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Background rates of adverse events of special interest for COVID-19 vaccines: A multinational Global Vaccine Data Network (GVDN) analysis

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ABSTRACT

Background: The Global COVID Vaccine Safety (GCoVS) project was established in 2021 under the multinational Global Vaccine Data Network (GVDN) consortium to facilitate the rapid assessment of the safety of newly introduced vaccines. This study analyzed data from GVDN member sites on the background incidence rates of conditions designated as adverse events of special interest (AESI) for COVID-19 vaccine safety monitoring.

Methods: Eleven GVDN global sites obtained data from national or regional healthcare databases using standardized methods. Incident events of 13 pre-defined AESI were included for a pre-pandemic period (2015–19) and the first pandemic year (2020). Background incidence rates (IR) and 95% confidence intervals (CI) were calculated for inpatient and emergency department encounters, stratified by age and sex, and compared between pre-pandemic and pandemic periods using incidence rate ratios.

Results: An estimated 197 million people contributed 1,189,652,926 person-years of follow-up time. Among inpatients in the pre-pandemic period (2015–19), generalized seizures were the most common neurological AESI (IR ranged from 22.15 [95% CI 19.01–25.65] to 278.82 [278.20–279.44] per 100,000 person-years); acute disseminated encephalomyelitis was the least common (<0.5 per 100,000 person-years at most sites). Pulmonary embolism was the most common thrombotic event (IR 45.34 [95% CI 44.85–45.84] to 93.77 [95% CI 93.46–94.08] per 100,000 person-years). The IR of myocarditis ranged from 1.60 [(95% CI 1.45–1.76) to 7.76 (95% CI 7.46–8.08) per 100,000 person-years. The IR of several AESI varied by site, healthcare setting, age and sex. The IR of some AESI were notably different in 2020 compared to 2015–19.

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Conclusion: Background incidence of AESIs exhibited some variability across study sites and between pre-pandemic and pandemic periods. These findings will contribute to global vaccine safety surveillance and research.

1. Introduction

The Coronavirus disease 2019 (COVID-19) pandemic was declared in March 2020. As of March 16, 2023, worldwide, there have been 760,360,956 confirmed cases, including 6,873,477 deaths [1]. The response to the pandemic ushered in a new era of vaccinology with vaccines based on newer technologies such as mRNA and viral vector platforms developed and authorized rapidly via parallel developmental processes [2]. COVID-19 immunization programs were implemented in some countries starting in December 2020, and progressed globally in early 2021, with 13,232,904,667 doses administered by March 13, 2023 [1].

Post-implementation monitoring is an essential component of safety evaluation during the life cycle of vaccines. It is especially important for detecting and characterizing rare adverse events following immunization (AEFI) that might not have been observed in clinical trials and for evaluating safety in a diverse population outside of a controlled clinical trial setting [3,4]. In the case of COVID-19 vaccines, safety signals for several rare, clinically significant AEFI were identified during post-implementation surveillance, in particular, thrombosis with thrombocytopenia syndrome (TTS) [5–7] following adenoviral vectored vaccines and myocarditis following mRNA vaccines [8]. Assessment of these signals and quantification of risk impacted regulatory decisions and policy recommendations in several regions [5,9–12].

Observed AEFI do not necessarily have a causal relationship with vaccination [13] and there is a baseline, background rate of these conditions. Quantifying the background rate allows reported AEFI to be assessed in context, considering what would be expected to be observed by chance following vaccination [14]. Evaluating whether observed incidence following vaccination differs from background incidence for a particular condition allows rapid assessment of emerging safety signals.

Establishing robust and reliable background rates requires a strategic and coordinated approach to first generate a list of adverse events of special interest (AESI) and then access appropriate electronic healthcare data [14]. The Safety Platform for Emergency vACcines (SPEAC) project developed a list of potential COVID-19 vaccine AESI in 2020. Pharmacovigilance authorities in several regions derived background rates for these conditions to support pharmacovigilance activities [14–19]. The Global Vaccine Data Network (GVDN), a multinational, investigator-led research consortium, established the Global Covid Vaccine Safety (GCoVS) project in 2021 to support vaccine pharmacovigilance and build capacity in other countries. This study aimed to determine the background rates for selected AESI across 11 diverse global sites.

Table 1
Characteristics of data sources and sites contributing data.

Site	Region	Site name	Database/s	Database description	Coding system
Sites providing inpatient data only					
Australia	State (New South Wales)	National Centre for Immunisation Research and Surveillance (NCIRS)	Admitted Patient Data Collection (APDC) (hospitalisations)	Linked healthcare records, population denominator	ICD-10-AM
Denmark	National	Statens Serum Institut (SSI), Copenhagen	Danish nationwide registers (Central Person Register, National Hospital Discharge Register)	Linked healthcare and person registries	ICD-10
England	National	UK Health Security Agency (UKHSA)	Hospital Episode Statistics (HES)	Linked healthcare records, population denominator	ICD-10
France	National	Institut National de la Santé et de la Recherche Médicale (INSERM)	Système National des Données de Santé (SNDS) administrative data	Linked healthcare data (hospital and claims data)	ICD-10
Scotland	National	Public Health Scotland	Scottish Morbidity Record 01 (SMR01) acute inpatient and day case dataset	Linked healthcare records, population denominator	ICD-10
Sites providing inpatient and emergency department data (separately)					
Argentina	State Tierra del Fuego	Hospital de Niños Ricardo Gutierrez Epidemiology Department Buenos Aires City	Hospital Episode Events	Linked healthcare records population denominator	ICD-10
Australia	State (Victoria)	Murdoch Children's Research Institute (MCRI)	Victorian Emergency Minimum Dataset (VEMD), Victorian Admitted Episodes Dataset (VAED)	Statewide linked healthcare records, population denominator	ICD-10-AM
Canada	Province (British Columbia)	British Columbia (BC) BC Centre for Disease Control (BCCDC)	Discharge Abstracts Database (DAD)[1]; National Ambulatory Care Reporting System (NACRS)[2]	Linked healthcare records, population denominator	ICD-10-CA
Canada	Province (Ontario)	ICES (formerly Institute for Clinical Evaluative Sciences)	Registered Persons Database; Discharge Abstracts Database (DAD); National Ambulatory Care Reporting System (NACRS)	Linked healthcare and person registries	ICD-10-CA
Taiwan	National	Health Data Research Center, National Taiwan University, Taipei	National Health Insurance data	Linked healthcare and person registries (claims data)	ICD-9-CM (2014–15), ICD-10-CM (2016–20)
Sites providing inpatient and emergency department data (combined)					
Finland	National	Finnish Institute for Health and Welfare THL, Helsinki	Linked national registers, including the Care register for Health Care (HILMO)	Linked healthcare and population registries	ICD-10

[1] Canadian Institute of Health Information [creator] (2020): Discharge Abstract Database (Hospital Separations). British Columbia Ministry of Health [publisher]. Data Extract. MOH (2020). https://www2.gov.bc.ca/gov/content/health/conducting-health-research-evaluation/data-access-health-data-central.

[2] British Columbia Ministry of Health [creator](2022). National Ambulatory Care Reporting System. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2022). https://www2.gov.bc.ca/gov/content/health/health-forms/online-services.

