Vaccine: X 15 (2023) 100418

Contents lists available at ScienceDirect

Vaccine: X

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

Risk of cardiac arrhythmia and cardiac arrest after primary and booster COVID-19 vaccination in England: A self-controlled case series analysis

Julia Stowe [a,*], Heather J. Whitaker [a], Nick J. Andrews [a], Elizabeth Miller FMedSci [b]

[a] UK Health Security Agency, 61 Colindale Avenue, London NW9 5EU, United Kingdom
[b] Department of Infectious Disease Epidemiology, Faculty of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine, Keppel St, London WC1E 7HT, UK

ARTICLE INFO

Keywords:
COVID-19 vaccine safety
Cardiac arrest
Arrhythmia
SARS-CoV-2 infection

ABSTRACT

Background: Various cardiac arrhythmias have been reported after COVID-19 infection and vaccination. We assessed the risk after primary immunisation with the ChAdOx1 adenovirus vectored vaccine, and primary and booster immunisation with an mRNA vaccine in 40 million vaccinated adults with 121 million doses (33.9% ChAdOx1 and 66.1% mRNA) in England.

Methods: Hospital admissions for a cardiac arrhythmia and emergency care attendance for a cardiac arrest in individuals aged 18 years and older on the 31st March 2021 were linked to the national COVID-19 immunisation register. The incidence of events 1–14 and 15–28 days after vaccination relative to a post-vaccination control period was estimated using the self-controlled case series method modified for fatal events. Outcomes were stratified by arrhythmia type, vaccine type, age group and dose number (up to five). Elevated relative incidence (RI) estimates with $p < 0.001$ were considered strong evidence of an association.

Findings: There was an increased risk of admission for arrhythmia events that were largely palpitations without myocarditis within 14 days of a second priming dose of an mRNA vaccine in 18–49 year olds with an RI of 1.66 (95 % confidence interval 1.47,1.86) for BNT162b2 and 3.75 (2.52,5.57) for mRNA-1273 ($p < 0.001$) and also after a first booster dose, 1.34 (1.17,1.53) and 1.75 (1.43,2.15) respectively ($p < 0.001$). No other cardiac arrhythmia, including cardiac arrest, showed an elevated incidence within 28 days of vaccination for any dose, age group or vaccine type. In contrast the risk of a cardiac arrhythmia of all types, including a cardiac arrest, was consistently elevated in those testing positive for SARS-CoV-2 infection.

Interpretation: Our study provides reassuring evidence of the safety of the ChAdOx1 and mRNA COVID-19 vaccines with respect to serious cardiac arrhythmias and of the favourable risk benefit of mRNA booster vaccination.

Background

Cardiac arrhythmias can affect any age group and ventricular arrhythmias may lead to cardiac arrest and sudden death. Various types of cardiac arrhythmia have been associated with COVID-19 illness, but whether their aetiology is specific to the SARS-CoV-2 virus or is a more generic manifestation of the inflammatory response associated with a systemic viral illness is unclear [1]. There are also case reports of cardiac arrhythmias occurring after mRNA and adenovirus vectored COVID-19 vaccines, in some cases associated with acute myocarditis, a confirmed signal associated with mRNA vaccines [2] or a pre-existing cardiac disorder [3–6]. Few COVID-19 vaccine safety studies have evaluated arrhythmia as an outcome, with a recent systematic review finding significant heterogeneity between the limited number of studies where this outcome was reported [7]. For example, one study in England showed no elevated risk after primary immunisation with the mRNA vaccine BNT162b2 in contrast to a study in Malaysia that found a significantly elevated risk within 21 days of a priming dose [8,9]. There is a paucity of information on the risk of a clinically significant arrhythmia after booster doses of vaccine although elevation of the heart rate has been shown within three days of a second booster dose of BNT162b2 in Israeli adults monitored remotely via smartwatches [10].

While an association between cardiac arrest and SARS-CoV-2 infection has been shown [11] few studies have assessed the risk of cardiac arrest in relation to COVID-19 vaccination. One study in Israel reported an increase in emergency department calls for cardiac arrest that

* Corresponding author.
E-mail address: Julia.stowe@ukhsa.gov.uk (J. Stowe).

https://doi.org/10.1016/j.jvacx.2023.100418
Received 30 May 2023; Received in revised form 28 November 2023; Accepted 30 November 2023
Available online 1 December 2023

