Characterizing the incidence of adverse events of special interest for COVID-19 vaccines across eight countries: a multinational network cohort study

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Comment on this paper

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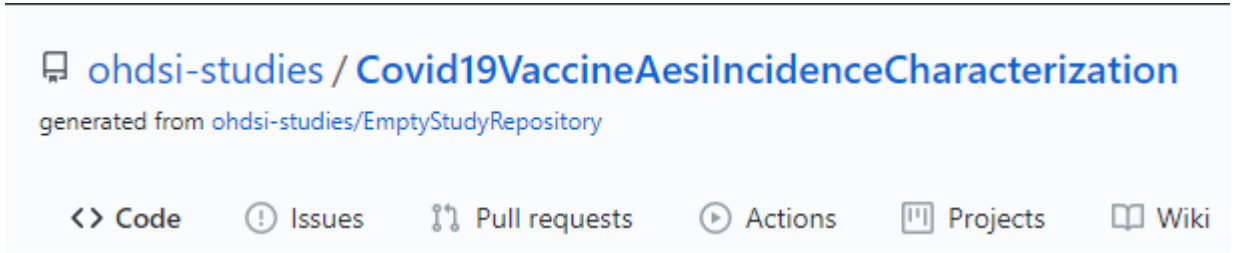
doi: https://doi.org/10.1101/2021.03.25.21254315