2. Methods

2.1. Data source and study population

The GVDN is a collaboration of 35 partner institutions across 27 countries. Within the GVDN, the GCoVS project collates electronic healthcare data on COVID-19 vaccine AESI across GVDN sites [20]. Eleven sites participated in this study, following the Background Rates of Adverse Events of Special Interest Following COVID-19 Vaccination Study Protocol [21]. Denmark, England, Finland, France, Scotland and Taiwan provided national-level data while state or provincial data were provided by Argentina (Tierra del Fuego), two sites in Australia (New South Wales and Victoria) and two sites in Canada (British Columbia and Ontario).

To the extent possible, standardized methods were employed across sites to obtain data. The healthcare setting was clearly defined and consistently applied across 10 of 11 sites. Ten sites contributed data on hospital inpatients, five were also able to contribute emergency department data, and Finland provided data on inpatient and emergency department patients combined. In Denmark, where data are not differentiated between outpatient, emergency department and inpatient visits, encounter duration (≥5 h) was used as a marker for inpatient admission; 5 h was determined as the appropriate cut-off based on patient flow within Denmark for the range of outcomes included. Only inpatient data from Denmark were included. In addition, data from outpatient and primary care settings were provided by three sites; these background rates are displayed on the GVDN dashboard [22] but not included in the current analysis due to small number of sites providing this type of data and the variability in data source.

All sites were able to capture person-level information for AESI through the use of linked data, such that AESI counts represent incident events in individuals (Table 1). To ensure only incident events were included, a 365-day washout duration was applied and only events more than 365 days after any previous event for the same AESI were included. Where sites were also able to capture person-level information on the source population through linkage of healthcare data and person registers, cohorts were constructed. Person-time at risk was then calculated as total time under observation for each individual taking into account loss to follow-up due to individuals exiting the study population (e.g., due to death or emigration). For sites that were unable to link person-level information on the source population, estimated population denominators for the region from which cases were ascertained were obtained for each year of the study period, with the mean 2015–19 population used for that time period.

2.2. Study period

The study period was standardized for all sites and included a pre-pandemic period (January 1, 2015 to December 31, 2019) and the first pandemic year (January 1, 2020 to December 31, 2020); most sites provided data for all study years. The pandemic year largely represents the period prior to introduction of COVID-19 vaccines (vaccines were rolled out in the UK, Europe, Canada and Argentina from mid-December 2020, and in other included sites from 2021). Data from 2014 were used as a look-back period for 2015, so that only incident events outside of the 365-day look-back were included.

2.3. Adverse events of special interest (AESI)

Thirteen conditions representing AESI were selected as a subset of those identified by the SPEAC Project, which included conditions with a known association with immunization or with a vaccine platform/adjuvant, theoretical concerns based on immunopathogenesis, viral replication during wild-type disease, or demonstration in an animal model using a candidate vaccine platform [23]. A limited set of AESI was selected to enable participation of sites exploring background incidence for the first time. Selected AESI represented those of particular relevance to current, real-world vaccine pharmacovigilance. Neurological conditions selected were Guillain-Barré syndrome (GBS), transverse myelitis (TM), Bell's palsy (BP), acute disseminated encephalomyelitis (ADEM), convulsions (generalized seizures [GS] and febrile seizures [FS]); potential safety signals have been identified for some of these conditions [5,8,24]. Specific thromboembolic conditions (cerebral venous sinus thrombosis [CVST], splanchnic vein thrombosis [SVT] and pulmonary embolism [PE]) were included; the unusual site thromboses (CVST and SVT) were selected as markers of potential TTS that could be accurately identified through diagnostic codes [7]. Both thrombocytopenia (TCP) and immune thrombocytopenia (ITP) were included due to their association with TTS and reports of ITP as an independent safety signal [25]. For cardiac conditions, both myocarditis and pericarditis were included and incidence was determined separately for each condition [10].

AESI were coded in all site databases using the International Classification of Diseases (ICD); most sites used Tenth Revision codes (ICD-10), including country-specific modifications, while data from Taiwan were coded by ICD-9-CM for the 2014–2015 period and ICD-10-CM for the 2016–2020 period (Table 1, Supplementary Table 1) in either the primary and/or secondary (associated or related) discharge diagnosis fields. Where sites did not use ICD coding for ED presentations, ED data were not included. Medical chart evaluation was not undertaken.

2.4. Statistical analysis

Background incidence rates (IR) were calculated by dividing the AESI count by person-years of follow-up. For sites that were unable to link person-level information on the source population, person-time at risk was calculated as one-year times the annual average population. Missing data on sex or age group were excluded from the analysis.

For each site, annual IR per 100,000 person-years were calculated for each AESI, with separate analyses conducted for each healthcare setting (inpatient and ED for most sites, and combined ED/inpatient data for Finland). Data from inpatient and ED settings were reported separately, where possible, due to potential differences in presentations and diagnostic practices, which are known to impact observed background rates [19].

Overall IR by site were calculated for the inpatient setting in the pre-pandemic (2015–19) and pandemic periods (2020) with incidence rate ratios (IRR) used to assess differences between the two periods. IR were stratified by sex and age group; IRR were used to compare incidence by sex. Some sites suppressed event counts below a certain threshold (e.g., less than 5) and the incidence rates were not calculated; three sites were unable to provide rates by 5- and 10-year age group due to local data suppression requirements. For consistency, all rates were reported in 20-year age groups for this study; more granular age group data by site are available on the GVDN dashboard [22].

Data from different sites were not pooled due to differences in geography, population demographics, and diagnostic and coding practices that may significantly affect background rates [14]. The reported country-specific background rates are likely to be more useful to local pharmacovigilance authorities and can be used as a comparator for similar populations in countries that do not participate in the GVDN.

For all IR, 95% confidence intervals (CI) were derived using the exact Poisson distribution [26]. Similarly for the ratio of the incidence rates, 95% confidence intervals were calculated using the exact Poisson method [27]. Data analysis was conducted in R version 4 (https://www.r-project.org/). The study protocol is available on the GVDN website [20].

2.5. Ethical approval

Human Research Ethics Committee approval was obtained or was waived from each of the participating sites (Supplementary Table 2).

Table 2
Incidence rate (IR) per 100,000 person years and incidence rate ratio (IRR) (with 95% confidence interval [CI]) of neurological conditions in the first pandemic year (2020) and pre-pandemic years (2015–19), by site, inpatients.