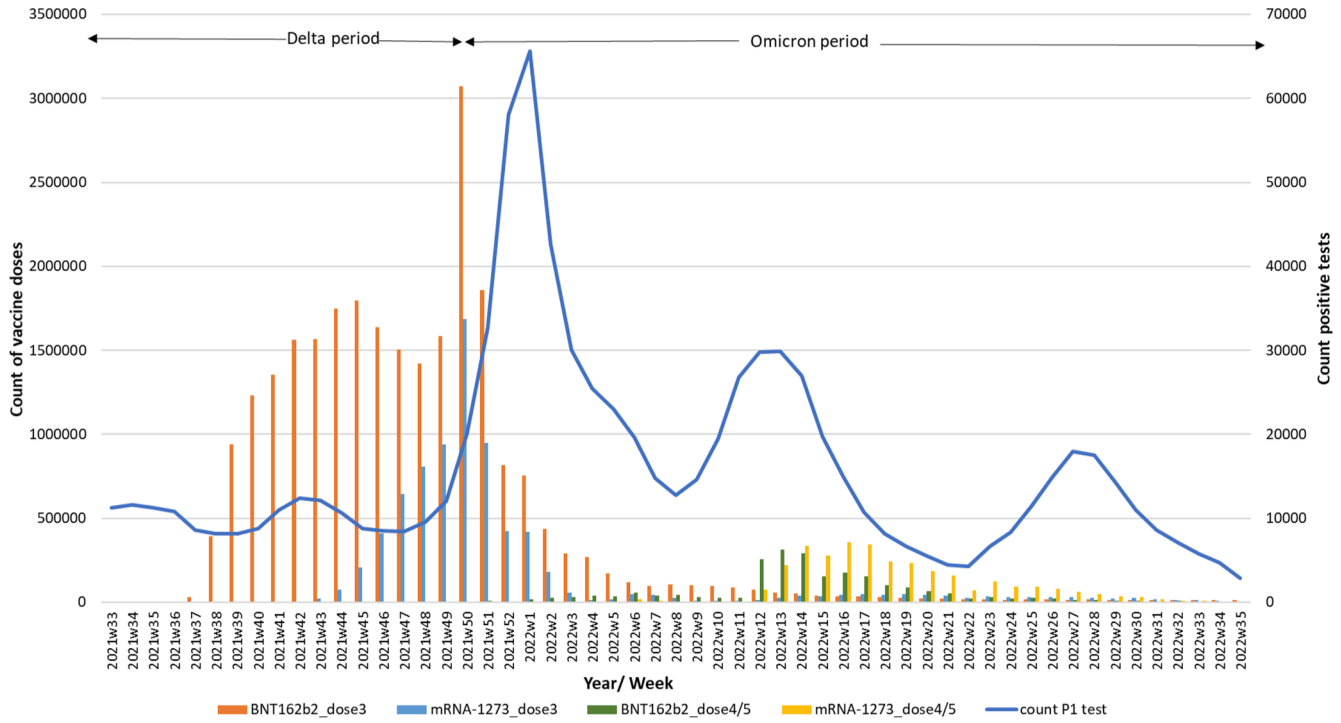

Fig. 1. Counts of Pillar 1 first positive tests and vaccine doses by week and year.

coincided with the roll out of primary courses of the BNT162b2 mRNA vaccine for 16–39 year olds and did not appear to be associated with COVID-19 infection rates [12]. Another study in Florida reported an elevated risk of a cardiac-related death of various aetiologies in 18–39 and ≥60 year olds after an mRNA vaccine but not an adenovirus vectored vaccine. [13]. In contrast a study of cardiac-related deaths in England in 12–29 year olds found no evidence of an elevated risk after an mRNA vaccine [14]. None of these studies investigated the risk after booster doses.

Based on the available evidence, the causal association, if any, between COVID-19 vaccination and the development of a cardiac arrhythmia or a cardiac-related death in adults has not been established. We investigate the risk of hospital admission for a cardiac arrhythmia after COVID-19 vaccination by age group, vaccine type and primary or booster vaccination in a national study in England in those aged 18 years and over. Since ventricular arrhythmias have a high fatality rate, we also investigated the association with COVID-19 vaccination among cardiac arrest patients brought to emergency care facilities in England. The risk of a cardiac arrhythmia or a cardiac arrest after a laboratory confirmed SARS-CoV-2 infection is also assessed.

Methods

Study population

The study population consisted of individuals resident in England aged 18 years and older on the 31st March 2021 who had received at least one dose of a COVID-19 vaccine.

Data sources

The Secondary Uses Service (SUS) database, which provides ICD-10 coded diagnoses for cases admitted to all National Health Service hospitals in England was used for case ascertainment [15]. Finished Consultant Admissions for a cardiac arrhythmia were categorised into five groups based on their primary diagnosis code: 1) Atrial fibrillation and flutter, 2) Atrioventricular block and conduction disorders, 3) Ventricular tachycardia, 4) Ventricular fibrillation and 5) Other cardiac arrhythmias (Supplementary Appendix Table 1). Admissions in the period 01/12/2020 to 31/08/2022 and with no prior admission for a cardiac arrhythmia event since 01/12/2019 were extracted from the SUS database.

The Emergency Care Dataset (ECDS) which captures all emergency care attendances at NHS hospitals in England was used to identify cases of cardiac arrest using the SNOMED Code: Cardiac Arrest 410429000 in any diagnosis field. ECDS attendances for a cardiac arrest in the study population between 01/12/2020 and 31/10/2022 were selected for individuals with no prior attendance for a cardiac arrest event between 01/12/2019 and 01/12/2022.

The UK Health Security Agency's (UKHSA) Second Generation Surveillance System (SGSS) [16] which collates results of PCR and LFT tests carried out in the community in England (termed Pillar 2), and PCR tests conducted in hospital patients, health care staff or other special groups (termed Pillar 1), was used to identify confirmed SARS-CoV-2 infections in the study population. Pillar 2 testing stopped in England on 31st March 2022. Repeat infections were defined as those in individuals with a second or subsequent positive test ≥90 days after a previous positive test.

Immunisation data were obtained from the National Immunisation Management System (NIMS) which records all COVID-19 vaccinations given in England. Primary vaccination was given with either the ChAdOx1, BNT162b2 or mRNA-1273 vaccines while only mRNA vaccines were used for boosting.

Deaths temporally associated with an outcome event were obtained using the death date in NIMS or the SNOMED emergency care destination code = mortuary 305398007 and emergency care status SNOMED code = Died in emergency care facility 75004002 or dead on arrival 63238001. The attendance date was used as the death date.

Data linkage

SUS admission records, ECDS consultations and SGSS SARS-CoV-2 cases were linked to the NIMS data set using NHS number. The extracted SUS admissions with the outcomes of interest that did not link with a

Table 1
Demographic and clinical features of the individuals with a hospital admission in SUS for cardiac arrhythmia within 90 days of a dose of a Covid-19 vaccine or a laboratory-confirmed SARS-CoV-2 infection between 1st December 2020 to 31st August 2022.

Demographic and Clinical features		Number	%
	All ages	75,772	100 %
Age Group (years)	**18 to 19**	325	0.43
	20 to 24	1,000	1.32
	25 to 29	1,165	1.54
	30 to 34	1,459	1.93
	35 to 39	1,654	2.18
	40 to 44	1,954	2.58
	45 to 49	2,342	3.09
	50 to 54	3,553	4.69
	55 to 59	4,654	6.14
	60 to 64	5,435	7.17
	65 to 69	6,359	8.39
	70 to 74	8,778	11.58
	75 to 79	12,198	16.10
	80 years plus	24,896	32.86
	All ages	75,772	100 %
Sex	**Male**	40,199	53.1 %
	Female	35,573	46.9 %
Ethnicity	**Asian**	2,963	3.9 %
	Black, African, Caribbean	959	1.3 %
	Mixed, Multiple	524	0.7 %
	NK	3,242	4.3 %
	Other	713	0.9 %
	White	67,371	88.9 %
Clinically Vulnerable		17,872	23.6 %
In an "at risk" group		16,447	21.7 %
Type of cardiac arrhythmia	**Atrial fibrillation and flutter: Group 1**	40,206	53.06 %
	AV block and conduction disorders: Group 2	12,295	16.23 %
	Ventricular tachycardia: Group 3	1698	2.24 %
	Ventricular fibrillation: Group 4	449	0.59 %
	Other cardiac arrhythmias: Group 5	21,124	27.88 %
Dose 4	**BNT162b2**	19,420	25.62 %
	mRNA-1273	14,398	19.00 %
Dose 5	**BNT162b2**	423	0.59 %
	mRNA-1273	1,570	2.07 %

NIMS record were excluded from the analysis; these comprised 0.5 % of the extracted SUS admissions.