https://www.medrxiv.org/content/10.1101/2021.03.25.21254315v2

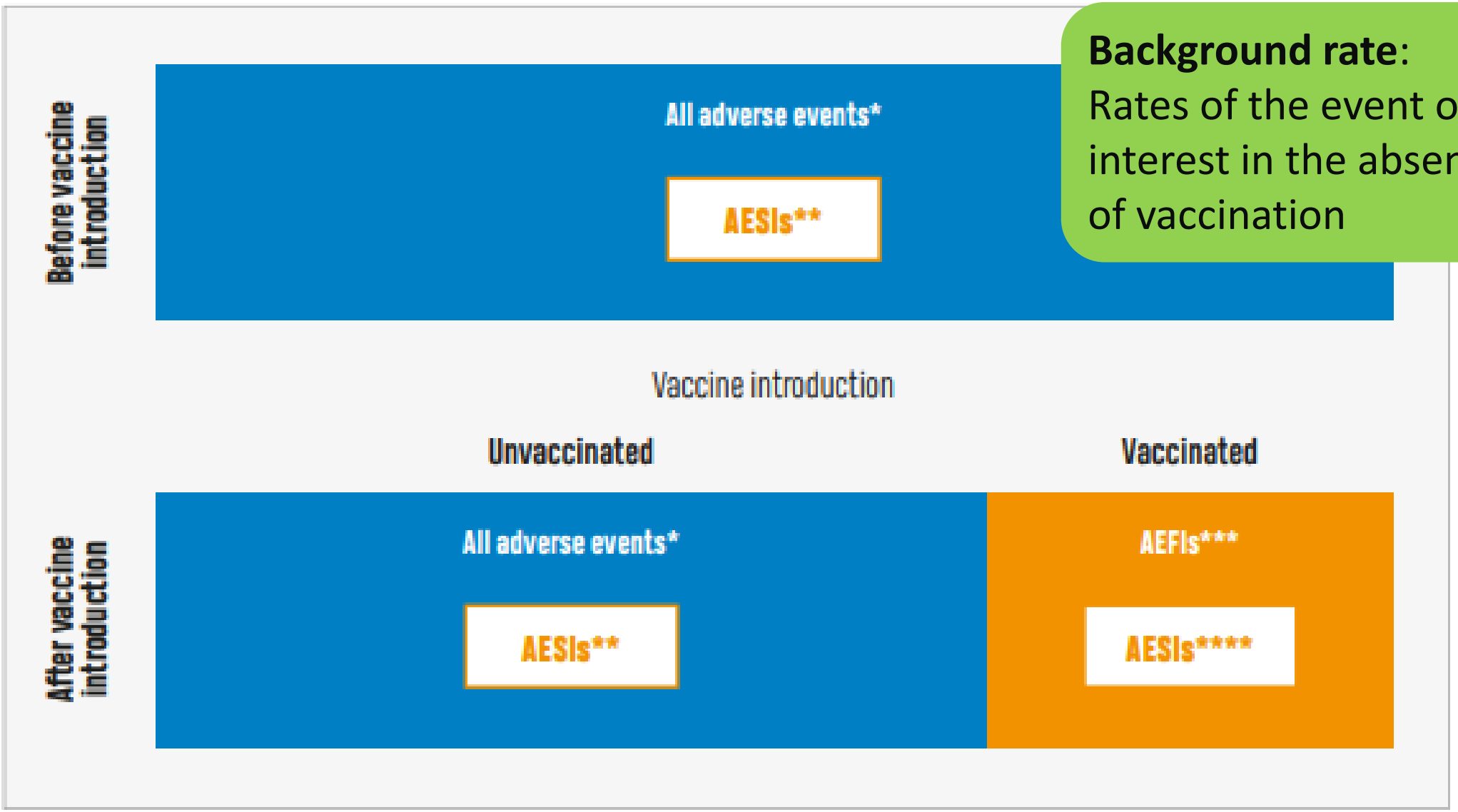


https://github.com/ohdsi-studies/Covid19VaccineAesiIncidenceCharacterization

Introduction

- Large-scale immunization programs against COVID-19 proceed around the world
- Raising news on media about COVID-19 vaccine safety concerns
- Use of **a**dverse **e**vents of **s**pecial **i**nterest (AESI) in vaccine safety surveillance

Fig 1: Schematic representation of the relationship between AESIs and AEFIs.



Background rate: Rates of the event of interest in the absence of vaccination

World Health Organization. Covid-19 vaccines: safety surveillance manual.

Background rates being used in current safety evaluation.

Bell's Palsy

The MHRA continues to review cases reporting Bell's Palsy and to analyse case reports against the number expected to occur by chance in the absence of vaccination (the 'natural rate'). The number of reports of facial paralysis received so far is similar to the expected natural rate and does not currently suggest an increased risk following the vaccines. We will continue to monitor these events, including through evaluation of electronic healthcare record data.

Medicines & Healthcare products Regulatory Agency

Research and analysis

Coronavirus vaccine - weekly summary of Yellow Card reporting

Updated 25 March 2021

https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting#annex-1-vaccine-analysis-print

Methods

- Retrospective cohort study
- 5 claims, 8 EHR databases from 8 countries (4 continents)
- Best estimate of background incidence rates from 2017 to 2019
- Estimates stratified by age, sex, database
- Pooled incidence rates using random effect meta-analysis, with 95% predicted confidence interval.

Outcomes (Events)

- Acute myocardial infarction (MI)
- Anaphylaxis
- Appendicitis
- Bell's palsy
- Deep vein thrombosis (DVT)
- Disseminated intravascular coagulation
- Encephalomyelitis
- Guillain-Barre syndrome (GBS)
- Hemorrhagic stroke
- Non-hemorrhagic stroke
- Immune thrombocytopenia
- Myocarditis/pericarditis
- Narcolepsy
- Pulmonary embolism (PE)
- Transverse myelitis

Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring

Draft Protocol

Food and Drug Administration

Center for Biologics Evaluation and Research (CBER)

Biologics Effectiveness and Safety (BEST) Initiative

Results

126,661,070 people
227,043,370 person-years of follow up (largest ever)

Within-source patient-level heterogeneity:

