Public Health 224 (2023) 1–7

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

COVID-19 vaccine safety in Scotland – background rates of adverse events of special interest

L.A. Cullen [a], Z. Grange [a], K. Antal [a], L. Waugh [a], M.S. Alsina [a], C.L. Gibbons [a], L.E. MacDonald [a, *], C. Robertson [b], J.C. Cameron [a], D. Stockton [a], M.C. O'Leary [a]

[a] Public Health Scotland, Glasgow, Edinburgh, UK
[b] University of Strathclyde and Public Health Scotland, Glasgow, UK

ARTICLE INFO

Article history:
Received 8 February 2023
Received in revised form
27 July 2023
Accepted 3 August 2023

Keywords:
Background rates
Vaccine safety
SARS-CoV-2
COVID-19 vaccination
Adverse events
Vaccine surveillance

ABSTRACT

Objectives: Mass COVID-19 vaccination commenced in December 2020 in Scotland. Monitoring vaccine safety relies on accurate background incidence rates (IRs) for health outcomes potentially associated with vaccination. This study aimed to quantify IRs in Scotland of adverse events of special interest (AESI) potentially associated with COVID-19 vaccination.

Study design and methods: IRs and 95% confidence intervals (CIs) for 36 AESI were calculated retrospectively for the pre-COVID-19 pandemic period (01 January 2015–31 December 2019) and the COVID-19 pandemic period (01 April 2020–30 November 2020), with age-sex stratification, and separately by calendar month and year. Incident cases were determined using International Classification of Diseases-10th Revision (ICD-10)–coded hospitalisations.

Results: Prepandemic population-wide IRs ranged from 0.4 (0.3–0.5 CIs) cases per 100,000 person-years (PYRS) for neuromyelitis optica to 478.4 (475.8–481.0 CIs) cases per 100,000 PYRS for acute renal failure. Pandemic population-wide IRs ranged from 0.3 (0.2–0.5 CIs) cases per 100,000 PYRS for Kawasaki disease to 483.4 (473.2–493.7 CIs) cases per 100,000 PYRS for acute coronary syndrome. All AESI IRs varied by age and sex. Ten AESI (acute coronary syndrome, acute myocardial infarction, angina pectoris, heart failure, multiple sclerosis, polyneuropathies and peripheral neuropathies, respiratory failure, rheumatoid arthritis and polyarthritis, seizures and vasculitis) had lower pandemic than prepandemic period IRs overall. Only deep vein thrombosis and pulmonary embolism had a higher pandemic IR.

Conclusion: Lower pandemic IRs likely resulted from reduced health-seeking behaviours and healthcare provision. Higher IRs may be associated with SARS-CoV-2 infections. AESI IRs will facilitate future vaccine safety studies in Scotland.

© 2023 The Authors. Published by Elsevier Ltd on behalf of The Royal Society for Public Health. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is associated with high levels of morbidity and mortality.[1] In order to slow the spread of the virus, stringent measures equating to a national lockdown were first introduced in Scotland on 23 March 2020.[2]

Given the severity of the disease (termed COVID-19) and the adverse impact of behavioural restrictions on the economy, several vaccines for COVID-19 were developed rapidly. These were granted emergency use authorisation in the UK, and the COVID-19 vaccination programme in Scotland commenced with the roll-out of the BNT162b2 (Comirnaty) vaccine on 08 December 2020.[3] Although the vaccines passed clinical trials, these are often conducted on populations with limited heterogeneity and follow-up time and without statistical power to detect very rare clinical adverse events associated with vaccination.[4] Therefore, some adverse events may not become apparent until after the vaccine is available to the general population. Health conditions reported or experienced following vaccination can increase vaccine hesitancy and even

* Corresponding author. Meridian Court, 5 Cadogan Street, Glasgow, G2 6QQ, UK. Tel.: +141 282 2913.
E-mail addresses: lucy.cullen@phs.scot (L.A. Cullen), zoe.grange@phs.scot (Z. Grange), karen.antal3@phs.scot (K. Antal), lynsey.waugh@phs.scot (L. Waugh), Marianne.simduwaalsina@phs.scot (M.S. Alsina), Cheryl.gibbons@phs.scot (C.L. Gibbons), laura.macdonald4@phs.scot (L.E. MacDonald), chris.robertson@strath.ac.uk (C. Robertson), claire.cameron2@phs.scot (J.C. Cameron), diane.stockton2@phs.scot (D. Stockton), Maureen.Oleary@phs.scot (M.C. O'Leary).

https://doi.org/10.1016/j.puhe.2023.08.006
0033-3506/© 2023 The Authors. Published by Elsevier Ltd on behalf of The Royal Society for Public Health. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Abbreviations

AESI	Adverse event of special interest
CIs	Confidence intervals
DPIA	Data Protection Impact Assessment
DVT	Deep vein thrombosis
GBS	Guillain-Barre Syndrome
ICD-10	International Classification of Diseases-10th Revision
ICMJE	International Committee for Medical Journal Editors
IR	Incidence rates
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
PE	Pulmonary embolism
PHS	Public Health Scotland
PYRS	Person-years
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SMR01	Scottish Morbidity Record 01
SMR02	Scottish Morbidity Record 02
SPEAC	Safety Platform for Emergency vACcines

result in temporary suspensions to vaccination,[5] requiring investigation to verify whether they are true adverse reactions or are merely temporally associated with vaccination.[6] As such, it is important to continue monitoring potential adverse events to further inform the safety and ensure the credibility of the vaccination programme.

