Contextualising adverse events of special interest to characterise the baseline incidence rates in 24 million patients with COVID-19 across 26 databases: a multinational retrospective cohort study

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Adverse Events of Special Interest (AESI)

- Acute myocardial infarction (MI)
- Anaphylaxis
- Appendicitis
- Bell's palsy
- Deep vein thrombosis (DVT)
- Encephalomyelitis
- Guillain-Barre syndrome (GBS)
- Hemorrhagic stroke

- Non-hemorrhagic stroke
- Immune thrombocytopenia
- Myocarditis/pericarditis
- Narcolepsy
- Pulmonary embolism (PE)
- Transverse myelitis
- Disseminated intravascular coagulation

The FDA Center for Biologics Evaluation and Research prioritized a list of outcomes

- Center for Biologics Evaluation and Research Office of Biostatistics and Epidemiology. CBER Surveillance Program Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring Protocol. https://www.bestinitiative.org/wp-content/ uploads/2021/02/C19-Vaccine-Safety-AESI-Background-RateProtocol-FINAL-2020.pdf (accessed 11 Mar 2021)

- bc-coordinator. Priority list of adverse events of special interest: COVID-19. 2020. https://brightoncollaboration.us/priority-list-aesicovid/ (accessed 11 Mar 2021).

Background

RESEARCH: SPECIAL PAPER

Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study

Xintong Li,[1] Anna Ostropolets,[2] Rupa Makadia,[3] Azza Shoaibi,[3] Gowtham Rao,[3] Anthony G Sena,[3,6] Eugenia Martinez-Hernandez,[4] Antonella Delmestri,[1] Katia Verhamme,[6,7] Peter R Rijnbeek,[6] Talita Duarte-Salles,[5] Marc A Suchard,[8,9] Patrick B Ryan,[2,3] George Hripcsak,[2] Daniel Prieto-Alhambra[1,6]

https://github.com/ohdsi-studies/Covid19VaccineAesiIncidenceCharacterization

The Study

- **Objective:** Quantify the occurrence of AESIs in subjects with COVID-19 overall and across specific age and sex groups.

- It is relevant to know how often these AESIs occur amongst patients who suffer the condition vaccines aim to prevent to assess the benefit risk profile of the vaccine.

- Protocol: https://ohdsi-studies.github.io/Covid19SubjectsAesiIncidenceRate/Protocol.html
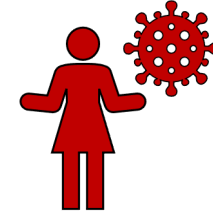
Design

- Retrospective cohort study

- Target Cohorts:
  - pre-pandemic background population (2017-2019)
  - First COVID-19 Event (positive test OR diagnosis)

- Outcome Cohorts:
  - AESIs

- Population Subgroups: age and sex

- Time at Risk: 90-days

- Outputs: Counts, Incidence Rates and Incidence Proportions of Outcomes

2017-2019

2017-2019

TARGET COHORT

Cohort #566 *(Read only)*

created by ryan@ohdsi.org on 2021-11-16 14:43

[COVID AESI] persons at risk at start of year 2017-2019 with 365d prior observation

| Definition | Concept Sets | Generation | Samples | Reporting | Export | Versions | Messages 3 |

Initial Event Cohort

People having any of the following:

- an observation period
  - using specified period: starting on 2017-01-01 and ending on 2017-01-01
    Note: only observation periods that encompass the start and end dates will be used.
- an observation period
  - using specified period: starting on 2018-01-01 and ending on 2018-01-01
    Note: only observation periods that encompass the start and end dates will be used.
- an observation period
  - using specified period: starting on 2019-01-01 and ending on 2019-01-01
    Note: only observation periods that encompass the start and end dates will be used.

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

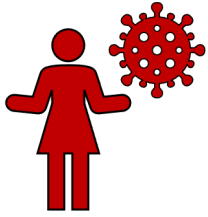Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort definition end date will be the index event's start date plus 0 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days

[COVID AESI] Persons with earliest COVID event based on positive test or diagnosis without neg test

Definition	Concept Sets	Generation	Samples	Reporting	Export	Versions	Messages 6

Initial Event Cohort

People having any of the following:

