 1,494 | 11 | 505 |
| Fatigue | 34,930 | 40,928 | 1,525 | 11,282 |
| Fever | 8,940 | 12,120 | 270 | 3578 |
| Fever with chills | 28 | 29 | 0 | 5 |
| Malaise | 8,797 | 10,935 | 173 | 2,252 |
| Oedema of face | 60 | 101 | 4 | 19 |
| Injection site | | | | |
| Injection site bruising | 0 | 0 | 0 | 0 |
| Injection site burning | 0 | 0 | 0 | 0 |
| Injection site erythema | 9 | 25 | 1 | 5 |
| Injection site induration | 0 | 3 | 0 | 0 |
| Injection site inflammation | 1 | 0 | 0 | 0 |
| Injection site irritation | 0 | 0 | 0 | 0 |
| Injection site pain | 16 | 57 | 2 | 6 |
| Injection site pruritus | 0 | 0 | 1 | 0 |
| Injection site rash | 2 | 5 | 1 | 1 |
| Injection site swelling | 16 | 27 | 4 | 2 |
| Injection site urticaria | 0 | 3 | 0 | 0 |
| Ear | | | | |
| Tinnitus | 7,972 | 11,901 | 368 | 2,081 |
| Gastrointestinal | | | | |
| Abdominal pain | 76,997 | 92,299 | 3,587 | 31,389 |
| Diarrhoea | 26,181 | 32,112 | 744 | 6,124 |
| Nausea | 9,541 | 10,620 | 288 | 4,060 |
| Vomiting | 10,588 | 12,798 | 378 | 6,096 |
| Immune | | | | |
| Anaphylaxis | 419 | 861 | 21 | 235 |
| Hypersensitivity reactions | 12,475 | 16,099 | 606 | 4,860 |

(continued)

**Table 2.** Continued.

| | BNT162b2 (1 or 2 doses) ($n = 300,641$) | ChAdOx1 (1 or 2 doses) ($n = 368,898$) | mRNA-1273 (1 or 2 doses) ($n = 12,024$) | Unvaccinated ($n = 99,637$) |
|---|---|---|---|---|
| Lymphatic | | | | |
| Lymphadenopathy | 4,290 | 3,986 | 286 | 1,508 |
| Metabolic/nutrition | | | | |
| Decrease in appetite | 4,746 | 5,899 | 90 | 1,872 |
| Musculoskeletal | | | | |
| Joint pain | 89,366 | 124,710 | 2,470 | 19,813 |
| Myalgia | 15,357 | 17,003 | 109 | 1,358 |
| Weakness | 1,064 | 1,494 | 11 | 505 |
| Neurological | | | | |
| Bell's palsy | 1,199 | 1,661 | 50 | 425 |
| Dizziness | 27,802 | 30,702 | 659 | 6,026 |
| Drowsiness | 916 | 1,175 | 30 | 303 |
| Guillain-Barre syndrome | 91 | 221 | 0 | 62 |
| Headache | 60,901 | 74,663 | 3,365 | 22,855 |
| Lethargy | 1,786 | 2,166 | 53 | 496 |
| Paraesthesia | 6,533 | 9,394 | 223 | 1,865 |
| Peripheral tremor | 3,633 | 4,752 | 50 | 597 |
| Psychiatric | | | | |
| Insomnia | 11,723 | 14,714 | 434 | 4,583 |
| Respiratory | | | | |
| Cough | 67,336 | 94,675 | 1,716 | 17,926 |
| Influenza-like illness | 3,349 | 4,990 | 122 | 1,561 |
| Sneezing | 255 | 233 | 6 | 110 |
| Sore throat | 19,406 | 19,338 | 1,056 | 8,221 |
| Skin | | | | |
| Angioedema | 647 | 1,003 | 25 | 214 |
| Eruption of skin | 49,270 | 57,713 | 2,075 | 14,383 |
| Hyperhidrosis | 828 | 623 | 34 | 420 |
| Vascular | | | | |

(continued)

