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Background rates of five thrombosis with thrombocytopenia syndromes of special interest for COVID-19 vaccine safety surveillance: Incidence between 2017 and 2019 and patient profiles from 38.6 million people in six European countries

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Abstract

Background: Thrombosis with thrombocytopenia syndrome (TTS) has been reported among individuals vaccinated with adenovirus-vectored COVID-19 vaccines. In this study, we describe the background incidence of non-vaccine induced TTS in six European countries.

Methods: Electronic medical records from France, the Netherlands, Italy, Germany, Spain, and the United Kingdom informed the study. Incidence rates of cerebral venous sinus thrombosis (CVST), splanchnic vein thrombosis (SVT), deep vein thrombosis (DVT), pulmonary embolism (PE), and myocardial infarction or ischemic stroke, all with concurrent thrombocytopenia, were estimated among the general population of persons in a database between 2017 and 2019. A range of additional potential adverse events of special interest for COVID-19 vaccinations were also studied in a similar manner.

Findings: A total of 38 611 617 individuals were included. Background rates ranged from 1.0 (95% CI: 0.7–1.4) to 8.5 (7.4–9.9) per 100 000 person-years for DVT with thrombocytopenia, from 0.5 (0.3–0.6) to 20.8 (18.9–22.8) for PE with thrombocytopenia, from 0.1 (0.0–0.1) to 2.5 (2.2–2.7) for SVT with thrombocytopenia, and from 1.0 (0.8–1.2) to 43.4 (40.7–46.3) for myocardial infarction or ischemic stroke with thrombocytopenia. CVST with thrombocytopenia was only identified in one database, with incidence rate of 0.1 (0.1–0.2) per 100 000 person-years. The incidence of non-vaccine induced TTS increased with age, and was typically greater among those with more comorbidities and greater medication use than the general population. It was also more often seen in men than women. A large proportion of those affected were seen to have been taking antithrombotic and anticoagulant therapies prior to their event.

Interpretation: Although rates vary across databases, non-vaccine induced TTS has consistently been seen to be a very rare event among the general population. While still remaining very rare, rates were typically higher among older individuals, and those affected were also seen to generally be male and have more comorbidities and greater medication use than the general population.

KEYWORDS
Covid-19, post vaccine, thrombosis-thrombocytopenia syndromes (TTS), vaccine

1 | INTRODUCTION

In little over a year since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, numerous vaccines against SARS-CoV-2 were developed based on several platforms.[1] Some have demonstrated a high degree of efficacy in large phase 3 clinical trials,[2–4] received conditional approvals from regulators, and together they have already been given to over a billion individuals.[5] The benefits of these vaccines are demonstrable. For example, a large study on mass vaccination in Israel finding the estimated effectiveness of BNT162b2 mRNA vaccine to be 94% for symptomatic COVID-19, 87% for hospitalisation, and 92% for severe COVID-19 from 7 days after the second dose.[6] Similarly, the use of the BNT162b2 mRNA and ChAdOx1 in Scotland have been associated with substantial reductions in the risk of developing severe COVID-19 disease.[7]

There remains, however, a need to assess the safety of vaccines against SARS-CoV-2 and assess safety signals as and when they arise. While phase 3 clinical trials provided valuable information on the rates of relatively common, but mostly mild, adverse reactions following vaccination against SARS-CoV-2, they were not powered to study the occurrence of rare adverse events of special interest. Although the risks of rare but serious adverse events might be low, nationwide vaccination campaigns where millions of people are inoculated can lead to a considerable absolute number of any such events to occur.

A particular area of concern has arisen relating to the occurrence of thrombosis (often cerebral or abdominal) with concomitant thrombocytopenia among individuals who had received adenovirus-based vaccine against SARS-CoV-2. As of the 28th April 2021, 242 instances of thromboembolic events with thrombocytopenia among individuals who had recently received the ChAdOx1 vaccine in the United Kingdom had been identified on the basis of spontaneous reports. Of these, cerebral venous sinus thrombosis (CVST) was reported in 93 of the cases.[8] Meanwhile, as of the 23rd April 2021, 15 confirmed reports of thrombosis with thrombocytopenia syndrome (TTS) had been identified for the Ad.26.COV2.S vaccine in the United States.[9] These spontaneous reports of TTS came at a time when 22.6 million first doses and 5.9 million second doses of the ChAdOx1 vaccine had been given in the United Kingdom and more than 8 million doses of the Ad.26.COV2.S had been given in the United States.[8,9]

TABLE 1 Database descriptions

Country	Database	Primary care data	Hospital linkage	Outpatient platelet measurements	Inpatient platelet measurements
France	IQVIA Longitudinal Patient Data (LPD) France	Yes	No	Yes	No
Germany	IQVIA Disease Analyser (DA) Germany	Yes	No	Yes	No
Italy	IQVIA Longitudinal Patient Data (LPD) Italy	Yes	No	Yes	No
The Netherlands	Integrated Primary Care Information (IPCI)	Yes	No	Yes	No
Spain	Information System for Research in Primary Care (SIDIAP) with minimum basic set of hospital discharge data (CMBD- HA)	Yes	Yes	Yes	No
United Kingdom	Clinical Practice Research Datalink (CPRD) Aurum	Yes	No	Yes	No
United Kingdom	Clinical Practice Research Datalink (CPRD) GOLD	Yes	No	Yes	No
United Kingdom	Health Informatics Centre at the University of Dundee (HIC Dundee)	Yes	Yes	Yes	Yes

TABLE 2 Characteristics of study populations

	CPRD Aurum	CPRD GOLD	HIC Dundee	IPCI	IQVIA DA Germany	IQVIA LPD France	IQVIA LPD Italy	SIDIAP CMBD-HA
N	13 178 959	3 913 071	948 561	1 299 288	8 459 098	3 951 633	1 066 230	5 794 777
Age (Median [IQR])	39 [22–57]	41 [22–59]	41 [23–59]	44 [23–60]	52 [32–67]	48 [28–65]	52 [37–68]	42 [25–59]
Sex: Male (*N* [%])	6 593 514 (50.0%)	1 937 858 (49.5%)	469 725 (49.5%)	636 386 (49.0%)	3 589 506 (42.4%)	1 669 415 (42.2%)	426 758 (40.0%)	2 859 044 (49.3%)
Years of prior observation time (Median [IQR])	8.9 [3.0–19.4]	11.9 [4.7–15.1]	8.0 [6.6–12.0]	3.2 [1.8–5.7]	4.8 [1.9–8.9]	4.6 [2.0–6.2]	6.3 [5.0–6.5]	11.0 [11.0–11.0]
Comorbidities prior to index date								
Autoimmune disease (*N* [%])	223 241 (1.7%)	70 604 (1.8%)	8040 (0.8%)	24 645 (1.9%)	238 985 (2.8%)	32 245 (0.8%)	45 567 (4.3%)	84 817 (1.5%)
Antiphospholipid syndrome (*N* [%])	4428 (0.0%)	1166 (0.0%)	<5	<5	<5	<5	<5	1011 (0.0%)
Thrombophilia (*N* [%])	11 893 (0.1%)	3039 (0.1%)	198 (0.0%)	0 (0.0%)	6474 (0.1%)	313 (0.0%)	<5	2796 (0.0%)
Asthma (*N* [%])	1 595 149 (12.1%)	484 991 (12.4%)	37 160 (3.9%)	138 777 (10.7%)	412 789 (4.9%)	222 161 (5.6%)	79 528 (7.5%)	353 485 (6.1%)
COPD (*N* [%])	243 501 (1.8%)	80 393 (2.1%)	14 225 (1.5%)	40 116 (3.1%)	358 047 (4.2%)	41 040 (1.0%)	27 119 (2.5%)	166 817 (2.9%)
Atrial fibrillation (*N* [%])	242 537 (1.8%)	76 091 (1.9%)	825 (0.1%)	31 801 (2.4%)	92 767 (1.1%)	13 412 (0.3%)	34 325 (3.2%)	137 843 (2.4%)
Diabetes mellitus (*N* [%])	728 420 (5.5%)	213 996 (5.5%)	25 891 (2.7%)	93 035 (7.2%)	597 233 (7.1%)	174 564 (4.4%)	95 611 (9.0%)	468 808 (8.1%)
Obesity (*N* [%])	372 593 (2.8%)	107 522 (2.7%)	9843 (1.0%)	40 395 (3.1%)	530 958 (6.3%)	15 634 (0.4%)	46 101 (4.3%)	927 483 (16.0%)
Heart disease (*N* [%])	895 638 (6.8%)	278 323 (7.1%)	56 966 (6.0%)	129 562 (10.0%)	936 730 (11.1%)	194 630 (4.9%)	165 172 (15.5%)	592 122 (10.2%)
Hypertensive disorder (*N* [%])	1 839 796 (14.0%)	558 671 (14.3%)	71 703 (7.6%)	222 433 (17.1%)	1 425 782 (16.9%)	498 244 (12.6%)	322 776 (30.3%)	1 145 518 (19.8%)
Renal impairment (*N* [%])	535 073 (4.1%)	168 610 (4.3%)	17 311 (1.8%)	27 555 (2.1%)	169 166 (2.0%)	13 064 (0.3%)	31 853 (3.0%)	230 896 (4.0%)
Malignant neoplastic disease (*N* [%])	633 639 (4.8%)	198 275 (5.1%)	51 307 (5.4%)	106 223 (8.2%)	534 352 (6.3%)	66 962 (1.7%)	86 645 (8.1%)	342 511 (5.9%)
Dementia (*N* [%])	109 915 (0.8%)	33 537 (0.9%)	5515 (0.6%)	7873 (0.6%)	95 957 (1.1%)	9217 (0.2%)	10 458 (1.0%)	72 696 (1.3%)
Medication use (183 days prior to 4 days prior)								
Non-steroidal anti-inflammatory drugs (*N* [%])	1 530 269 (11.6%)	900 092 (23.0%)	247 182 (26.1%)	211 464 (16.3%)	928 497 (11.0%)	1 056 021 (26.7%)	293 188 (27.5%)	1 617 103 (27.9%)
Cox-2 inhibitors (*N* [%])	6223 (0.0%)	7126 (0.2%)	2469 (0.3%)	8165 (0.6%)	33 006 (0.4%)	13 769 (0.3%)	21 899 (2.1%)	27 048 (0.5%)
Systemic corticosteroids (*N* [%])	701 368 (5.3%)	404 443 (10.3%)	95 032 (10.0%)	139 482 (10.7%)	269 020 (3.2%)	315 054 (8.0%)	84 587 (7.9%)	337 121 (5.8%)
Antithrombotic and anticoagulant therapies (*N* [%])	199 014 (1.5%)	114 246 (2.9%)	72 557 (7.6%)	44 985 (3.5%)	213 378 (2.5%)	175 535 (4.4%)	110 079 (10.3%)	112 901 (1.9%)
Lipid modifying agents (*N* [%])	304 903 (2.3%)	143 424 (3.7%)	103 695 (10.9%)	54 039 (4.2%)	191 407 (2.3%)	197 031 (5.0%)	83 234 (7.8%)	81 743 (1.4%)
Antineoplastic and immunomodulating agents (*N* [%])	207 230 (1.6%)	124 080 (3.2%)	44 853 (4.7%)	54 941 (4.2%)	210 390 (2.5%)	94 702 (2.4%)	36 792 (3.5%)	64 163 (1.1%)