- a measurement of SARS-CoV-2 test[2]
  - occurrence start is: after 2019-12-01
  - value as concept is any of: Detected, Detected, Positive, Positive, Present, Present
- a condition occurrence of COVID-19[1]
  - occurrence start is: after 2019-12-01
  - Having any of the following criteria:
    - exactly 0 occurrences of: a measurement of SARS-CoV-2 test[2]
      - value as concept is any of: Negative, Not detected, Not detected in pooled specimen, Absent, Negative, Not detected, Absent
      where event starts between 0 days Before and 3 days After index start date

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **earliest event per person.**

Inclusion Rules

Inclusion Criteria #(1): Continuous Observation of at least 365d
Having all of the following criteria:

- at least 1 occurrences of: an observation period
  where event starts between All days Before and 365 days Before index start date and event ends between 0 days After and All days After index start date

Inclusion Criteria #(2): No COVID-19/SARS-CoV-2 Tests Prior to Index
Having all of the following criteria:

- exactly 0 occurrences of: a measurement of SARS-CoV-2 test[2]
  - value as concept is any of: Detected, Detected, Positive, Positive, Present, Present
  where event starts between All days Before and 1 days Before index start date
- and exactly 0 occurrences of: a condition occurrence of COVID-19[1]
  Having any of the following criteria:
    - exactly 0 occurrences of: a measurement of SARS-CoV-2 test[2]
      - value as concept is any of: Negative, Not detected, Not detected in pooled specimen, Absent, Negative, Not detected, Absent
      where event starts between All days Before and 3 days After index start date
  where event starts between All days Before and 1 days Before index start date

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort definition end date will be the index event's start date plus 3 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days

TARGET COHORT

Outcomes (AESIs)

- Acute myocardial infarction (MI)
- Anaphylaxis
- Appendicitis
- Bell's palsy
- Deep vein thrombosis (DVT)
- Encephalomyelitis
- Guillain-Barre syndrome (GBS)
- Hemorrhagic stroke
- Non-hemorrhagic stroke

- Immune thrombocytopenia
- Myocarditis/pericarditis
- Narcolepsy
- Pulmonary embolism (PE)
- Transverse myelitis
- Disseminated intravascular coagulation
- Thrombosis with Thrombocytopenia (TWT)**

Methods: Data Sources

- Data were obtained from 26 databases

- These databases represent 11 countries:

  - Belgium
  - Estonia
  - France
  - Germany

  - Japan
  - The Netherlands
  - Serbia
  - Spain

  - Turkey
  - United Kingdom (UK)
  - United States of America (US)

Methods: Data Sources

- **Administrative Claims:**
IBM® MarketScan® Commercial Claims and Encounters Database (IBM_CCAE); IBM® MarketScan® Multi-State Medicaid Database (IBM_MDCD); IBM® MarketScan® Medicare Supplemental and Coordination of Benefits Database (IBM_MDCR); IQVIA LRxDX Open Claims (IQVIA_OPENCLAIMS); IQVIA Pharmetrics (IQVIA_PHARMETRICS); JMDC; Optum De-Identified Clinformatics® Data Mart Database - Socio-Economic Status (SES) (OPTUM_SES); and University of Tartu (U_OF_TARTU).
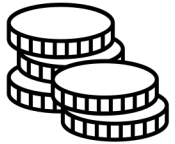
- **General Practitioner:**
Clinical Practice Research Datalink AURUM (CPRD_AURUM); Integrated Primary Care Information (IPCI); IQVIA® Disease Analyzer France (IQVIA_FRANCE_DA); IQVIA® Disease Analyzer Germany (IQVIA_GERMAN_DA); and The Information System for Research on Primary Care (SIDIAP).

- **Electronic Health Records:**
Health Data Warehouse of Assistance Publique - Hopitaux de Marseille (APHM); University of Colorado Anschutz Medical Campus- Health Data Compass (CU_AMC); Columbia University Irving Medical Center (CUIMC); Fundación para la Investigación e Innovación Biosanitaria en Atención Primaria COVID19 (FIIBAP); Health Informatics Centre (HIC); Parc de Salut Mar Barcelona Information System (IMASIS); Istanbul Faculty of Medicine, Istanbul University (IU); Medaman Hospital Data (MHD); Optum® de-identified Electronic Health Record Dataset (OPTUM_EHR); STAnford medicine Research data Repository (STARR); University Clinical Center of Serbia (UCCS); and University of California Health Data Warehouse (UCHEALTHDW).

Electronic Health Records with Registry:
UK Biobank (UK_BIOBANK).

