Update on TTS and vaccine studies

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AGENDA

- Distributed network analysis: the very basics
- Background rates of AESI (ROC13)
- Observed VS Expected Rates of VTE/ATE/TTS (ROC13)
- Preliminary findings from ROC22
- Upcoming work

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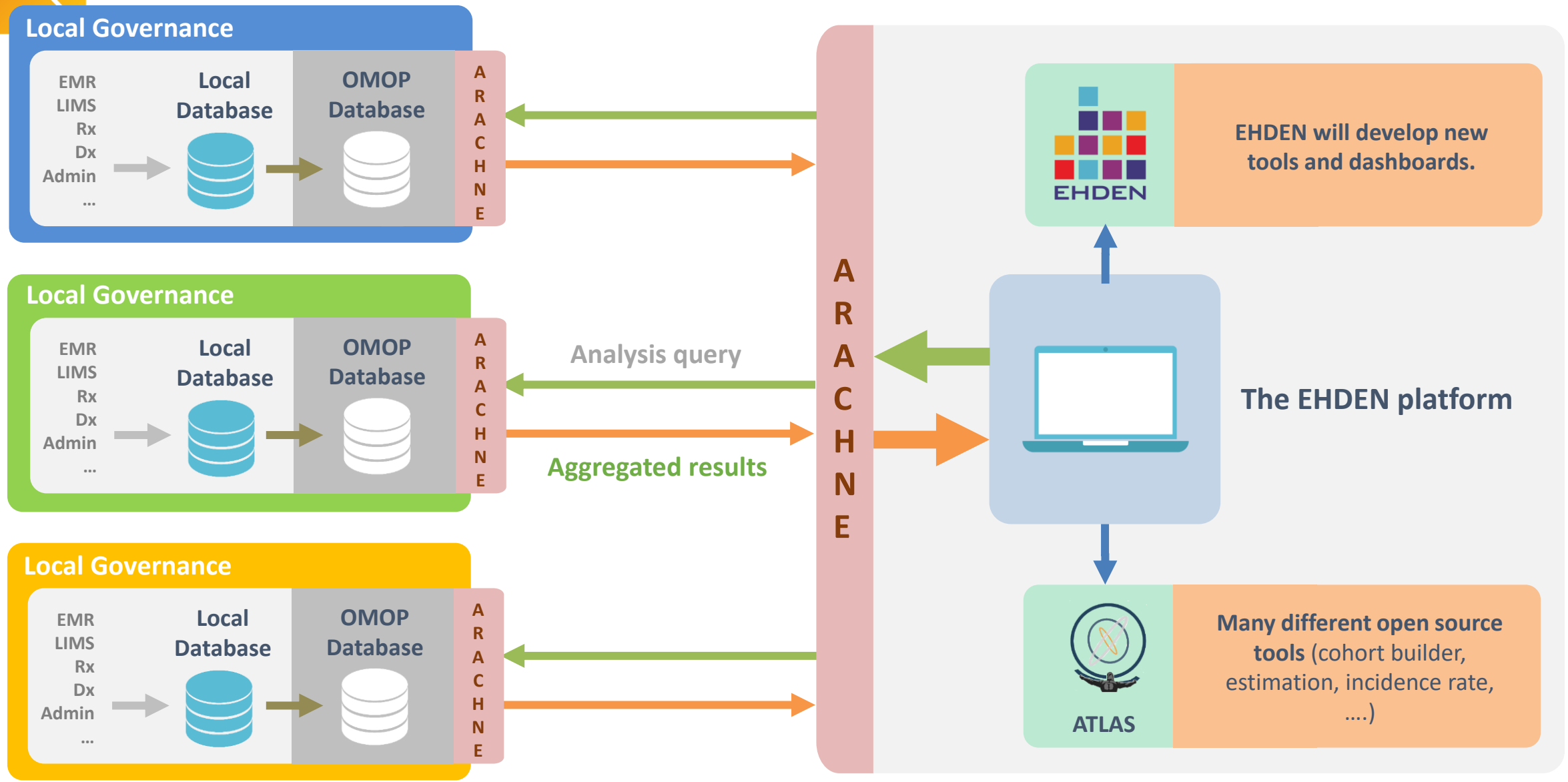
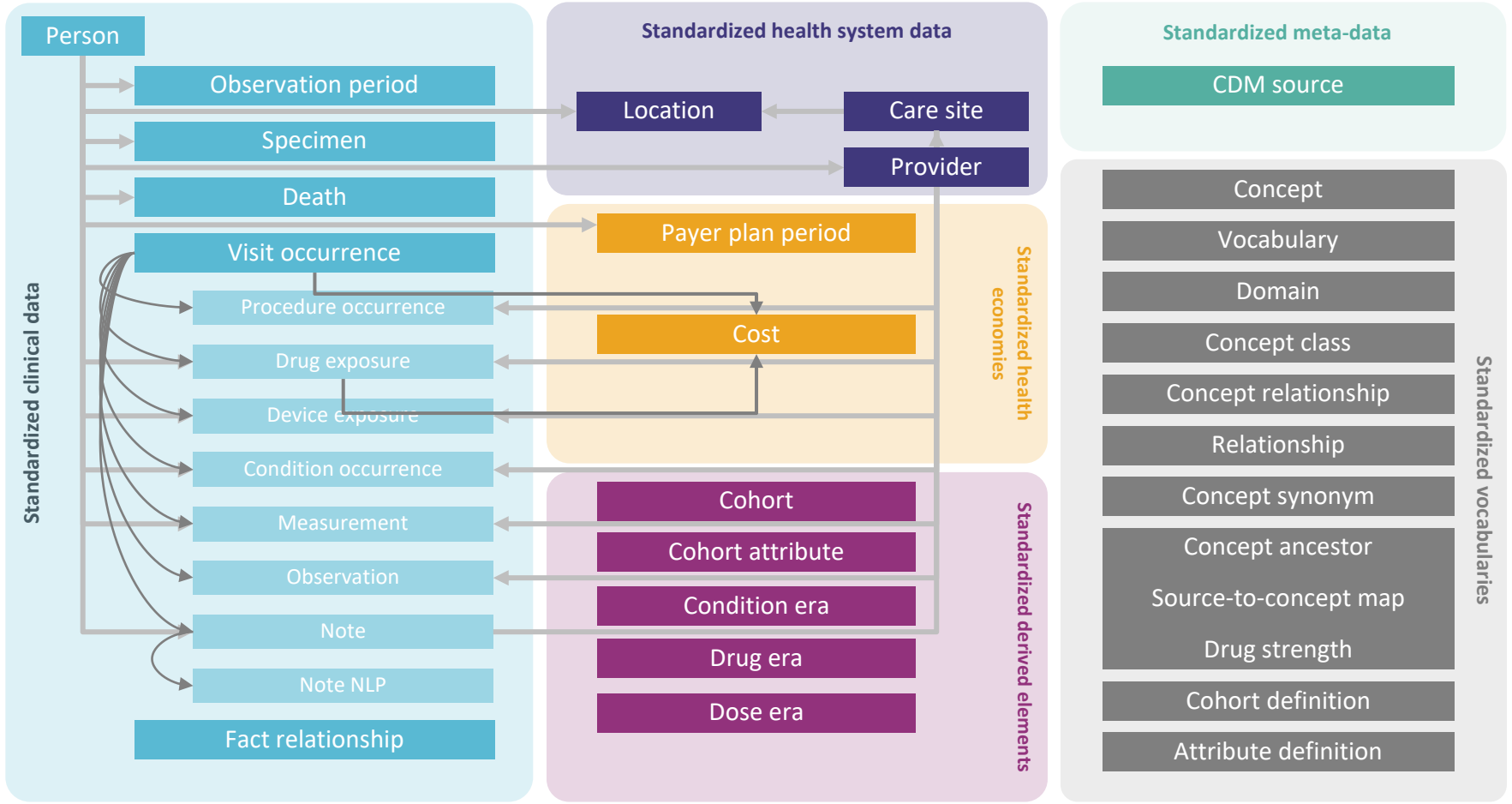
The EHDEN Federated Data Network