(Continues)

TABLE 2 (Continued)

	CPRD Aurum	CPRD GOLD	HIC Dundee	IPCI	IQVIA DA Germany	IQVIA LPD France	IQVIA LPD Italy	SIDIAP CMBD-HA
Hormonal contraceptives for systemic use (*N* [%])	304 094 (2.3%)	173 708 (4.4%)	51 084 (5.4%)	47 983 (3.7%)	169 549 (2.0%)	98 852 (2.5%)	18 740 (1.8%)	46 834 (0.8%)
Tamoxifen (*N* [%])	2904 (0.0%)	2141 (0.1%)	1666 (0.2%)	865 (0.1%)	3761 (0.0%)	826 (0.0%)	684 (0.1%)	1230 (0.0%)
Sex hormones and modulators of the genital system (*N* [%])	372 384 (2.8%)	213 023 (5.4%)	63 019 (6.6%)	55 810 (4.3%)	228 846 (2.7%)	141 501 (3.6%)	29 750 (2.8%)	58 987 (1.0%)

Note: CPRD: Clinical Practice Research Datalink, IQVIA DA GERMANY: IQVIA Disease Analyser Germany, IQVIA LPD France: IQVIA Longitudinal Patient Data France, IPCI: Integrated Primary Care Information, IQVIA LPD Italy: IQVIA Longitudinal Patient Data Italy, SIDIAP CMBD-HA: Information System for Research in Primary Care with hospital linkage. COPD: chronic obstructive pulmonary disease.

Although our understanding of pathogenesis of TTS after vaccination against SARS-CoV-2 is still evolving, current evidence indicates its mechanism includes the formation of antibodies directed against the cationic platelet chemokine, platelet factor 4 (PF4), that act against platelet antigens which result in massive platelet activation, aggregation, and consumption, which reduces platelet count and results in thrombosis.[10] In TTS, the location of thrombosis appears to often be atypical, with CVST and splanchnic vein thrombosis (SVT) observed in many cases.[11] This clinical presentation of TTS after vaccination shares important similarities with immune heparin-induced thrombocytopenia (HIT) and other spontaneous HIT syndromes, but remains itself a novel disorder.[12] The degree to which the reported TTS events after vaccination against SARS-CoV-2 exceed the number of non-vaccine induced TTS otherwise expected to happen is not yet well-known, nor is how the profiles of the persons with such events after vaccination have differed from those who typically experience them. Establishing the rates of non-vaccine induced TTS events among the general population in previous years will help to provide context for the observed rates being seen among those vaccinated.[13] Moreover, a description of the characteristics of the individuals who have had non-vaccine induced TTS events in the past will also help to inform a consideration of whether the profiles of individuals with TTS after a vaccination against COVID-19 differ to those who typically have such events.

In this study, we set out to estimate the background incidence rates of non-vaccine induced TTS and to describe the profiles of individuals who typically have these types of events. We did this using electronic medical records collected between 2017 and 2019 and covering over 38 million people across six European countries. In addition, we performed similar analyses for a range of other embolic and thrombotic events and coagulopathies of special interest for COVID-19 vaccinations.

2 | METHODS

2.1 | Study design

A cohort study using routinely-collected primary care data from across Europe. Data were mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM), which allowed for the study to be run in a distributed manner, with common analytic code run by each site and aggregated results returned, all without the need to share patient-level data.[14–16]

2.2 | Data sources

Data from seven electronic medical records databases from France, Netherlands, Italy, Germany, Spain, and the United Kingdom informed the analysis. The Clinical Practice Research Datalink (CPRD) GOLD and Aurum databases contains data contributed by general practitioners (GP) from the United Kingdom.[17,18] The Health Informatics Centre at the University of Dundee (HIC Dundee) database includes linked primary care and hospital data of persons from the Tayside region of Scotland, capturing around 20% of the Scottish population. The Integrated Primary Care Information (IPCI) database is collected from electronic healthcare records of patients registered with GPs throughout the Netherlands. IQVIA Longitudinal Patient Data (LPD) Italy includes anonymised patient records collected from software used by GPs during an office visit to document patients´ clinical records. IQVIA LPD France is a computerised network of physicians including GPs who contribute to a centralised database of anonymised patient electronic medical records.[19] IQVIA Disease Analyser (DA) Germany is collected from extracts of patient management software used by general medicine and specialists practicing in ambulatory care settings. The Information System for Research in Primary Care (SIDIAP; www.sidiap.org) is a primary care records database that covers approximately 80% of the population of Catalonia, North-East Spain. SIDIAP can be linked to the minimum basic set of hospital discharge data (CMBD- HA), which includes diagnosis and procedures registered during hospital admissions.[20] Results for SIDIAP CMBD-HA are presented in this manuscript, with results for SIDIAP alone reported in the Supporting Information for comparison.

In summary, all the included databases captured outpatient diagnoses and outpatient lab measurements. SIDIAP CMBD-HA and HIC Dundee also directly captured diagnoses from linked hospital data. HIC Dundee was the only database that, in addition, included hospital lab measurements (Table 1).