Name	Country	Data Provenance	Dates Covered YYYY/MM	Total Persons	% F	Ages Covered Mean Age (IQR)	Subjects with COVID-19 #	Pre-Pandemic Background Population #	Measure-ments With Values
APHM	FR	EHR	1998/11-2021/07	2,465,265	51.9	40 (21-60)	11,431	673,031	N
CPRD_AURUM	UK	GP	1995/01-2021/03	39,879,547	51.8	31 (18-44)	587,886	14,094,032	Y
CU_AMC	US	EHR	2011/01-2022/04	4,795,392	54.0	39 (22-56)	72,648	830,579	Y
CUIMC	US	EHR	1985/03-2021/08	6,808,470	55.8	38 (21-56)	28,044	1,197,983	Y
FIIBAP*	ES	EHR	2001/03-2021/10	292,305	54.7	41 (23-58)	7,138	78	N
HIC	SC	EHR	2005/01-2021/12	1,254,464	50.4	45 (28-66)	11,813	885,236	Y
IBM_CCAE	US	Claims	2000/01-2021/07	159,440,276	51.1	31 (17-46)	983,089	23,483,191	N
IBM_MDCD	US	Claims	2006/01-2020/12	32,806,887	56.2	24 (5-38)	196,997	11,810,505	N
IBM_MDCR	US	Claims	2000/01-2021/07	10,356,249	55.3	72 (65-77)	41,542	1,467,963	N
IMASIS	ES	EHR	1990/02-2021/07	976,524	47.4	38 (23-54)	9,330	198,012	Y
IPCI	NL	GP	2006/01-2021/06	2,529,355	51.2	37 (18-55)	91,759	1,329,674	N
IQVIA_FRANCE_DA	FR	GP	2016/07-2021/06	3,767,012	52.3	38 (18-56)	2,859	1,394,912	N
IQVIA_GERMANY_DA	DE	GP	2011/04-2021/03	30,780,239	55.7	44 (25-62)	45,508	9,040,531	N
IQVIA_OPENCLAIMS	US	Claims	2000/01-2021/10	306,000,000	52.6	34 (14-52)	17,848,443	306,000,000	N
IQVIA_PHARMETRICS	US	Claims	2013/01-2021/09	166,422,594	50.6	38 (19-50)	1,593,578	46,947,246	N
IU	TR	EHR	2018/01-2021/10	899,515	53.0	35 (18-52)	6,194	619	Y
JMDC	JP	Claims	2005/01-2021/03	12,541,088	48.6	32 (19-46)	17,564	6,680,196	N
MHD	BE	EHR	2015/07-2021/12	117,131	50.9	52 (29-70)	203	23,754	N
OPTUM_EHR	US	EHR	2007/01-2021/03	99,454,715	53.3	37 (19-56)	693,334	41,281,147	Y
OPTUM_SES	US	Claims	2000/05-2021/06	90,285,937	50.5	36 (19-52)	899,986	17,212,611	Y
SIDIAP	ES	GP	2003/01-2021/06	8,022,374	50.1	35 (17-51)	495,237	5,934,449	Y
STARR	US	EHR	2008/01-2022/04	3,475,673	53.6	36 (18-54)	31,928	1,118,549	Y
U_OF_TARTU†	EE	Claims	2021/01-2021/02	386,557	53.2	39 (21-57)	84,957	376,842	N
UCCS	RS	EHR	2018/10-2021/03	823,962	54.1	51 (35-67)	16,764	49,643	N
UCHDW*	US	EHR	2012/01-2022/05	316,119	53.8	37 (12-54)	61,037	240,831	Y
UK_BIOBANK	UK	EHR + Registry	1970/02-2020/07	502,504	54.4	34 (25-43)	1,717	458,889	Y
Total	-	-	-	945,520,607	-	-	*23,840,986*	*492,730,503*	-

* COVID only subset, † COVID + Controls

Pooled Estimated Age and Sex Stratified Incidence Rates Per 100,000 person years (with 95% prediction intervals), calculated from meta-analyses
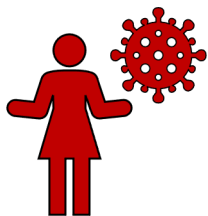
2017-2019

CIOMS Frequency Classification

Very Rare (<1/10000)	
Rare (>=10000 to <1/1000)	
Uncommon (>= 1/1000 to <1/100)	
Common (>= 1/100 to <1/10)	
Very Common (>=1 /10)	