	Argentina	Australia:Victoria	Australia:NSW	Canada:BC	Canada:Ontario	Denmark	England	France	Scotland	Taiwan
Guillain-Barre syndrome (GBS)										
IR 2015–19	0	2.79	2.66	1.90	1.58	2.29	3.80	3.82	2.83	4.07
	–	(2.61–2.98)	(2.50–2.82)	(1.73–2.08)	(1.49–1.68)	(2.12–2.46)	(3.73–3.88)	(3.76–3.88)	(2.63–3.03)	(3.95–4.19)
IR 2020	0	1.91	–	1.71	1.16	1.55	3.28	3.20	2.41	1.96
	–	(1.59–2.27)	–	(1.37–2.11)	(0.99–1.35)	(1.24–1.90)	(3.14–3.44)	(3.07–3.33)	(2.02–2.86)	(1.79–2.15)
IRR	–	0.68	–	0.90	0.73	0.68	0.86	0.84	0.85	0.48
	–	(0.56–0.82)	–	(0.71–1.13)	(0.62–0.86)	(0.54–0.84)	(0.82–0.91)	(0.80–0.87)	(0.70–1.03)	(0.44–0.53)
Transverse myelitis (TM)										
IR 2015–19	0	0.96	0.93	1.01	0.61	0.84	1.29	0.57	0.69	1.64
	–	(0.86–1.08)	(0.84–1.03)	(0.89–1.14)	(0.55–0.67)	(0.74–0.95)	(1.25–1.34)	(0.55–0.59)	(0.60–0.80)	(1.57–1.71)
IR 2020	0	1.06	–	0.76	0.62	0.22	1.14	0.61	0.73	0.54
	–	(0.83–1.34)	–	(0.54–1.04)	(0.50–0.76)	(0.12–0.38)	(1.06–1.23)	(0.55–0.67)	(0.52–1.00)	(0.45–0.64)
IRR	–	1.10	–	0.75	1.02	0.26	0.88	1.07	1.06	0.33
	–	(0.84–1.44)	–	(0.52–1.05)	(0.80–1.27)	(0.14–0.46)	(0.81–0.96)	(0.96–1.18)	(0.73–1.50)	(0.27–0.39)
Bell's palsy (BP)										
IR 2015–19	0	8.60	8.57	3.12	2.74	16.13	21.16	18.18	11.25	8.38
	–	(8.28–8.93)	(8.28–8.86)	(2.90–3.35)	(2.62–2.87)	(15.68–16.59)	(20.99–21.34)	(18.04–18.31)	(10.85–11.66)	(8.21–8.55)
IR 2020	0.58	10.66	9.28	3.87	3.59	6.83	20.92	17.14	9.48	5.29
	(0.01–3.21)	(9.89–11.48)	(8.63–9.97)	(3.35–4.44)	(3.29–3.91)	(6.17–7.53)	(20.54–21.30)	(16.85–17.44)	(8.68–10.33)	(5.00–5.59)
IRR	–	1.24	1.08	1.24	1.31	0.42	0.99	0.94	0.84	0.63
	–	(1.14–1.35)	(1.00–1.17)	(1.05–1.45)	(1.19–1.44)	(0.38–0.47)	(0.97–1.01)	(0.93–0.96)	(0.77–0.92)	(0.59–0.67)
Acute disseminated encephalomyelitis (ADEM)										
IR 2015–19	0.12	0.35	0.46	0.21	0.18	0.14	0.26	0.27	0.17	0.51
	(0.00–0.69)	(0.28–0.42)	(0.40–0.54)	(0.16–0.28)	(0.15–0.21)	(0.10–0.18)	(0.24–0.28)	(0.25–0.29)	(0.12–0.22)	(0.47–0.55)
IR 2020	0	0.32	–	0.16	0.10	0.03	0.15	0.19	0.05	0.30
	–	(0.20–0.49)	–	(0.07–0.31)	(0.05–0.16)	(0.00–0.12)	(0.12–0.19)	(0.16–0.23)	(0.01–0.16)	(0.24–0.38)
IRR	–	0.91	–	0.76	0.56	0.21	0.58	0.70	0.29	0.59
	–	(0.54–1.46)	–	(0.30–1.56)	(0.31–0.97)	(0.03–0.94)	(0.45–0.72)	(0.58–0.84)	(0.06–1.01)	(0.45–0.75)
Febrile seizures (FS)										
IR 2015–19	10.33	12.83	11.95	3.50	3.39	22.69	18.25	16.07	15.14	2.66
	(8.23–12.80)	(12.44–13.23)	(11.61–12.30)	(3.27–3.74)	(3.26–3.53)	(22.15–23.23)	(18.09–18.40)	(15.94–16.20)	(14.68–15.61)	(2.57–2.76)
IR 2020	4.61	2.69	–	2.10	2.12	11.21	8.76	9.97	7.06	1.25
	(1.99–9.09)	(2.31–3.12)	–	(1.72–2.53)	(1.89–2.37)	(10.37–12.10)	(8.52–9.01)	(9.75–10.20)	(6.37–7.80)	(1.11–1.40)
IRR	0.45	0.21	–	0.60	0.63	0.49	0.48	0.62	0.47	0.47
	(0.19–0.92)	(0.18–0.24)	–	(0.49–0.73)	(0.55–0.70)	(0.46–0.54)	(0.47–0.49)	(0.61–0.64)	(0.42–0.52)	(0.42–0.53)
Generalized seizures (GS)										
IR 2015–19	22.15	147.29	132.12	54.19	59.25	147.97	278.82	177.91	206.96	69.00
	(19.01–25.65)	(145.95–148.64)	(130.99–133.26)	(53.27–55.11)	(58.68–59.82)	(146.60–149.35)	(278.20–279.44)	(177.49–178.34)	(205.25–208.68)	(68.51–69.48)
IR 2020	23.06	142.45	119.58	51.03	56.51	62.14	245.24	160.03	190.36	21.42
	(16.48–31.41)	(139.58–145.36)	(117.22–121.97)	(49.10–53.02)	(55.30–57.74)	(60.15–64.19)	(243.94–246.53)	(159.13–160.94)	(186.72–194.05)	(20.83–22.01)
IRR	1.04	0.97	0.91	0.94	0.95	0.42	0.88	0.90	0.92	0.31
	(0.72–1.47)	(0.95–0.99)	(0.89–0.92)	(0.90–0.98)	(0.93–0.98)	(0.41–0.43)	(0.87–0.88)	(0.89–0.90)	(0.90–0.94)	(0.30–0.32)

BC: British Columbia; NSW: New South Wales. IR were not calculated when the site suppressed low event counts, and CI was not calculated when IR = 0. IRR is 2020 compared to 2015–19.

Table 3
Incidence rate (IR) per 100,000 person years and incidence rate ratio (IRR) (with 95% confidence interval [CI]) of neurological conditions in the first pandemic year (2020) and pre-pandemic years (2015–19), by site, emergency department patients.