**Table 2.** Continued.

| | BNT162b2 (1 or 2 doses) ($n = 300,641$) | ChAdOx1 (1 or 2 doses) ($n = 368,898$) | mRNA-1273 (1 or 2 doses) ($n = 12,024$) | Unvaccinated ($n = 99,637$) |
|---|---|---|---|---|
| Capillary leak syndrome | 0 | 0 | 0 | 0 |
| Myocarditis | 220 | 258 | 8 | 46 |
| Pericarditis | 429 | 597 | 21 | 177 |

**Table 3.** Relative incidence of medically attended AEIs in the pre-exposure and risk periods for both doses by vaccine brand.

| | BNT162b2 | ChAdOx1 | mRNA-1273 |
|---|---|---|---|
| Model 1 | | | |
| D1: −7 to −1 | 0.96 (0.94–0.98)*** | 0.96 (0.94–0.98)*** | 1.02 (0.96–1.09) |
| D1: 0 to 7 | 0.92 (0.90–0.94)*** | 0.96 (0.94–0.97)*** | 1.05 (1.00–1.12) |
| D2: −7 to −1 | 0.91 (0.89–0.93)*** | 0.96 (0.94–0.98)*** | 1.00 (0.94–1.07) |
| D2: 0 to 7 | 0.94 (0.92–0.96)*** | 0.95 (0.94–0.97)*** | 1.07 (1.01–1.14)* |
| Model 2 | | | |
| D1: −7 to −1 | 0.96 (0.94–0.98)*** | 0.97 (0.95–0.98)*** | 1.16 (0.95–1.41) |
| D1: 0 to 7 | 0.93 (0.91–0.94)*** | 0.97 (0.95–0.98)*** | 1.20 (1.00–1.44)* |
| D2: −7 to −1 | 0.92 (0.90–0.94)*** | 0.96 (0.95–0.98)*** | 1.07 (0.95–1.35) |
| D2: 0 to 7 | 0.96 (0.94–0.98)*** | 0.97 (0.95–0.98)*** | 1.13 (0.91–1.39) |
| D1: −7 to −1 × age | 0.9978 (0.9970–0.9987)*** | 0.9988 (0.9978–0.9999)* | 1.0094 (0.9990–1.0199) |
| D1: 0 to 7 × age | 0.9973 (0.9965–0.9982)*** | 0.9982 (0.9973–0.9992)*** | 1.0035 (0.9944–1.0128) |
| D2: −7 to −1 × age | 0.9981 (0.9972–0.9991)*** | 0.9993 (0.9982–1.0004) | 1.0062 (0.9932–1.0193) |
| D2: 0 to 7 × age | 0.9965 (0.9956–0.9973)*** | 0.9979 (0.9968–0.9989)*** | 0.9988 (0.9874–1.0103) |

Age centred at 50 years in Model 2.
*$p < 0.05$, ***$p < 0.001$.

dose of BNT162b2, which was not observed with the other brand.

The strength of this study is the well-established ORCHID practice network,[27] with high data quality as practices get feedback through practice visits (currently largely virtual) and dashboards.[28] The NIMS has ensured that COVID-19 vaccination records are reliably captured and posted back into primary care CMRs; this system has ensured that only a very small proportion of people did not have their vaccine brand recorded (0.5% for the first dose and 0.6% for the second dose) compared with influenza vaccination (1.4%).[29]

However, there are always uncertainties about data quality and whether all relevant events have been captured, resulting in an underestimation of the incidence of medically attended AEIs. In this study, only events requiring medical attention and involving a general practitioner (GP) consultation have been captured. Moreover, since the base

**Table 4.** Relative incidence of medically attended AEIs in the pre-exposure and risk periods for both doses by category and vaccine brand.