Outcome by Sex	0-5 Years	6-17 Years	18-34 Years	35-54 Years	55-64 Years	65-74 Years	75-84 Years	>=85 Years
Acute Myocardial Infarction (AMI)								
Female	6 (0 to 250)	3 (0 to 40)	11 (3 to 41)	53 (14 to 211)	151 (41 to 550)	237 (94 to 600)	532 (241 to 1172)	996 (241 to 4111)
Male	6 (0 to 219)	3 (0 to 19)	18 (6 to 52)	152 (54 to 432)	400 (166 to 965)	539 (242 to 1202)	789 (354 to 1758)	1306 (292 to 5847)
Non-hemorrhagic Stroke								
Female	12 (2 to 87)	6 (2 to 21)	19 (6 to 61)	67 (16 to 278)	152 (36 to 643)	274 (95 to 792)	647 (285 to 1472)	1412 (322 to 6185)
Male	12 (3 to 48)	8 (2 to 28)	17 (5 to 59)	93 (29 to 301)	252 (83 to 769)	417 (173 to 1008)	774 (334 to 1791)	1246 (243 to 6382)
Deep Vein Thrombosis (DVT)								
Female	10 (2 to 58)	8 (3 to 25)	52 (19 to 141)	91 (33 to 251)	146 (55 to 393)	224 (90 to 560)	387 (169 to 888)	378 (82 to 1753)
Male	11 (2 to 57)	10 (3 to 30)	48 (17 to 134)	107 (40 to 289)	251 (105 to 602)	302 (124 to 735)	437 (188 to 1019)	408 (81 to 2046)
Pulmonary Embolism (PE)								
Female	5 (0 to 111)	3 (1 to 11)	43 (16 to 114)	90 (32 to 253)	155 (59 to 407)	238 (120 to 475)	430 (227 to 815)	492 (161 to 1496)
Male	5 (0 to 118)	3 (1 to 13)	29 (10 to 85)	98 (37 to 256)	199 (90 to 439)	280 (143 to 549)	409 (205 to 819)	419 (124 to 1424)
Hemorrhagic Stroke								
Female	17 (2 to 118)	7 (2 to 23)	15 (4 to 55)	32 (10 to 103)	64 (22 to 184)	88 (33 to 232)	196 (84 to 457)	363 (84 to 1564)
Male	14 (3 to 65)	10 (3 to 37)	21 (6 to 66)	44 (15 to 124)	94 (35 to 253)	128 (55 to 298)	272 (121 to 612)	403 (85 to 1901)
Bell's Palsy								
Female	19 (7 to 53)	23 (11 to 47)	44 (20 to 96)	62 (25 to 158)	79 (32 to 198)	82 (30 to 224)	100 (33 to 301)	97 (29 to 321)
Male	18 (6 to 54)	20 (10 to 42)	42 (19 to 92)	64 (26 to 157)	84 (34 to 209)	93 (35 to 244)	100 (33 to 302)	106 (31 to 365)
Appendicitis								
Female	33 (13 to 82)	161 (71 to 363)	140 (69 to 286)	89 (44 to 178)	76 (38 to 153)	55 (26 to 116)	46 (20 to 105)	40 (10 to 171)
Male	37 (18 to 77)	211 (119 to 371)	152 (80 to 287)	92 (48 to 177)	70 (35 to 140)	59 (28 to 121)	49 (23 to 105)	47 (12 to 189)
Myocarditis Pericarditis								
Female	9 (1 to 68)	9 (2 to 38)	20 (6 to 66)	29 (10 to 85)	39 (14 to 108)	41 (15 to 112)	49 (18 to 133)	43 (6 to 295)
Male	9 (1 to 66)	11 (4 to 36)	40 (14 to 112)	44 (15 to 132)	53 (18 to 155)	57 (21 to 154)	64 (20 to 205)	51 (8 to 338)
Thrombosis with Thrombocytopenia (TWT)								
Female	7 (0 to 779)	3 (0 to 170)	7 (1 to 91)	12 (1 to 146)	26 (2 to 281)	37 (3 to 410)	80 (8 to 810)	174 (43 to 701)
Male	6 (0 to 328)	3 (0 to 140)	7 (0 to 148)	23 (1 to 422)	54 (4 to 737)	81 (6 to 1069)	146 (14 to 1568)	320 (88 to 1155)
Immune Thrombocytopenia (ITP)								
Female	18 (6 to 52)	12 (5 to 30)	23 (7 to 73)	23 (8 to 71)	30 (11 to 87)	36 (13 to 101)	50 (18 to 141)	45 (11 to 185)
Male	20 (8 to 52)	11 (4 to 31)	11 (3 to 37)	17 (5 to 56)	29 (10 to 89)	45 (15 to 137)	76 (26 to 218)	85 (22 to 334)
Anaphylaxis								
Female	85 (7 to 1002)	66 (3 to 1556)	47 (11 to 195)	41 (11 to 146)	38 (9 to 154)	30 (9 to 95)	25 (8 to 78)	15 (2 to 99)
Male	124 (9 to 1628)	72 (2 to 3305)	31 (7 to 134)	26 (6 to 106)	28 (5 to 168)	25 (6 to 107)	17 (6 to 44)	12 (4 to 35)
Narcolepsy								
Female	5 (0 to 386)	8 (3 to 27)	28 (8 to 95)	23 (7 to 80)	19 (6 to 60)	15 (5 to 44)	16 (5 to 49)	15 (3 to 81)
Male	5 (0 to 179)	8 (2 to 26)	20 (6 to 61)	19 (6 to 61)	18 (6 to 56)	15 (5 to 45)	18 (6 to 55)	21 (5 to 94)
Disseminated Intravascular Coagulation (DIC)								
Female	9 (0 to 397)	4 (0 to 82)	8 (0 to 141)	9 (1 to 102)	13 (2 to 94)	14 (3 to 77)	19 (5 to 72)	25 (4 to 156)
Male	9 (0 to 369)	5 (0 to 109)	5 (0 to 51)	11 (1 to 106)	19 (2 to 161)	21 (3 to 165)	28 (7 to 117)	34 (8 to 145)
Encephalomyelitis								
Female	10 (2 to 68)	9 (2 to 54)	7 (1 to 37)	8 (1 to 45)	13 (3 to 64)	14 (4 to 48)	16 (4 to 59)	25 (4 to 179)
Male	9 (2 to 57)	10 (2 to 57)	8 (2 to 39)	8 (2 to 37)	15 (3 to 66)	15 (4 to 53)	22 (5 to 95)	29 (6 to 151)
Guillain-Barré Syndrome (GBS)								
Female	7 (0 to 507)	3 (0 to 43)	4 (1 to 16)	4 (1 to 15)	6 (2 to 24)	7 (2 to 28)	9 (3 to 32)	16 (2 to 137)
Male	8 (0 to 275)	3 (0 to 20)	3 (1 to 11)	5 (2 to 16)	9 (3 to 26)	10 (4 to 28)	16 (5 to 53)	19 (5 to 65)
Transverse Myelitis								
Female	4 (0 to 290)	2 (0 to 20)	5 (1 to 16)	7 (2 to 24)	7 (3 to 20)	7 (3 to 20)	5 (2 to 15)	7 (0 to 198)
Male	4 (0 to 283)	2 (0 to 18)	3 (1 to 8)	4 (1 to 15)	6 (2 to 20)	5 (2 to 13)	6 (1 to 22)	7 (1 to 35)