The Brighton Collaboration, an international voluntary collaboration of healthcare professionals currently funded by the Coalition for Epidemic Preparedness Innovation to develop vaccine safety protocols for emerging vaccines,[7] identified a number of health outcomes that could potentially be adverse events associated with COVID-19 vaccination. These are known as adverse events of special interest (AESI).[8] They were identified because they have previously been or theoretically could be associated with vaccination, or because they are associated with COVID-19 disease. Accurate population background rates of AESI are required to monitor vaccine safety.[4] They provide estimates of the incidence of AESI in the absence of the vaccine, so they can be used to estimate the expected incidental rate of AESI in the vaccinated population.[4] Ideally, rates should be from a time period with comparable healthcare use to the period of vaccine administration in the population.[9] If the AESI incidence in the vaccinated population is observed to be higher than the expected rate, this may signal a safety issue for further investigation. Whereas passive surveillance systems, such as the Medicine and Healthcare products Regulatory Agency's (MHRA) Yellow Card Scheme or the US Vaccine Adverse Events Reporting System, rely on voluntary reporting and are most useful for generating hypotheses surrounding potential adverse events following vaccination,[10] background rates facilitate studies that can provide more robust evidence regarding vaccine safety. These, in turn, can improve vaccine confidence and limit vaccine hesitancy.[6]

This study aimed to quantify background incidence rates (IRs) of conditions identified as AESI in the safety monitoring of new COVID-19 vaccinations, including BNT162b2 (Comirnaty), ChAdOx1 nCoV-19 (AZD1222; Vaxzevria) and mRNA-1273 (Spikevax), to inform and enable future vaccine safety analyses.

Methods

Thirty-six AESI were included based on outcomes recommended for monitoring by the Safety Platform for Emergency vACcines (SPEAC) and further informed by discussions with the MHRA and outcomes previously monitored for influenza vaccination.[11] AESI were defined by the International Classification of Diseases-10th Revision (ICD-10)[12] diagnostic codes (Supplemental Table 1) advised by the Public Health Scotland (PHS) terminology service, who routinely validate these codes to ensure they are recorded consistently and accurately.[13] Clinicians within PHS and the University of Glasgow agreed the final selection of AESI and their definitions.

Patients hospitalised with an AESI were identified retrospectively using the Scottish Morbidity Record 01[14] (SMR01) and 02 (SMR02)[15] national data sets. SMR01 includes discharge diagnoses data for all inpatient and day patient episodes from acute specialty hospitals, excluding obstetric and psychiatric specialties. SMR02 includes episode-level data every time a person attends hospital for an obstetric event (antenatal, delivery or postnatal).

Episode-level data were extracted from SMR01 and SMR02 for the period 01 June 2013 to 08 September 2021 and filtered to remove episodes with unknown or unspecified patient sex. An episode is a period of hospital care initiated by a referral or admission and ended by a discharge.[16] AESI events were identified by an ICD-10 code within any diagnosed condition from an episode.[16] The initial data extract covered a longer period than the study periods to account for hospital stays that overlapped with but started or ended outside these dates.

SMR01 episodes were aggregated to hospital stay level for individuals based on their unique Community Health Index number, counting multiple events within a stay once for each AESI. SMR02 data were retained at episode level.

Incident cases were identified using a similar approach to the Centre for Biologics Evaluation and Research.[17] The time between multiple admissions for an individual for the same AESI was calculated using the earliest admission dates from each SMR01 stay and SMR02 episode. AESI events were included if an individual was not previously admitted with a diagnosis of the same AESI within a prespecified time period (clean window). The clean window was verified with clinicians and based on the aetiology of each outcome event (Supplemental Table 1). For example, Guillain-Barre Syndrome's (GBS) clean window was 365 days. For a patient admitted on 01 April 2018 and again on 01 June 2018 with a GBS diagnosis, only the earlier admission was identified as a case (Fig. 1). Individuals contributed multiple incident cases if their events were separated by a period greater than the clean window. The longest clean window was 365 days, so hospitalisations from 01 January 2014 were used to identify incident cases from 01 January 2015 onwards.

For each AESI, IRs per 100,000 PYRS (person-years) and 95% confidence intervals (CIs) were calculated by calendar month and year and overall by age group (0–11, 12–15, 16–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80+ years, all ages) and sex (male, female) for two study periods. The pre-COVID-19 pandemic period was 01 January 2015 to 31 December 2019. The COVID-19 pandemic period was 01 April 2020 to 30 November 2020, before the vaccination programme in Scotland started. Denominator data were National Records of Scotland mid-year population estimates.[18] Until the end of March 2020, confirmed COVID-19 infection rates in Scotland were low; therefore, 01 January 2020 to 31 March 2020 was excluded from the prepandemic and pandemic study periods. IRs for this period were calculated separately for information only.

IRs for each AESI were compared between the prepandemic and pandemic periods. IRs were defined as higher where the IR and 95%