	Argentina	Australia:Victoria	Canada:BC	Canada:Ontario	Taiwan
Guillain-Barre syndrome (GBS)					
IR 2015–19	0.12 (0.00–0.69)	1.05 (0.94–1.17)	0.40 (0.33–0.49)	0.16 (0.13–0.19)	7.09 (6.93–7.24)
IR 2020	0.58 (0.01–3.21)	0.58 (0.41–0.79)	0.41 (0.25–0.62)	0.12 (0.07–0.18)	3.76 (3.52–4.02)
IRR	4.83 (0.06–363.75)	0.55 (0.38–0.77)	1.02 (0.60–1.64)	0.75 (0.44–1.26)	0.53 (0.49–0.57)
Transverse myelitis (TM)					
IR 2015–19	0 (–)	0.50 (0.42–0.58)	0 (–)	0.11 (0.09–0.14)	2.02 (1.94–2.11)
IR 2020	0 (–)	0.39 (0.26–0.58)	0 (–)	0.10 (0.06–0.17)	0.94 (0.82–1.07)
IRR	– (–)	0.78 (0.50–1.20)	– (–)	0.91 (0.49–1.61)	0.47 (0.40–0.53)
Bell's palsy					
IR 2015–19	20.90 (17.86–24.32)	17.57 (17.11–18.04)	14.62 (14.15–15.10)	25.01 (24.64–25.38)	98.92 (98.34–99.50)
IR 2020	34.02 (25.90–43.88)	20.42 (19.35–21.54)	16.92 (15.81–18.08)	27.74 (26.89–28.60)	83.01 (81.85–84.17)
IRR	1.63 (1.19–2.20)	1.16 (1.09–1.23)	1.16 (1.07–1.25)	1.11 (1.07–1.15)	0.84 (0.83–0.85)
Acute disseminated encephalomyelitis (ADEM)					
IR 2015–19	0 (–)	– (–)	0 (–)	0.01 (0.00–0.02)	0.62 (0.57–0.67)
IR 2020	0 (–)	– (–)	0 (–)	0.01 (0.00–0.04)	0.55 (0.46–0.65)
IRR	– (–)	– (–)	– (–)	1.00 (0.02–5.32)	0.89 (0.73–1.07)
Febrile seizures (FS)					
IR 2015–19	0 (–)	37.62 (36.95–38.30)	9.66 (9.28–10.06)	21.15 (20.82–21.50)	67.45 (66.98–67.93)
IR 2020	0 (–)	18.32 (17.30–19.38)	5.92 (5.28–6.63)	10.91 (10.38–11.45)	29.92 (29.23–30.62)
IRR	– (–)	0.49 (0.46–0.52)	0.61 (0.54–0.69)	0.52 (0.49–0.54)	0.44 (0.43–0.45)
Generalised seizures (GS)					
IR 2015–19	13.44 (11.02–16.23)	147.03 (145.69–148.37)	75.56 (74.48–76.65)	79.75 (79.09–80.41)	463.59 (462.34–464.84)
IR 2020	8.65 (4.84–14.27)	137.27 (134.46–140.13)	75.37 (73.02–77.78)	66.44 (65.13–67.77)	157.60 (156.01–159.21)
IRR	0.64 (0.35–1.11)	0.93 (0.91–0.95)	1.00 (0.96–1.03)	0.83 (0.82–0.85)	0.34 (0.34–0.34)

BC: British Columbia. IR were not calculated when the site suppressed low event counts, and CI was not calculated when IR = 0. IRR is 2020 compared to 2015–19.

3. Results

The total number of person-years included in the study across all sites and all study years was 1,189,652,926. Distribution of person-years by age group and sex across sites is available in Supplementary Table 3. France contributed the highest number of person-years of data.

3.1. Neurological conditions

The AESI with the highest incidence among inpatients at all sites was GS (IR across sites ranged from point estimates of 22.15 to 278.82 per 100,000 person-years among inpatients in the pre-pandemic period) (Table 2). The incidence of GS was also highest for combined patient types (Finland) and across most sites providing ED data (Tables 3 and 4). FS were less common than GS (point estimate IR per 100,000 ranged from 2.66 to 22.69, among inpatients in 2015–19) (Table 2). The incidence of FS was higher among ED patients than among inpatients for sites that reported data from both healthcare settings (point estimates of 9.66 to 67.45 per 100,000 among ED patients in 2015–19). BP was also reported more frequently among ED patients compared to inpatients for sites that reported data from both settings (point estimates ranged from 14.62 to 98.92 among ED patients) (Tables 2 and 3). The incidence of GBS was low, with point estimates between 1.58 and 4.07 per 100,000 person-years among inpatients in the pre-pandemic era, with no cases reported from the Argentina site in this period. ADEM and TM were rare with incidence <0.5 per 100,000 person-years for ADEM at almost all sites, and incidence for TM up to 1.64 per 100,000 person-years among inpatients (Table 2).

The incidence of FS was significantly lower in 2020 than in 2015–19 among inpatients and ED patients at all sites in 2020 (Tables 2, 3). The IR of GS and GBS was lower in the inpatient setting at most sites in 2020, compared to the earlier time period (Table 2). The incidence of BP was slightly higher among ED patients in 2020 at most sites; this pattern was not seen among inpatients (Fig. 1, Tables 2 and 3).

The incidence of GS, BP and GBS increased with age, although GBS declined in the oldest age group (80 years and over) at some sites (Supplementary Fig. 1, Supplementary Table 4). TM peaked in the 40–59- or 60–79-year age group at most sites. FS occurred, by definition, in childhood and ADEM was more common in younger people (under 20 years of age) at most sites. There was a male predominance for GS and GBS at almost all sites (Supplementary Tables 4 and 5).

3.2. Hematological conditions

Among thromboembolic conditions, PE was the most common with most site point estimates between 45.34 and 93.77 per 100,000 person-years among inpatients in the pre-pandemic years, excluding Taiwan and Argentina, where the IR was notably lower (Tables 4 and 5). CVST was rare with IR point estimates generally in the range of 0.21–1.72 per 100,000 person-years in 2015–19 (with no cases from the Argentina site) and IR less than 1 per 100,000 person-years at most inpatient sites (n = 8). SVT was more common than CVST with IR point estimates ranging from 0.12 to 13.84 in the pre-pandemic period (Table 5). The incidence of thromboembolic conditions was higher in inpatients than ED patients for most sites that provided data from both healthcare settings (Table 6). Thrombocytopenia was more common than ITP among inpatients and was more common among inpatients than ED patients at most sites providing data from both settings (Table 5 and 6).

The incidence of PE was higher among inpatients at most (n = 6) sites in 2020 compared to the pre-pandemic era, and among combined patients in Finland, but this increase was not seen for all sites (Table 5, Fig. 2). SVT also increased at most, but not all, sites in 2020. No clear pattern was seen for CVST, thrombocytopenia or ITP (Tables 4 and 5, Fig. 2).

Table 4
Incidence rate (IR) per 100,000 person years and incidence rate ratio (IRR) (with 95% confidence interval [CI]) of neurological, hematological and cardiac conditions in the first pandemic year (2020) and pre-pandemic years (2015–19), Finland, combined inpatient and emergency department patients.

	Neurological conditions	Hematological and cardiac conditions
	Guillain-Barre syndrome (GBS)	*Thrombocytopenia (TCP)*
IR 2015–19	2.74 (2.55–2.94)	15.09 (14.64–15.56)
IR 2020	2.11 (1.75–2.53)	14.47 (13.50–15.50)
IRR	0.77 (0.63–0.94)	0.96 (0.89–1.03)
	Transverse myelitis (TM)	*Idiopathic thrombocytopenia (ITP)*
IR 2015–19	0.22 (0.17–0.28)	17.71 (17.22–18.21)
IR 2020	0.14 (0.06–0.28)	14.29 (13.32–15.32)
IRR	0.64 (0.27–1.35)	0.81 (0.75–0.87)
	Bell's palsy (BP)	*Pulmonary embolism (PE)*
IR 2015–19	41.50 (40.75–42.26)	87.81 (86.71–88.91)
IR 2020	42.32 (40.63–44.05)	90.97 (88.50–93.50)
IRR	1.02 (0.98–1.07)	1.04 (1.01–1.07)
	Acute disseminated encephalomyelitis (ADEM)	*Cerebral venous sinus thrombosis (CVST)*
IR 2015–19	0.16 (0.12–0.21)	2.45 (2.27–2.64)
IR 2020	0.16 (0.07–0.30)	2.24 (1.86–2.66)
IRR	1.00 (0.43–2.07)	0.91 (0.75–1.11)
	Febrile seizures (FS)	*Splanchnic vein thrombosis (SVT)*
IR 2015–19	18.44 (17.94–18.95)	5.81 (5.53–6.10)
IR 2020	9.41 (8.63–10.25)	5.72 (5.11–6.38)
IRR	0.51 (0.47–0.56)	0.98 (0.87–1.11)
	Generalized seizures (GS)	*Myocarditis*
IR 2015–19	240.05 (238.25–241.87)	10.48 (10.11–10.87)
IR 2020	221.43 (217.56–225.35)	7.09 (6.41–7.82)
IRR	0.92 (0.90–0.94)	0.68 (0.61–0.75)
		Pericarditis
IR 2015–19		3.98 (3.75–4.22)
IR 2020		4.10 (3.59–4.67)
IRR		1.03 (0.89–1.19)

IRR is 2020 compared to 2015–19.