TABLE 3 Incidence rates per 100 000 person-years for thrombosis and non-vaccine induced thrombosis with thrombocytopenia

	N	PYs	Number of events	Incidence rate (95% CI) per 100 000 PYs
Cerebral venous sinus thrombosis (CVST)				
CPRD Aurum	13 178 767	35 268 555	432	1.2 (1.1–1.3)
CPRD GOLD	3 913 025	9 676 085	118	1.2 (1.0–1.5)
IQVIA DA Germany	8 459 044	19 369 671	95	0.5 (0.4–0.6)
IQVIA LPD France	3 951 606	8 210 128	26	0.3 (0.2–0.5)
SIDIAP CMBD-HA	5 794 764	16 751 651	121	0.7 (0.6–0.9)
Cerebral venous sinus thrombosis (CVST) with thrombocytopenia				
SIDIAP CMBD-HA	5 794 777	16 751 791	16	0.1 (0.1–0.2)
Deep vein thrombosis (DVT)				
CPRD Aurum	13 164 316	35 185 059	35 778	101.7 (100.6–102.7)
CPRD GOLD	3 909 649	9 656 721	9071	93.9 (92.0–95.9)
HIC Dundee	948 184	2 153 442	1186	55.1 (52.0–58.3)
IQVIA DA Germany	8 451 032	19 329 175	16 600	85.9 (84.6–87.2)
IPCI	1 296 310	3 402 027	6367	187.2 (182.6–191.8)
IQVIA LPD Italy	1 063 587	2 639 975	3891	147.4 (142.8–152.1)
SIDIAP CMBD-HA	5 790 802	16 722 842	14 408	86.2 (84.8–87.6)
Deep vein thrombosis (DVT) with thrombocytopenia				
CPRD Aurum	13 178 808	35 268 706	537	1.5 (1.4–1.7)
CPRD GOLD	3 913 031	9 676 132	127	1.3 (1.1–1.6)
HIC Dundee	948 498	2 153 995	184	8.5 (7.4–9.9)
IQVIA DA Germany	8 458 995	19 369 390	225	1.2 (1.0–1.3)
IPCI	1 299 274	3 418 833	34	1.0 (0.7–1.4)
IQVIA LPD Italy	1 066 209	2 651 714	39	1.5 (1.0–2.0)
SIDIAP CMBD-HA	5 794 559	16 750 224	1037	6.2 (5.8–6.6)
Myocardial infarction or ischemic stroke				
CPRD Aurum	13 148 520	35 109 906	60 805	173.2 (171.8–174.6)
CPRD GOLD	3 907 225	9 642 096	16 143	167.4 (164.8–170.0)
IQVIA DA Germany	8 433 598	19 257 191	39 468	205.0 (202.9–207.0)
IQVIA LPD France	3 933 628	8 154 546	10 917	133.9 (131.4–136.4)
HIC Dundee	946 414	2 142 566	9633	449.6 (440.7–458.7)
IPCI	1 289 281	3 377 441	10 684	316.3 (310.4–322.4)
IQVIA LPD Italy	1 058 436	2 626 927	3952	150.4 (145.8–155.2)
SIDIAP CMBD-HA	5 777 909	16 639 142	55 854	335.7 (332.9–338.5)
Myocardial infarction or ischemic stroke (with thrombocytopenia 10 days pre to 10 days post)				
CPRD Aurum	13 178 584	35 267 614	847	2.4 (2.2–2.6)
CPRD GOLD	3 913 036	9 676 204	95	1.0 (0.8–1.2)
IQVIA DA Germany	8 458 789	19 368 273	696	3.6 (3.3–3.9)
IQVIA LPD France	3 951 515	8 209 629	229	2.8 (2.4–3.2)
HIC Dundee	948 362	2 153 011	935	43.4 (40.7–46.3)
IPCI	1 299 257	3 418 730	96	2.8 (2.3–3.4)
IQVIA LPD Italy	1 066 181	2 651 560	94	3.5 (2.9–4.3)
SIDIAP CMBD-HA	5 793 878	16 745 114	4205	25.1 (24.4–25.9)
Pulmonary embolism (PE)				
CPRD Aurum	13 167 997	35 208 213	28 612	81.3 (80.3–82.2)
CPRD GOLD	3 910 531	9 662 585	7149	74.0 (72.3–75.7)
HIC Dundee	947 984	2 151 351	2823	131.2 (126.4–136.2)

(Continues)

TABLE 3 (Continued)

	N	PYs	Number of events	Incidence rate (95% CI) per 100 000 PYs
IQVIA DA Germany	8 449 246	19 325 600	17 204	89.0 (87.7–90.4)
IQVIA LPD France	3 947 450	8 195 137	4700	57.4 (55.7–59.0)
IPCI	1 297 807	3 410 984	3141	92.1 (88.9–95.4)
IQVIA LPD Italy	1 064 532	2 645 601	1748	66.1 (63.0–69.2)
SIDIAP CMBD-HA	5 792 195	16 734 624	9590	57.3 (56.2–58.5)
Pulmonary embolism (PE) with thrombocytopenia				
CPRD Aurum	13 178 867	35 269 146	344	1.0 (0.9–1.1)
CPRD GOLD	3 913 042	9 676 256	84	0.9 (0.7–1.1)
HIC Dundee	948 459	2 153 685	447	20.8 (18.9–22.8)
DA Germany	8 458 971	19 369 265	286	1.5 (1.3–1.7)
IQVIA LPD France	3 951 605	8 210 109	39	0.5 (0.3–0.6)
IPCI	1 299 282	3 418 860	21	0.6 (0.4–0.9)
IQVIA LPD Italy	1 066 222	2 651 761	17	0.6 (0.4–1.0)
SIDIAP CMBD-HA	5 794 594	16 750 449	985	5.9 (5.5–6.3)
Splanchnic vein thrombosis (SVT)				
CPRD Aurum	13 178 697	35 267 889	1040	2.9 (2.8–3.1)
CPRD GOLD	3 913 005	9 675 960	233	2.4 (2.1–2.7)
HIC Dundee	948 541	2 154 020	112	5.2 (4.3–6.3)
IQVIA DA Germany	8 458 941	19 369 177	398	2.1 (1.9–2.3)
IQVIA LPD France	3 951 594	8 210 016	122	1.5 (1.2–1.8)
IQVIA LPD Italy	1 066 207	2 651 684	58	2.2 (1.7–2.8)
SIDIAP CMBD-HA	5 794 483	16 749 703	1718	10.3 (9.8–10.8)
Splanchnic vein thrombosis (SVT) with thrombocytopenia				
CPRD Aurum	13 178 944	35 269 606	47	0.1 (0.1–0.2)
CPRD GOLD	3 913 070	9 676 375	5	0.1 (0.0–0.1)
HIC Dundee	948 553	2 154 098	40	1.9 (1.3–2.5)
IQVIA DA Germany	8 459 086	19 369 887	16	0.1 (0.0–0.1)
SIDIAP CMBD-HA	5 794 721	16 751 354	412	2.5 (2.2–2.7)

Note: CPRD: Clinical Practice Research Datalink, IQVIA DA GERMANY: IQVIA Disease Analyser Germany, IQVIA LPD France: IQVIA Longitudinal Patient Data France, IPCI: Integrated Primary Care Information, IQVIA LPD Italy: IQVIA Longitudinal Patient Data Italy, SIDIAP CMBD-HA: Information System for Research in Primary Care with hospital linkage.

2.3 | Study participants and time at risk

The primary study cohort consisted of individuals present in a database as of the 1st January 2017, with this date used as the index date for all study participants. These individuals were followed up to whichever came first: the outcome of interest, exit from the database, or the 31st December 2019 (the end of study period). A second study cohort which was made up of active patients was used for a sensitivity analysis, where individuals entered the cohort on the date of their first visit occurrence after 1st January 2017. As with the primary study cohorts these individuals were followed up to whichever came first: the outcome of interest, exit from the database, or 31st December 2019. As a further sensitivity analysis, study cohorts were also generated with the additional requirement that individuals had a minimum of 1 year of history available in the database prior to their index date.