age and sex patterns

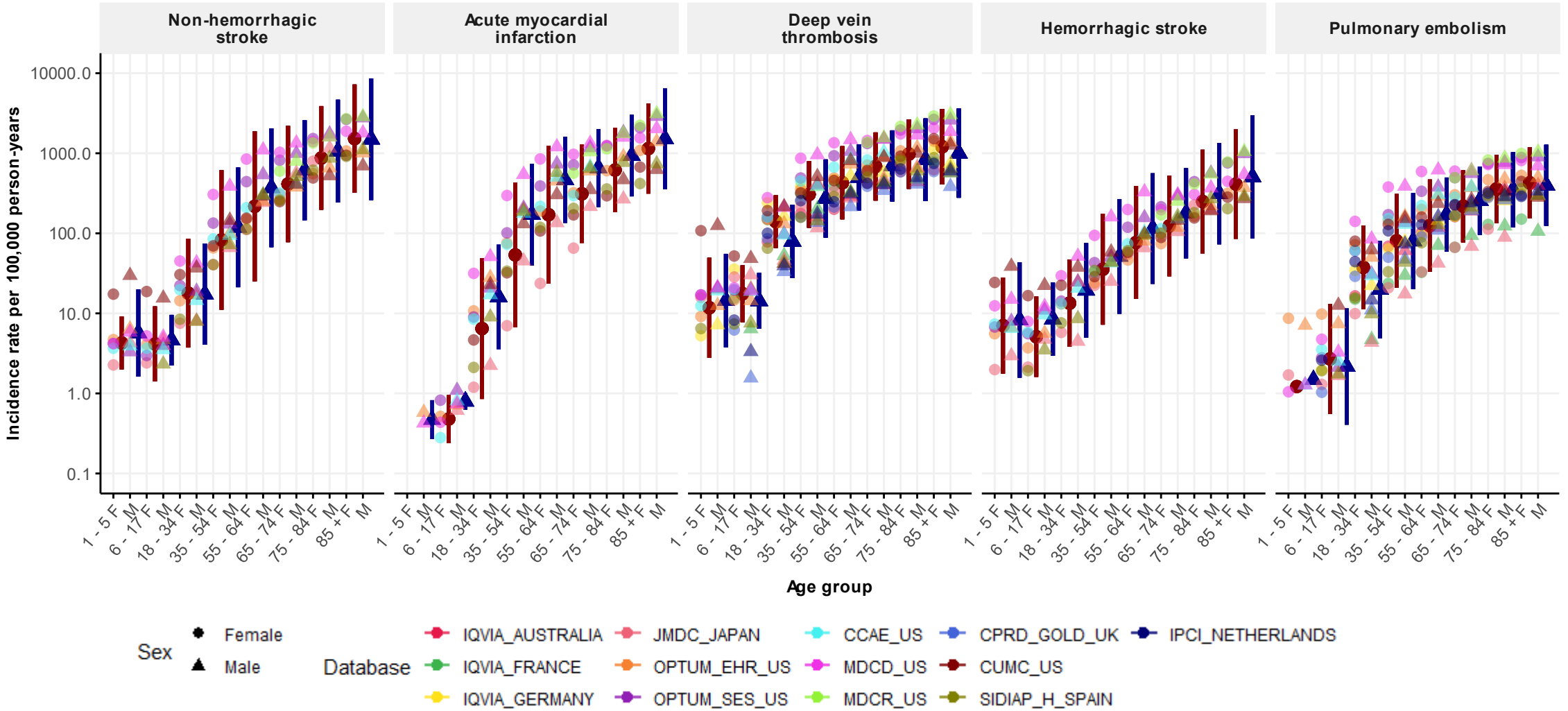
Population-level heterogeneity between databases

CIOMS Frequency classification
Very rare: <1/10,000
Rare: >1/10,000 AND <1/1,000
Uncommon: >1/1,000 AND <1/100
Common: >1/100 AND <1/10
Very common: >1/10