CIOMS: Council of International Organizations of Medical Sciences

Pooled Estimated Age and Sex Stratified Incidence Rates Per 100,000 person years (with 95% prediction intervals), calculated from meta-analyses

CIOMS Frequency Classification

Classification
Very Rare (<1/10000)
Rare (>=10000 to <1/1000)
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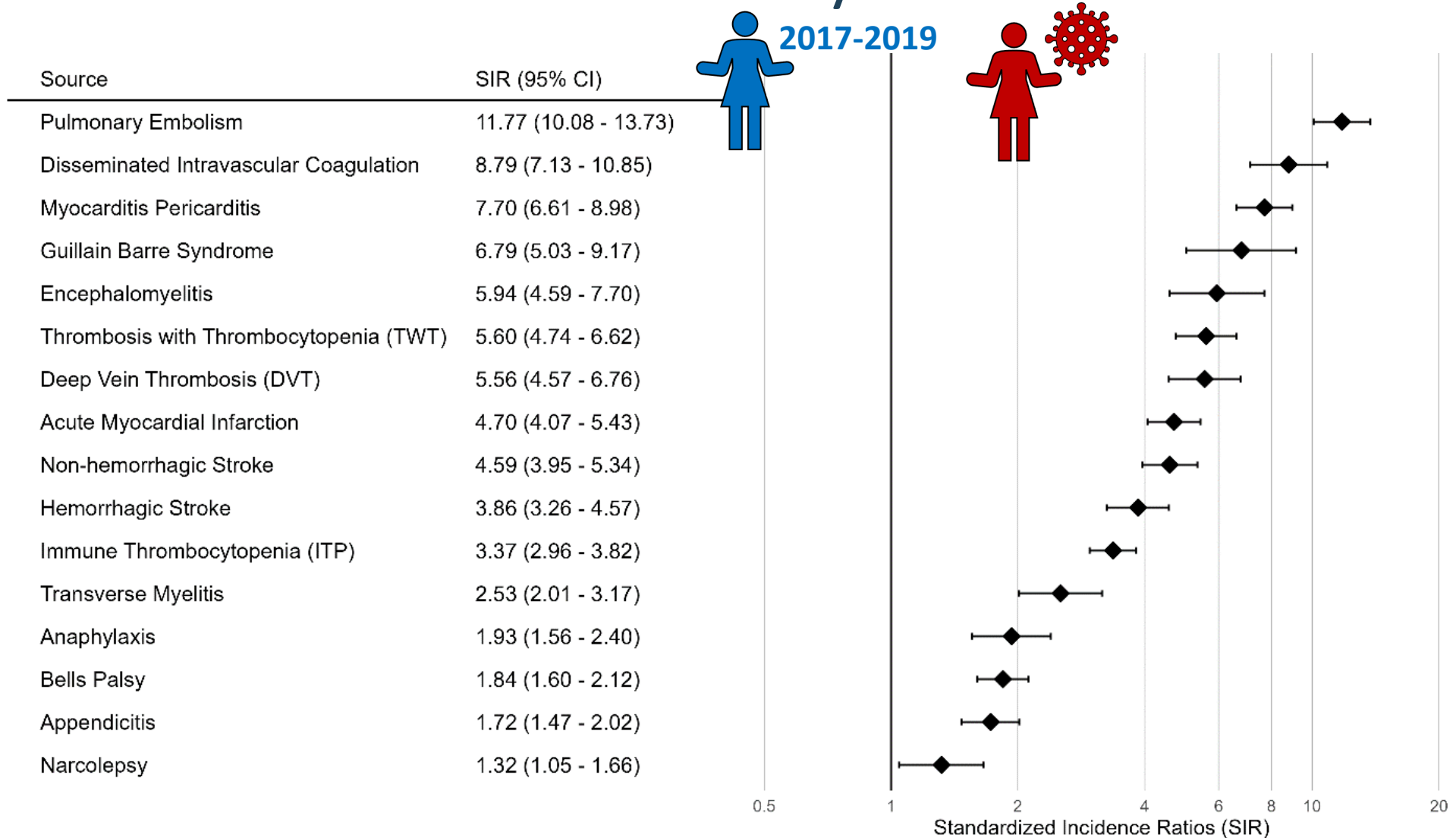| Outcome by Sex	0-5 Years	6-17 Years	18-34 Years	35-54 Years	55-64 Years	65-74 Years	75-84 Years	>=85 Years
Acute Myocardial Infarction								
Female	527 (2 to 116345)	151 (5 to 4281)	84 (28 to 253)	335 (123 to 910)	940 (374 to 2365)	2047 (1044 to 4014)	3940 (1969 to 7882)	4960 (2090 to 11772)
Male	469 (2 to 121380)	139 (4 to 5421)	167 (44 to 639)	827 (333 to 2053)	1991 (954 to 4153)	3526 (1945 to 6391)	5721 (2717 to 12046)	8198 (2782 to 24155)
Non-hemorrhagic Stroke								
Female	552 (3 to 95794)	153 (6 to 3663)	96 (21 to 441)	356 (105 to 1209)	839 (223 to 3156)	1790 (829 to 3866)	3723 (1677 to 8265)	4928 (1974 to 12303)
Male	547 (4 to 79312)	162 (8 to 3148)	121 (16 to 924)	575 (155 to 2135)	1422 (476 to 4249)	2965 (1532 to 5739)	5009 (2421 to 10361)	6524 (2225 to 19132)
Deep Vein Thrombosis (DVT)								
Female	478 (5 to 44031)	245 (25 to 2399)	287 (97 to 847)	817 (337 to 1979)	1638 (743 to 3610)	2839 (1549 to 5203)	3908 (1968 to 7763)	3781 (1467 to 9750)
Male	425 (8 to 23054)	217 (24 to 1935)	346 (81 to 1468)	1364 (490 to 3794)	2993 (1479 to 6057)	3994 (2213 to 7211)	4538 (2113 to 9750)	4504 (1789 to 11342)
Pulmonary Embolism								
Female	504 (5 to 53649)	168 (17 to 1697)	409 (124 to 1346)	1119 (493 to 2539)	2025 (1021 to 4014)	3650 (2533 to 5259)	4782 (3044 to 7515)	4718 (2353 to 9460)
Male	444 (3 to 67053)	170 (13 to 2194)	521 (109 to 2491)	1686 (652 to 4358)	3438 (2014 to 5868)	5230 (3953 to 6920)	6504 (4119 to 10269)	6480 (3914 to 10726)