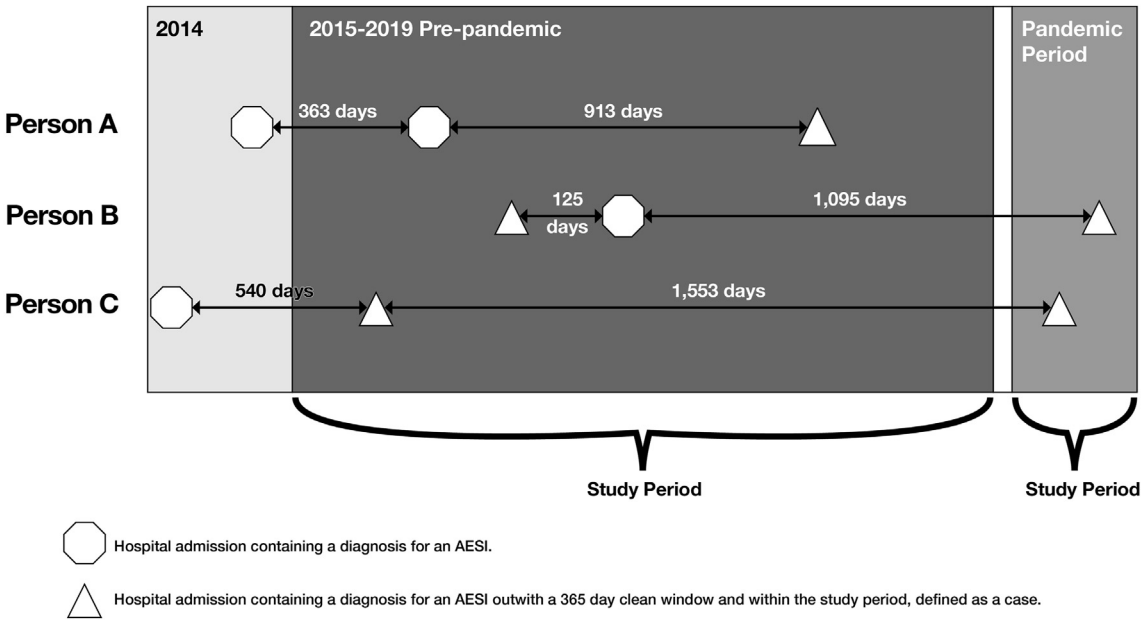

Fig. 1. Identifying cases from three individuals' hospital admissions for Guillain-Barre Syndrome using a 365-day clean window.

CIs were above those of a comparison rate with no overlap between them. The reverse was defined as lower. Comparisons of IRs by calendar month were used to identify seasonal trends. Analyses were conducted in R version 3.6.1, using the tidyverse,[19] lubridate,[20] janitor,[21] epitools[22] and dplyr[23] packages.

Results

Prepandemic period population estimates ranged from 5,373,000 to 5,463,300 (mean = 5,420,780). The pandemic period population estimate was 3,644,000.[18] As expected, IRs varied substantially across the 36 AESI. Prepandemic population-wide IRs (without age or sex stratification) ranged from 0.4 (0.3–0.5 CIs) cases per 100,000 PYRS for neuromyelitis optica to 478.4 (475.8–481.0 CIs) cases per 100,000 PYRS for acute renal failure (Supplemental Figure 1; Supplemental Table 2). Pandemic period population-wide IRs ranged from 0.3 (0.2–0.5 CIs) cases per 100,000 PYRS for Kawasaki disease to 483.4 (473.2–493.7 CIs) cases per 100,000 PYRS for acute coronary syndrome (Supplemental Fig. 2; Supplemental Table 3).

Prepandemic versus pandemic IRs

Deep vein thrombosis (DVT) and pulmonary embolism (PE) was the only AESI with a higher IR during the pandemic period (pandemic period = 101.8 [98.6–105.1 CIs]; prepandemic period = 91.1 [89.9–92.2 CIs] cases per 100,000 PYRS) (Table 1). This was largely driven by the 40- to 69-year-old age groups (Supplemental Table 1; Supplemental Table 2).

Ten AESI (acute coronary syndrome, acute myocardial infarction, angina pectoris, heart failure, multiple sclerosis, polyneuropathies and peripheral neuropathies, respiratory failure, rheumatoid arthritis and polyarthritis, seizures and vasculitis) had lower IRs overall during the pandemic period (Table 1).

Age and sex

Differences occurred in all AESI IRs when age and sex-stratified (Supplemental Figs. 1-2; Supplemental Tables 2-3). In the prepandemic period, there was a sex difference in IRs for 23 AESI, whereby 12 AESI had higher IRs in males (Supplemental Fig. 1; Supplemental Table 2): acute coronary syndrome, acute myocardial infarction, acute renal failure, angina pectoris, GBS, heart failure, myocarditis and pericarditis, other arterial thromboembolism, polyneuropathies and peripheral neuropathies, seizures, stroke (ischemic) and subsequent myocardial infarction. The other 11 AESI had higher overall IRs in females: autoimmune thyroiditis, chronic fatigue syndrome, demyelination, DVT and PE, facial palsy including Bell's palsy, fibromyalgia, multiple sclerosis, optic neuritis, other venous thromboembolism, respiratory failure and rheumatoid arthritis and polyarthritis (Supplemental Fig. 1; Supplemental Table 2). During the pandemic period, six AESI no longer had sex differences observed in the prepandemic period, including five which were previously higher in females (DVT and PE, facial palsy including Bell's palsy, optic neuritis, other venous thromboembolism, rheumatoid arthritis and polyarthritis), and one that was higher in males (subsequent myocardial infarction).

For most AESI, sex differences varied across age groups except for autoimmune thyroiditis where the IR was consistently higher in females, and seizures where the IR was consistently higher in males (Supplemental Fig. 1, Supplemental Table 2). This pattern was observed in both study periods.

Kawasaki disease and vasculitis were the only AESI predominantly seen in children aged under 12 years for both sexes in both study periods (Figs. 1 and 2; Supplemental Tables 2-3). This pattern was less apparent in the pandemic period for both AESI due to a smaller number of events resulting in wider CIs.

Seasonal trends

Respiratory failure and vasculitis had seasonal trends in both study periods, with higher IRs during winter months (Supplemental Fig. 3; Supplemental Table 4).

Discussion

Estimated IRs from hospitalisations for 36 AESI potentially related to COVID-19 vaccination provide important contextual

Table 1
IRs and 95% CIs of AESI throughout the prepandemic and pandemic periods.