Statistical methods

A statistical analysis plan using the self-controlled case series method (SCCS) was drawn up in advance as part of the protocol (Supplementary Appendix). All analyses used date of admission or date of ECDS consultation as the index date.

Due to the high risk of event-related deaths for some of the cardiac events which will censor future vaccine exposures, a modified SCCS method was employed as described by Kuhnert et al. where observation periods are defined post-exposure, as in a self-controlled risk interval study [17]. An observation window for each vaccine exposure was defined from vaccination up to the minimum separation between vaccine doses, regardless of whether the patient died. For doses 2–5 the minimum separation was 90 days; for the very small number of individuals who did receive another dose before this time the reference window was curtailed at the next dose. Dose 1 was not included in the analysis as the average separation from dose 2 was less than 90 days. A minimum separation of 90 days also applied to infections, since a new infection was defined as a new positive test at least 90 days since any previous new infection. The data set for the analysis comprised individuals who had received a least one dose of COVID-19 vaccine. Vaccinated individuals who had received a mixed primary schedule, first and 2nd doses <19 days apart, second, third, fourth, fifth doses <56 days apart, or a third ChAdOx1 dose, or a 3rd dose before 1st September 2021, or a 1st dose before 8th December 2020 were excluded, as were any recipients with missing vaccine manufacturer information and of other COVID-19 vaccines or vaccines which may have been given as part of a vaccine trial. Immunosuppressed individuals were eligible to receive up to five doses within the study period and as dose five numbers were very small doses four and five were combined.

The SCCS analysis assessed as the main outcome whether there was an increased incidence of admission to hospital with a cardiac arrhythmia in each of the five diagnostic groups 1–28 days after the second and subsequent doses of any of the three COVID-19 vaccines used in England relative to the incidence in post-vaccination periods outside these risk periods (42-90 days post vaccination).The 1–28 day risk period was based on the signal raised in the earlier study by Patone et al [8]. The period 29–41 days was analysed separately as a washout period. Emergency care records for cardiac arrest were analysed in the same way. Analyses were stratified by dose, vaccine type (ChAdOx1, BNT162b2 or mRNA-1273 vaccine) and age group categorised as 18–49, 50–74 and ≥75 years. These age groups were selected to broadly reflect the sequential roll out of the vaccine and also due to have adequate power for the conditions of interest. When considering the combinations of doses, vaccines and conditions for the 1–28 risk period there are over 100 tests. Many of these tests will be correlated so an a priori decision was made that only relative incidence (RI) estimates with $p < 0.001$ would be considered as strong statistical evidence of an association which allows for 50 independent comparisons. In a secondary analysis the 1–28 day period was further split into 1–14 and 15–28 day periods, as the risk for myocarditis was found to be highest in the first two weeks after vaccination in an earlier study in England using the same data sources [18]. Events on Day 0, the day of vaccination, were assigned a separate risk window. The risk of a cardiac arrhythmia after a confirmed SARS-CoV-2 infection was assessed in the period 1–14 and 15–41 days after infection with the day of positive test (Day 0) assessed separately. COVID-19 infection and vaccination effects were fitted simultaneously, as separate exposures in the same model, so that the effect of COVID-19 infection was accounted for when this overlapped with any period 0–90 days post vaccination and vice versa.

Governance

UKHSA has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for national surveillance of communicable diseases and as such, individual patient consent is not required. Data Availability.

The raw study data are protected and are not available due to data privacy laws. This work is carried out under Regulation 3 of The Health Service ((Control of Patient Information) (Secretary of State for Health, 2002)) [19] using patient identification information without individual patient consent. Data cannot be made publicly available for ethical and legal reasons, i.e. public availability would compromise patient confidentiality as data tables list single counts of individuals rather than aggregated data.

Results

The weekly number of doses delivered since the start of the booster programme in September 2021 is shown in Fig. 1 by manufacturer, together with the weekly number of confirmed SARS-CoV-2 infections in the Pillar 1 surveillance system. The majority of the first booster doses (dose three) of the BNT162b2 vaccine were given before the start of the

