Risk of venous thrombotic events and thrombocytopenia in sequential time periods after ChAdOx1 and BNT162b2 COVID-19 vaccines: A national cohort study in England

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Summary

Background Thrombosis with thrombocytopenia, or thrombocytopenia on its own, have been reported after Covid-19 vaccines. We assessed the risk after ChAdOx1 adenovirus-vector and BNT162b2 mRNA vaccines in a national cohort study in England.

Methods Hospital admissions for a cerebral venous thrombosis (CVT), other venous thrombosis or thrombocytopenia between 30th November 2020 and 18th April 2021 were linked to the national Covid-19 immunisation register. The incidence of events by dose in pre-defined post-vaccination risk periods relative to the unvaccinated cohort was estimated after adjustment for age, gender, co-morbidities, care home residency and health/social care worker status. Elevated relative incidence (RI) estimates with p<0.001 were considered strong evidence of an association.

Findings The RI for CVT after a first ChAdOx1 dose in 15-39 and 40-64 year olds was 8.7 (95% confidence interval 5.8-13.0) and 2.2 (1.4-3.2) respectively, p<0.001. The elevated risk period in 15-39 year olds was highest 4-13 days post-vaccination (16.3, 9.9-27.0). The attributable risk (AR) was 16.1 per million doses for 15-39 and 3.2 per million for 40-64 year olds. RIs for other thrombosis admissions were elevated in these age groups with ARs of 36.3 and 16.4 per million respectively as were RIs for thrombocytopenia, with ARs of 11.3 and 10.1 per million respectively. No elevated RIs were found for 65+ year olds or after a second ChAdOx1 dose, nor for BNT162b2 vaccine recipients of any age.

Interpretation This epidemiological study shows an increased risk of thrombotic episodes and thrombocytopenia in adults under 65 years of age within a month of a first dose of ChAdOx1 vaccine but not after the BNT162b2 vaccine.

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Keywords: Covid-19 vaccine safety; thrombosis with thrombocytopenia syndrome; thrombocytopenia post-Covid-19 vaccine

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Research in context

Evidence before this study

We searched PubMed on 2nd September 2021, for published research articles using the search terms "COVID vaccine" and "safety", or "thrombosis" or "thrombocytopenia". After exclusion of review articles and case reports we identified four population-based epidemiological studies that assessed the risk of thrombosis or thrombocytopenia after COVID-19 vaccines. The first conducted in Norway and Denmark used record linkage methods to assess the risk in 281,264 first dose recipients aged 18-64 years of the ChAdOx1 adenovirus vector vaccine compared with a historical cohort from 2016 to 2019 (reference 3 in main paper). Marginally elevated standardised morbidity ratios (SMRs) for admission for a venous thrombosis were found largely attributable to cerebral venous sinus thromboses, SMR 20.25 (8.14 to 41.73). A second study using a matched case control design in a Scottish population in which 2.53 million people had received a first dose of ChAdOx1 or BNT162b2 mRNA vaccine found evidence of an increased risk of thrombocytopenia after a first dose of ChAdOx1 vaccine (reference 12 in main paper). Both studies lacked power to stratify by age and onset after vaccination. A third study, which used the self-controlled case series method to analyse a national data set of hospital admissions in England, found increased risks of haematological and vascular events after a first dose of both the ChAdOx1 and BNT162b2 vaccines (reference 19 in the main paper). The fourth study from Israel using a matched cohort design assessed the safety of BNT162b2 vaccine for a number of outcomes and found no evidence of an elevated risk of thrombotic or thrombocytopenic events after either a first and second dose (reference 20 in main paper).

Added value of this study

We conducted a retrospective cohort study of hospital admissions for a venous thrombotic event or thrombocytopenia in a national cohort of over 45 million COVID-19 vaccine eligible individuals in England of whom 61% (over 27 million) had received at least one dose of either the ChAdOx1 or BNT162b2 vaccine. The large study population provided sufficient power to estimate risks by vaccine type, age group and interval after vaccination. The results showed an association between receipt of a first dose of the ChAdOx1 vaccine and cerebral venous thromboses, and venous thromboses at other sites, in those aged 15-64 years of age with the greatest elevated risk within 4-13 days after vaccination in those aged 15-39 years. No elevated risks for these events were found after the BNT162b2 vaccine or in recipients aged 65 years and over of the ChAdOx1 vaccine. An elevated risk of admissions for thrombocytopenia without an accompanying venous thrombosis was also found in under 65 year olds with a similar risk in those aged 15-39 and 40-64 years.

Implications of all the available evidence

The available epidemiological evidence, together with the characteristic haematological and clinical features of the cases reported as vaccine-induced thrombotic thrombocytopenia (VITT), are supportive of a causal association between receipt of a first dose of ChAdOx1 vaccine and development of a venous thrombosis or thrombocytopenia. The age-stratified attributable risk estimates from our study provide a basis for conducting risk-benefit analyses for the use of the ChAdOx1 vaccine in different age groups when taken in the context of the high protection afforded by the vaccine, the risk of acquiring COVID-19 infection and the availability of alternative vaccines. Our study was the first to assess the risk of thrombosis or thrombocytopenia after a second dose of the ChAdOx1 vaccine and while no evidence of an elevated risk was found more post-dose two data are needed to confirm this.

The epidemiological studies so far conducted lack information on the clinical and haematological features of the thrombosis cases to assess the proportion that have a low platelet count, elevated D dimers and anti-platelet factor 4 antibodies - features reported to be characteristic of VITT. Further epidemiological studies in which such additional clinical and haematological information is sought are needed.