2.4 | Outcomes

Here we summarise results for five specific TTS events of interest: CVST with thrombocytopenia, DVT with thrombocytopenia, PE with thrombocytopenia, SVT with thrombocytopenia, and myocardial infarction or ischemic stroke with thrombocytopenia. Occurrences of CVST, DVT, PE, SVT, myocardial infarction and stroke were identified on the basis of diagnostic codes. Thrombocytopenia was identified either by SNOMED CT codes (which are used as the standard codes for conditions in the OMOP CDM) or a measurement of between 10 000 and 150 000 platelets per microliter of blood and observed during a time window starting 10 days prior to the event of interest up to 10 days afterwards. For comparison, we also provide results for each of the above outcomes without thrombocytopenia. In addition, we provide background rates for coagulopathies that have been identified as potential causes for TTS: HIT, disseminated intravascular

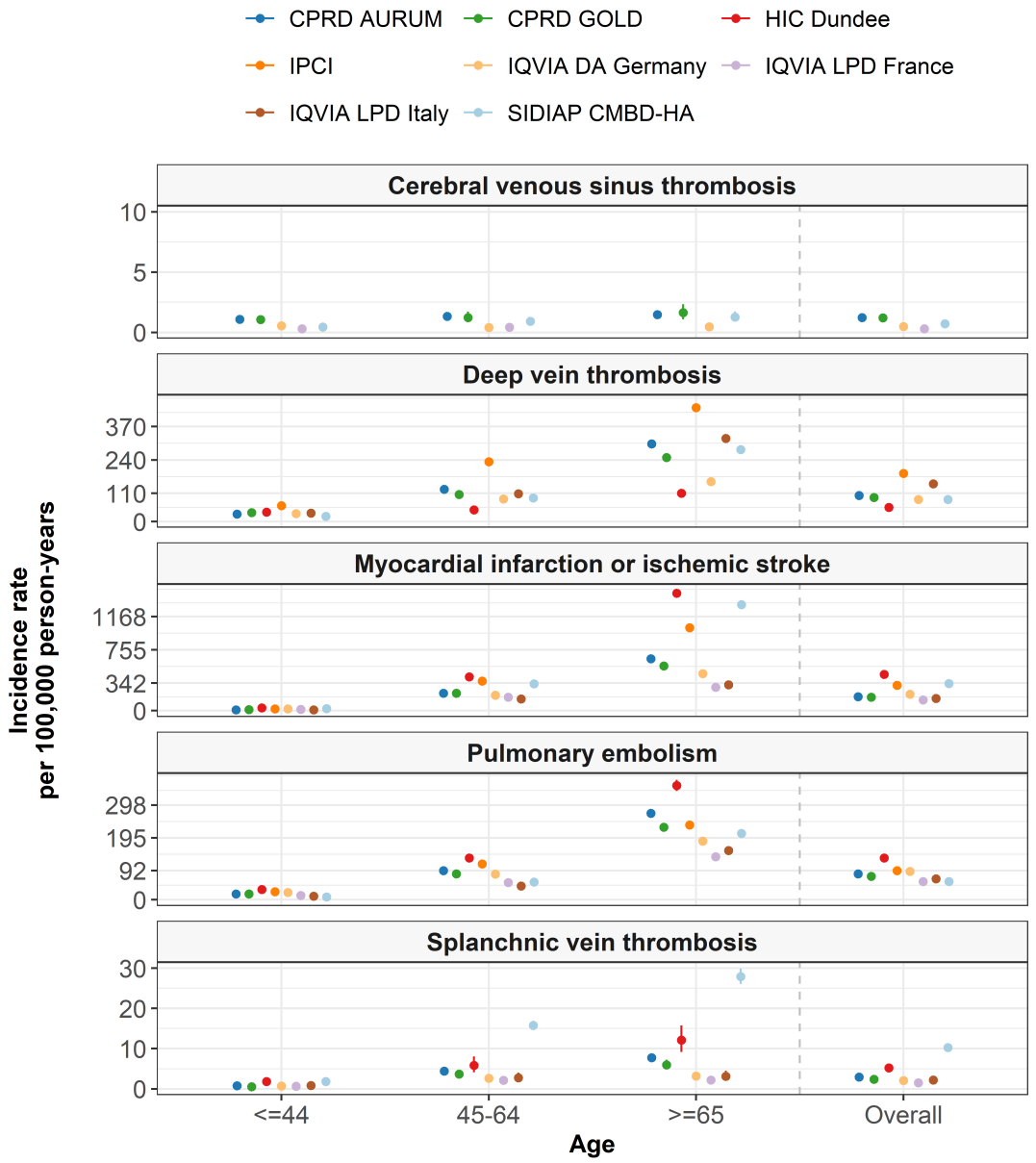

FIGURE 1 Incidence rates (with 95% confidence intervals) per 100 000 of arterial and venous thromboembolism among the general population, stratified by age and sex

coagulation (DIC), immune thrombocytopenia, and thrombotic thrombocytopenic purpura (TTP). Our definition of TTP included hemolytic uremic syndrome.

The outcomes described here are taken from a wider set of adverse events of special interest (AESI) for COVID-19 vaccinations. Three sets of outcome events were identified: (1) venous thromboembolic events; (2) arterial thromboembolic events; and (3) rare embolic, coagulopathies, and TTS events. For venous thromboembolic events, instances of DVT (with one broad definition and another narrow) and PE events were identified, with venous thromboembolism events defined as the occurrence of either DVT or PE. In this manuscript, we describe results for the narrow definition of DVT. For arterial thromboembolic events, instances of myocardial infarction and ischemic stroke were identified, along with a composite outcome of either of these events. Instances of stroke, either ischemic or hemorrhagic, were also identified. A wide set of rare embolic and thrombotic events and thrombocytopenias and platelet disorders were considered: DIC, immune thrombocytopenia, TTP, HIT, thrombocytopenia, platelet disorders, CVST, splenic vein thrombosis, splenic artery thrombosis, splenic infarction, hepatic vein thrombosis, hepatic artery thrombosis, portal vein thrombosis, intestinal infarction, mesenteric vein thrombosis, celiac artery thrombosis, visceral vein thrombosis, and SVT.

All study outcome definitions were reviewed with the aid of the CohortDiagnostics R package,[21] so as to identify additional codes of interest and to remove those highlighted as irrelevant based on feedback from regulators (e.g., puerperium and pregnancy-related disease) through an iterative process during the initial stages of analyses. A detailed description of the definitions used to identify the outcomes

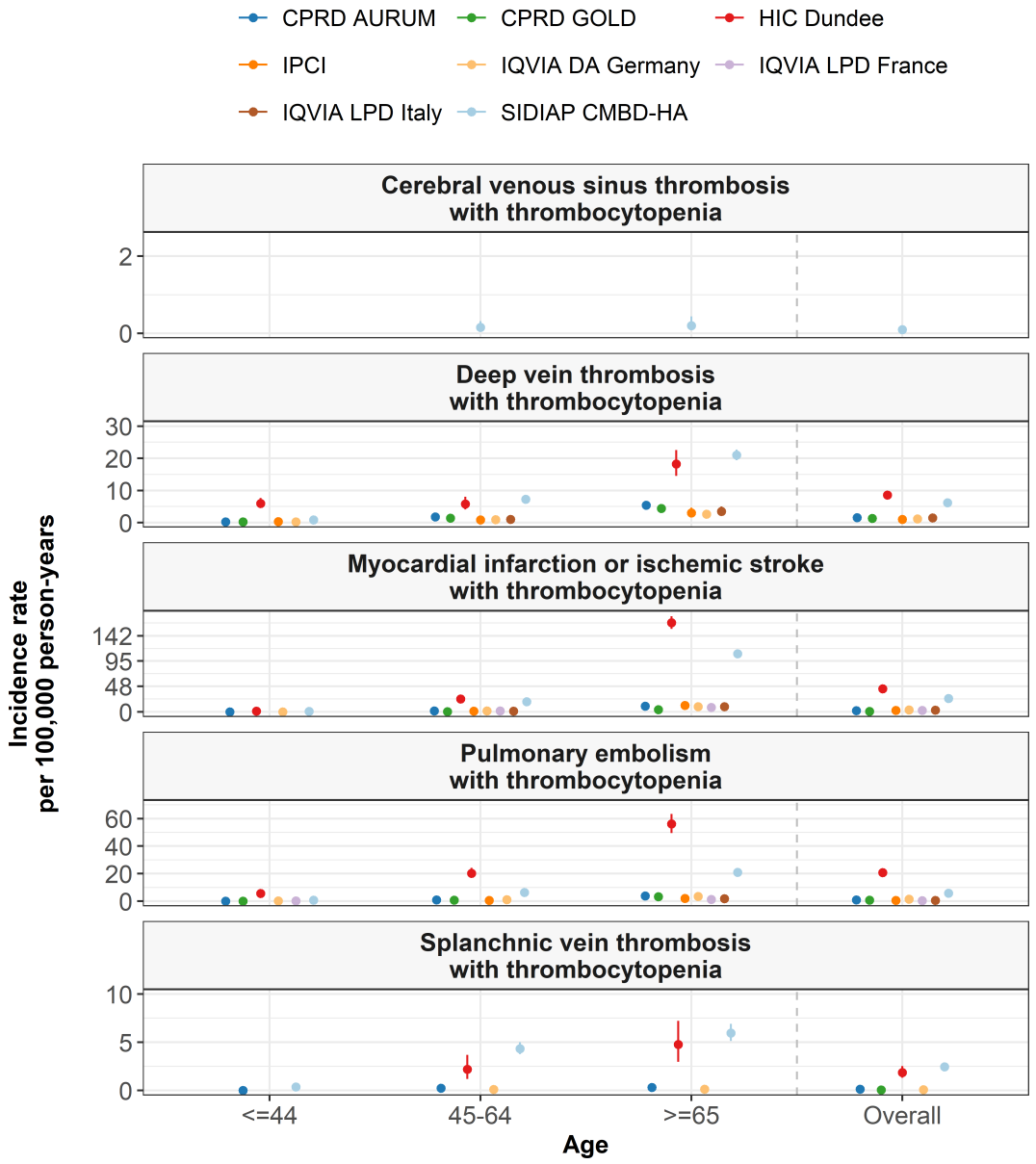

FIGURE 2 Incidence rates (with 95% confidence intervals) per 100 000 of non-vaccine induced thrombocytopenia syndrome among the general population, stratified by age and sex

of the study is provided at https://livedataoxford.shinyapps.io/CovCoagOutcomesCohorts/. This application summarises the codes used to identify outcomes and their frequency in the databases, the overlap between cohorts in the databases as a whole, and a detailed summary of the profiles of all the individuals with a code of interest in each of the databases.