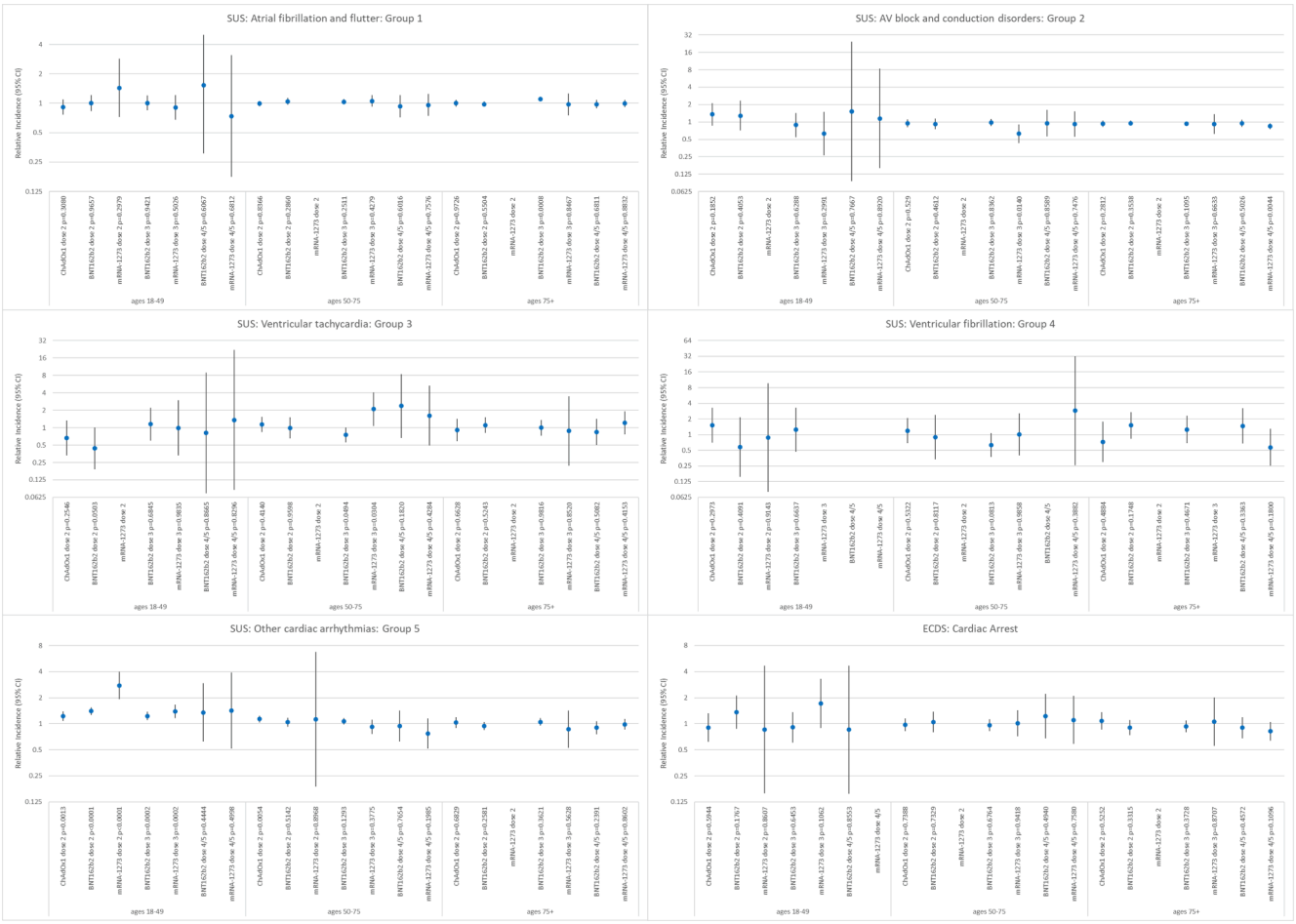

Fig. 2. Relative incidence (RI) of admission for a cardiac arrhythmia in one of the five diagnostic categories in the 1–28 day post-vaccination risk period, stratified by age group, dose and vaccine type.

Omicron BA.1/2 wave in December 2021 with the Spring 2022 booster campaigns for mRNA-1273 and BNT162b2 largely coinciding with the waves associated with the emergence of the Omicron BA.4/5 sub-lineages.

Of the 210,329 admissions with a diagnosis of cardiac arrhythmia in COVID-19 vaccinated individuals aged 18 years and over, 75,772 (36.0 %) fell within a 90-day post-vaccination or post-infection period (Table 1). The number of cases increased with age, consistent with the known age-related risk of an arrhythmia in the population [20]. Over half had a diagnosis of atrial fibrillation or flutter. The proportion with a fatal outcome as measured by death within 7 days of an admission was under 2 % in each group with the exception of ventricular fibrillation (group 4) for which 16.3 % of those admitted died within 7 days (Supplementary Appendix Table 2). At least two doses of a COVID-19 vaccine had been received by 75,488 (99.6 %) of those admitted to hospital within 90 days of vaccination with only 284 (0.4 %) receiving just one dose.

Fig. 2 shows the relative incidence (RI) of admission for a cardiac arrhythmia in one of the five diagnostic categories in the 1–28 day post-vaccination risk period, stratified by age group, dose and vaccine type. With the exception of diagnoses in group 5 in 18–49 year olds no other diagnostic grouping showed strong statistical evidence of an association ($p < 0.001$). Further breakdown of group 5 admissions into 1–14 and 15–28 day periods showed the elevated RIs in the 18–49 age group were restricted to the 1–14 day period (Table 2). Attributable risk (with 95 % confidence intervals) per million doses in the 18–49 year age group for this outcome were calculated based on total second and third doses given in the study period in England. These risks were: BNT162b2 dose 2: 14 [11,16]; dose 3: 8 [5,11]; mRNA-1273 dose2: 30 [25,34]; dose 3:14 [10,17]. In this age group, the majority of the group 5 diagnoses (range 84 % to 96 %) in this post-vaccination interval were coded as palpitations or a non-specific tachycardia; none of the secondary or tertiary diagnosis codes indicated myocarditis. In 50–74 year olds and those aged 75 years and older there was no post-vaccination outcomes within 1–14 or 15–28 days of vaccination with $p < 0.001$ in any of the other diagnostic groups (Supplementary Appendix Table 3).

To further assess the elevated risk for group 5 arrhythmias in under 50 year olds and its potential association with myocarditis an ad hoc analysis was conducted with age stratification into 18–24 and 25 to 49 year olds This showed similar RIs between the two age groups (Supplementary Appendix Table 4).

The RI for ventricular fibrillation (group 4) in ≥75 year olds in the washout period 29–41 days after the first booster dose of BNT162b2 (dose 3) was 2.7 (95 % CI 1.48, 4.94, $p = 0.001$) based on a total of 11 cases in this time interval (Supplementary Appendix Table3). Since individuals with ventricular fibrillation may die before admission, this finding was investigated further by analysing cardiac arrests in the ECDS data set. For the 5344 ECDS cases with a cardiac arrest in individuals who had received two or more doses of a COVID-19 vaccine, 3973 (74.3 %) were fatal. This ECDS analysis showed no elevated risk within 28 days of vaccination for any vaccine or dose (Table 3). The RI in the 29–41 day washout period after the third dose of BNT162b2 for those aged 75 years and over was 1.28 (1.06, 1.54), $p = 0.011$.

For SARS-CoV-2 infection, RIs for those testing positive on the day of admission (Day 0) were raised for all types of cardiac arrhythmia in all age groups with exception of ventricular fibrillation in 18–49 year olds;

Table 2
Relative incidence (RI) of admissions with Cardiac Arrhythmia in SUS using the SCCS analysis in risk intervals after a COVID-19 vaccine stratified by age group (* $p < 0.001$).