AESI	2015	2016	2017	2018	2019	Prepandemic period (2015–2019 average)	Pandemic period (01 April 2020 to 30 November 2020)
Acute and Subacute Hepatic Failure	2.9 (2.4–3.4)	3.0 (2.6–3.5)	3.2 (2.7–3.7)	3.7 (3.2–4.3)	3.6 (3.1–4.1)	3.3 (3.1–3.5)	3.6 (3.1–4.3)
Acute Coronary Syndrome	454.9 (449.2–460.6)	442.9 (437.3–448.5)	445.9 (440.3–451.6)	434.1 (428.6–439.7)	443 (437.4–448.6)	444.1 (441.6–446.6)	394.4 (388–400.9)
Acute Myocardial Infarction	202.3 (198.5–206.1)	204.4 (200.6–208.2)	205.3 (201.5–209.1)	201.6 (197.9–205.4)	203.0 (199.2–206.8)	203.3 (201.6–205)	192.0 (187.5–196.5)
Acute Renal Failure	433.4 (427.8–439.0)	483.6 (477.8–489.5)	499.8 (493.9–505.8)	487.6 (481.7–493.5)	487.1 (481.3–493.0)	478.4 (475.8–481)	449.8 (442.9–456.7)
Angina Pectoris	278.7 (274.3–283.2)	263.3 (259.0–267.7)	256.0 (251.8–260.3)	243.4 (239.2–247.6)	248.8 (244.6–253.0)	258.0 (256.1–259.9)	211.6 (206.9–216.3)
Autoimmune Thyroiditis	2.9 (2.5–3.4)	3.0 (2.6–3.5)	2.9 (2.5–3.4)	3.9 (3.4–4.4)	3.5 (3.1–4.1)	3.3 (3–3.5)	3.1 (2.5–3.7)
Chronic Fatigue Syndrome	5.5 (4.9–6.1)	5.7 (5.1–6.4)	4.7 (4.2–5.3)	4.3 (3.8–4.9)	4.2 (3.7–4.8)	4.9 (4.6–5.2)	4.0 (3.4–4.7)
Demyelination	2.8 (2.4–3.3)	2.5 (2.1–3.0)	2.8 (2.4–3.3)	2.6 (2.2–3.1)	2.2 (1.8–2.6)	2.6 (2.4–2.8)	2.4 (1.9–2.9)
Disseminated Intravascular Coagulation	1.2 (0.9–1.5)	1.1 (0.8–1.4)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.8 (0.6–1.1)	1.0 (0.8–1.1)	1.3 (0.9–1.7)
Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)	85.8 (83.4–88.3)	88.9 (86.4–91.5)	93.7 (91.2–96.3)	93.2 (90.6–95.8)	93.6 (91.1–96.2)	91.1 (89.9–92.2)	101.8 (98.6–105.1)
Encephalitis including Acute Disseminated Encephalomyelitis (ADEM)	3.6 (3.1–4.1)	3.3 (2.8–3.8)	3.5 (3.0–4.0)	3.5 (3.1–4.1)	3.6 (3.1–4.1)	3.5 (3.3–3.7)	2.6 (2.1–3.2)
Facial Palsy including Bell's Palsy	15.0 (14.0–16.1)	14.8 (13.8–15.9)	13 (12.0–14.0)	13.4 (12.5–14.5)	13.8 (12.8–14.8)	14.0 (13.6–14.5)	10.9 (9.9–12.1)
Fibromyalgia	34.2 (32.7–35.8)	37.4 (35.8–39.0)	38.0 (36.4–39.6)	44.1 (42.3–45.9)	49.8 (47.9–51.7)	40.7 (40–41.5)	47.5 (45.3–49.8)
Guillain-Barre Syndrome (GBS)	3.0 (2.5–3.5)	3.2 (2.7–3.7)	3 (2.5–3.5)	2.7 (2.3–3.2)	2.9 (2.5–3.4)	2.9 (2.7–3.2)	2.3 (1.8–2.8)
Heart Failure	259.0 (254.7–263.3)	263.5 (259.2–267.8)	269.4 (265.1–273.8)	264.7 (260.4–269.1)	277.5 (273.1–282.0)	266.9 (264.9–268.8)	249.0 (243.9–254.2)
Intracranial Venous Thrombosis	1.2 (0.9–1.5)	1.6 (1.3–2.0)	1.5 (1.2–1.9)	1.9 (1.5–2.3)	1.7 (1.4–2.1)	1.6 (1.4–1.7)	1.8 (1.4–2.3)
Kawasaki Disease	0.4 (0.3–0.6)	0.4 (0.2–0.5)	0.5 (0.3–0.7)	0.6 (0.4–0.9)	0.5 (0.4–0.8)	0.5 (0.4–0.6)	0.3 (0.2–0.5)
Multiple Sclerosis	35.8 (34.2–37.5)	35.5 (34.0–37.2)	36.3 (34.7–37.9)	38.8 (37.2–40.5)	37.3 (35.7–39.0)	36.8 (36–37.5)	31.3 (29.5–33.2)
Myasthenia Gravis	5.0 (4.4–5.7)	5.4 (4.8–6.1)	5.5 (4.9–6.2)	5.6 (5.0–6.3)	6.1 (5.5–6.8)	5.5 (5.3–5.8)	4.6 (4–5.4)
Myocarditis and Pericarditis	7.8 (7.1–8.6)	7.1 (6.4–7.8)	7.8 (7.1–8.6)	8.7 (7.9–9.5)	9 (8.2–9.8)	8.1 (7.7–8.4)	8.9 (8–9.9)
Narcolepsy	0.7 (0.5–0.9)	0.6 (0.4–0.9)	0.6 (0.4–0.9)	0.5 (0.3–0.7)	0.5 (0.3–0.7)	0.6 (0.5–0.7)	0.5 (0.3–0.8)
Neuromyelitis Optica	0.3 (0.1–0.4)	0.5 (0.3–0.7)	0.3 (0.2–0.5)	0.4 (0.2–0.6)	0.6 (0.4–0.8)	0.4 (0.3–0.5)	0.5 (0.3–0.8)
Optic Neuritis	1.8 (1.4–2.2)	1.9 (1.6–2.4)	1.2 (1.0–1.6)	1.8 (1.5–2.2)	1.8 (1.4–2.2)	1.7 (1.6–1.9)	1.2 (0.9–1.6)
Other Arterial Thromboembolism	21.7 (20.5–23.0)	22.5 (21.3–23.8)	25.5 (24.2–26.9)	25.9 (24.6–27.3)	24.8 (23.5–26.2)	24.1 (23.5–24.7)	20.6 (19.2–22.2)
Other Venous Thromboembolism	23.3 (22.1–24.7)	24.1 (22.8–25.4)	24.3 (23.0–25.7)	23.2 (21.9–24.5)	25.9 (24.6–27.3)	24.2 (23.6–24.8)	22.1 (20.6–23.7)
Polyneuropathies and Peripheral Neuropathies	33.4 (31.9–35.0)	34.8 (33.3–36.5)	33.7 (32.2–35.3)	33.3 (31.8–34.9)	34.9 (33.3–36.5)	34.0 (33.3–34.7)	27.0 (25.3–28.7)
Respiratory Failure	69.5 (67.3–71.8)	78.4 (76.1–80.8)	84.8 (82.3–87.2)	82.4 (80.0–84.8)	83.4 (81.0–85.8)	79.7 (78.6–80.8)	56.4 (54–58.9)
Rheumatoid Arthritis and Polyarthritis	80.5 (78.1–82.9)	75.5 (73.2–77.8)	72.7 (70.5–75.0)	71.4 (69.2–73.7)	73.3 (71.0–75.6)	74.7 (73.6–75.7)	50.1 (47.9–52.5)
Seizures	338.8 (333.9–343.8)	347.9 (343.0–352.9)	347.6 (342.7–352.6)	340.8 (335.9–345.8)	353.8 (348.8–358.8)	345.8 (343.6–348)	299.5 (293.9–305.2)
Stroke (Haemorrhagic)	48.9 (47.0–50.8)	49.9 (48.0–51.8)	48.0 (46.2–49.9)	50.3 (48.4–52.2)	51.1 (49.2–53.0)	49.6 (48.8–50.5)	46.6 (44.4–48.8)
Stroke (Ischemic)	181.1 (177.5–184.7)	181.5 (177.9–185.1)	184.3 (180.7–188.0)	183.9 (180.4–187.6)	185.4 (181.8–189.1)	183.3 (181.7–184.9)	182.5 (178.1–186.9)
Subsequent Myocardial Infarction	3.5 (3.0–4.0)	2.8 (2.3–3.2)	2.3 (1.9–2.7)	2.5 (2.1–3.0)	2.5 (2.1–2.9)	2.7 (2.5–2.9)	2.5 (2–3.1)
Thrombocytopenia	34.7 (33.2–36.3)	33.7 (32.2–35.3)	33 (31.5–34.5)	31.2 (29.7–32.7)	32.7 (31.2–34.2)	33.1 (32.4–33.7)	28.5 (26.8–30.3)
Transient Ischaemic Attack	52.5 (50.6–54.5)	55.7 (53.8–57.8)	59.9 (57.9–62.0)	59.5 (57.4–61.5)	63.1 (61.0–65.3)	58.2 (57.3–59.1)	54.1 (51.7–56.5)
Transverse Myelitis	0.6 (0.4–0.9)	0.7 (0.5–1.0)	0.8 (0.5–1.0)	0.8 (0.6–1.0)	0.6 (0.4–0.9)	0.7 (0.6–0.8)	0.9 (0.6–1.2)
Vasculitis	8.0 (7.3–8.8)	9.7 (8.9–10.5)	8.2 (7.5–9.0)	8.4 (7.6–9.2)	8.2 (7.5–9.0)	8.5 (8.2–8.9)	5.0 (4.3–5.8)