Background

The rapid development and deployment of safe and effective vaccines to prevent COVID-19 has been a remarkable achievement with over five billion doses administered worldwide by end of August 2021.[1] The United Kingdom (UK) was the first country to start a national COVID-19 vaccination programme on 8th December 2020 and the end of August over 88% of adults aged 16 years of age and over had received at least one dose,[2] the majority with either the Oxford-AstraZeneca adenovirus vector vaccine (ChAdOx1) or the Pfizer-BioNTech mRNA vaccine (BNT162b2).

Following rare cases of venous thrombosis with thrombocytopenia occurring within a month of the ChAdOx1 vaccine, first reported from Norway and Denmark,[3] the UK Joint Committee on Vaccination and Immunisation advised on 7th April 2021 that mRNA vaccines were preferred for healthy individuals under 30 years of age.[4] On 7th May 2021 this advice was extended to healthy under 40 year olds based on a review of cases reported to the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and predictions about the likely timing and size of a third wave of SARS-CoV-2 infection in the UK.[5] A causal association between rare thrombotic events and the ChAdOx1 vaccine was considered plausible based on the clinical and haematological features of the reported cases and the presence of anti-platelet factor 4 (anti-PF4) antibodies in many of those who were tested.[6–8] Symptom onset in reported cases is usually within five to 24 days of vaccination with a median of 10-12 days.[9]

Public Health England (PHE) through its COVID-19 surveillance remit has access to the national denominator database of over 45 million individuals in England aged 16 years and over eligible to receive a COVID-19 vaccine together with daily updates of the dates and type of each COVID-19 vaccine given to the eligible population.[10] PHE also has access to the national electronic hospital dataset that provides ICD-10 diagnoses for cases admitted to all National Health Service hospitals in England within a few weeks of an admission. We linked the national immunisation dataset with the hospital admissions dataset to assess the risk of admission for a venous thromboembolic event after a first or second dose of ChAdOx1 or BNT162b2 vaccines. We also assessed the risk of thrombocytopenia which has been reported as a suspected adverse event after mRNA vaccines in the United States and also showed evidence of an excess risk 0-27 days after a first dose of ChAdOx1 vaccine in Scotland.[11,12]

Methods

Study population and study design

The study population comprised the resident population in England eligible to receive a COVID-19 vaccine. The study design was a retrospective cohort analysis of the incidence of venous thrombosis or thrombocytopenia resulting in hospital admission according to COVID-19 vaccination status.

Study period

Dates of admission for the outcomes of interest were from 30th November 2020 to 18th April 2021

Vaccination database

Individuals eligible for COVID-19 vaccination in England (aged 16 years as at 31st March 2021) comprised the denominator population for the National Immunisation Management Systems (NIMS). The NIMS database of eligible individuals was constructed using National Health Service (NHS) numbers of individuals identified in electronic NHS records.[13] Since the NHS is the universal health care provider in the UK free at the point of access to all UK residents it has near complete coverage of the resident population. The NIMS denominator population is updated weekly to reflect known changes in the resident population including deaths. In addition to demographic information, the NIMS denominator used information from primary care and other electronic health records to flag those in a clinically extremely vulnerable (CEV) group for which COVID-19 vaccination was recommended irrespective of age, those who were residents in care homes, and health and social care workers - occupations considered at high risk of exposure to infection and/or transmission to vulnerable individuals. This allowed the programme to be rolled out in groups of descending order of priority based on age, CEV status, place of residence and occupation. The co-morbidities included in the CEV category, and the timing of the roll out to these priority groups are given in Appendix 1. Daily updates of vaccinations (date, batch number and manufacturer) given to the eligible population were provided by NIMS.

Hospital admissions database

Hospital inpatient admissions for the outcomes of interest were identified from the national electronic database of hospital admissions that provides timely updates of ICD-10 codes for completed hospital stays for all NHS hospitals in England, termed the Secondary Uses Service -SUS.[14] Up to 24 ICD-10 diagnoses fields can be completed in SUS for each admission with the first diagnosis field indicating the primary reason for admission.

Clinical outcomes

SUS admissions from 30th November 2020 to 18th April 2021 in patients of all ages with an ICD-10 diagnosis code that indicated an admission for a cerebral venous thrombosis (CVT), a non-cerebral venous thrombosis (thrombophlebitis, deep venous or splanchnic vein thrombosis or pulmonary embolism- here termed "other venous thrombosis") or thrombocytopenia were identified in the SUS database. In a sensitivity analysis additional code sets that were potentially more sensitive (expanded CVT code set) or more specific (CVT or other venous thrombosis with a thrombocytopenia code) were used. For the full list of ICD-10 codes and groupings see Appendix 2 Table A1. In line with the Scottish analysis,[12] individuals with a prior admission with a thrombotic or thrombocytopenic code in any of the first five diagnosis fields between 1st December 2019 and 29th November 2020 were excluded respectively from the thrombosis and thrombocytopenia analyses to ensure that only incident cases were included.