2.5 | Patient profiles

The characteristics of the study population were extracted relative to their index date, as were those of individuals with a particular outcome of interest relative to the date of their event. The age and sex of individuals was identified, along with their history of conditions and medication use. Using all of an individual's prior observation time, prior diagnosis of autoimmune disease, antiphospholipid syndrome, thrombophilia, asthma, atrial fibrillation, malignant neoplastic disease, diabetes mellitus, obesity, heart disease, hypertensive disorder, renal impairment, chronic obstructive pulmonary disease (COPD), or dementia were identified on the basis of SNOMED CT codes and all their hierarchical descendants. Prior medication use was identified using anatomical therapeutic chemical (ATC) codes using a time window of 183 to 4 days prior the index date. Any use of antithrombotic and anticoagulant therapies, non-steroidal anti-inflammatory drugs, Cox-2 inhibitors, systemic corticosteroids, lipid modifying agents, antineoplastic and immunomodulating agents, hormonal contraceptives for systemic use, tamoxifen, and sex hormones and modulators of the genital system overlapping with this time window were identified.

	Age <=44	Age 45-64	Age >=65	Overall	
Cerebral venous sinus thrombosis with thrombocytopenia		2 (1 to 3)	2 (1 to 4)	1 (1 to 2)	SIDIAP CMBD-HA
Deep vein thrombosis with thrombocytopenia	2 (1 to 3)	18 (15 to 21)	53 (48 to 59)	15 (14 to 16)	CPRD AURUM
	2 (1 to 4)	14 (10 to 19)	43 (34 to 54)	13 (11 to 15)	CPRD GOLD
	59 (45 to 75)	58 (40 to 79)	179 (143 to 222)	84 (72 to 97)	HIC Dundee
	3 (1 to 7)	9 (4 to 16)	30 (18 to 46)	10 (7 to 14)	IPCI
	2 (1 to 3)	9 (7 to 12)	26 (22 to 31)	11 (10 to 13)	IQVIA DA Germany
		10 (4 to 18)	34 (23 to 49)	14 (10 to 20)	IQVIA LPD Italy
	8 (7 to 10)	72 (64 to 80)	207 (191 to 224)	61 (57 to 65)	SIDIAP CMBD-HA
Myocardial infarction or ischemic stroke with thrombocytopenia	1 (0 to 1)	20 (17 to 23)	105 (97 to 114)	24 (22 to 25)	CPRD AURUM
		5 (3 to 9)	43 (34 to 54)	10 (8 to 12)	CPRD GOLD
	14 (8 to 23)	238 (202 to 279)	1,641 (1,527 to 1,762)	428 (401 to 456)	HIC Dundee
		13 (7 to 21)	118 (94 to 147)	28 (22 to 34)	IPCI
	2 (1 to 3)	20 (16 to 23)	98 (90 to 106)	35 (33 to 38)	IQVIA DA Germany
		19 (14 to 25)	82 (70 to 95)	27 (24 to 31)	IQVIA LPD France
		14 (7 to 24)	99 (78 to 123)	35 (28 to 43)	IQVIA LPD Italy
	10 (8 to 12)	188 (176 to 201)	1,072 (1,036 to 1,110)	248 (240 to 255)	SIDIAP CMBD-HA
Pulmonary embolism with thrombocytopenia	1 (1 to 2)	10 (8 to 12)	37 (33 to 43)	10 (9 to 11)	CPRD AURUM
	1 (0 to 2)	8 (5 to 12)	32 (25 to 42)	9 (7 to 11)	CPRD GOLD
	55 (42 to 71)	201 (167 to 238)	553 (488 to 625)	205 (186 to 224)	HIC Dundee
		6 (2 to 13)	21 (11 to 35)	6 (4 to 9)	IPCI
	2 (1 to 3)	11 (9 to 14)	35 (30 to 40)	15 (13 to 16)	IQVIA DA Germany
	2 (1 to 4)		13 (9 to 19)	5 (3 to 6)	IQVIA LPD France
			18 (10 to 30)	6 (4 to 10)	IQVIA LPD Italy
	7 (6 to 9)	62 (55 to 70)	207 (191 to 224)	58 (54 to 62)	SIDIAP CMBD-HA
Splanchnic vein thrombosis with thrombocytopenia	0 (0 to 1)	2 (2 to 4)	3 (2 to 5)	1 (1 to 2)	CPRD AURUM
				1 (0 to 1)	CPRD GOLD
		22 (12 to 37)	47 (29 to 71)	18 (13 to 25)	HIC Dundee
		1 (0 to 2)	1 (1 to 3)	1 (0 to 1)	IQVIA DA Germany
	4 (3 to 5)	43 (37 to 49)	59 (51 to 68)	24 (22 to 27)	SIDIAP CMBD-HA

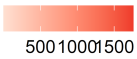

FIGURE 3 Expected cases (with 95% confidence intervals) of non-vaccine induced thrombocytopenia syndrome per 36 days in a population of 10 000 000 people in a given age strata or overall. Blank cells are where there were fewer than five people with the event and incidence rates were not estimated

2.6 | Statistical methods

The profiles of the study cohorts and those with an outcome of interest were summarised, with median and interquartile range (IQR) used for continuous variables and counts and percentages used for categorical variables. For each study outcome, the number of events, the observed time at risk, and the incidence rate per 100 000 person-years are summarised along with 95% confidence intervals. For a given outcome, any study participants with the outcome in the year prior were excluded from the analysis of that outcome. These results are provided for the study cohorts and stratified by data source as a whole and by age (≤44, 45–64, or ≥65 years old) and sex. To aid in comparison with rates being reported after vaccinations, the expected number of events per 36 days for a population of 10 million were calculated based on the incidence rates calculated for the overall study cohorts and age strata.

2.7 | Code availability

All analytic code used for the study is available at https://github.com/oxford-pharmacoepi/CovCoagBackgroundIncidence. Code lists are provided in the Appendix S1.

2.8 | Role of funding source

This study was funded by the European Medicines Agency (EMA). This document expresses the opinion of the authors of the paper, and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties. The study outcomes were chosen in collaboration with the EMA so as to best reflect the events of interest. The study protocol was reviewed by the EMA and registered in the European Union

TABLE 4 Characteristics of patients with non-vaccine induced thrombosis with thrombocytopenia