			18–49				50–74				75+			
			SUS: Other cardiac arrhythmias: Group 5											
Vaccination status		**Interval (days)**	**case count**	**person years**	**RI (95 % CI)**	**p-value**	**case count**	**person years**	**RI (95 % CI)**	**p-value**	**case count**	**person years**	**RI (95 % CI)**	**p-value**
ChAdOx1	**Dose 2**	**1 to 14**	218	296.8	1.28 (1.1, 1.5)	0.002	384	605.4	1.06 (0.95, 1.19)	0.291	117	225.3	0.83 (0.68, 1.02)	0.079
		15 to 28	199	296.8	1.17 (1, 1.38)	0.052	434	605.4	1.2 (1.08, 1.34)	0.001	172	225.3	1.23 (1.03, 1.46)	0.021
		29 to 41	185	275.6	1.17 (0.99, 1.38)	0.059	342	562.1	1.02 (0.9, 1.15)	0.75	145	209.2	1.11 (0.93, 1.34)	0.254
BNT162b2	**Dose 2**	**1 to 14**	**398**	**431.4**	**1.66 (1.47, 1.86)** *	**<0.001**	205	301.3	1.02 (0.87, 1.19)	0.797	249	368.1	0.92 (0.8, 1.06)	0.272
		15 to 28	275	431.2	1.15 (1, 1.31)	0.049	213	301.2	1.06 (0.91, 1.24)	0.446	257	368.1	0.95 (0.83, 1.1)	0.507
		29 to 41	216	400.2	0.97 (0.84, 1.13)	0.693	185	279.7	0.99 (0.84, 1.16)	0.907	202	341.8	0.79 (0.68, 0.92)	0.002
mRNA-1273	**Dose 2**	**1 to 14**	**51**	**30.6**	**3.75 (2.52, 5.57)***	**<0.001**	1	1.8	1.11 (0.12, 10.7)	0.927	0	0.3		
		15 to 28	24	30.5	1.77 (1.08, 2.9)	0.022	1	1.8	1.14 (0.12, 10.95)	0.911	0	0.3		
		29 to 41	18	28.2	1.44 (0.83, 2.47)	0.191	1	1.6	1.25 (0.13, 12)	0.848	1	0.2	3.44 (0.21, 55.33)	0.383
BNT162b2	**Dose 3**	**1 to 14**	**298**	**392.7**	**1.34 (1.17, 1.53)***	**<0.001**	426	689.7	1.11 (1, 1.24)	0.051	276	538.9	0.98 (0.85, 1.12)	0.725
		15 to 28	251	392.2	1.13 (0.98, 1.3)	0.094	391	689.5	1.03 (0.92, 1.15)	0.673	316	538.9	1.12 (0.99, 1.27)	0.077
		29 to 41	205	363.7	0.99 (0.85, 1.15)	0.868	363	640.2	1.02 (0.91, 1.15)	0.731	270	500.3	1.03 (0.9, 1.18)	0.665
mRNA-1273	**Dose 3**	**1 to 14**	**141**	**143.9**	**1.75 (1.43, 2.15)** *	**<0.001**	90	143.4	0.99 (0.78, 1.25)	0.944	14	23.3	1.01 (0.56, 1.83)	0.979
		15 to 28	84	143.4	1.05 (0.82, 1.34)	0.71	77	143.3	0.85 (0.66, 1.09)	0.198	10	23.3	0.72 (0.37, 1.43)	0.349
		29 to 41	88	132.1	1.18 (0.93, 1.5)	0.176	58	132.9	0.69 (0.52, 0.91)	0.008	12	21.6	0.93 (0.5, 1.75)	0.827
BNT162b2	**Dose 4/5**	**1 to 14**	2	9.3	0.45 (0.1, 1.96)	0.286	16	40.3	0.83 (0.48, 1.44)	0.51	96	197.9	0.89 (0.71, 1.11)	0.298
		15 to 28	10	9	2.29 (1.01, 5.15)	0.046	20	39.9	1.05 (0.63, 1.74)	0.846	98	197.3	0.91 (0.73, 1.14)	0.429
		29 to 41	5	8.2	1.26 (0.45, 3.5)	0.659	21	36.6	1.2 (0.73, 1.97)	0.469	98	182.4	0.99 (0.79, 1.24)	0.917
mRNA-1273	**Dose 4/5**	**1 to 14**	4	9	1.4 (0.41, 4.78)	0.594	27	46.2	1.06 (0.67, 1.66)	0.816	138	282	0.95 (0.79, 1.15)	0.592
		15 to 28	4	8.8	1.44 (0.42, 4.92)	0.562	12	45.4	0.48 (0.26, 0.89)	0.019	148	281.2	1.03 (0.85, 1.23)	0.795

(*continued on next page*)

Table 2 (*continued*)

		18–49				50–74				75+			
		SUS: Other cardiac arrhythmias: Group 5											
Vaccination status	**Interval (days)**	**case count**	**person years**	**RI (95 % CI)**	**p-value**	**case count**	**person years**	**RI (95 % CI)**	**p-value**	**case count**	**person years**	**RI (95 % CI)**	**p-value**
	29 to 41	3	7.8	1.21 (0.31, 4.7)	0.779	17	40.6	0.76 (0.44, 1.29)	0.308	137	259.6	1.03 (0.85, 1.24)	0.777

RIs for some conditions were also raised in later post-infection periods (Supplementary Appendix Table 4). The risk of a cardiac arrest after a confirmed COVID-19 infection was elevated within 42 days of a positive test in both 50–74 and ≥75 year olds (Supplementary Appendix Table 4).

Discussion

In this national study we assessed the association between COVID-19 vaccination and hospital admission for a cardiac arrhythmia in the 40.4 million individuals aged 18 years and over who received at least one dose of one of the three vaccines used for widespread immunisation in England. A range of cardiac arrhythmias was investigated grouped by anatomical site and aetiology. The only evidence we found of an association within a month of any vaccine dose was the increased risk of admission, largely for palpitations or tachycardia, within 14 days of a second priming dose and first booster dose of the two mRNA vaccines in 18–49 year olds.

In the United States a data-mining exercise exploring adverse events after primary immunisation using health maintenance organisation databases found a clustering of admissions or emergency room consultations for palpitations in the first week after receipt of an mRNA vaccine in young adults [21]. Palpitations are common and do not necessarily indicate underlying cardiac pathology. The short-term prognosis of patients with palpitations is good with low rates of death and stroke at a year, though recurrence of symptoms is common [22]. As in our study, the US analysis did not suggest an association with myocarditis.