Data extraction and linkage

SUS cases were linked to the NIMS data set by NHS number using data extracted from both databases on 11th May 2021 when discharge diagnoses for admissions up to the end of the study period of 18th April were judged to be at least 40% complete. In both the SUS and NIMS datasets provided to PHE the NHS numbers had all been checked as valid using the final digit checksum which detects erroneous NHS numbers and which could lead to invalid linkage. The extracted SUS cases with the outcomes of interest that did not link with a NIMS record were excluded from the analysis; these comprised 0.48% of the extracted SUS admissions. All linked admissions had an age in years, and a completed

CEV, health or social care worker, or care home residency flag (coded as Yes/No)

Construction of the study cohort

NIMS data (monthly denominator data and daily vaccination data) were used to construct the cumulative vaccination status of the population by day from 30th November 2020 to 18th April 2021 stratified by age, vaccine type and post-vaccination intervals (derived from interval between date of vaccination and date of admission) of 0-3, 4-13, 14-27, 28+ days after dose 1 and any time after dose 1 and 0-27 and 28+ days after dose 2, or unvaccinated. The post-vaccination risk periods were chosen based on the range and median intervals between vaccination and symptom onset from a large series of passively reported cases of the putative vaccine-induced immune thrombocytopenia and thrombosis (VITT) syndrome in the UK [9] with allowance for a delay of a few days between onset and admission. Cumulative counts of individuals in each vaccination status category from the NIMS denominator database were stratified by age (5 year bands), gender, care home residency, health or social care worker and whether in a clinically extremely vulnerable (CEV) group. Thrombosis events were stratified by the same factors and were merged to obtain a dataset of event counts and population denominators by day. This process produced a cohort with person time and events between 30th November 2020 and 18th April 2021 stratified by the covariates. Individuals who remained unvaccinated during the study period, as well as those who were initially unvaccinated but then received a vaccine in the study period, contributed person time to the unvaccinated group. Subsequent admissions for the same outcome during the study period were excluded. For computational simplicity, due to the rarity of the outcome events in the vaccinated and unvaccinated cohorts, person time was censored at 18th April for both cohorts rather than at event date for those with an outcome of interest. Individuals who died were removed from the cohort at the end of the month in which they died using information on deaths in the NIMS denominator files.

Statistical analysis

A statistical analysis plan was drawn up in advance as part of the protocol (Appendix 3 – Study protocol, version 1.1). All analyses used date of admission as the index date. Poisson regression was used to estimate the relative incidence (RI) of events in the pre-specified post-vaccination risk periods compared with the unvaccinated period with an offset for population at risk (person days). Adjustment for covariates was by age (5 year bands or broader bands for rare events), sex, period (week), or for rare events four weekly period, CEV status, care home residency for those aged 65+ years and HCW status for those aged <65 years. RIs are shown with 95% confidence intervals but due to the large number of risk intervals being examined, elevated RIs with $p<0.01$ were considered as evidence of a signal and only those with $p<0.001$ were considered as strong evidence of an association. Adjusted RIs were not estimated for risk periods with <2 cases. An early analysis was also conducted using only admissions to March 7th 2021 as a signal strengthening exercise when reports of a thrombotic signal first emerged.

To investigate gender effects the post-first dose relative incidence was compared for each age group between males and females using an interaction term and a likelihood ratio test. Where p-values were <0.05 this was further investigated by stratification.

Attributable cases in the risk intervals with significantly raised RIs ($p<0.001$) were estimated from the attributable fraction AF= (RI-1)/RI multiplied by the number of cases in that interval. Attributable risk was then calculated from the attributable cases divided by the number of doses administered.

Role of the funding source

The funders had no role in study design, data collection, data analysis, interpretation or writing of the report.

Results

The number of admissions for CVT, other venous thromboses or thrombocytopenia are shown in Figure 1 by week beginning December 1st 2020 and ending on April 18th 2021. There was some suggestion of a drop in cases in the last 3 weeks of the study period consistent with delays in allocating discharge diagnosis to the most recent admissions, delays in hospitals uploading data into SUS and prolonged durations of stay that were not completed by the time of the data extract on May 11th 2020. The total number of individuals who had received at least one dose of either the ChAdOx1 or BNT162b2 vaccine by 18th April was 27,378,384 of whom 3,886,541 were aged <40 years, 13,535,979 were 40-64 and 9,955,864 were aged 65 years and older. The vaccine doses given by study week, and by age and priority grouping, are shown in Appendix 2 (Figures A1 and A2) and the unvaccinated and vaccinated person-time for the study population, stratified by clinical outcome, dose, vaccine type and the variables used in the adjusted analyses are shown in Appendix 2, Table A2.

The numbers of admissions and risk per 100,000 person years for each outcome event are shown in Table 1 for the unvaccinated cohort and for the vaccinated cohort according to the pre-specified post-vaccination risk periods after a first dose. The risk of a non-CVT venous thrombosis or thrombocytopenia in the unvaccinated group increased 11 and 6 fold respectively with age, but showed little change with age for CVT events. For CVT admissions there was a significantly raised