	N	Age (median [IQR])	Sex: male (*N* [%])
CPRD Aurum			
Study population	13 178 959	39 [22–57]	6 593 514 (50.0%)
Deep vein thrombosis with thrombocytopenia	537	69 [58–78]	369 (68.7%)
Myocardial infarction or ischemic stroke with thrombocytopenia	847	74 [65–82]	672 (79.3%)
Pulmonary embolism with thrombocytopenia	344	70 [60–78]	217 (63.1%)
Splanchnic vein thrombosis with thrombocytopenia	47	61 [52–72]	26 (55.3%)
CPRD GOLD			
Study population	3 913 071	41 [22–59]	1 937 858 (49.5%)
Deep vein thrombosis with thrombocytopenia	127	70 [56–80]	70 (55.1%)
Myocardial infarction or ischemic stroke with thrombocytopenia	95	78 [68–86]	73 (76.8%)
Pulmonary embolism with thrombocytopenia	84	71 [62–79]	50 (59.5%)
Splanchnic vein thrombosis with thrombocytopenia	5	59 [52–59]	<5
HIC Dundee			
Study population	948 561	41 [23–59]	469 725 (49.5%)
Deep vein thrombosis with thrombocytopenia	184	58 [37–75]	99 (53.8%)
Myocardial infarction or ischemic stroke with thrombocytopenia	935	77 [67–83]	611 (65.3%)
Pulmonary embolism with thrombocytopenia	447	68 [53–78]	247 (55.3%)
Splanchnic vein thrombosis with thrombocytopenia	40	65 [52–72]	27 (67.5%)
IQVIA DA Germany			
Study population	8 459 098	52 [32–67]	3 589 506 (42.4%)
Deep vein thrombosis with thrombocytopenia	225	71 [60–80]	143 (63.6%)
Myocardial infarction or ischemic stroke with thrombocytopenia	696	76 [67–81]	520 (74.7%)
Pulmonary embolism with thrombocytopenia	286	72 [62–80]	183 (64.0%)
Splanchnic vein thrombosis with thrombocytopenia	16	64 [60–73]	11 (68.8%)
IQVIA LPD France			
Study population	3 951 633	48 [28–65]	1 669 415 (42.2%)
Myocardial infarction or ischemic stroke with thrombocytopenia	229	74 [65–80]	193 (84.3%)
Pulmonary embolism with thrombocytopenia	39	72 [57–83]	23 (59.0%)
IPCI			
Study population	1 299 288	44 [23–60]	636 386 (49.0%)
Deep vein thrombosis with thrombocytopenia	34	70 [54–81]	20 (58.8%)
Myocardial infarction or ischemic stroke with thrombocytopenia	96	77 [70–82]	76 (79.2%)
Pulmonary embolism with thrombocytopenia	21	70 [54–73]	12 (57.1%)
IQVIA LPD Italy			
Study population	1 066 230	52 [37–68]	426 758 (40.0%)
Deep vein thrombosis with thrombocytopenia	39	76 [62–82]	20 (51.3%)
Myocardial infarction or ischemic stroke with thrombocytopenia	94	76 [70–83]	67 (71.3%)
Pulmonary embolism with thrombocytopenia	17	78 [69–81]	9 (52.9%)

TABLE 4 (Continued)

	N	Age (median [IQR])	Sex: male (*N* [%])
SIDIAP CMBD-HA			
Study population	5 794 777	42 [25–59]	2 859 044 (49.3%)
Cerebral venous sinus thrombosis with thrombocytopenia	16	62 [49–67]	8 (50.0%)
Deep vein thrombosis with thrombocytopenia	1037	69 [58–79]	617 (59.5%)
Myocardial infarction or ischemic stroke with thrombocytopenia	4205	75 [66–83]	2964 (70.5%)
Pulmonary embolism with thrombocytopenia	985	70 [59–79]	584 (59.3%)
Splanchnic vein thrombosis with thrombocytopenia	412	62 [54–72]	295 (71.6%)

Note: CPRD: Clinical Practice Research Datalink, IQVIA DA GERMANY: IQVIA Disease Analyser Germany, IQVIA LPD France: IQVIA Longitudinal Patient Data France, IPCI: Integrated Primary Care Information, IQVIA LPD Italy: IQVIA Longitudinal Patient Data Italy, SIDIAP CMBD-HA: Information System for Research in Primary Care with hospital linkage. For complete set of characteristics of those with an event of interest during follow-up see https://livedataoxford.shinyapps.io/CovCoagBackgroundIncidence/

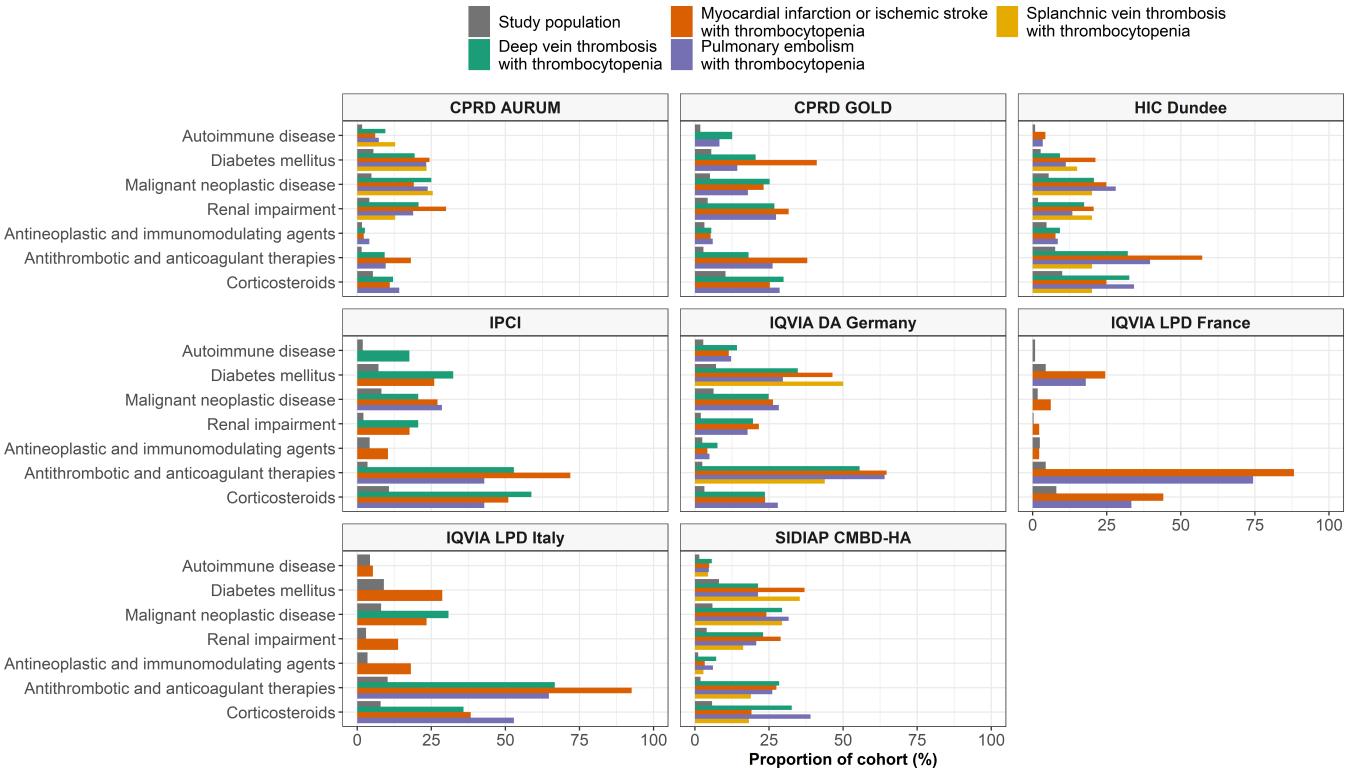

FIGURE 4 Comorbidities and prior medication use among patients with non-vaccine induced thrombocytopenia syndrome compared to the overall study population. Any characteristic seen in less than five people in a cohort is not reported

electronic Register of Post-Authorisation Studies (EU PAS Register®): http://www.encepp.eu/encepp/viewResource.htm?id=40415

3 | RESULTS

A total of 38 611 617 individuals were included in the study (13 178 959 from CPRD Aurum, 3 913 071 from CPRD GOLD, 948561 from HIC Dundee, 8 459 098 DA Germany, 3 951 633 LPD France, 1 299 288 IPCI, 1066230 LPD Italy, and 5 794 777 from SIDIAP CMBD-HA). The median age of the study populations ranged from 39 in CPRD Aurum to 52 in DA Germany and LPD Italy. More detailed characteristics of each of these populations are summarised in Table 2.