Hemorrhagic Stroke								
Female	574 (3 to 101501)	145 (5 to 4607)	60 (14 to 248)	155 (41 to 590)	328 (123 to 874)	592 (295 to 1186)	935 (401 to 2178)	1175 (556 to 2482)
Male	568 (4 to 72465)	150 (7 to 3149)	109 (25 to 484)	263 (75 to 925)	550 (193 to 1567)	781 (371 to 1644)	1452 (738 to 2855)	1948 (487 to 7798)
Bell's Palsy								
Female	539 (8 to 34829)	189 (17 to 2091)	91 (59 to 143)	153 (77 to 304)	212 (98 to 457)	300 (71 to 1261)	383 (82 to 1787)	403 (65 to 2519)
Male	464 (5 to 46723)	166 (18 to 1513)	91 (35 to 236)	182 (86 to 384)	240 (87 to 666)	310 (98 to 978)	378 (73 to 1958)	648 (68 to 6176)
Appendicitis								
Female	580 (27 to 12353)	355 (175 to 719)	260 (145 to 467)	181 (100 to 326)	159 (71 to 356)	200 (57 to 700)	269 (49 to 1487)	334 (30 to 3778)
Male	561 (29 to 10808)	432 (195 to 961)	345 (153 to 780)	210 (123 to 359)	159 (86 to 292)	201 (69 to 588)	292 (47 to 1834)	450 (31 to 6580)
Myocarditis Pericarditis								
Female	650 (19 to 22601)	268 (74 to 965)	329 (76 to 1418)	290 (122 to 688)	344 (131 to 904)	383 (142 to 1037)	404 (132 to 1242)	425 (88 to 2052)
Male	529 (24 to 11794)	362 (106 to 1237)	469 (164 to 1340)	330 (147 to 742)	374 (167 to 840)	498 (208 to 1191)	709 (207 to 2423)	798 (131 to 4842)
Thrombosis with Thrombocytopenia (TWT)								
Female	457 (3 to 62013)	146 (1 to 17082)	57 (6 to 546)	116 (17 to 794)	312 (47 to 2069)	582 (84 to 4015)	964 (74 to 12496)	1476 (94 to 23167)
Male	430 (2 to 74298)	137 (1 to 21627)	89 (10 to 803)	280 (35 to 2221)	600 (80 to 4488)	1143 (135 to 9644)	1741 (146 to 20754)	2096 (173 to 25442)
Immune Thrombocytopenia (ITP)								
Female	506 (5 to 55485)	161 (4 to 6440)	67 (24 to 188)	110 (36 to 340)	189 (62 to 580)	286 (87 to 947)	452 (99 to 2058)	409 (71 to 2366)
Male	480 (4 to 59121)	150 (3 to 6553)	52 (17 to 160)	127 (45 to 361)	204 (90 to 464)	361 (122 to 1065)	517 (125 to 2145)	754 (136 to 4193)