		Incidence rate (per 100,000 person-years) by age group							
Outcome	Sex	1 - 5	6 - 17	18 - 34	35 - 54	55 - 64	65 - 74	75 - 84	85+
Non-hemorrhagic stroke	Female	4 (2-9)	4 (1-12)	18 (4-86)	83 (11-617)	217 (25-1882)	413 (77-2198)	874 (197-3884)	1523 (320-7239)
	Male	6 (2-20)	5 (2-10)	17 (4-75)	119 (21-664)	370 (67-2046)	612 (145-2578)	1063 (242-4662)	1495 (260-8607)
Acute myocardial infarction	Female	<1 (<1-1)	<1 (<1-1)	6 (1-49)	54 (7-430)	171 (24-1235)	312 (76-1280)	617 (184-2069)	1144 (313-4184)
	Male	<1 (<1-1)	1 (1-1)	16 (4-72)	172 (40-740)	467 (135-1611)	653 (214-1994)	934 (290-3013)	1514 (356-6432)
Deep vein thrombosis	Female	12 (3-50)	18 (8-40)	140 (66-298)	306 (117-797)	428 (150-1224)	683 (257-1820)	975 (360-2642)	1206 (407-3572)
	Male	14 (4-55)	14 (6-32)	80 (28-228)	272 (88-836)	499 (194-1289)	695 (250-1931)	831 (254-2720)	1003 (278-3616)
Hemorrhagic stroke	Female	7 (2-28)	5 (2-16)	13 (4-47)	36 (7-175)	77 (15-389)	124 (29-527)	249 (56-1108)	412 (85-1986)
	Male	8 (2-43)	8 (3-24)	19 (5-76)	51 (10-268)	115 (23-562)	178 (49-650)	312 (73-1340)	506 (86-2961)
Pulmonary embolism	Female	1 (<1-36)	3 (1-13)	38 (11-124)	81 (21-309)	125 (33-470)	217 (77-611)	358 (135-951)	427 (154-1184)
	Male	1 (<1-24)	2 (<1-12)	20 (5-80)	80 (20-318)	171 (59-497)	256 (96-683)	349 (119-1030)	398 (124-1277)
Appendicitis	Female	32 (12-84)	154 (55-430)	134 (69-260)	85 (42-172)	66 (28-156)	53 (20-143)	40 (13-124)	35 (12-98)
	Male	38 (17-85)	194 (101-372)	146 (81-266)	88 (49-159)	65 (32-132)	57 (23-144)	47 (15-152)	45 (14-143)
Bells palsy	Female	15 (9-27)	25 (12-51)	44 (23-84)	61 (26-140)	76 (31-184)	86 (29-256)	101 (31-330)	92 (31-274)
	Male	15 (10-24)	21 (13-34)	43 (29-64)	68 (37-125)	86 (43-172)	94 (35-252)	92 (29-291)	100 (34-292)
Anaphylaxis	Female	49 (16-150)	50 (16-154)	39 (16-95)	34 (13-91)	35 (14-85)	29 (11-76)	23 (7-73)	12 (4-36)
	Male	74 (26-209)	56 (18-175)	29 (14-63)	24 (11-53)	25 (11-53)	24 (9-68)	18 (7-49)	10 (2-50)
Immune thrombocytopenia	Female	12 (8-19)	9 (4-21)	14 (6-36)	15 (5-43)	18 (6-53)	25 (8-82)	30 (8-110)	36 (11-118)
	Male	17 (12-23)	8 (3-19)	8 (2-23)	10 (3-35)	19 (6-57)	30 (9-105)	41 (10-170)	56 (15-210)
Myocarditis pericarditis	Female	6 (1-25)	7 (2-21)	16 (8-32)	22 (9-53)	31 (13-72)	35 (12-97)	39 (11-138)	34 (8-143)
	Male	7 (1-32)	11 (5-24)	37 (16-88)	37 (16-87)	45 (20-102)	49 (17-139)	54 (15-193)	41 (9-193)
Disseminated intravascular coagulation	Female	2 (<1-104)	2 (<1-48)	4 (<1-99)	5 (<1-75)	10 (1-89)	14 (2-97)	19 (4-94)	16 (3-82)
	Male	3 (<1-137)	2 (<1-44)	4 (<1-31)	5 (1-56)	12 (1-120)	17 (2-154)	23 (4-152)	24 (5-126)
Encephalomyelitis	Female	5 (2-15)	5 (2-16)	5 (2-19)	6 (1-44)	9 (1-61)	11 (2-62)	12 (2-77)	14 (2-100)
	Male	5 (2-12)	5 (2-14)	5 (2-17)	7 (1-55)	12 (3-58)	16 (3-73)	18 (3-101)	16 (1-180)
Narcolepsy	Female	1 (<1-5)	7 (3-17)	15 (4-52)	11 (2-55)	9 (2-42)	10 (2-46)	8 (1-49)	9 (2-42)
	Male	1 (<1-5)	6 (2-18)	13 (4-40)	10 (2-47)	11 (3-44)	10 (2-50)	10 (2-68)	10 (2-60)
Guillain-Barre syndrome	Female	1 (<1-8)	1 (<1-2)	3 (1-5)	3 (1-11)	5 (1-18)	6 (2-19)	6 (3-16)	7 (2-22)
	Male	2 (<1-18)	1 (<1-3)	2 (1-4)	4 (2-7)	7 (4-14)	8 (3-25)	11 (3-40)	12 (2-68)
Transverse myelitis	Female	1 (<1-3)	1 (<1-3)	3 (1-8)	4 (1-12)	4 (2-13)	4 (2-13)	4 (1-11)	2 (1-9)
	Male	1 (<1-2)	1 (<1-3)	2 (1-6)	3 (1-10)	4 (1-10)	4 (1-11)	4 (1-13)	4 (1-11)