An increased risk of myocarditis in the first week after mRNA COVID-19 vaccines has been documented [8,18,23]. Arrhythmia can acutely occur in patients with myocarditis [24] but in this analysis we did not find any concomitantly coded myocarditis in the "Other cardiac arrhythmia" group within 14 days of a second priming dose and first booster dose of the two mRNA vaccines in 18–49 year olds where a strong statistical evidence of an association ($p < 0.001$] was demonstrated. Moreover, the elevated risk in the "other cardiac arrhythmia" group was similar in 18–24 and 25–49 year olds, unlike the myocarditis risk which in an earlier study in England was shown to be higher in the younger age group [18]. These findings suggest that whatever the etiology of the vaccine-associated admissions for palpitations or tachycardia it does not appear to be associated with vaccine-induced myocarditis and has a different causal mechanism. Although we did not find any concomitantly coded myocarditis and arrhythmic admissions we did not assess if the patient had previously been diagnosed with myocarditis for which arrhythmia may be a long-term risk due to scarring [25].

There have been a number of claims about mRNA vaccines causing sudden death with some calling for the withdrawal of all mRNA vaccines from the market [26]. In our analysis we assessed the risk of admission for ventricular fibrillation which can result in sudden death but found no evidence of an increased risk within a month of vaccination for any vaccine or dose. There was a possible signal in those aged 75 years and older in the period 29–41 days after a third dose of the BNT162b2 vaccine but not after the mRNA-1273 vaccine. This was not a pre-specified risk period in the analysis but was denoted a washout period to allow for any carryover effect to dissipate should there be an increased risk in the first month after vaccination. We investigated this finding further by analysing cardiac arrests recorded in ECDS which will include cases that die before or during an emergency care consultation. There was a marginally elevated RI in the washout period after a third dose of BNT162b2 in those aged 75 years and over though the p-value did not meet our criterion of evidence of an association. In contrast, testing positive for SARS-CoV-2 infection on the day of admission or ECDS consultation was associated with a 63-fold increased risk of ventricular fibrillation and 42-fold increased risk of cardiac arrest respectively. The marginally elevated risks of ventricular fibrillation or cardiac arrest in the washout period between 4 and 6 weeks after a third dose of the BNT162b2 mRNA vaccine has not been reported elsewhere and may have been associated with undiagnosed SARS-CoV-2 infection since for many recipients of this booster dose the washout period coincided with the large wave of Omicron BA.1/2 that began in November 2021.

The risk of cardiac arrhythmias of all types was consistently elevated in those testing positive for SARS-CoV-2 infection with the highest RIs on Day 0. The practice of testing patients admitted to hospital for any reason as part of infection control procedures will lead to enhanced ascertainment of cases admitted on Day 0. While some of these admissions may not be causally related to the SARS-CoV-2 infection, the very high RIs observed would suggest that the majority are likely to be a consequence of it. The cessation of widespread community testing for those with symptoms of SARS-CoV-2 at the end of March 2022 will also inflate the Day 0 incidence relative to the incidence in the later post-vaccination risk and the baseline periods.

There is high case fatality rate associated with some cardiac arrhythmias, with 16.3 % of those admitted with ventricular fibrillation dying within a week of admission and 75.9 % of those attending emergency care with a cardiac arrest. When analysing events after sequential doses of vaccine this results in event-dependent attrition and violates key assumptions of the conventional SCCS method that an event should not alter either subsequent exposure or the observation period. We therefore used a modification of the SCCS method that can be applied in situations where the outcome event is associated with death and where sequential doses of vaccine are separated by specified minimum intervals [17]. For this, only the post-vaccination period after each dose is used in the analysis with a pre-specified post-vaccination risk interval, followed by a washout period and then a baseline period of fixed length which in our analysis was between 42 and 90 days. Day 0 (the day of vaccination) was analysed separately and not included as a risk period as it could include events that occurred either before or a few hours after vaccination. Proceeding with vaccination in an individual who presents with an acute onset cardiac arrhythmia is unlikely and in our study few events were detected on day 0 for which RI estimates were consistently below 1. With the short interval between the first and second doses in the primary course we could only include second and booster doses in our analysis which used a fixed post-vaccination interval of 42 to 90 days as the comparator. A study of death registrations in England in individuals aged 12–29 years suggested a possible increase in all cause and cardiac-related deaths in females in the 12 weeks after a first dose of the ChAdOx1 vaccine but no analysis of deaths within sequential time periods after vaccination in young women was conducted due to power limitations [14]. Most studies of vaccine safety have focussed on risk windows of within four or six weeks of

Table 3
Relative incidence (RI) of attendances with Cardiac Arrest in ECDS using the SCCS analysis in risk intervals after a COVID-19 vaccine.