information for monitoring and providing reassurance regarding vaccine safety. If concerns around serious adverse events occurring post-vaccination are reported through social media, passive reporting or anecdotally, these estimates facilitate quick comparisons of observed number of events in the vaccinated population with the expected number of events. Lower event rates among vaccinees than the background rates provide reassurance that events may have occurred coincidentally. However, it is important that background rates used reflect the IRs of AESI in the absence of vaccination as closely as possible.

Ten AESI (acute coronary syndrome, acute myocardial infarction, angina pectoris, heart failure, multiple sclerosis, polyneuropathies and peripheral neuropathies, respiratory failure, rheumatoid arthritis and polyarthritis, seizures and vasculitis) had lower IRs following the emergence of COVID-19 and associated behavioural restrictions (Table 1; Supplemental Figure 3). To our knowledge, this study is the first to examine changes in IRs for polyneuropathies and peripheral neuropathies and vasculitis following the COVID-19 pandemic. However, findings for the remaining eight AESI that had lower pandemic period IRs align with other studies examining the same conditions.[24–28]

Reasons for observing lower pandemic period IRs are likely to be multifactorial. These are important to consider when choosing comparison periods for vaccine safety analyses. Several studies have attributed reduced IRs to health-seeking behaviour changes during the pandemic, suggesting anxiety around SARS-CoV-2 infection may prevent or delay presentation at hospital, particularly during the early pandemic period.[24,28,29] This was evidenced by research showing decreased self-referrals but increased ambulance admissions to hospital with heart failure during 2020 compared with prior years.[30] These findings indicate a shift in patients seeking medical care only for more serious events during the pandemic rather than a true reduction in IRs.

Lower pandemic IRs are also likely caused by the National Health Service (NHS) being placed on emergency footing from 17 March 2020.[31] Many healthcare services were paused to allocate resources to managing COVID-19 cases. This affected referral and treatment patterns, and all non-urgent elective treatment was suspended. Indeed, several AESI that were lower during the pandemic were related to the circulatory system (acute coronary syndrome, acute myocardial infarction, heart failure, angina pectoris, vasculitis). Elective cardiac surgery and cardiology were among the paused services, and their staged return only began mid-June 2020.[32] Accordingly, we observed that most AESI with lower pandemic IRs gradually increased throughout the pandemic period, returning to levels more closely resembling prepandemic IRs around the same time NHS services recommenced (Supplemental Figure 3). Similarly, community deaths from heart failure were higher and hospitalisations were lower during the period February to May 2020 compared with equivalent 2018 and 2019 time periods in England.[29] Other factors causing reduced IRs could include individuals practicing better self-care over the pandemic period[33] if they had more available time compounded with the incentive to stay healthy in case of SARS-CoV-2 infection. For others, reduced physical activity due to behavioural restrictions could have masked the symptoms from cardiovascular AESI,[34] meaning individuals were less aware of a need to attend hospital.