CIOMS: Council of International Organizations of Medical Sciences

Age-sex stratified incidence rates, overall and per database



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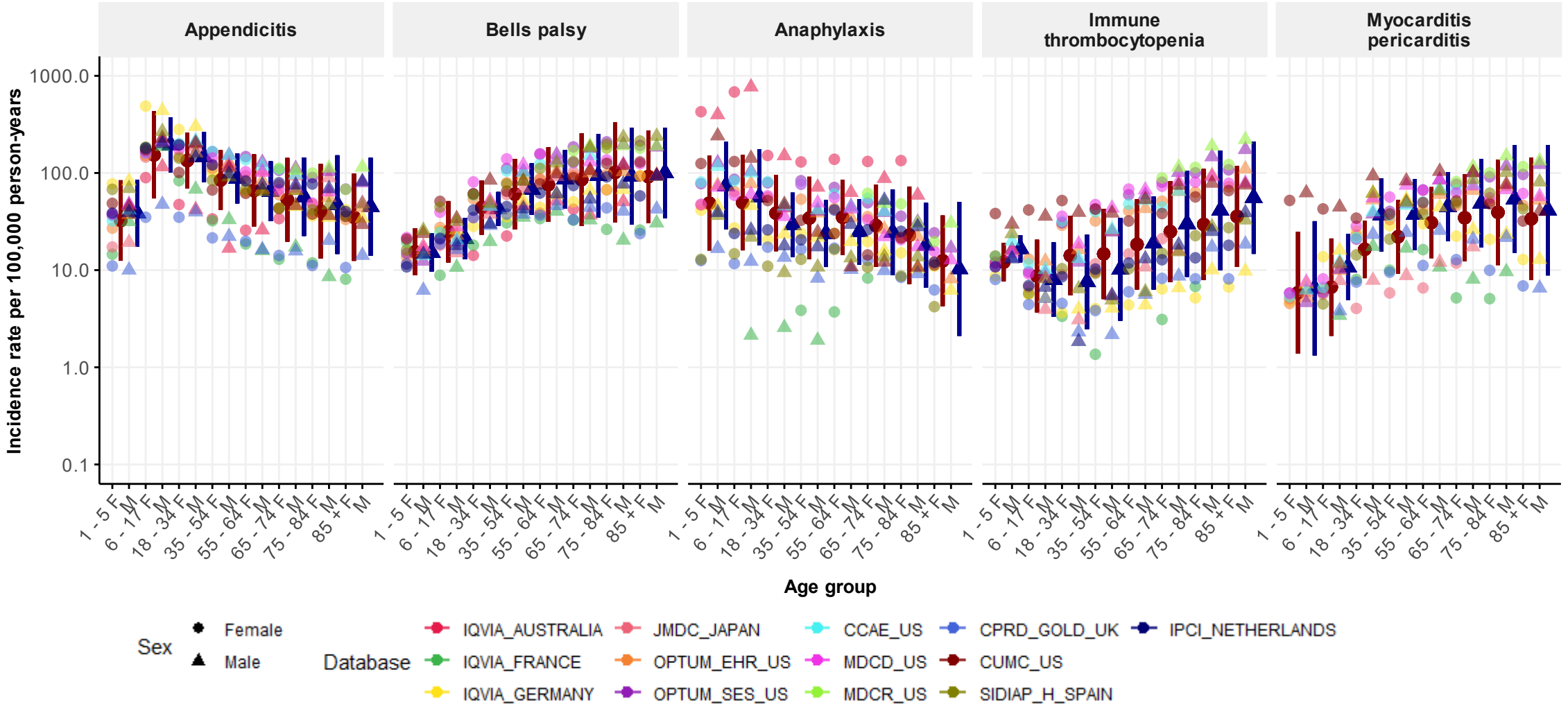
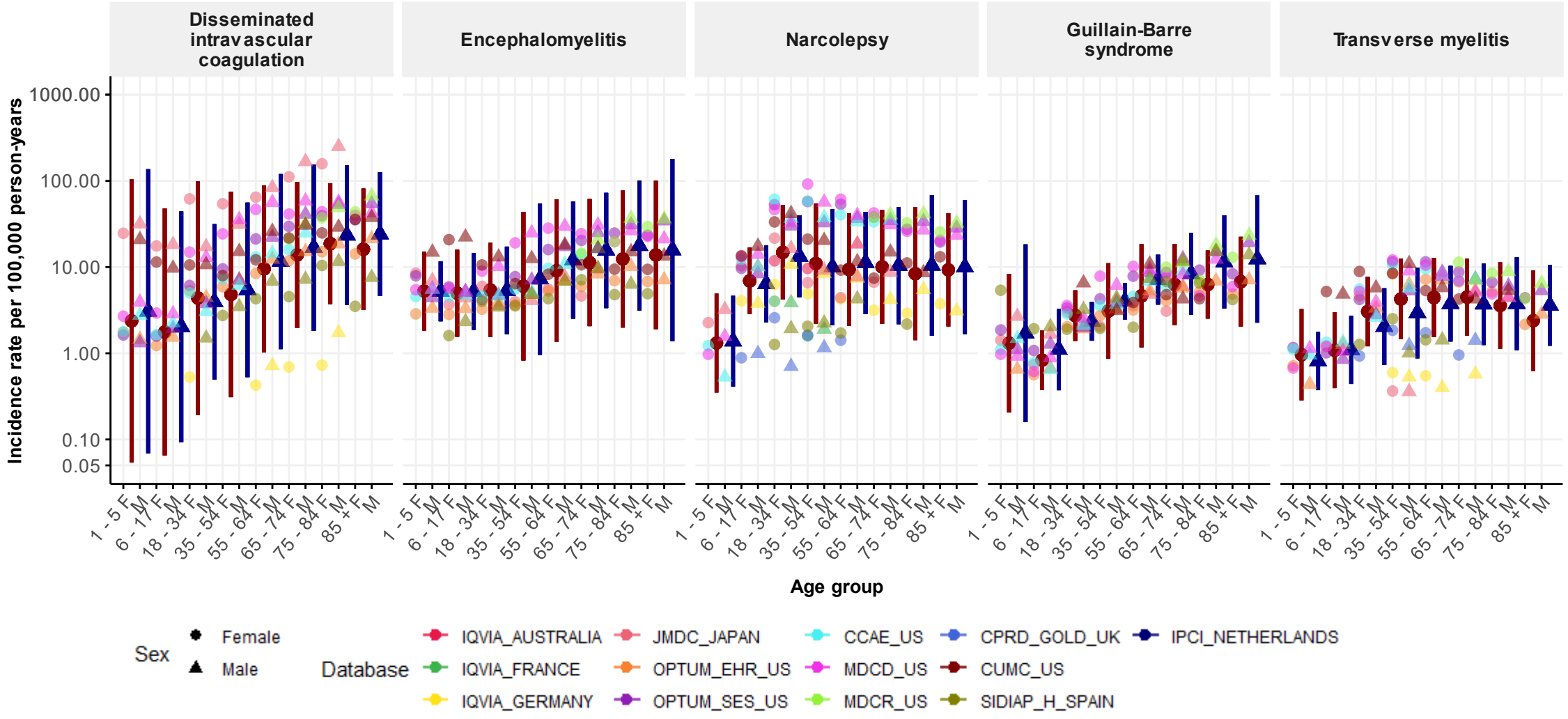