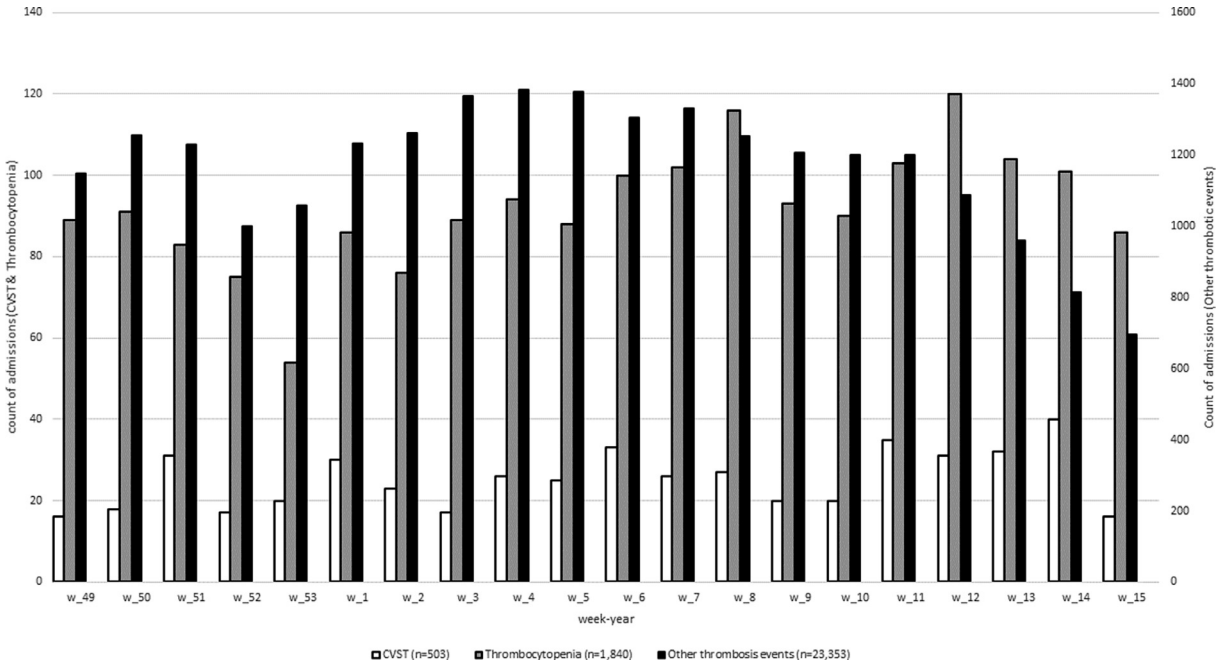

Figure. 1. Distribution of events by week in the study period and ICD diagnosis set.

adjusted RI (p<0.001) in the 4-13, 14-27 and 28+ day post-vaccination risk periods after the ChAdOx1 but not the BNT162b2 vaccine. The elevated risk after the ChAdOx1 vaccine was confined to those aged 15-39 and 40-64 years. The overall adjusted RI for any time after a first ChAdOx1 dose in these two age groups was 8.7 (5.8 – 13.0) and 2.2 (1.4-5.3, p<0.001 respectively. For other venous thromboses there was also a raised adjusted RI (p<0.001) in the same age groups within 4-27 days (Table 1). For both these outcomes crude and adjusted analyses were similar. Five individuals with a primary diagnosis code in the other venous thrombosis group were also recorded as having a CVT of which two were in the 14-27 day period after a first dose of ChAdOx1 vaccine. For admissions with a primary diagnosis code of thrombocytopenia there was an elevated risk after the first dose of ChAdOx1 vaccine in 15-39 and 40-64 year olds; six individuals with a primary diagnosis code of thrombocytopenia also had a thrombosis code for that admission indicating a CVT of which 5 were within the 4-27 day period after a first dose of ChAdOx1 vaccine (one unvaccinated).

There was no evidence of a gender effect for any outcomes after a first dose of ChAdOx1 vaccine. There was possible evidence of a gender effect for BNT162b2 vaccine for other (i.e non CVT) venous thromboses in 15 to 39 year olds (interaction p=0.009). The relative incidences (95% CI) for days 4-13, 14-27 and 28+ after the first dose were 2.2 (1.1-4.1), 1.3 (0.6-2.7), and 1.6 (1.0-2.5) for males compared to 0.8 (0.4-1.5), 0.9 (0.5-1.5), and 0.8 (0.6-1.2) for females, respectively. The p-value for the elevated risk after BNT162b2 vaccine in males in the 4-13 day period was 0.017 which did not meet the protocol criterion of p<0.01 for evidence of a signal of elevated risk.

In both the ChAdOx1 and BNT162b2 vaccine groups, the outcome of other (ie non-CVT) venous thrombosis in those aged 65 years and over had adjusted RIs below 1 with p values <0.0001 (Table 1). Adjusted RIs below 1 were observed at all intervals after vaccination, including the 0-3 day risk window.

There were no signals of an increased risk of a thrombotic event or thrombocytopenia after a second dose of either vaccine (i.e. none with p<0.01) but the available person-years were substantially lower than after the first dose and many risk intervals had <2 cases for which RIs were not estimated (Appendix 4, Table B1).

The attributable risks estimates based on the thrombotic or thrombocytopenic events with elevated RI estimates at the p<0.001 threshold at any time after a first dose of the ChAdOx1 vaccine are shown in Table 2. For thrombotic events, ARs were higher in the 15-39 than the 40-64 year age group for all outcomes but similar by age for thrombocytopenia at 11.3 and 10.1 per million doses respectively.

In the sensitivity analysis using an expanded set of codes to identify potential CVT cases the RI estimates were similar with only a few extra cases identified

a)