			18–49				50–74				75+			
			ECDS: Cardiac Arrest											
Vaccination status		Interval (days)	n cases	person years	RI (95 % CI)	p-value	n cases	person years	RI (95 % CI)	p-value	n cases	person years	RI (95 % CI)	p-value
ChAdOx1	Dose 2	1 to 14	14	29.4	0.63 (0.36, 1.11)	0.112	88	159.1	0.82 (0.65, 1.04)	0.099	52	80	0.99 (0.73, 1.35)	0.939
		15 to 28	26	29.4	1.17 (0.75, 1.83)	0.483	120	159.1	1.12 (0.91, 1.38)	0.27	61	80	1.17 (0.88, 1.56)	0.287
		29 to 41	14	27.3	0.68 (0.38, 1.2)	0.184	108	147.7	1.09 (0.88, 1.35)	0.437	45	74.3	0.93 (0.67, 1.28)	0.645
BNT162b2	Dose 2	1 to 14	15	20.7	1.15 (0.64, 2.07)	0.631	40	65.8	1.01 (0.71, 1.44)	0.948	70	110.8	0.87 (0.67, 1.13)	0.282
		15 to 28	20	20.7	1.56 (0.92, 2.65)	0.097	43	65.8	1.09 (0.77, 1.53)	0.637	76	110.8	0.95 (0.73, 1.22)	0.664
		29 to 41	19	19.3	1.6 (0.94, 2.74)	0.084	39	61.1	1.06 (0.74, 1.51)	0.749	59	102.8	0.78 (0.59, 1.03)	0.082
mRNA-1273	Dose 2	1 to 14	1	1.7	0.89 (0.1, 8)	0.92	1	0.2			0	0		
		15 to 28	1	1.7	0.82 (0.09, 7.35)	0.857	0	0.2			0	0		
		29 to 41	1	1.6	0.87 (0.1, 7.86)	0.905	0	0.2			0	0		
BNT162b2	Dose 3	1 to 14	18	19.7	0.9 (0.54, 1.52)	0.703	106	115.8	0.86 (0.69, 1.06)	0.159	121	112.6	0.98 (0.8, 1.2)	0.822
		15 to 28	17	19.7	0.91 (0.53, 1.55)	0.725	133	115.8	1.08 (0.89, 1.31)	0.456	109	112.6	0.88 (0.72, 1.09)	0.249
		29 to 41	16	18.2	0.9 (0.52, 1.56)	0.712	130	107.5	1.13 (0.93, 1.37)	0.226	145	104.6	1.28 (1.06, 1.54)	0.011
mRNA-1273	Dose 3	1 to 14	11	6.4	2.15 (1.01, 4.57)	0.046	27	25	1.08 (0.7, 1.66)	0.742	4	5.9	0.56 (0.19, 1.62)	0.285
		15 to 28	7	6.4	1.29 (0.53, 3.09)	0.574	24	25	0.95 (0.6, 1.49)	0.818	11	5.9	1.57 (0.77, 3.19)	0.218
		29 to 41	4	5.9	0.81 (0.27, 2.4)	0.704	24	23.1	0.97 (0.62, 1.53)	0.913	8	5.5	1.23 (0.55, 2.73)	0.616
BNT162b2	Dose 4/5	1 to 14	1	0.8	0.84 (0.09, 7.57)	0.878	10	5.7	1.22 (0.59, 2.55)	0.592	39	20.7	0.93 (0.65, 1.33)	0.71
		15 to 28	1	0.8	0.86 (0.1, 7.75)	0.895	10	5.7	1.24 (0.59, 2.58)	0.572	36	20.5	0.86 (0.6, 1.25)	0.437
		29 to 41	2	0.7	1.86 (0.34, 10.24)	0.474	12	5.2	1.63 (0.82, 3.24)	0.165	34	19	0.91 (0.62, 1.32)	0.609
mRNA-1273	Dose 4/5	1 to 14	0	0.5			10	5	1.2 (0.56, 2.56)	0.646	55	26	0.9 (0.66, 1.21)	0.482
		15 to 28	0	0.5			8	4.9	1.02 (0.45, 2.3)	0.971	44	26	0.74 (0.53, 1.03)	0.071
		29 to 41	0	0.4			4	4.4	0.53 (0.18, 1.55)	0.247	58	23.9	1.07 (0.8, 1.44)	0.654

vaccination, as in our study, as this is considered the most biologically plausible interval for vaccine-attributable effects. Moreover, use of the ChAdOx1 vaccine in young adults in settings where the risk of cardiac-related deaths can be assessed has been limited due to the risk of thrombosis with thrombocytopenia in this age group [27]. Corroboration of the signal of a potential increase in cardiac-related deaths in young women within three months of a first dose of the ChAdOx1 vaccine is therefore lacking.

Our analysis has the strength of being a national study that captures all vaccine doses and hospital admissions for the outcomes of interest in the vaccine-eligible adult population in England thus providing sufficient power to stratify results by dose, vaccine type, age and type arrhythmia. With the multiplicity of outcome measures we focussed on those with a p-value of <0.001 as providing evidence of an association and did not formally adjust p-values for multiple comparisons. However, there were only three elevated RIs for a hospital admission within the 1–28 day risk period with a p-value that fell between 0.01 and 0.001, one in group 1 in those aged 75 years and over after a third dose of BNT162b2 vaccine and two in group 5 after a second dose of ChAdOx1 vaccine with one in 18–49 and one in 50–74 year olds. This contrasts with the consistency of the findings of elevated risks in group 5 in the 1–14 day post-vaccination period after second and third doses of each mRNA vaccine in those aged 18–49 years when using a $p < 0.001$ threshold and provides some reassurance that vaccine-attributable effects have been reliably identified in our study.

Ours is an observational study so is prone to selection bias and confounding. While time-invariant individual level confounders are automatically adjusted for in the self-controlled case series design it is unable to control for time varying confounders (though such effects were considered unlikely in the short interval within 90 days of vaccination) nor for selection biases such as those discussed above associated with day 0 effects and changes in SARS-CoV-2 practice over time. Selection bias may also arise if a clinical decision to admit a patient with a cardiac arrhythmia is influenced by knowledge of the patient's vaccination status the effect of which may be to mask a true association or generate a spurious one. While this cannot be ruled out for the less serious cardiac arrhythmias such as palpitations it seems unlikely for the more serious arrhythmias with a higher case fatality rate. Those who have an out-of-hospital cardiac arrest for which resuscitation is not attempted may not be transferred to hospital and will not therefore be included in our ECDS dataset but it seems unlikely that such cases would be biased with respect to vaccination status. In addition an ecological study from Australia has demonstrated no correlation between out- of hospital cardiac arrest and COVID-19 vaccine [28].

In conclusion, our study provides reassuring evidence of the safety of the adenovirus vector ChADOx1 and the two mRNA vaccines with respect to hitherto unidentified serious cardiac events and of the favourable risk benefit of COVID-19 booster vaccination.

Funding

EM receives support from the National Institute for Health Research Health Protection Research Unit in Immunisation at the London School of Hygiene and Tropical Medicine in partnership with UKHSA (Grant Reference NIHR200929).

CRediT authorship contribution statement

Julia Stowe: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Heather J. Whitaker:** Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Nick J. Andrews:** Conceptualization, Formal analysis, Methodology, Writing – original draft. **Elizabeth Miller FMedSci:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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

Data availability

The data that has been used is confidential.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2023.100418.