Reduced physical activity may have also contributed to the observed increased rates of DVT and PE during the pandemic period.[34] It is also notable that SARS-CoV-2 infection has been associated with PE and may therefore have increased relative to increasing infection rates.[35] Although DVT and PE was the only AESI that was higher overall during the pandemic than prepandemic period, rates of several other AESI (including acute renal failure, GBS, disseminated intravascular coagulation) were also likely affected during the pandemic given their association with COVID-19.[36–38]

Consistent with other research, IRs varied substantially by age and sex.[21] Generally, IRs were highest in adults across both prepandemic and pandemic periods (Supplemental Fig. 1; Supplemental Fig. 2). Exceptions were Kawasaki disease and vasculitis where IRs were highest in under 12-year-olds in the prepandemic period. The majority of AESI also had higher IRs in one sex during the prepandemic period (Supplemental Fig. 1). Prepandemic IRs for acute myocardial infarction, myocarditis and pericarditis and GBS were higher in males than females, matching findings in a UK study of IRs from 2017 to 2019.[21] However, sex differences in general were less apparent during the pandemic period (Supplemental Fig. 2). For some AESI, including thrombocytopenia, sex differences were age-dependent such that the IR was higher in younger females than males, but the reverse occurred in older age groups.

For certain conditions, substantial differences in IRs occur throughout the year due to the seasonal nature of the disease, which needs to be considered and accounted for when undertaking safety analyses.[39] Winter peaks observed for respiratory failure in both prepandemic and pandemic periods align with the influenza season (Supplemental Figure 3).[40,41] The marked reduction in respiratory failure throughout the pandemic period (Table 1; Supplemental Figure 3) mirrors the reduction observed in non-COVID-19 respiratory pathogens circulating throughout the pandemic.[41] The lower incidence has been attributed to COVID-19 behavioural restrictions, which prevented the usual transmission of infection observed in previous years.[41]

The study included many AESI identified as relevant to the COVID-19 vaccination programme. By using national data and standardised definitions for identifying AESI, IRs are likely to be reflective of and generalisable to the Scottish population. SMR records are produced for all inpatients and day cases in Scotland and are therefore unbiased towards particular geographical areas or other subsets of patients that may influence IRs. Furthermore, AESI were identified from all episodes within a hospital stay. This increased the likelihood of including stays involving an AESI regardless of severity. The use of a clean window, defined accordingly for each AESI, limited the possibility of identifying repeat admissions for individuals with a history of the condition.

The provision of age and sex-stratified rates will allow future studies to rapidly assess vaccine safety in specific cohorts. By calculating prepandemic and pandemic IRs separately, the pandemic's impact on the incidence of AESI can also be reviewed. This will be particularly important when selecting comparison periods for and interpretation of follow-up vaccine safety analysis. The availability of AESI IRs and the insights into the pandemic's influence and seasonal trends provided will also aid safety studies for other vaccine programmes, such as influenza, and support public health planning in the event of potential future pandemics.[39]

Study limitations

For some AESI, hospitalisation may be unnecessary, and patients are seen in primary care or outpatient settings instead, so they are not counted in IRs. Additionally, some individuals may not seek healthcare, or their hospitalisation might differ based on age, sex or other risk factors for serious disease or complications. While this may have been a particular bias throughout the pandemic period, the data presented likely underestimate the true IRs for some or all conditions across both study periods. Although many AESI were included, the list was not exhaustive, and other adverse events may emerge as safety concerns associated with COVID-19 vaccination. Identification of hospitalisations for the included AESI may have

also been affected if any changes occurred to the ICD-10 codes used during the study periods. The clean window length chosen for each AESI will also have influenced IRs, potentially underestimating admissions counted as cases.

2020 mid-year population estimates were also likely affected by higher mortality rates caused by SARS-CoV-2 infections,[42] resulting in the denominator overestimating the true population. Furthermore, excess deaths may have occurred among cohorts most at risk for the AESI investigated. Combined, these could have resulted in lower IRs throughout the pandemic period without any true change in incidence.

Caution should be applied when comparing IRs calculated using different methods and/or databases and from different geographical areas. For example, our prepandemic IR of 2.9 GBS cases per 100,000 PYRS (2.7–3.2 CIs) is higher than UK-wide estimates from 2016 to 2019 calculated using prescriptions of intravenous immunoglobulin for treating GBS in hospital.[43] Our study identified any condition that develops during a stay or affects a patient's management, so it may have included patients with a GBS diagnosis that never received specific GBS treatment. Furthermore, IRs can vary substantially across data sources even when controlling for other confounders.[44] Future research using the IRs made available here should ideally use the same SMR data sets to calculate postvaccination IRs of AESI.

Conclusion

Estimates are provided for potential AESI identified for monitoring in relation to COVID-19 vaccine safety. The findings presented illustrate the effect of age, sex and time period on AESI incidence, which must be considered in future analysis. Appropriately stratified IRs provided will enable rapid assessment of vaccine safety in Scotland, for example in observed versus expected studies, which monitor IRs postvaccination to signal potential safety concerns. Such analyses are commonly used in vaccine vigilance when quick decision-making is required, and reviewing large case numbers individually would be inefficient. This enables public confidence in vaccination to be maintained. The IRs also provide insight into behaviour changes (i.e. likelihood of visiting hospital and being admitted) and the possible impact of COVID-19 on health when comparing prepandemic and pandemic periods.