Age group	Vaccination status	Person years	Cerebral venous thrombosis				
			Cases	risk per 100,000 person years	Crude RI	Adjusted RI[1]	P- value
15 to 39	**unvaccinated**	7316283	138	1.89	baseline	baseline	
	AZ 0-3 days	26577	2	7.53	4.0	3.9 (1.0-15.8)	0.059
	AZ 4-13 days	64972	20	30.78	16.3	**16.3 (9.9-27)****	**<0.0001**
	AZ 14-27 days	80017	9	11.25	6.0	**6.1 (3.0-12.5)****	**<0.0001**
	AZ 28+ days	105340	13	12.34	6.5	**6.6 (3.5-12.5)****	**<0.0001**
	PF 0-3 days	15164	0	0.00	0.0	N <2	
	PF 4-13 days	37282	1	2.68	1.4	N <2	
	PF 14-27 days	50547	2	3.96	2.1	1.9 (0.5-8.0)	0.36
	PF 28+ days	136472	4	2.93	1.6	1.6 (0.6-4.5)	0.38
40 to 64	**unvaccinated**	5831379	141	2.42	1.0	baseline	
	AZ 0-3 days	110033	3	2.73	1.1	1.1 (0.3-3.5)	0.88
	AZ 4-13 days	265801	18	6.77	2.8	**2.7 (1.6-4.6)****	**0.00032**
	AZ 14-27 days	340292	24	7.05	2.9	**2.8 (1.7-4.7)****	**0.0001**
	AZ 28+ days	344276	13	3.78	1.6	1.4 (0.7-2.7)	0.32
	PF 0-3 days	35802	0	0.00	0.0	N <2	
	PF 4-13 days	89087	2	2.24	0.9	0.8 (0.2-3.4)	0.79
	PF 14-27 days	122191	3	2.46	1.0	0.9 (0.3-2.9)	0.86
	PF 28+ days	306783	6	1.96	0.8	0.7 (0.3-1.7)	0.44
65 +	**unvaccinated**	1950335	48	2.46	1.0	baseline	
	AZ 0-3 days	58333	2	3.43	1.4	1 .0(0.2-4.4)	0.97
	AZ 4-13 days	145509	2	1.37	0.6	0.4 (0.1-1.7)	0.22
	AZ 14-27 days	202486	13	6.42	2.6	1.9 (0.9-4.0)	0.10
	AZ 28+ days	580777	11	1.89	0.8	0.5 (0.2-1.3)	0.15
	PF 0-3 days	51471	0	0.00	0.0	N <2	
	PF 4-13 days	128621	5	3.89	1.6	1.3 (0.5-3.4)	0.57
	PF 14-27 days	173229	7	4.04	1.6	1.3 (0.5-3.0)	0.59
	PF 28+ days	539798	11	2.04	0.8	0.6 (0.3-1.4)	0.25

b)

Age group	Vaccination status	Person years	Other venous thrombosis				
			Cases	risk per 100,000 person years	Crude RI	Adjusted RI[1]	P- value
15 to 39	**unvaccinated**	7316283	2027	27.71	baseline	baseline	
	AZ 0-3 days	26577	17	63.97	2.3	1.7 (1.1-2.7)	0.031
	AZ 4-13 days	64972	52	80.03	2.9	**2.2 (1.7-3.0)****	**<0.0001**
	AZ 14-27 days	80017	62	77.48	2.8	**2.3 (1.8-3.0)****	**<0.0001**
	AZ 28+ days	105340	55	52.21	1.9	1.4 (1.1-1.9)	0.016
	PF 0-3 days	15164	6	39.57	1.4	0.9 (0.4-2.0)	0.79
	PF 4-13 days	37282	19	50.96	1.8	1.2 (0.7-1.8)	0.55
	PF 14-27 days	50547	23	45.50	1.6	1.0 (0.7-1.6)	0.90
	PF 28+ days	136472	55	40.30	1.5	1.0 (0.8-1.4)	0.82
40 to 64	**unvaccinated**	5831379	6364	109.13	1.0	baseline	
	AZ 0-3 days	110033	75	68.16	0.6	0.6 (0.5-0.7)	<0.0001
	AZ 4-13 days	265801	374	140.71	1.3	**1.3 (1.1-1.4)****	**<0.0001**
	AZ 14-27 days	340292	427	125.48	1.1	**1.3 (1.1-1.4)****	**<0.0001**
	AZ 28+ days	344276	463	134.49	1.2	1.2 (1.1-1.4)*	0.0018
	PF 0-3 days	35802	29	81.00	0.7	0.6 (0.4-0.8)	0.0021
	PF 4-13 days	89087	127	142.56	1.3	1.0 (0.9-1.2)	0.87
	PF 14-27 days	122191	187	153.04	1.4	1.1 (1.0-1.3)	0.11
	PF 28+ days	306783	341	111.15	1.0	1.0 (0.9-1.1)	0.78

(*continued*)

Table 1 (Continued)

b)

Age group	Vaccination status	Person years	Other venous thrombosis				
			Cases	risk per 100,000 person years	Crude RI	Adjusted RI[1]	P- value
65 +	**unvaccinated**	1950335	6133	314.46	1.0	baseline	
	AZ 0-3 days	58333	171	293.14	0.9	0.8 (0.7-0.9)	0.00093
	AZ 4-13 days	145509	504	346.37	1.1	0.9 (0.8-1.0)	0.012
	AZ 14-27 days	202486	659	325.45	1.0	0.8 (0.7-0.9)	<0.0001
	AZ 28+ days	580777	1630	280.66	0.9	0.8 (0.7-0.8)	<0.0001
	PF 0-3 days	51471	102	198.17	0.6	0.5 (0.4-0.6)	<0.0001
	PF 4-13 days	128621	390	303.22	1.0	0.7 (0.7-0.8)	<0.0001
	PF 14-27 days	173229	520	300.18	1.0	0.7 (0.6-0.8)	<0.0001
	PF 28+ days	539798	1620	300.11	1.0	0.7 (0.6-0.7)	<0.0001

c)