Anaphylaxis								
Female	546 (34 to 8722)	224 (38 to 1298)	120 (57 to 252)	135 (46 to 393)	134 (39 to 457)	165 (31 to 886)	209 (15 to 2851)	299 (10 to 9177)
Male	670 (105 to 4273)	222 (40 to 1228)	90 (29 to 281)	100 (21 to 487)	101 (17 to 588)	144 (18 to 1139)	272 (7 to 10999)	430 (6 to 31495)
Narcolepsy								
Female	508 (4 to 66259)	182 (2 to 18808)	69 (29 to 163)	73 (27 to 194)	98 (15 to 621)	186 (18 to 1892)	213 (14 to 3336)	337 (7 to 16043)
Male	459 (3 to 81397)	169 (1 to 20837)	59 (16 to 220)	73 (17 to 308)	103 (15 to 710)	167 (12 to 2232)	302 (11 to 8349)	495 (10 to 25617)
Disseminated Intravascular Coagulation								
Female	509 (4 to 65261)	148 (4 to 5549)	48 (10 to 229)	91 (9 to 920)	163 (32 to 820)	302 (41 to 2226)	326 (71 to 1500)	397 (33 to 4751)
Male	452 (4 to 55867)	127 (3 to 5681)	67 (7 to 679)	164 (11 to 2349)	294 (33 to 2653)	487 (68 to 3504)	613 (82 to 4595)	536 (93 to 3076)
Encephalomyelitis								
Female	575 (4 to 93365)	145 (3 to 6015)	49 (7 to 348)	76 (12 to 503)	91 (24 to 347)	148 (31 to 713)	257 (40 to 1673)	344 (24 to 4934)
Male	495 (3 to 84065)	146 (8 to 2571)	56 (13 to 253)	85 (18 to 408)	134 (34 to 520)	180 (56 to 583)	379 (55 to 2614)	563 (43 to 7329)
Guillain Barre Syndrome								
Female	508 (2 to 133569)	131 (1 to 20989)	34 (9 to 130)	52 (9 to 292)	88 (19 to 403)	150 (22 to 1018)	181 (13 to 2611)	295 (7 to 12936)
Male	441 (2 to 96492)	126 (1 to 25674)	51 (3 to 826)	73 (11 to 473)	106 (38 to 301)	162 (44 to 591)	295 (39 to 2229)	478 (14 to 16304)
Transverse Myelitis								
Female	456 (2 to 87635)	117 (1 to 21552)	30 (4 to 206)	35 (6 to 190)	47 (10 to 231)	96 (7 to 1379)	121 (3 to 4442)	168 (2 to 12892)
Male	406 (2 to 66668)	112 (1 to 22746)	40 (1 to 1354)	41 (4 to 414)	52 (7 to 388)	89 (5 to 1743)	172 (3 to 11116)	283 (6 to 12779)