| | BNT162b2 | ChAdOx1 |
|---|---|---|
| General / injection site / skin | | |
| D1: −7 to −1 | 0.97 (0.92–1.01) | 0.96 (0.92–1.00) |
| D1: 0 to 7 | 0.98 (0.94–1.02) | 1.07 (1.03–1.11)*** |
| D2: −7 to −1 | 0.95 (0.90–0.99)* | 0.98 (0.94–1.03) |
| D2: 0 to 7 | 0.98 (0.94–1.03) | 0.96 (0.93–1.01) |
| Gastrointestinal / metabolic / nutrition | | |
| D1: −7 to −1 | 0.89 (0.86–0.93)*** | 0.95 (0.91–0.99)** |
| D1: 0 to 7 | 0.87 (0.84–0.91)*** | 0.93 (0.90–0.97)*** |
| D2: −7 to −1 | 0.88 (0.84–0.92)*** | 0.96 (0.92–1.00)* |
| D2: 0 to 7 | 0.87 (0.83–0.90)*** | 0.93 (0.89–0.97)*** |
| Immune / lymphatic | | |
| D1: −7 to −1 | 1.16 (1.04–1.28)** | 1.20 (1.09–1.32)*** |
| D1: 0 to 7 | 1.32 (1.20–1.45)*** | 1.55 (1.43–1.68)*** |
| D2: −7 to −1 | 0.89 (0.78–1.01) | 1.00 (0.89–1.11) |
| D2: 0 to 7 | 1.41 (1.28–1.56)*** | 1.07 (0.97–1.78) |
| Musculoskeletal | | |
| D1: −7 to −1 | 1.01 (0.96–1.06) | 1.01 (0.97–1.05) |
| D1: 0 to 7 | 0.92 (0.88–0.97)*** | 0.87 (0.84–0.91)*** |
| D2: −7 to −1 | 0.92 (0.87–0.97)** | 1.06 (1.02–1.11)** |
| D2: 0 to 7 | 0.97 (0.92–1.01) | 1.00 (0.96–1.04) |
| Neurological / psychiatric | | |
| D1: −7 to −1 | 0.99 (0.95–1.03) | 0.94 (0.91–0.98)** |
| D1: 0 to 7 | 0.92 (0.88–0.95)*** | 1.00 (0.97–1.04) |
| D2: −7 to −1 | 0.91 (0.87–0.95)*** | 0.91 (0.87–0.94)*** |
| D2: 0 to 7 | 0.94 (0.90–0.98)** | 1.03 (0.99–1.07) |
| Respiratory / ear | | |
| D1: −7 to −1 | 0.91 (0.86–0.95)*** | 0.87 (0.83–0.91)*** |
| D1: 0 to 7 | 0.87 (0.83–0.91)*** | 0.82 (0.79–0.86)*** |
| D2: −7 to −1 | 0.89 (0.84–0.93)*** | 0.90 (0.86–0.95)*** |
| D2: 0 to 7 | 0.93 (0.88–0.97)** | 0.84 (0.80–0.88)*** |

(continued)

**Table 4.** Continued.

| | BNT162b2 | ChAdOx1 |
|---|---|---|
| Vascular | | |
| D1: −7 to −1 | 0.61 (0.27–1.34) | 0.66 (0.38–1.16) |
| D1: 0 to 7 | 0.88 (0.51–1.51) | 0.77 (0.47–1.26) |
| D2: −7 to −1 | 0.97 (0.51–1.82) | 0.60 (0.31–1.17) |
| D2: 0 to 7 | 1.24 (0.72–2.12) | 0.46 (0.23–0.94)* |

Age centred at 50 years.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

population is built on GP registrations, the denominator may have been inflated, including 'ghosts' who cannot get sick. It is also likely that the seven-day risk period selected will not capture all AEIs presented; we used this window because it is the window selected by the EMA for surveillance of AEIs post-influenza vaccination.[12] We do not have access to data about whether those vaccinated were healthcare workers, of which most were vaccinated with the BNT162b2 vaccine, and may have had greater exposure to the SARS-CoV-2 virus, or reported more adverse events.[30] Finally, we have not taken into account SARS-CoV-2 infections prior to vaccination or during the study period, which can be associated with some of these AEIs, and it remains unknown whether prior infection is associated with a higher or lower incidence of AEIs.