Author statements

Acknowledgements

Clinical support was provided by Dr Lynda Fenton (Public Health Scotland), Dr Rachael Wood (Public Health Scotland and University of Edinburgh) and Professor Emma Thomson (University of Glasgow Centre for Virus Research) to review the adverse events of special interest included in this paper, along with the diagnostic codes and clean windows used for their identification.

Author contributions

All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors (ICMJE). MCO conceived and designed the study and supported the conduct of the analysis. LAC, KA and LW conducted the data analysis. LAC produced the data visualisations. LAC, ZG, KA, CLG, LEM, MSA and MCO contributed to the interpretation of results. LAC drafted and revised the manuscript. In addition, all authors provided revisions to manuscript drafts and guidance throughout the analysis and paper writing process. All authors have read and approved the final manuscript and agree for it to be published.

Ethical approval

The Public Health Scotland Order 2019 in Article 9 (2)(i) places an obligation on Public Health Scotland to engage in the control of the spread of infectious diseases in accordance with section 43 of the National Health Service (Scotland) Act 1978. In accordance with Sections 15, 16 (5), and 21 (2) of the Public Health etc. (Scotland) Act 2008, PHS is obliged to process data in relation to notifiable diseases, health risk states of patients, notifiable organisms, and carrying out public health investigations, and as such, individual patient consent is not required. A Data Protection Impact Assessment (DPIA) allows Public Health Scotland staff to link existing data sets. This study was approved under COVID-19 Rapid DPIA 2122-0077.

Consent for publication

Not applicable.

Availability of data and materials

All data generated during this study are included in this published article and its supplementary information files. R scripts used to produce supplementary figures 1-3 will be made available on GitHub upon publication. Please contact the corresponding author (LEM) for assistance accessing these.

Funding

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.08.006.

References

1. Kang SJ, Jung SI. Age-related morbidity and mortality among patients with COVID-19. *Infect Chemother* 2020;**52**(2):154–64. Jun 12.
2. Timeline of Coronavirus (COVID-19) in Scotland – SPICe Spotlight | Solas air SPICe [Internet]. [cited 2022 Jan 24]. Available from: https://spice-spotlight.scot/2022/01/21/timeline-of-coronavirus-covid-19-in-scotland/.
3. First COVID-19 vaccinations in Scotland take place. - gov.scot [Internet]. [cited 2022 Jan 31]. Available from: https://www.gov.scot/news/first-covid-19-vaccinations-in-scotland-take-place/.
4. Black SB, Law B, Chen RT, Dekker CL, Sturkenboom M, Huang W-T, et al. The critical role of background rates of possible adverse events in the assessment of COVID-19 vaccine safety. *Vaccine* 2021 May 6;**39**(19):2712–8.
5. Wise J. Covid-19: European countries suspend use of Oxford-AstraZeneca vaccine after reports of blood clots. Mar 11 *BMJ* 2021;**372**. n699.
6. Marti M, de Cola M, MacDonald NE, Dumolard L, Duclos P. Assessments of global drivers of vaccine hesitancy in 2014-Looking beyond safety concerns. *PLoS One* 2017;**12**(3):e0172310. Mar 1.
7. Brighton Collaboration – Home Page - Brighton Collaboration [Internet]. [cited 2022 May 4]. Available from: https://brightoncollaboration.us/.
8. COVID-19 - Brighton Collaboration [Internet]. [cited 2022 Apr 6]. Available from: https://brightoncollaboration.us/covid-19/.
9. Hampton LM, Aggarwal R, Evans SJW, Law B. General determination of causation between Covid-19 vaccines and possible adverse events. *Vaccine* 2021;**39**(10):1478–80. Mar 5.
10. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the vaccine adverse event reporting system (VAERS). *Vaccine* 2015;**33**(36):4398–405. Aug 26.
11. Simpson CR, Lone N, Kavanagh K, Ritchie LD, Robertson C, Sheikh A, et al. *Seasonal Influenza Vaccine Effectiveness (SIVE): an observational retrospective cohort study – exploitation of a unique community-based national-linked database to determine the effectiveness of the seasonal trivalent influenza vaccine.* Southampton (UK): NIHR Journals Library; 2013.