The incidence of thrombocytopenia, ITP and PE increased with age, while SVT increased to age 60–79 years then stabilized or declined (Supplementary Table 6, Supplementary Fig. 2). CVST also increased with age at most sites in the pre-pandemic period; in 2020, an increase in incidence to 60–79 years followed by decline in the elderly was seen at some sites (Supplementary Fig. 2, Supplementary Table 4). There was a male predominance for thrombocytopenia at most sites; this was not seen for ITP. PE was slightly more common in females compared to male inpatients at most (n = 7) sites in the pre-pandemic period; however, this sex difference was not seen at most of these sites in 2020 (Supplementary Table 6). CVST was more common among male than female inpatients at four sites in the pre-pandemic period; in 2020, this sex difference was no longer seen at three sites. SVT was more common among males at all sites in 2015–19 and this difference persisted in 2020 (Supplementary Table 6).

3.3. Cardiac conditions

Pericarditis was more common than myocarditis at most sites (n = 6) (Tables 4 and 5). In the pre-pandemic period, the point estimate IR of myocarditis ranged from 1.6 to 7.76 per 100,000 person-years among inpatients (with no cases reported from the Argentina site); incidence was lower in ED patients at most sites that reported data from both settings (Tables 5 and 6). No clear trend over time was seen for myocarditis although the incidence decreased in 2020 among ED patients at three of four sites with reported cases (Fig. 2, Table 6). While pericarditis rates increased with age, myocarditis rates peaked in young adults at most sites and remained high throughout adulthood (Supplementary Fig. 2). Myocarditis was more common in males at almost all sites in 2015–19 and in 2020 (Supplementary Tables 4 and 6).

4. Discussion

This study presents a systematically coordinated analysis of background rates based on inpatient and ED encounters for selected COVID-19 AESI across 11 sites in 9 countries. While background rates for COVID-19 AESI have previously been published for individual countries or regions [18,19,28–31], this study encompasses large regional or national databases from countries in Europe, Asia, North and South America and Oceania, capturing the heterogeneity of background rates across different geographical locations and populations. While two other studies have similarly included diverse countries globally [32,33], these included a range of data sources (such as administrative claims databases and primary care), while we consistently derived rates from available linked inpatient and ED data, and used consistent ICD codes and standardized methods for obtaining incident cases.

Similar to the European vACCine covid-19 monitoring readinESS (ACCESS) study [19], we analyzed data by healthcare setting (ED or inpatient), accounting for variations in background rates in different healthcare settings (depending on whether the condition leads to hospital admission) and retaining the usefulness of the results for observed versus expected analyses of data from these settings. Our study also included a consistent time period across almost all sites, incorporating five pre-pandemic years and the first pandemic year (prior to

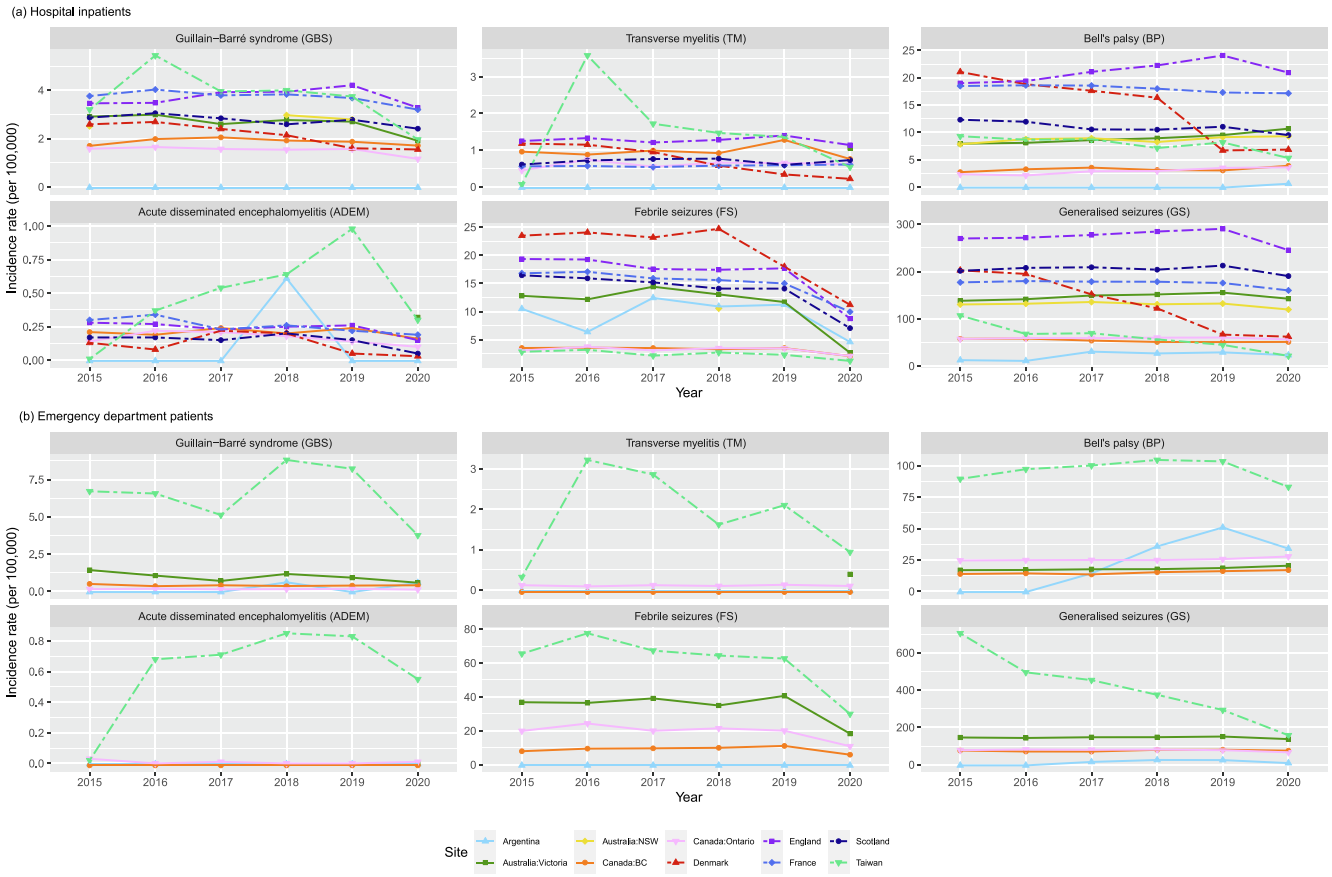

Fig. 1. Incidence rate (IR) per 100,000 person-years of neurological conditions over time (2015–20), by site. (a) Inpatients. (b) Emergency department patients.

vaccination) enabling analysis of the changing incidence of some AESI in 2020 and providing the most relevant data to be used for observed versus expected analysis. Granular data were provided by sites enabling calculation of background rates by age group and sex over time. All data are publicly available via the GVDN dashboard [20], and can be used by pharmacovigilance authorities in COVID-19 and other vaccine safety surveillance.