Our sensitivity analysis suggested it was reasonable to focus on the first seven days after vaccination as is EMA recommendations for enhanced surveillance post influenza vaccination.[11–13,15] However, given the novelty of COVID-19 vaccination and the suggestion that AEIs may have a higher incidence in the periods of days 8 to 14 and days 15 to 21 post-second vaccination for one of the vaccines, this should be considered in future analyses.

We did not include the rare but serious adverse events associated with COVID-19 vaccines as already reported[5–7,9] and our method excluded conditions associated with mortality during the observation period to prevent violation of the event independence assumption of the SCCS design. Our overall conclusion about low RI of AEIs should not ignore these rare but important risks.[6,7]

Our COVID-19 vaccine data may provide a benchmark for future years as COVID-19 become endemic and there is a likely need for ongoing vaccination. It is possible that either enhanced passive surveillance, where questionnaires are additionally used,[15] or adding text searches using natural language processing (NLP) might increase AEI capture.[31] One study increased AEI capture using NLP by around 15%.[32] Where we have conducted enhanced passive surveillance for influenza, we have detected more AEIs, particularly local reactions that may not have reached the threshold for medical attendance.[15]

Though others have reported more serious AEIs in males, studies present mixed findings over the effect of age.[33,34] Lymphadenopathy and myocarditis have also been reported in a national study of the BNT162b2 vaccine, but without a comparator.[35] Likewise, Bell's palsy, paraesthesia and Guillain-Barré syndrome have inconclusive associations with vaccination.[36,37]

General practice appointments dipped but then have recovered nearly back to normal after the COVID-19 pandemic, with a greater proportion of appointments taking place over the phone.[38] We have seen no evidence to suggest that this would have differently affected the pre- and post-vaccination window.

Sentinel networks may be well placed to provide contemporary passive surveillance data about AEIs after vaccination, with the potential to enhance this surveillance through additional data collection or by adding NLP.

## Conclusion

There is a need to establish a vaccine safety surveillance for reporting common AEIs after the administration of COVID-19 vaccines, similar to that of influenza vaccines. While it is recognised that COVID-19 vaccines are associated with a small increase in incidence of rare but serious adverse events, there has been less reporting of other AEIs. Against a list of prespecified medically attended AEIs, we found there was no increase in incidence. Standardised reporting of AEIs, possibly via sentinel

systems, could provide safety data complementary to other mechanisms for monitoring vaccine safety.

## Declarations

**Competing Interests:** SdeL is Director of the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) and has received funding from AstraZeneca, GSK, Sanofi and Seqirus and been member of advisory boards for AstraZeneca, Sanofi and Seqirus all through his University. The AstraZeneca studies include ATTEST, a study of Thrombotic Thrombocytopenia. SdeL is PI and FDRH Co-PI. DTB is on secondment to the Department of Health (Northern Ireland) and has been a member or observer on the UK Scientific Advisory Group for Emergencies and many of its subgroups. RKO is a member of the National Institute for Health and Care Excellence (NICE) Technology Appraisal Committee (TAC) and has served as a paid consultant to the pharmaceutical industry, providing methodological advice and support unrelated to this research. AS is a member of the Scottish Government's CMO COVID-19 Advisory Group and its Standing Committee on Pandemics; he was a member of AstraZeneca's Thrombotic Thrombocytopenic Taskforce. All AS' roles are unremunerated.

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**Ethics approval:** This study was ethically approved (REC reference: 21/HRA/2786).

**Guarantor:** UA.

**Contributorship:** SdeL, MJ, RT and AS conceived the study with input into the design from the DaCVaP study team. RT and SdeL drafted the first version. RT, SdeL and UA led the revisions of the article. RT with input from MJ conducted the analysis. RB and RT created the data tables for the analysis. JW was responsible for variable curation. All authors read and commented on the draft paper. AS is the PI for DaCVaP.

**Data sharing statement:** The statistical analysis plan, R scripts used for the analysis and meta-data are available upon request. The data that support the findings of this study are not publicly available because they are based on pseudonymised sentinel network clinical records. These data are, however, available by application via ORCHID https://orchid.phc.ox.ac.uk. The terminology lists for the variables are available at Supplementary Table S1.

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