Adverse events following first and second dose COVID-19 vaccination in England, October 2020 to September 2021

Adverse events following first and second dose COVID-19 vaccination in England, October 2020 to September 2021: a national vaccine surveillance platform self-controlled case series study

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Citation style for this article:
Tsang Ruby SM, Joy Mark, Byford Rachel, Robertson Chris, Anand Sneha N, Hinton William, Mayor Nikhil, Kar Debasish, Williams John, Victor William, Akbari Ashley, Bradley Declan T, Murphy Siobhan, O'Reilly Dermot, Owen Rhiannon K, Chuter Antony, Beggs Jillian, Howsam Gary, Sheikh Aziz, Hobbs FD Richard, de Lusignan Simon. Adverse events following first and second dose COVID-19 vaccination in England, October 2020 to September 2021: a national vaccine surveillance platform self-controlled case series study. Euro Surveill. 2023;28(3):pii=2200195. https://doi.org/10.2807/1560-7917.ES.2023.28.3.2200195

Article submitted on 23 Feb 2022 / accepted on 01 Nov 2022 / published on 19 Jan 2023

Background: Post-authorisation vaccine safety surveillance is well established for reporting common adverse events of interest (AEIs) following influenza vaccines, but not for COVID-19 vaccines. Aim: To estimate the incidence of AEIs presenting to primary care following COVID-19 vaccination in England, and report safety profile differences between vaccine brands. Methods: We used a self-controlled case series design to estimate relative incidence (RI) of AEIs reported to the national sentinel network, the Oxford-Royal College of General Practitioners Clinical Informatics Digital Hub. We compared AEIs (overall and by clinical category) 7 days pre- and post-vaccination to background levels between 1 October 2020 and 12 September 2021. Results: Within 7,952,861 records, 781,200 individuals (9.82%) presented to general practice with 1,482,273 AEIs, 4.85% within 7 days post-vaccination. Overall, medically attended AEIs decreased post-vaccination against background levels. There was a 3–7% decrease in incidence within 7 days after both doses of Comirnaty (RI: 0.93; 95% CI: 0.91–0.94 and RI: 0.96; 95% CI: 0.94–0.98, respectively) and Vaxzevria (RI: 0.97; 95% CI: 0.95–0.98). A 20% increase was observed after one dose of Spikevax (RI: 1.20; 95% CI: 1.00–1.44). Fewer AEIs were reported as age increased. Types of AEIs, e.g. increased neurological and psychiatric conditions, varied between brands following two doses of Comirnaty (RI: 1.41; 95% CI: 1.28–1.56) and Vaxzevria (RI: 1.07; 95% CI: 0.97–1.78).Conclusion: COVID-19 vaccines are associated with a small decrease in medically attended AEI incidence. Sentinel networks could routinely report common AEI rates, contributing to reporting vaccine safety.

Introduction

The coronavirus disease (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 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, of third and later further vaccinations, also commenced in September 2021. The vaccines currently being used until December 2022 in the UK are Comirnaty (BNT162b2 mRNA, BioNTech-Pfizer), Vaxzevria (ChAdOx1-S, Oxford-AstraZeneca) and Spikevax (mRNA-1273, Moderna). Studies have

shown that these vaccines are highly effective at reducing severe COVID-19 [1-4].

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 [5-7]. However, to detect rarer adverse events of interest (AEIs) following immunisations, post-licensure follow-up is needed in larger general populations. Examples include the extremely rare adverse event of concurrent thrombosis and thrombocytopenia ('thrombotic thrombocytopenia syndrome' (TTS)) that has been reported following vaccination with the first dose of Vaxzevria, and myocarditis and acute pericarditis reported after Comirnaty or Spikevax vaccination. The former was only detected as national immunisation programmes rolled out worldwide, which led the JCVI to advise that adults aged under 40 years of age should be offered an alternative in May 2021 [8]. A summary of adverse events associated with COVID-19 vaccines that were detected post-licensure is presented in the **Box** below.