Accurate and consistent background rates are a critical component in the conduct of reliable observed versus expected analyses. However, rates may vary across different populations [18], geographical regions [32,33], and over time, which was seen in our study and may relate to underlying differences in populations, care-seeking behavior, access to care (for example, there are no primary care systems in Taiwan), diagnostic and coding practices. Given the variability across geographical regions, background rates used for observed versus expected analysis should be from the most comparable population or region, or ideally, from the same data source.

The background rates for many conditions were similar to those seen in other studies, validating our findings. For neurological conditions, similar to the ACCESS study [19], we found that GS were relatively common compared to the rarer conditions of ADEM and TM. Although our rates were generally slightly higher than those reported in the ACCESS study [19], they were similar to those reported from the FDA Biologics Effectiveness and Safety (BEST) initiative [18] and a previous literature review [34]. GBS was rare, and rates were consistent with those reported from the ACCESS study [19] and BEST initiative [18], although at a number of sites, rates were higher than those reported in an earlier literature review (1–2 per 100,000 per year) [34].

While PE was the most common thromboembolic condition in our study, rates were lower than in the BEST study but similar to Canadian and Australian background rates studies [28,31]. The ACCESS study found that venous thromboembolism was common and higher among inpatients compared to ED patients, similar to our findings in relation to PE [19]. Our background rates for CVST were similar to other studies [19,28]; others have not generally assessed SVT. Although the incidence of PE among inpatients was lower in Taiwan than at other sites, this was not seen for unusual site thromboses. The background rates for TCP and ITP differed from those found in the ACCESS [19] and BEST [18] studies although rates of ITP were generally consistent with rates reported from Canada [28], which may represent differences in ICD codes used and in coding practices between regions. The rate of myocarditis at some of our study sites was higher than that identified among inpatients in the ACCESS study [19] but consistent with findings from the literature [34].

The incidence of some AESI may have been impacted by the COVID-19 pandemic, with declines due to reduced healthcare utilization and/or transmission of other infectious diseases and increases due to an association with COVID-19 disease. Where this has occurred, it is important to select the most appropriate background rate for observed versus expected analysis [14]. For conditions that declined in incidence in 2020, comparison of post-vaccination rates with pre-pandemic rates may mean safety signals are obscured; conversely, for conditions that increased during the pandemic, comparison of post-vaccination rate with earlier data may generate a false signal.

The background incidence rates varied over time in this study. Febrile seizures decreased in incidence in 2020, consistent with evidence of decreased circulation of respiratory viruses as a result of public health measures against COVID-19 [35]. Similar to the BEST study [18], the rate of GBS declined at most sites in our study in 2020. Conversely, the incidence of PE and SVT increased at most sites in 2020, consistent with the known association between COVID-19 disease and thromboembolism and the findings of the BEST background rates study [18,36]. However, despite a known association between myocarditis and COVID-

Table 5
Incidence rate (IR) per 100,000 person years and incidence rate ratio (IRR) (with 95% confidence interval [CI]) of hematological and cardiac conditions in the first pandemic year (2020) and pre-pandemic years (2015–19), by site, inpatients.