Age group	Vaccination status	Person years	Thrombocytopenia				
			Cases	risk per 100,000 person years	Crude RI	Adjusted RI[1]	P- value
15 to 39	**unvaccinated**	7316283	230	3.14	baseline	baseline	
	AZ 0-3 days	26577	2	7.53	2.4	1.30 (0.3-5.3)	0.71
	AZ 4-13 days	64972	14	21.55	6.9	**3.7 (2.1-6.4)****	**<0.0001**
	AZ 14-27 days	80017	15	18.75	6.0	**3 .0(1.7-5.2)****	**<0.0001**
	AZ 28+ days	105340	16	15.19	4.8	1.6 (0.9-2.8)	0.11
	PF 0-3 days	15164	3	19.78	6.3	3.8 (1.2-12.0)	0.024
	PF 4-13 days	37282	0	0.00	0.0	N<2	
	PF 14-27 days	50547	7	13.85	4.4	2.5 (1.2-5.5)	0.020
	PF 28+ days	136472	11	8.06	2.6	1.4 (0.7-2.6)	0.32
40 to 64	**unvaccinated**	5831379	382	6.55	1.0	baseline	
	AZ 0-3 days	110033	10	9.09	1.4	1.2 (0.6-2.3)	0.57
	AZ 4-13 days	265801	39	14.67	2.2	**1.9 (1.4-2.8)****	**0.00023**
	AZ 14-27 days	340292	72	21.16	3.2	**2.8 (2.1-3.8)****	**<0.0001**
	AZ 28+ days	344276	73	21.20	3.2	**1.8 (1.3-2.4)****	**0.00084**
	PF 0-3 days	35802	4	11.17	1.7	1.3 (0.5-3.4)	0.65
	PF 4-13 days	89087	11	12.35	1.9	1.4 (0.8-2.5)	0.30
	PF 14-27 days	122191	12	9.82	1.5	1.1 (0.6-2.0)	0.78
	PF 28+ days	306783	35	11.41	1.7	1.2 (0.8-1.8)	0.38
65 +	**unvaccinated**	1950335	390	20.00	1.0	baseline	
	AZ 0-3 days	58333	17	29.14	1.5	1.2 (0.8-2.1)	0.39
	AZ 4-13 days	145509	40	27.49	1.4	1.2 (0.8-1.7)	0.45
	AZ 14-27 days	202486	45	22.22	1.1	0.9 (0.7-1.3)	0.73
	AZ 28+ days	580777	120	20.66	1.0	0.9 (0.7-1.3)	0.73
	PF 0-3 days	51471	13	25.26	1.3	1.1 (0.6-1.9)	0.74
	PF 4-13 days	128621	27	20.99	1.0	0.9 (0.6-1.3)	0.58
	PF 14-27 days	173229	32	18.47	0.9	0.8 (0.5-1.1)	0.16
	PF 28+ days	539798	132	24.45	1.2	1.1 (0.8-1.4)	0.71

***Table 1*: Relative incidence (RI) of admission with a) Cerebral venous thrombosis b) Other venous thrombosis c) Thrombocytopenia after a first dose of AstraZeneca (AZ) ChAdOx1 or Pfizer-BioNTech (PF) BNT162b2 vaccine by post-vaccination risk interval.**

1RIs adjusted for age (5 year bands or broader bands for rare events), sex, period (week) or four weekly period for rare events, CEV status, care home residency for those aged 65+ years and HCW status for those aged <65 years.

* significant at the P<0.01 level;

** significant at the P<0.001 level

Event	Age group	RI at any time after a first dose (95% CI)	Attributable fraction (95% CI)	Events in risk period	Attributable events	Doses	Attributable risk per 1 million doses (95% CI)
Cerebral venous thrombosis	15-39 year olds	8.7 (5.8-13.0)	0.89 (0.83-0.92)	44	39	2425111	16.1 (15.0-17.7)
	40-64 year olds	2.2 (1.4-3.2)	0.55 (0.29-0.69)	58	43	10040475	3.2 (1.7-4.0)
Other venous thrombosis	15-39 year olds	1.9 (1.6-2.2)	0.47 (0.38-0.55)	186	88	2425111	36.3 (28.8-41.8)
	40-64 year olds	1.1 (1.1-1.2)	0.12 (0.06-0.19)	1339	164	10040475	16.4 (7.5-24.9)
Thrombocytopenia	15-39 year olds	2.4 (1.6-3.5)	0.58 (0.38-0.71)	47	27	2425111	11.3 (7.3-13.8)
	40-64 year olds	2.1 (1.6-2.6)	0.52 (0.38-0.62)	194	102	10040475	10.1 (7.2-11.9)

***Table 2*: Attributable risk estimates (95% Confidence intervals, CIs) per dose for events with relative incidence estimates with p<0.001 after a first dose of ChAdOx1 Covid-19 vaccine.**

(Table 3). When restricting admissions to those with both a thrombosis code (CVT or other venous thrombosis) and a code indicating thrombocytopenia the RI estimates are considerably greater though the attributable risk estimates were lower due to the fewer number of events in the post-vaccination risk periods.