References

[1] Dewland TA, Marcus GM. SARS-CoV-2 infection and cardiac arrhythmias. Nat Cardiovasc Res 2022;1(12):1109–10.
[2] Alami A, Krewski D, Farhat N, Mattison D, Wilson K, Gravel CA, et al. Risk of myocarditis and pericarditis in mRNA COVID-19-vaccinated and unvaccinated populations: a systematic review and meta-analysis. BMJ Open 2023;13(6):e065687.
[3] Nashashibi S, Priesler O, Levinger U, Habib G. High degree atrio-ventricular block following COVID-19 vaccination. Isr Med Assoc J 2022;24(10):627–8.
[4] Lim KH, Park JS. COVID-19 Vaccination-Induced Ventricular Fibrillation in an Afebrile Patient With Brugada Syndrome. J Korean Med Sci 2022;37(42):e306.
[5] Bassareo PP, Mihali K, Walsh KP. Ventricular tachycardia triggered by the first dose of an adenoviral vector-based COVID-19 vaccine in an adult patient with congenital heart disease. Clin Case Rep 2022;10(9):e6064.
[6] Lin W, Yip ACL, Evangelista LKM, Wong RCC, Tan HC, Lim TW, et al. Ventricular tachycardia from myocarditis following COVID-19 vaccination with tozinameran (BNT162b2, Pfizer-BioNTech). Pacing Clin Electrophysiol 2022;45(9):1097–100.
[7] Abutaleb MH, Makeen HA, Meraya AM, Alqahtani SS, Al-Mass BI, Aljazaeri RO, et al. Risks of Cardiac Arrhythmia Associated with COVID-19 Vaccination: A Systematic Review and Meta-Analysis. Vaccines (Basel) 2023;11(1).
[8] Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med 2022;28(2):410–22.
[9] Ab Rahman N, Lim MT, Lee FY, Lee SC, Ramli A, Saharudin SN, et al. Risk of serious adverse events after the BNT162b2, CoronaVac, and ChAdOx1 vaccines in Malaysia: A self-controlled case series study. Vaccine 2022;40(32):4394–402.
[10] Yechezkel M, Mofaz M, Painsky A, Patalon T, Gazit S, Shmueli E, et al. Safety of the fourth COVID-19 BNT162b2 mRNA (second booster) vaccine: a prospective and retrospective cohort study. Lancet Respir Med 2023;11(2):139–50.
[11] Scquizzato T, Landoni G, Scandroglio AM, Franco A, Calabro MG, Paoli A, et al. Outcomes of out-of-hospital cardiac arrest in patients with SARS-CoV-2 infection: a systematic review and meta-analysis. Eur J Emerg Med 2021;28(6):423–31.
[12] Sun CLF, Jaffe E, Levi R. Increased emergency cardiovascular events among under-40 population in Israel during vaccine rollout and third COVID-19 wave. Sci Rep 2022;12(1):6978.
[13] The Florida Department of Health (Department). Exploring the relationship between all-cause and cardiac-related mortality following COVID-19 vaccination or infection in Florida residents: a self-controlled case series study 2022 [Available from: https://floridahealthcovid19.gov/wp-content/uploads/2022/10/20221007-guidance-mrna-covid19-vaccines-analysis.pdf. (accessed 27/11/2023).
[14] Nafilyan V, Bermingham CR, Ward IL, Morgan J, Zaccardi F, Khunti K, et al. Risk of death following COVID-19 vaccination or positive SARS-CoV-2 test in young people in England. Nat Commun 2023;14(1):1541.
[15] NHS Digital. Secondary Uses Service (SUS) 2022 [Available from: https://digital.nhs.uk/services/secondary-uses-service-sus.] (accessed 27/11/2023).
[16] UK Health Security Agency. Laboratory reporting to UKHSA. A guide for diagnostic laboratories [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1159953/UKHSA_Laboratory_reporting_guidelines_May_2023.pdf.] (accessed 27/11/2023).
[17] Kuhnert R, Hecker H, Poethko-Muller C, Schlaud M, Vennemann M, Whitaker HJ, et al. A modified self-controlled case series method to examine association between multidose vaccinations and death. Stat Med 2011;30(6):666–77.
[18] Stowe J, Miller E, Andrews N, Whitaker HJ. Risk of myocarditis and pericarditis after a COVID-19 mRNA vaccine booster and after COVID-19 in those with and without prior SARS-CoV-2 infection: A self-controlled case series analysis in England. PLoS Med 2023;20(6):e1004245.
[19] UK Statutory Instruments: The Health Service (Control of Patient Information) Regulations 2002 [Available from: https://www.legislation.gov.uk/uksi/2002/1438/regulation/3/made.] (accessed 27/11/2023).
[20] Hatch F, Lancaster MK, Jones SA. Aging is a primary risk factor for cardiac arrhythmias: disruption of intracellular Ca2+ regulation as a key suspect. Expert Rev Cardiovasc Ther 2011;9(8):1059–67.
[21] Yih WK, Daley MF, Duffy J, Fireman B, McClure D, Nelson J, et al. A broad assessment of covid-19 vaccine safety using tree-based data-mining in the vaccine safety datalink. Vaccine 2023;41(3):826–35.

[22] Weber BE, Kapoor WN. Evaluation and outcomes of patients with palpitations. Am J Med 1996;100(2):138–48.
[23] Wong HL, Hu M, Zhou CK, Lloyd PC, Amend KL, Beachler DC, et al. Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases. Lancet (London, England) 2022;399(10342):2191–9.
[24] Peretto G, Sala S, Rizzo S, De Luca G, Campochiaro C, Sartorelli S, et al. Arrhythmias in myocarditis: State of the art. Heart Rhythm 2019;16(5):793–801.
[25] Pelargonio G, Pinnacchio G, Narducci ML, Pieroni M, Perna F, Bencardino G, et al. Long-Term Arrhythmic Risk Assessment in Biopsy-Proven Myocarditis. JACC Clin Electrophysiol 2020;6(5):574–82.
[26] Karmakar S. COVID-19 Vaccines Can Cause Sudden Cardiac Deaths: Warns Expert, Calls For Its Withdrawal From Market 2023 [Available from: https://www.thehealthsite.com/news/covid-19-vaccines-can-cause-sudden-cardiac-deaths-warns-expert-calls-for-its-withdrawal-from-market-942361/.] (accessed 27/11/2023).
[27] Andrews NJ, Stowe J, Ramsay ME, Miller E. Risk of venous thrombotic events and thrombocytopenia in sequential time periods after ChAdOx1 and BNT162b2 COVID-19 vaccines: A national cohort study in England. Lancet Reg Health Eur 2022;13:100260.
[28] Paratz ED, Nehme Z, Stub D, La Gerche A. No Association Between Out-of-Hospital Cardiac Arrest and COVID-19 Vaccination. Circulation 2023;147(17):1309–11.