	Argentina	Australia:Victoria	Australia:NSW	Canada:BC	Canada:Ontario	Denmark	England	France	Scotland	Taiwan
Thrombocytopenia (TCP)										
IR 2015–19	1.00	67.98	80.34	25.56	35.09	10.73	54.16	97.30	22.64	37.77
	(0.43–1.96)	(67.07–68.89)	(79.46–81.24)	(24.93–26.20)	(34.65–35.53)	(10.37–11.11)	(53.88–54.43)	(96.99–97.62)	(22.08–23.22)	(37.41–38.13)
IR 2020	0	74.68	85.02	28.81	38.95	6.21	60.24	97.28	20.07	23.18
	–	(72.61–76.80)	(83.04–87.05)	(27.36–30.31)	(37.95–39.97)	(5.59–6.88)	(59.60–60.88)	(96.57–97.99)	(18.90–21.29)	(22.57–23.80)
IRR	–	1.10	1.06	1.13	1.11	0.58	1.11	1.00	0.89	0.61
	–	(1.06–1.13)	(1.03–1.09)	(1.06–1.19)	(1.08–1.14)	(0.52–0.65)	(1.10–1.13)	(0.99–1.01)	(0.83–0.95)	(0.60–0.63)
Idiopathic thrombocytopenia (ITP)										
IR 2015–19	0.75	8.48	7.55	0.39	4.58	7.11	14.24	10.85	8.76	10.38
	(0.27–1.63)	(8.16–8.81)	(7.28–7.83)	(0.31–0.47)	(4.43–4.74)	(6.81–7.42)	(14.10–14.38)	(10.74–10.95)	(8.41–9.12)	(10.19–10.57)
IR 2020	0	7.87	7.26	0.39	3.60	4.67	12.76	9.80	7.83	5.47
	–	(7.21–8.58)	(6.69–7.87)	(0.24–0.60)	(3.30–3.92)	(4.13–5.26)	(12.47–13.06)	(9.58–10.03)	(7.11–8.61)	(5.18–5.77)
IRR	–	0.93	0.96	1.00	0.79	0.66	0.90	0.90	0.89	0.53
	–	(0.84–1.02)	(0.88–1.05)	(0.58–1.63)	(0.72–0.86)	(0.58–0.74)	(0.87–0.92)	(0.88–0.93)	(0.80–0.99)	(0.50–0.56)
Pulmonary embolism (PE)										
IR 2015–19	0.50	62.47	70.75	57.15	45.34	78.59	74.65	93.77	89.55	13.47
	(0.14–1.27)	(61.60–63.35)	(69.92–71.58)	(56.21–58.11)	(44.85–45.84)	(77.59–79.60)	(74.33–74.97)	(93.46–94.08)	(88.43–90.69)	(13.26–13.68)
IR 2020	1.15	71.13	73.23	56.39	51.24	70.40	88.78	111.57	101.68	8.73
	(0.14–4.17)	(69.11–73.19)	(71.39–75.11)	(54.36–58.48)	(50.09–52.41)	(68.27–72.57)	(88.00–89.56)	(110.82–112.33)	(99.03–104.39)	(8.36–9.11)
IRR	2.30	1.14	1.04	0.99	1.13	0.90	1.19	1.19	1.14	0.65
	(0.21–16.17)	(1.10–1.18)	(1.01–1.06)	(0.95–1.03)	(1.10–1.16)	(0.87–0.93)	(1.18–1.20)	(1.18–1.20)	(1.10–1.17)	(0.62–0.68)
Cerebral venous sinus thrombosis (CVST)										
IR 2015–19	0	0.21	0.50	0.49	0.51	1.57	0.38	1.72	0.24	0.82
	–	(0.16–0.27)	(0.43–0.58)	(0.41–0.59)	(0.46–0.57)	(1.43–1.71)	(0.35–0.40)	(1.67–1.76)	(0.18–0.30)	(0.77–0.88)
IR 2020	0	0.27	–	0.62	0.62	1.21	0.62	2.25	0.38	0.63
	–	(0.16–0.43)	–	(0.43–0.88)	(0.50–0.76)	(0.94–1.52)	(0.56–0.69)	(2.14–2.36)	(0.24–0.59)	(0.53–0.74)
IRR	–	1.29	–	1.27	1.22	0.77	1.63	1.31	1.58	0.77
	–	(0.73–2.22)	–	(0.83–1.88)	(0.95–1.53)	(0.59–0.99)	(1.44–1.84)	(1.24–1.38)	(0.93–2.66)	(0.64–0.92)
Splanchnic vein thrombosis (SVT)										
IR 2015–19	0.12	5.21	5.14	5.14	5.07	3.94	6.83	12.06	5.47	13.84
	(0.00–0.69)	(4.96–5.46)	(4.92–5.37)	(4.87–5.44)	(4.90–5.24)	(3.72–4.17)	(6.73–6.92)	(11.95–12.17)	(5.19–5.75)	(13.62–14.06)
IR 2020	0	6.16	–	5.92	6.05	2.90	8.39	13.08	6.26	9.24
	–	(5.58–6.79)	–	(5.28–6.63)	(5.66–6.46)	(2.48–3.37)	(8.16–8.64)	(12.82–13.34)	(5.61–6.96)	(8.86–9.64)
IRR	–	1.18	–	1.15	1.19	0.74	1.23	1.08	1.14	0.67
	–	(1.06–1.32)	–	(1.01–1.31)	(1.11–1.28)	(0.62–0.87)	(1.19–1.27)	(1.06–1.11)	(1.01–1.29)	(0.64–0.70)
Myocarditis										
IR 2015–19	0	7.76	2.89	2.38	1.64	3.46	2.92	5.35	1.60	2.06
	–	(7.46–8.08)	(2.73–3.07)	(2.19–2.58)	(1.55–1.74)	(3.26–3.68)	(2.85–2.98)	(5.27–5.42)	(1.45–1.76)	(1.98–2.15)
IR 2020	0	8.80	3.35	2.86	1.44	2.84	3.44	5.84	1.39	0.91
	–	(8.10–9.54)	(2.97–3.78)	(2.41–3.36)	(1.25–1.65)	(2.42–3.30)	(3.28–3.59)	(5.66–6.01)	(1.10–1.74)	(0.79–1.04)
IRR	–	1.13	1.16	1.20	0.88	0.82	1.18	1.09	0.87	0.44
	–	(1.03–1.24)	(1.01–1.33)	(0.99–1.44)	(0.75–1.02)	(0.69–0.97)	(1.12–1.24)	(1.06–1.13)	(0.67–1.11)	(0.38–0.51)
Pericarditis										
IR 2015–19	0.25	1.94	7.08	4.22	5.28	10.71	1.86	16.88	4.94	0.45
	(0.03–0.90)	(1.79–2.10)	(6.82–7.35)	(3.97–4.49)	(5.11–5.45)	(10.35–11.09)	(1.81–1.91)	(16.75–17.02)	(4.68–5.22)	(0.41–0.49)
IR 2020	0	2.27	7.26	3.96	6.01	9.05	1.92	14.87	6.09	0.15
	–	(1.92–2.66)	(6.69–7.87)	(3.44–4.55)	(5.62–6.42)	(8.30–9.85)	(1.80–2.03)	(14.60–15.15)	(5.46–6.78)	(0.11–0.21)
IRR	–	1.17	1.03	0.94	1.14	0.85	1.03	0.88	1.23	0.33
	–	(0.97–1.40)	(0.94–1.12)	(0.80–1.09)	(1.06–1.23)	(0.77–0.93)	(0.97–1.10)	(0.86–0.90)	(1.09–1.39)	(0.23–0.47)

BC: British Columbia; NSW: New South Wales. IR were not calculated when the site suppressed low event counts, and CI was not calculated when IR = 0. IRR is 2020 compared to 2015–19.

Table 6
Incidence rate (IR) per 100,000 person years and incidence rate ratio (IRR) (with 95% confidence interval [CI]) of hematological and cardiac conditions in the first pandemic year (2020) and pre-pandemic years (2015–19), by site, emergency department patients.

	Argentina	Australia:Victoria	Canada:BC	Canada:Ontario	Taiwan
Thrombocytopenia (TCP)					
IR 2015–19	0.25 (0.03–0.90)	5.61 (5.36–5.88)	3.27 (3.05–3.51)	6.76 (6.57–6.95)	76.51 (76.01–77.02)
IR 2020	0.58 (0.01–3.21)	4.62 (4.11–5.17)	3.75 (3.24–4.32)	5.39 (5.02–5.78)	42.42 (41.59–43.25)
IRR	2.32 (0.04–44.51)	0.82 (0.73–0.93)	1.15 (0.97–1.34)	0.80 (0.74–0.86)	0.55 (0.54–0.57)
Idiopathic thrombocytopenia (ITP)					
IR 2015–19	0.87 (0.35–1.79)	2.91 (2.73–3.11)	0 (–)	1.70 (1.61–1.80)	15.15 (14.92–15.37)
IR 2020	0 (–)	1.94 (1.62–2.30)	0 (–)	1.30 (1.13–1.50)	7.26 (6.92–7.61)
IRR	– (–)	0.67 (0.55–0.80)	– (–)	0.76 (0.65–0.89)	0.48 (0.46–0.50)
Pulmonary embolism (PE)					
IR 2015–19	0 (–)	35.48 (34.83–36.15)	16.65 (16.14–17.16)	19.85 (19.52–20.18)	53.60 (53.18–54.03)
IR 2020	0 (–)	33.23 (31.86–34.65)	19.21 (18.03–20.45)	20.52 (19.79–21.26)	31.33 (30.63–32.05)
IRR	– (–)	0.94 (0.89–0.98)	1.15 (1.08–1.24)	1.03 (0.99–1.08)	0.58 (0.57–0.60)
Cerebral venous sinus thrombosis (CVST)					
IR 2015–19	0 (–)	– (–)	0 (–)	0.04 (0.02–0.05)	3.48 (3.37–3.59)
IR 2020	0 (–)	– (–)	0 (–)	0.08 (0.04–0.14)	2.74 (2.54–2.96)
IRR	– (–)	– (–)	– (–)	2.00 (0.95–4.16)	0.79 (0.72–0.86)
Splanchnic vein thrombosis (SVT)					
IR 2015–19	0 (–)	– (–)	0 (–)	0.71 (0.65–0.78)	10.33 (10.15–10.52)
IR 2020	0 (–)	– (–)	0 (–)	0.79 (0.66–0.95)	7.21 (6.88–7.56)
IRR	– (–)	– (–)	– (–)	1.11 (0.90–1.36)	0.70 (0.66–0.73)
Myocarditis					
IR 2015–19	0 (–)	2.03 (1.88–2.19)	1.28 (1.14–1.43)	0.25 (0.22–0.29)	8.97 (8.79–9.14)
IR 2020	0 (–)	1.62 (1.33–1.96)	1.15 (0.87–1.48)	0.14 (0.08–0.21)	6.26 (5.94–6.58)
IRR	– (–)	0.80 (0.64–0.98)	0.90 (0.67–1.18)	0.56 (0.34–0.90)	0.70 (0.66–0.74)
Pericarditis					
IR 2015–19	0 (–)	– (–)	4.91 (4.63–5.19)	2.17 (2.06–2.28)	2.04 (1.96–2.13)
IR 2020	0.58 (0.01–3.21)	– (–)	5.56 (4.93–6.24)	1.98 (1.75–2.22)	1.64 (1.48–1.81)
IRR	– (–)	– (–)	1.13 (0.99–1.29)	0.91 (0.80–1.04)	0.80 (0.72–0.89)