Age group	Vaccination status	Person years	Expanded CVT codes			Thrombosis with thrombocytopenia		
			Cases	Crude RI	Adjusted RI	Cases	Crude RI	Adjusted RI
15 to 39	**unvaccinated**	7316283	148	1.0	baseline	34	1.0	Baseline
	AZ 0-3 days	26577	3	5.6	5.2 (1.7-16.6)	0	0.0	N<2
	AZ 4-13 days	64972	21	16.0	**15.4 (9.5-25.2)****	12	39.7	**38.2 (17.6-82.9)****
	AZ 14-27 days	80017	9	5. 6	**5.5 (2.7-11.2)****	9	24.2	**22.1 (9.3-52.5)****
	AZ 28+ days	105340	15	7.0	**6.8 (3.7-12.4)****	4	8.2	**5.8 (1.7-19.3)***
	PF 0-3 days	15164	0	0.00	N <2	0	0.0	N<2
	PF 4-13 days	37282	1	1.3	N <2	1	5.8	N<2
	PF 14-27 days	50547	2	2.0	1.8 (0.4-7.3)	1	4.3	N<2
	PF 28+ days	136472	4	1. 5	1.4 (0.5-4)	2	3.2	3 (0.6-13.8)
40 to 64	**unvaccinated**	5831379	214	1.0	baseline	68	1.0	baseline
	AZ 0-3 days	110033	4	1.0	1.1 (0.4-3)	1	0.8	N<2
	AZ 4-13 days	265801	22	2.3	**2.6 (1.6-4.2)****	19	6.1	**5.4 (3-9.7)****
	AZ 14-27 days	340292	28	2.2	**2.8 (1.8-4.5)****	24	6.1	**5.2 (2.9-9.3)****
	AZ 28+ days	344276	16	1.3	1.5 (0.8-2.8)	14	3.5	1.9 (0.9-3.9)
	PF 0-3 days	35802	0	0.0	N <2	1	2.4	N<2
	PF 4-13 days	89087	2	0.6	0.6 (0.1-2.3)	1	1.0	N<2
	PF 14-27 days	122191	7	1.6	1.5 (0.7-3.2)	5	3.5	2.7 (1.1-7.1)
	PF 28+ days	306783	6	0.5	0.6 (0.3-1.4)	6	1.7	1.1 (0.4-2.8)
65 +	**unvaccinated**	1950335	185	1.0	baseline	64	1.0	baseline
	AZ 0-3 days	58333	5	0.9	0.9 (0.3-2.1)	1	0.5	N<2
	AZ 4-13 days	145509	15	1.1	1 (0.6-1.8)	11	2.3	2.1 (1-4.5)
	AZ 14-27 days	202486	23	1.2	1.3 (0.8-2.1)	11	1.7	1.7 (0.8-3.7)
	AZ 28+ days	580777	45	0.8	1.2 (0.7-1.9)	10	0.5	0.6 (0.3-1.5)
	PF 0-3 days	51471	1	0.2	N <2	1	0.6	N<2
	PF 4-13 days	128621	12	1.0	1.0 (0.5-1.7)	3	0.7	0.6 (0.2-1.9)
	PF 14-27 days	173229	18	1.1	1.1 (0.6-1.8)	4	0.7	0.6 (0.2-1.8)
	PF 28+ days	539798	59	1.2	1.5 (1-2.3)	20	1.1	1.2 (0.6-2.5)

***Table 3*: Relative incidence (RI) of admission in the sensitivity analysis using the expanded CVT code set, and codes indicating thrombosis with thrombocytopenia, after a first dose of ChAdOx1 (AZ) or BNT162b2 (PF) vaccine by post-vaccination risk interval.**

* significant at the P<0.01 level

** significant at the P<0.001 level

Using the adjusted RI for any time after a first ChAdOx1 dose in the 15-39 and 40-64 year age groups of 18.9 (9.4-38.2) and 3.8 (2.3 and 6.2) respectively), the attributable risk estimates for admissions with both a thrombosis and thrombocytopenia code are respectively 9.8 and 4.3 per million doses.

The RI estimates in each age group after the first dose using admissions to March 7th 2021 are shown in Appendix 4, Table B2 Relative incidence estimates were generally lower with only CVT admissions in 15-39 year olds 4-13 days after a first dose of ChAdOx1 vaccine showing an elevated risk at the p<0.001 level.

Discussion

This record linkage study in England provides epidemiological evidence of an elevated risk of CVT and other thrombotic events after a first dose of ChAdOx1 vaccine in adults aged under 65 years. There was no evidence of an elevated risk in those aged 65 years and over nor in those of any age who received the BNT162b2 vaccine. Attributable risk estimates were higher for 15-39 year olds than for 40-64 year olds and were higher for venous thromboses involving peripheral, splanchnic or portal veins than cerebral venous thromboses. Admissions for thrombocytopenia were also elevated after a first dose of ChAdOx1 vaccine, the majority in the absence of an accompanying thrombosis code. None of the outcomes with an elevated risk after the ChAdOx1 vaccine showed a difference by gender. There were substantially fewer second doses of either the ChAdOx1 or BNT162b2 vaccines given in the study period due to the policy adopted in the UK of delaying the 2nd dose to maximise the public health benefit as the vaccine programme was rolled out.[15] This limited the power to assess events after a second dose though based on the available numbers there was no signal of an increase in thrombotic events after a second dose of either vaccine.

In this epidemiological analysis we did not attempt to verify discharge diagnoses nor did we seek additional information on any haematological tests carried out during the admission such as D Dimers, platelet counts, prothrombin time, fibrinogen levels or, if done, anti-PF4 antibodies. This information is being sought via haematologists in a subset to obtain further clinical information on the outcome events identified in SUS by the ICD-coding in vaccinated and unvaccinated individuals. While lack of specificity in identifying cases of the putative vaccine-induced thrombosis with thrombocytopenia (VITT) syndrome would reduce the RI estimates due to misclassification bias, this would not affect estimates of attributable risk. When restricting outcomes to those with both a thrombosis and thrombocytopenia code (Table 3) the RI estimates were higher but the attributable risk estimates lower than for thrombotic events without an additional thrombocytopenia code. They were also below the risk estimated by the MHRA based on passively reported cases of thrombo-embolic events with concurrent thrombocytopenia - 20.5 per million doses in those aged 18-49 years[16] which suggests incomplete recording of concomitant thrombocytopenia for thrombotic events in the SUS database. The existence of the syndrome first received widespread publicity among health care professionals and the public in the UK on 7th April 2021 and it is possible that this may have influenced health care seeking behaviour or diagnostic investigations and ICD-10 coding among those admitted after this date. An initial analysis of admissions by 7th March 2021 produced somewhat lower RIs for CVT for the 15-39 year age group than the analysis of admissions up to 18th April 2021 though with overlapping confidence intervals (Supplementary Appendix Table SC4) but there was insufficient power to assess risks in older age groups or for other thrombotic events at this early time point. In adults under 65 years of age the majority of the cases reported to the MHRA by clinicians have been of CVT which makes it unlikely that the significantly raised RI estimates in under 65 year olds for the non-CVT events in our analysis reflects ascertainment bias due to alert clinicians looking for cases temporally-associated with ChAdOx1 vaccine.