12. ICD-10 Version:2019 [Internet]. [cited 2022 Jan 24]. Available from: https://icd.who.int/browse10/2019/en.
13. ISD Services | Terminology Services and Clinical Coding | Coding & Terminology Systems | ISD Scotland [Internet]. [cited 2023 Jul 20]. Available from: https://www.isdscotland.org/Products-and-Services/Terminology-Services/.
14. SMR Datasets | SMR01 - General/Acute Inpatient and Day Case | ISD Scotland | Data Dictionary [Internet]. [cited 2022 Mar 21]. Available from: https://www.ndc.scot.nhs.uk/Data-Dictionary/SMR-Datasets/SMR01-General-Acute-Inpatient-and-Day-Case/.
15. SMR Datasets | SMR02 - Maternity Inpatient and Day Case | ISD Scotland | Data Dictionary [Internet]. [cited 2022 Mar 21]. Available from: https://www.ndc.scot.nhs.uk/Data-Dictionary/SMR-Datasets/SMR02-Maternity-Inpatient-and-Day-Case/.
16. ISD Scotland | Information Services Division [Internet]. [cited 2022 Jan 26]. Available from: https://www.ndc.scot.nhs.uk/Dictionary-A-Z/Definitions/index.asp?Search=E&ID=241&Title=Episode%20of%20Care.
17. Vaccines & Allergenics – BEST Initiative [Internet]. [cited 2022 Mar 21]. Available from: https://www.bestinitiative.org/vaccines-and-allergenics.
18. Mid-Year Population Estimates | National Records of Scotland [Internet]. [cited 2022 Jan 24]. Available from: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/population/population-estimates/mid-year-population-estimates.
19. Wickham H, Averick M, Bryan J, Chang W, McGowan L, François R, et al. Welcome to the tidyverse. *JOSS* 2019;**4**(43):1686.
20. Grolemund G, Wickham H. Dates and times made easy with lubridate. *J Stat Softw* 2011;**40**(3).
21. Firke S. *Simple tools for examining and cleaning dirty data [R package janitor version 2.1.0*. 2021. Jan 5.
22. Aragon TJ. *Epidemiology Tools [R package epitools version 0.5-10.1*. 2020. Mar 22.
23. A Grammar of Data Manipulation [R package dplyr version 1.0.8] [Internet]. 2022 [cited 2022 Mar 21]. Available from: https://cran.r-project.org/web/packages/dplyr/index.html.
24. Leung WCY, Lau EHY, Kwan P, Chang RS-K. Impact of COVID-19 on seizure-related emergency attendances and hospital admissions - a territory-wide observational study. *Epilepsy Behav* 2021;**115**:107497. Feb.
25. He L, Lu F, Du X, Long D, Sang C, Tang R, et al. Impact of COVID-19 pandemic on hospital admissions of acute coronary syndrome: A Beijing inpatient database study. *Lancet Reg Health West Pac* 2022;**19**:100335. Feb.
26. Bodilsen J, Nielsen PB, Søgaard M, Dalager-Pedersen M, Speiser LOZ, Yndigegn T, et al. Hospital admission and mortality rates for non-covid diseases in Denmark during covid-19 pandemic: nationwide population based cohort study. May 24 *BMJ* 2021;**373**. n1135.
27. Frankfurter C, Buchan TA, Kobulnik J, Lee DS, Luk A, McDonald M, et al. Reduced rate of hospital presentations for heart failure during the COVID-19 pandemic in Toronto, Canada. *Can J Cardiol* 2020;**36**(10):1680–4. Oct.
28. Richter D, Faissner S, Bartig D, Tönges L, Hellwig K, Ayzenberg I, et al. The impact of the COVID-19 pandemic on hospitalizations and plasmapheresis therapy in multiple sclerosis and neuromyelitis optica spectrum disorder: a nationwide analysis from Germany. *Ther Adv Neurol Disord* 2021;**14**:17562864211030656. Jul 7.
29. Severino P, D'Amato A, Saglietto A, D'Ascenzo F, Marini C, Schiavone M, et al. *Reduction in heart failure hospitalization rate during coronavirus disease 19 pandemic outbreak*. ESC Heart Fail; 2020. Oct 23.
30. Kubica J, Ostrowska M, Stolarek W, Kasprzak M, Grzelakowska K, Kryś J, et al. *Impact of COVID-19 pandemic on acute heart failure admissions and mortality: a multicentre study (COV-HF-SIRIO 6 study)*. ESC Heart Fail; 2021.
31. NHS Scotland placed on emergency footing - gov.scot [Internet]. [cited 2022 Mar 11]. Available from: https://www.gov.scot/news/nhs-scotland-placed-on-emergency-footing/.
32. Restarting more health services - gov.scot [Internet]. [cited 2022 Mar 11]. Available from: https://www.gov.scot/news/restarting-more-health-services/.
33. Chang Y-K, Hung C-L, Timme S, Nosrat S, Chu C-H. Exercise behavior and mood during the COVID-19 pandemic in Taiwan: lessons for the future. *Int J Environ Res Public Health* 2020;(19):17.
34. Sokolski M, Gajewski P, Zymliński R, Biegus J, Berg JMT, Bor W, et al. Impact of coronavirus disease 2019 (COVID-19) outbreak on acute admissions at the emergency and cardiology departments across Europe. *Am J Med* 2021;**134**(4):482–9. Apr.
35. Salihi S, Perçin B, Erkengel HI, Özalp B, Saçlı H, Kara I. Does COVID-19 infection increase the risk of pulmonary embolism in ambulatory patients with deep vein thrombosis. *Vascular* 2021:17085381211052207. Dec 4.
36. Raza A, Estepa A, Chan V, Jafar MS. Acute renal failure in critically ill COVID-19 patients with a focus on the role of renal replacement therapy: a review of what we know so far. *Cureus* 2020;**12**(6):e8429. Jun 3.
37. Caress JB, Castoro RJ, Simmons Z, Scelsa SN, Lewis RA, Ahlawat A, et al. COVID-19-associated Guillain-Barré syndrome: the early pandemic experience. *Muscle Nerve* 2020;**62**(4):485–91. Oct.
38. Mortus JR, Manek SE, Brubaker LS, Loor M, Cruz MA, Trautner BW, et al. Thromboelastographic results and hypercoagulability syndrome in patients with coronavirus disease 2019 who are critically ill. *JAMA Netw Open* 2020;**3**(6):e2011192. Jun 1.
39. Black S, Eskola J, Siegrist C-A, Halsey N, MacDonald N, Law B, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. *Lancet* 2009;**374**(9707):2115–22. Dec 19.
40. The flu vaccine | The flu vaccine [Internet]. [cited 2022 Mar 11]. Available from: https://www.nhsinform.scot/flu-vaccine/the-vaccines/the-flu-vaccine/.
41. HPS weekly national seasonal respiratory report.
42. Deaths involving coronavirus (COVID-19) in Scotland | National Records of Scotland [Internet]. [cited 2022 Feb 21]. Available from: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/general-publications/weekly-and-monthly-data-on-births-and-deaths/deaths-involving-coronavirus-covid-19-in-scotland.
43. Keddie S, Pakpoor J, Mousele C, Pipis M, Machado PM, Foster M, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. *Brain* 2021;**144**(2):682–93. Mar 3.
44. Li X, Ostropolets A, Makadia R, Shoaibi A, Rao G, Sena AG, et al. Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study. *BMJ* 2021:n1435. Jun 14.