BC: British Columbia. IR were not calculated when the site suppressed low event counts, and CI was not calculated when IR = 0. IRR is 2020 compared to 2015–19.

19 disease [37], there was no clear trend over time at most sites and declines at some ED sites, possibly related to decreased circulation of other viruses [37].

The background rates of various AESI varied with age and/or sex and were generally consistent with other background rates studies. GBS was more common in males and increased with age [18,19,31,32,34], and PE (or venous thromboembolism in some studies) also increased with age [19,28,31,32]. Myocarditis was more common in males [18,19,30–32,34]. Detailed data on these age and sex specific differences are critical in the evaluation of safety signals through observed versus expected analysis, such as the safety signal for myocarditis following mRNA COVID-19 vaccines in young adult males [38].

This study was limited by the data restrictions at each site, including age groups and healthcare setting available, and different abilities of sites to link patient and population level data, impacting the calculation of person-years used in denominators. Data were derived from inpatient and emergency department encounters; outpatient settings were excluded. Estimates are based on electronically coded data and were not chart-validated. Chart review is planned for GVDN association studies on myocarditis, pericarditis and TTS, which will be published separately. Data were captured annually so variation in background rate by season was not captured. Practices in relation to ICD-10 coding and diagnostic trends, along with healthcare access and utilization, may have varied across sites. The variation in IR across sites may limit the utility and generalizability of the totality of the data.

5. Conclusion

The GVDN background rates study provides granular background rates for key AESI by year, age, and sex for nine countries and from different global regions. Comparison with other background rates studies demonstrates the validity of the data. Rates are described by healthcare setting enabling use of the most appropriate data source for individual safety signals, depending on the healthcare setting where each condition is likely to be diagnosed. Data are publicly available via a dashboard, enabling rapid use in real-time global vaccine safety surveillance, with the potential to expand to capture additional AESI and include additional sites. Availability of background rates also provides useful information to inform communications such as framing of key messages during vaccine programs. The GVDN is currently collating data on the incidence of these same AESI in the post-COVID-19 vaccine era, including for observed versus expected analyses.

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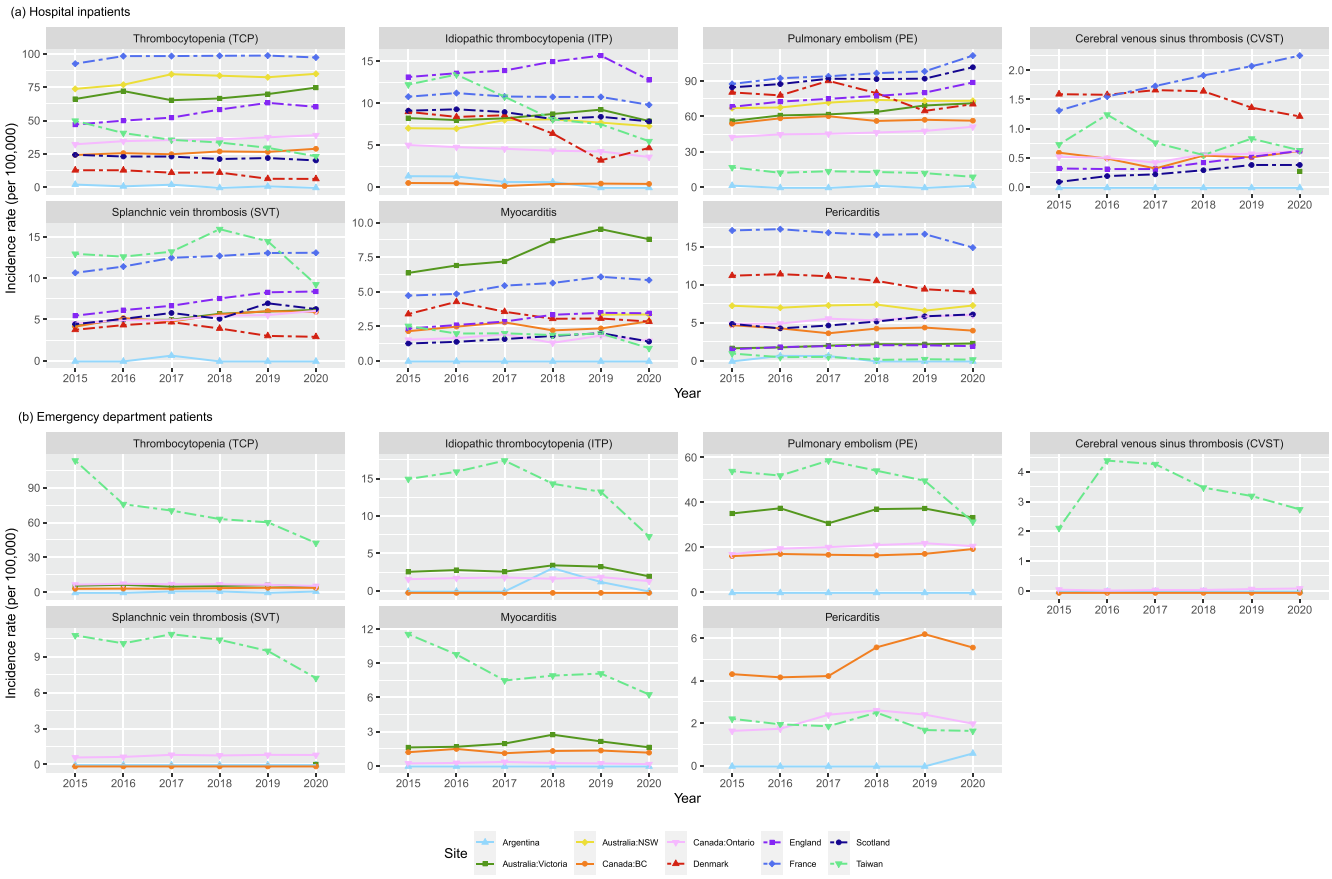

Fig. 2. Incidence rate (IR) per 100,000 person-years of hematological and cardiac conditions over time (2015–20), by site. (a) Inpatients. (b) Emergency department patients.

Disclaimer

All analyses, inferences drawn, opinions, conclusions, and statements are those of the authors and do not necessarily represent the official views of, nor an endorsement by, CDC/HHS, or the U.S. Government. For more information, please visit cdc.gov.

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Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.08.079.

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