COVID-19 disease can itself be associated with thrombotic events.[17] In this analysis we did not attempt to identify thrombotic events associated with COVID-19 which may have occurred in some vaccine recipients before protection started at around 14-21 days post-vaccination.[18] However, admissions with a COVID-19-induced thrombotic event should not be more likely in the early post-vaccination period than in the unvaccinated. To place any vaccine-associated risks of thrombosis or thrombocytopenia in context it is important to compare these with the risks of developing such complications with COVID-19 disease. A recent study in the UK showed substantially higher risks of thrombotic events and thrombocytopenia after SARS-CoV-2 infection than after a Covid-19 vaccine in the same population.[19]

A record linkage study combining data from Norway and Denmark also found evidence of an increased risk of admission for a thrombotic episode in recipients of the ChAdOx1 vaccine in individuals 18-65 years, though no comparative data was available for older adults nor for recipients of mRNA vaccines.[3] This study did not adjust for underlying clinical conditions and was based on standardised morbidity ratios just adjusted for age, gender and country compared with a historical cohort from 2016 to 2019. A large number of outcome measures were presented with many showing a lower 95% CI just above one; significance levels adjusted for multiple testing were not provided. In our analysis, given the number of risk periods and outcomes investigated, we adopted a cautious approach of only considering elevated RIs with a p value of <0.001 as providing

strong evidence of an association. An analysis of admissions in Scotland after a first dose of ChAdOx1 or BNT162b2 vaccines for thrombotic events or thrombocytopenia failed to show an elevated risk of venous thrombosis but the study lacked power; a potential association between thrombocytopenia after a first-dose of the ChAdOx1 vaccine was identified though the attributable risk by age and risk interval could not be assessed.[12] A self-controlled case series analysis of hospital admissions in England for thrombocytopenia and thromboembolism reported elevated risks of a cerebral venous sinus thrombosis after both the ChAdOx1 and BNT162b2 vaccines, and an elevated risk of arterial thromboembolism after BNT162b2. However, pre-vaccination time was used as the control period which could introduce bias as the occurrence of the event may affect the likelihood of subsequent vaccination; a sensitivity analysis using only the post-vaccination period from 28 days showed no elevated risks for any vaccine outcome.[19] A study from Israel using a matched cohort design found no elevated risks of a thrombotic event or thrombocytopenia after either a first or second dose of BNT162b2 vaccine.[20]

Ours is an observational study and has limitations. While we adjusted for clinical conditions that were flagged as CEV (as listed in Appendix 1) we did not adjust for a wider range of co-morbidities that were subsequently added to the NIMS denominator dataset after the vaccination programme had started and which allowed individuals with these conditions to receive vaccination irrespective of their age when adults aged 60-64 years became eligible. These additional conditions were retrospectively flagged in mid-March and there was evidence that in some cases the thrombosis event itself had resulted in individuals being given this additional "at-risk" flag after the event which would result in bias if used in the analysis. We were also unable to adjust for socioeconomic status and ethnic group though the lack of an elevated risk with the BNT162b2 vaccine suggests that they are not potential confounders. The relative incidence estimates below one for both vaccines in those aged 65 years and older suggests bias from unmeasured confounders, for example associated with a healthy vaccinee effect,[21] as a true protective effect from vaccine seems unlikely. Use of the self-controlled case series would control for unmeasured time-invariant confounders but when the analysis was conducted there was insufficient post-event observation time to use as the control period and we did not consider it valid to use the pre-event time as the control period, as in the recent analysis by Hippisley-Cox et al[19], because of the likelihood that the event itself would influence subsequent vaccination in an unpredictable way. For example initially the event might have made vaccination more likely if it then flagged the person as in a risk group, but later when the potential risk was known it may have become a reason individuals did not get vaccinated. Our study only included events that were severe enough to warrant hospital admission so will have missed any cases treated in primary care and we did not have access to platelet counts which constitute a key component of the VITT case definition. Also we did not investigate arterial thrombotic events for which no signal had been raised at the time we planned our study.

In conclusion, this analysis provides epidemiological evidence of an increased risk of a CVT or other thrombotic event, or thrombocytopenia after a first dose of ChAdOx1 vaccine. The attributable risk for a thrombotic event was highest in under 40 year olds, at 16.1 and 36.3 per million doses respectively for a CVT or other thrombosis event. These low risks can be mitigated by rapid diagnosis and appropriate treatment[22] and need to be judged in the context of the benefit afforded by the vaccine during periods of increased COVID-19 incidence and in the absence of an available alternative vaccine.

Governance

PHE 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.

Role of the funding source

None.

Author Contributions

All authors developed the study protocol. JS carried out the data management and descriptive analysis. NA conducted the statistical analysis and EM wrote the first draft of the paper. Authors NA and JS have verified the underlying data. All authors contributed to subsequent revisions and approved the final version. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication

Data sharing statement

This work is carried out under Regulation 3 of The Health Service (Control of Patient Information) (Secretary of State for Health, 2002))(3) 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

Declaration of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanepe.2021.100260.

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