Post authorisation surveillance is required to continually assess vaccine safety in the real world and to maintain public confidence in vaccines, including for COVID-19 [9]. While such surveillance platforms are well established in influenza vaccination [10,11], often using computerised medical record (CMR) data [12], no equivalent systems have been established for COVID-19 vaccination in the UK beyond the generic adverse events reporting systems. This study was conducted to estimate the incidence of a list of prespecified AEIs presenting to general practice following 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 profiles between vaccine brands.

Methods

Data source

We used data from the Oxford-Royal College of General Practitioners Clinical Informatics Digital Hub (ORCHID), England [13], which were derived from pseudonymised extracts of computerised primary care records. Such a 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 [14]. The UK has registration-based primary care, where one patient registers with a single general practice, and CMRs have been in routine use for over 20 years. 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 general practice CMR directly or via NHS Digital's Data Processing Service (DPS) (**Figure 1**). In addition, the ORCHID receives direct feed from the National Immunisation Management System (NIMS), and while there were differences between data sources at the start of vaccination December 2019 to March 2020, the direct DPS transfer route is reliable.

Prespecified adverse events of interest

Using the pseudonymised data, patients were retrospectively followed up for consultations (attendance in primary care) for prespecified AEIs that were determined based on adverse events reported in clinical trials and post-licensure surveillance (see **Table 1** for the included conditions). This list was developed through mapping potential adverse events listed in the regulatory approval documents published by the Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA) to Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT). The SNOMED CT concept IDs used within the study are shown in Supplementary Table S1. 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 [15,16].

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 and 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 patients aged 16 and over on the study index date (1 October 2020; n=1,819,782) 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). We described these attendances as 'medically attended events' or 'medically attended AEIs'. The age cut-off of 16 years was selected based on vaccination guidelines at the time of the study.

Patients were excluded if they: (i) were not registered with a general practice on 1 October 2020, (ii) died on or before 1 October 2020, (iii) had less than 14 days of follow-up after their first dose vaccination because of deregistration or death, (iv) their first dose of any COVID-19 vaccine recorded before 8 December 2020, (v) their first dose Vaxzevria vaccine recorded before 4 January 2021, (vi) their first dose Spikevax vaccine

KEY PUBLIC HEALTH MESSAGE

What did you want to address in this study?

We wanted to compare how frequently a selected list of adverse events occurred in the 7 days after people received their first and second doses of a COVID-19 vaccine compared to background levels, using real-world data from general practices in England. We also examined differences in safety profiles between the vaccine brands.

What have we learnt from this study?

We found that the rates of general practitioner consultations for these adverse events decreased by 3–7% after two doses of Comirnaty or Vaxzevria in the 7 days after vaccination, but increased by 20% after the first dose of Spikevax. The specific types of adverse events reported differed slightly by vaccine brand.

What are the implications of your findings for public health?

The rates of adverse events following COVID-19 vaccination appear to be generally low across the three vaccines used in the United Kingdom. Using computerised medical records to study patterns of vaccine adverse events will be important in the future as COVID-19 becomes endemic and ongoing vaccination is required.

Box

Summary of COVID-19 vaccine safety signals detected in post-licensure surveillance from October 2020–September 2021

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 cause 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 Vaxzevria vaccination [38,50], with the signal later being confirmed in population studies [15,39]. During the investigations, a number of countries suspended the use of Vaxzevria, and later restricted their use to certain age groups.

Myocarditis and pericarditis

Cases of myocarditis and pericarditis have been reported following Comirnaty and Spikevax vaccination [39,51]. Large observational studies have since been conducted across different countries, which observed a short-term increase in risk of myocarditis and pericarditis, particularly in younger individuals. The evidence is mixed with regards to whether males or females are at higher risk of experiencing these adverse events [32-34].

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 Vaxzevria vaccination were identified in an English cohort, with the association between Vaxzevria and GBS replicated in an independent Scottish cohort [35]. Subsequent studies describe rare and generally minor neurological events following vaccination [36,37].