CIOMS: Council of International Organizations of Medical Sciences

Standardized Incidence Ratios Forest Plot with Meta Analysis of AESIs

2017-2019

Source	SIR (95% CI)
Pulmonary Embolism	11.77 (10.08 - 13.73)
Disseminated Intravascular Coagulation	8.79 (7.13 - 10.85)
Myocarditis Pericarditis	7.70 (6.61 - 8.98)
Guillain Barre Syndrome	6.79 (5.03 - 9.17)
Encephalomyelitis	5.94 (4.59 - 7.70)
Thrombosis with Thrombocytopenia (TWT)	5.60 (4.74 - 6.62)
Deep Vein Thrombosis (DVT)	5.56 (4.57 - 6.76)
Acute Myocardial Infarction	4.70 (4.07 - 5.43)
Non-hemorrhagic Stroke	4.59 (3.95 - 5.34)
Hemorrhagic Stroke	3.86 (3.26 - 4.57)
Immune Thrombocytopenia (ITP)	3.37 (2.96 - 3.82)
Transverse Myelitis	2.53 (2.01 - 3.17)
Anaphylaxis	1.93 (1.56 - 2.40)
Bells Palsy	1.84 (1.60 - 2.12)
Appendicitis	1.72 (1.47 - 2.02)
Narcolepsy	1.32 (1.05 - 1.66)

Standardized Incidence Ratios (SIR)

0.5 1 2 4 6 8 10 20

Conclusions

- To our knowledge this is the largest study to date on the descriptive epidemiology of AESIs among the COVID-19 population.

- **Considerable heterogeneity in the IR** among the COVID-19 cohort by geographic areas and databases

- **Considerable variability with age and some with sex groups** emphasizing the need for age and sex stratification when assessing risks and benefits of COVID 19 vaccines

- **Thrombotic events** such as AMI, strokes, DVT, and pulmonary embolism were more frequent compared to other AESIs and **were "uncommon" to "common" in older COVID-19 subjects**.

- In most databases, the **risk of these thrombotic events was higher among COVID-19 subjects when compared to the 'pre-pandemic background population'** of the data sources with a pooled standardized incidence ratio above.

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