Incidence rates for the different outcomes of thrombosis and non-vaccine induced TTS across the databases are summarised in

TABLE 5 Incidence rates per 100 000 person-years for coagulopathy

	N	PYs	Number of events	Incidence rate per 100, 000 PYs
Disseminated intravascular coagulation				
CPRD Aurum	13 178 947	35 269 622	36	0.1 (0.1–0.1)
CPRD GOLD	3 913 067	9 676 361	15	0.2 (0.1–0.3)
HIC Dundee	948 555	2 154 105	32	1.5 (1.0–2.1)
IQVIA DA Germany	8 459 041	19 369 706	79	0.4 (0.3–0.5)
IQVIA France LPD	3 951 611	8 210 148	34	0.4 (0.3–0.6)
IQVIA Italy LPD	1 066 206	2 651 697	37	1.4 (1.0–1.9)
SIDIAP CMBD-HA	5 794 596	16 750 823	641	3.8 (3.5–4.1)
Heparin-induced thrombocytopenia				
CPRD Aurum	13 178 819	35 269 050	299	0.8 (0.8–0.9)
CPRD GOLD	3 912 943	9 675 822	302	3.1 (2.8–3.5)
HIC Dundee	948 500	2 153 919	165	7.7 (6.5–8.9)
IQVIA DA Germany	8 458 456	19 366 573	1513	7.8 (7.4–8.2)
IQVIA France LPD	3 951 623	8 210 192	20	0.2 (0.1–0.4)
IQVIA Italy LPD	1 066 144	2 651 425	171	6.4 (5.5–7.5)
SIDIAP CMBD-HA	5 792 945	16 739 615	6351	37.9 (37.0–38.9)
Immune thrombocytopenia				
CPRD Aurum	13 177 523	35 262 293	2519	7.1 (6.9–7.4)
CPRD GOLD	3 912 708	9 674 616	759	7.8 (7.3–8.4)
HIC Dundee	948 447	2 153 668	333	15.5 (13.8–17.2)
IQVIA DA Germany	8 457 949	19 364 321	2264	11.7 (11.2–12.2)
IQVIA LPD France	3 951 527	8 209 807	175	2.1 (1.8–2.5)
IPCI	1 299 133	3 418 075	267	7.8 (6.9–8.8)
SIDIAP CMBD-HA	5 792 354	16 736 041	7816	46.7 (45.7–47.7)
Thrombotic thrombocytopenic purpura				
CPRD Aurum	13 178 867	35 269 192	175	0.5 (0.4–0.6)
CPRD GOLD	3 913 059	9 676 289	52	0.5 (0.4–0.7)
HIC Dundee	948 560	2 154 123	9	0.4 (0.2–0.8)
IQVIA DA Germany	8 458 805	19 368 465	552	2.8 (2.6–3.1)
IQVIA LPD France	3 951 599	8 210 086	52	0.6 (0.5–0.8)
IQVIA LPD Italy	1 066 176	2 651 585	45	1.7 (1.2–2.3)
SIDIAP CMBD-HA	5 794 674	16 751 190	272	1.6 (1.4–1.8)

Note: CPRD: Clinical Practice Research Datalink, IQVIA DA GERMANY: IQVIA Disease Analyser Germany, IQVIA LPD France: IQVIA Longitudinal Patient Data France, IPCI: Integrated Primary Care Information, IQVIA LPD Italy: IQVIA Longitudinal Patient Data Italy, SIDIAP CMBD-HA: Information System for Research in Primary Care with hospital linkage.

Table 3. The incidence rates for CVST ranged from 0.3 (95% CI: 0.2–0.5) to 1.2 (1.0–1.5) per 100 000 person-years; CVST with thrombocytopenia was only seen in SIDIAP CMBD-HA, where the incidence rate was 0.1 (0.1–0.2) per 100 000 person-years. The incidence rates for SVT ranged from 1.5 (1.2–1.8) to 10.3 (9.8–10.8), and from 0.1 (0.0–0.1) to 2.5 (2.2–2.7) per 100 000 person-years for SVT with thrombocytopenia. The incidence rates for DVT ranged from 85.9 (84.6–87.2) to 187.2 (182.6–191.8), and from 1.0 (0.7–1.4) to 8.5 (7.4–9.9) per 100 000 person-years for DVT with thrombocytopenia. The incidence rates for PE ranged from 66.1 (63.0–69.2) to 131.2 (126.4–136.2), and from 0.5 (0.3–0.6) to 20.8 (18.9–22.8) per 100 000 person-years for PE with thrombocytopenia. Lastly, the incidence rates for myocardial infarction or ischemic stroke ranged from 133.9 (131.4–136.4) to 449.6 (440.7–458.7), and from 1.0 (0.8–1.2) to 43.4 (40.7–46.3) per 100 000 person-years for myocardial infarction or ischemic stroke with thrombocytopenia. As with thrombosis in general, see Figure 1, incidence rates for non-vaccine induced TTS were typically higher for older age groups, see Figure 2.

Based on the highest estimates for the overall study cohorts, one would expect approximately 1 case of CVST with thrombocytopenia, 24 of SVT with thrombocytopenia, 84 of DVT with thrombocytopenia, 205 of PE with thrombocytopenia, and 428 of myocardial infarction or ischemic stroke with thrombocytopenia among a general population of 10 million individuals per 36 days. For a cohort of the

same size aged 65 or over, this would rise to 59 of SVT with thrombocytopenia, 207 of DVT with thrombocytopenia, 553 of PE with thrombocytopenia, and 1641 of myocardial infarction or ischemic stroke with thrombocytopenia, see Figure 3.

The age and sex profiles of those with non-vaccine induced TTS are summarised in Table 4 and the prevalence of comorbidities and prior medication are presented in Figure 4, along with those of the study populations. The median age of the 16 individuals with CVST with thrombocytopenia in SIDIAP CMBD-HA was 62 years old. The median age of those with DVT with thrombocytopenia ranged from 58 to 76 across the databases, from 68 to 78 for PE with thrombocytopenia, from 59 to 64 for SVT with thrombocytopenia, and from 73 to 78 for stroke with thrombocytopenia. Men generally predominated the affected cohorts, accounting for 50.0%–71.6% of those with different TTS in the contributing databases. The prevalence of comorbidities and prior medication use was higher for patients with TTS than in the general population. In CPRD GOLD, for example, 1.8% of the study population had an autoimmune disease, 5.1% had a history of cancer, 5.5% had diabetes, 4.3% had renal impairment. These compared to 12.6%, 25.2%, 20.5%, and 26.8% for patients with DVT with thrombocytopenia. Similarly, while 2.9% of the study population were taking antithrombotic and anticoagulant therapies in the months preceding their index date, 18.1% of patients with DVT with thrombocytopenia were. Requiring a year of prior history for study participants to be included in the analysis and defining study populations based on their first visit after 2017 had only a small effect on the results.

Incidence rates for DIC, HIT, immune thrombocytopenia, and TTP are summarised in Table 5. The incidence rate for DIC ranged from 0.1 (0.1–0.1) to 3.8 (3.3–4.1) per 100 000 person-years, from 0.2 (0.1–0.4) to 37.9 (37.0–38.) for HIT, from 2.1 (1.8–2.5) to 46.7 (45.7–47.7) for immune thrombocytopenia, and from 0.4 (0.2–0.8) to 2.8 (2.6–3.1) for thrombotic thrombocytopenic purpura.

The incidence rates for all study outcomes are summarised in the Supporting Information and in a web application: https://livedataoxford.shinyapps.io/CovCoagBackgroundIncidence/, where the characteristics of outcome cohorts are also described.

4 | DISCUSSION

4.1 | Key results

In this study, we have analysed data for over 38 million people from across six European countries to establish the background incidence of non-vaccine induced TTS. With incidence rates of less than 35 per 100 000 person-years, this condition can be considered as a very rare event. These events can generally be expected to occur in older persons, with the average age of those over 60 for most events in most of the databases studied. Moreover, those affected typically had a higher prevalence of comorbidities, such as autoimmune diseases, cancer, and diabetes. They also had a high prevalence of use of medications indicated for the prevention of thrombosis including antithrombotic and anticoagulant therapies, as well as some potentially associated with an increased risk of TTS such as systemic glucocorticoids.

Coagulopathies potentially associated with TTS were mostly rare: immune thrombocytopenia was the most common with rates up to almost 47 per 100 000 person-years, followed by HIT (up to 38 per 100 000), DIC (up to 4 per 100 000), and TTP (up to 3 per 100 000).

4.2 | Findings in context

A number of previous studies have estimated the incidence of venous thromboembolism in the general population, with its incidence rate estimated to be around 100 cases per 100 000 person-years.[22] Approximately two-thirds of venous thromboembolism can be expected to present as DVT, with the other third presenting as PE with or without DVT.[23] Meanwhile the incidence of myocardial infarction has been seen to be above 20 cases per 100 000 person-years,[24] while the incidence of stroke generally estimated to be more than 100 persons per 100 000 person-years.[25,26] The incidence of each of these events is seen to be much higher among older persons. The incidence of SVT and CVST is far less well-known. Estimates for the incidence of CVST have ranged from 0.2 to 2 per 100 000 person-years.[27–30] Meanwhile there is little research describing the incidence of SVT in the general population, although the incidence of portal vein thrombosis, the most commonly involved vein, has been estimated at around 3 per 100 000 person-years, while the incidence of Budd-Chiari syndrome was estimated at around 2 per 100 000 person-years in the same study.[31]

In one recent study, data from Denmark and Norway was used to assess 28-day rates of thromboembolic events and coagulation disorders among a cohort of people who had received the ChAdOx1 vaccine and in historical comparator cohorts.[32] In the historical comparator population, which covered 2016–2018 for Denmark and 2018–2019 for Norway, the incidence rate of CVST, PE, lower limb venous thrombosis, and SVT were estimated at 2, 57, 94, and 4 per 100 000 person-years, respectively. Meanwhile the incidence rate for idiopathic thrombocytopenia purpura and DIC were 7 and 1 per 100 000. These estimates are all fall within the range of estimates seen across databases in our study.