Appendicitis
Bells palsy
Anaphylaxis
Immune thrombocytopenia
Myocarditis pericarditis
Incidence rate per 100,000 person-years
1000.0
100.0
10.0
1.0
0.1
1 - 5 F
M
6 - 17 F
M
18 - 34 F
M
35 - 54 F
M
55 - 64 F
M
65 - 74 F
M
75 - 84 F
M
85 + F
M
Age group
Sex
Female
Male
Database
IQVIA_AUSTRALIA
IQVIA_FRANCE
IQVIA_GERMANY
JMDC_JAPAN
OPTUM_EHR_US
OPTUM_SES_US
CCAE_US
MDCD_US
MDCR_US
CPRD_GOLD_UK
CUMC_US
SIDIAP_H_SPAIN
IPCI_NETHERLANDS

Cont.


Disseminated intravascular coagulation
Encephalomyelitis
Narcolepsy
Guillain-Barre syndrome
Transverse myelitis
Incidence rate per 100,000 person-years
1000.00
100.00
10.00
1.00
0.10
0.05
1 - 5 F
M
6 - 17 F
M
18 - 34 F
M
35 - 54 F
M
55 - 64 F
M
65 - 74 F
M
75 - 84 F
M
85 + F
M
Age group
Sex
Female
Male
Database
IQVIA_AUSTRALIA
IQVIA_FRANCE
IQVIA_GERMANY
JMDC_JAPAN
OPTUM_EHR_US
OPTUM_SES_US
CCAE_US
MDCD_US
MDCR_US
CPRD_GOLD_UK
CUMC_US
SIDIAP_H_SPAIN
IPCI_NETHERLANDS

Conclusions

- Single classification for each event is not enough
- Age effect is strong enough that **must** adjust for it
  - Small differences in age distribution can produce large effects
- Databases difference (beyond age and sex): consider within-database comparisons
- Individual study estimates should be interpreted with caution
- Systematic error associated with database choice should be incorporated into any analysis.