Another recent European network study has also assessed the background incidence of thromboembolic events, coagulation disorders, and non-vaccine induced TTS.[33] There is some overlap in data sources used, with their study also including data from CPRD GOLD and SIDIAP CMBD-HA. Although in many instances our estimates are comparable to theirs, there are discrepancies. These seem to be driven primarily by differences in cohort definitions. For example, they estimated the incidence of rate of CVST to be 0.6 (0.3–1.1) and 0.1 (0.0–0.3) per 100 000 person-years for SIDIAP CMBD-HA and CPRD GOLD respectively, which compared to our estimates of 0.7 (0.6–0.9) and 1.2 (1.0–1.5). While the estimates for SIDIAP CMBD-HA are similar, the difference between results for CPRD GOLD appears to be due to the code "Nonpyogenic venous sinus thrombosis," which was

included in our definition of CVST (and was the most common code that led to cohort entry in CPRD GOLD) but does not appear to have been included in their definition. Meanwhile, even greater differences were seen for estimates of non-vaccine induced TTS. Their estimate of venous thromboembolism with thrombocytopenia for SIDIAP CMBD-HA was 2.4 (1.7–3.4), which is less than both our estimates for DVT and PE with thrombocytopenia in SIDIAP CMBD-HA (estimated to be 6.2 [5.8–6.6] and 5.9 [5.5–6.3], respectively). This discrepancy appears to be due to their reliance on diagnostic codes to identify cases of thrombocytopenia, whereas in our study we used both diagnostic codes and platelet measurements. Indeed, as can be seen in our study diagnostics, the vast majority of cases of thrombocytopenia are identified by platelet measurement records rather than diagnostic codes in both SIDIAP CMBD-HA and CPRD GOLD. The impact of this can be seen with their estimates of the incidence rate of thrombocytopenia, which were 142.42 (136.47–148.56) and 21.63 (20.15–23.20) for SIDIAP CMBD-HA and CPRD GOLD respectively, far lower than our estimates of 1185.9 (1180.6–1191.2) and 523.1 (518.5–527.8).

Spontaneous reports identified 93 cases of CVST with thrombocytopenia among individuals who had recently received the ChAdOx1 vaccine in the United Kingdom.[8] The profile of patients with TTS after vaccination also appears to differ to the typical profiles of those with TTS as seen in our data. While in this study we have seen those with TTS to typically be older than the general population of people in the database, more commonly male, and with more comorbidities and greater prior medication use, initial studies describing the profiles of patients with vaccine-induced TTS have most often presented the cases of people who were aged under 60, more often female, and with relatively few comorbidities described.[11,34–36] This dissimilarity in patient profiles of those with TTS in previous years and those for whom it has been reported following a vaccination is notable.

Substantial heterogeneity can though be seen in estimates of across databases, particularly where platelet measurements are required to identify an outcome. For PE, for example, a twofold difference was seen between the databases with the highest and lowest incidence rates. This increased to a more than 20-fold difference between databases for PE with thrombocytopenia. This heterogeneity was observed even though we used data mapped to a common data model and applied the same analytic code across the databases. Given that the data sources used come from different countries some differences in estimates can be expected. However, the heterogeneity in results seen here can also be explained by substantial differences in data capture across databases and source coding systems. Two of the databases had patient-level linkage to hospital records and one of these also captured inpatient platelet measurements. Incidence rates were often higher for these two databases. Moreover, while the databases were mapped to a common data model the source data used different medical vocabularies. For example, while read codes were used to represent condition-related concepts in CPRD GOLD, ICD-9 was used in IQVIA LPD Italy and ICD-10CM in SIDIAP. These coding systems differ in the granularity by which they describe clinical events, and this can have a meaningful impact on research findings. This can be seen in the literature by the impact on research findings when databases switched from using ICD-9 to ICD-10 codes for instance.[37] This all further underlines the importance of using consistent data sources in vaccine safety research with a historical comparator design. In the case of TTS it can also be expected that full linkage capturing both outpatient and inpatient lab measurements is required for accurate outcome ascertainment.

4.3 | Study limitations

This study relies on routinely-collected health care data and while this has allowed for the inclusion of a large study population, the recording of TTS has not previously been evaluated in the databases used. A degree of measurement error can thus be expected, and further research is required to validate the recording of TTS. This includes not only the identification of the constituent events themselves, but also the time period over which they can be considered concurrent. The findings from this study demonstrate that data sources that do not capture inpatient lab measurements can be expected to underestimate the true incidence of TTS. Studies that rely solely on records of diagnoses can be expected to miss many of the cases of thrombocytopenia that can be observed from available measurements of platelet counts.

The degree to which the TTS events being described after vaccinations against SARS-CoV-2 are comparable to non-vaccine induced TTS events previously seen in the general population is as yet unclear. TTS after vaccination appears to occur at unusual sites, with a large proportion of spontaneous reports and case series describing cerebral or abdominal thromboses, and with high levels of antibodies to platelet factor 4 often observed despite the absence of an exposure to heparin.[11,38] In this study we have focused on specific sites of thrombosis with concomitant thrombocytopenia. We believe that this is more instructive than providing a singular background incidence rate for venous thromboembolism with thrombocytopenia, which would be driven in large part by commonly seen events (such as DVT and PE) and would not necessarily reflect the presentation of TTS after vaccination. In particular, we do not have measurements of anti-PF4 antibodies and so could not use this for defining study outcomes. As the pathophysiology of TTS after vaccination becomes better understood, definitions of the appropriate historical comparator can also be expected to evolve so as to best match the condition being described among those who have been recently vaccinated. In particular this may mean the exclusion of patients with history of other rare disorders who may present with TTS without proximate heparin, such as patients with antiphospholipid syndrome.

5 | CONCLUSION

Based on data from over 38 million people from six European databases, non-vaccine induced TTS has been seen to be very rare. While rates varied across databases, the highest incidence rates for DVT, PE,

and stroke with thrombocytopenia were 8.5, 20.8, and 30.9 per 100 000 person-years, respectively. Meanwhile the highest incidence rates for CVST and SVT with thrombocytopenia were 0.1 and 2.5 per 100 000 person-years. Non-vaccine induced TTS was typically seen among individuals older, more often male, and in worse health than the general population. While these findings help to provide context for the rates of adverse events being reported by spontaneous reports following vaccinations against SARS-CoV-2, a full assessment of the safety signal for TTS would benefit from within-database comparisons which account for individual-level characteristics such as age and sex.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors were involved in the study conception and design, interpretation of the results, and the preparation of the manuscript. Edward Burn led the data analysis and wrote the initial draft of the manuscript with Daniel Prieto-Alhambra. Edward Burn, Talita Duarte-Salles, Carlen Reyes, María Aragón, and Sergio Fernandez-Bertolin had access to the SIDIAP data. Edward Burn, Xintong Li, Antonella Delmestri, and Daniel Prieto-Alhambra had access to the CPRD data. Daniel R. Morales and Scott Horban had access to the HIC Dundee data. Peter Rijnbeek and Katia Verhamme had access to the IPCI data, and Kristin Kostka, Henry Morgan Stewart, Carlen Reyes, Sarah Seager had access to LPD France, LPD Italy, and DA Germany.

ETHICS STATEMENT

The protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol number 20_000211), the IDIAPJGol Clinical Research Ethics Committee (project code: 21/007-PCV), and the IPCI governance board (application number 3/2021). Some databases used (IQVIA LPD Italy, IQVIA LPD France, IQVIA DA Germany) in these analyses are commercially available, syndicated data assets that are licenced by contributing authors for observational research. These assets are de-identified commercially available data products that could be purchased and licenced by any researcher. As these data are deemed commercial assets, there is no Institutional Review Board applicable to the usage and dissemination of these result sets or required registration of the protocol with additional ethics oversight. Compliance with Data Use Agreement terms, which stipulate how these data can be used and for what purpose, is sufficient for the licencing commercial entities. Further inquiry related to the governance oversight of these assets can be made with the respective commercial entity, IQVIA (iqvia.com). For HIC Dundee, institutional review board approval for the use of de-identified data for this project was granted by the Tayside Health Informatics Centre.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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