The OMOP common data model



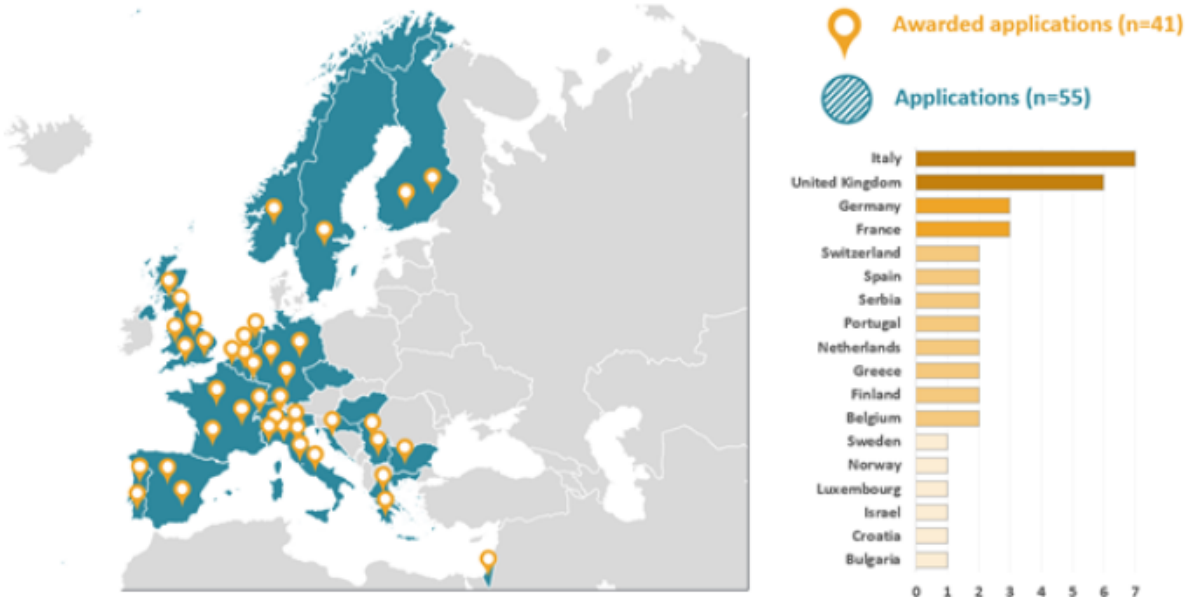
- Patient-centric
- Tabular
- Extendable
- Built for analytics
- Relational design

v 5.0.1

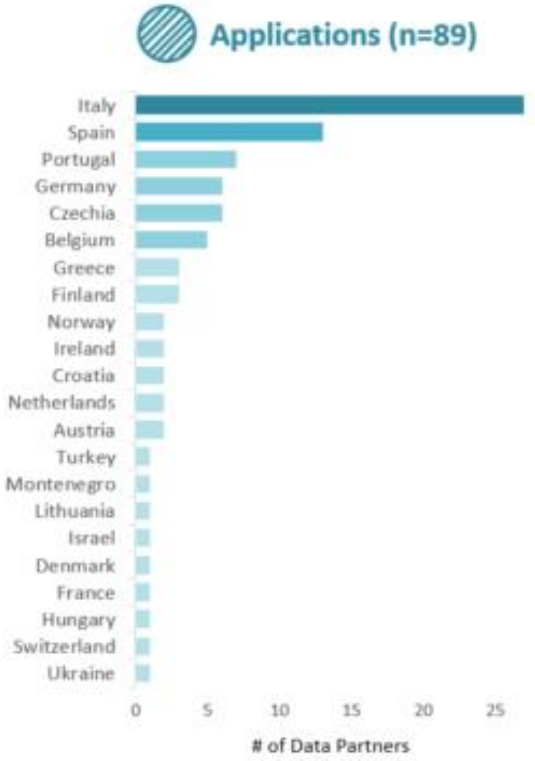
EHDEN grows its federated network by adding 41 new data partners, reaching a total of 98 data partners in 22 countries.

16th June 2021

The EHDEN Consortium is pleased to announce that a total of 41 data partners have been selected in our latest open call for data partners. Having received a total of 55 eligible applications, these 41 applications were selected by the EHDEN Data Source Prioritisation Committee. Combined, the 41 selected data partners represent over 78 million patient records, originating from various care settings.



- And the network keeps growing!!
- 89 apps to DP call #5



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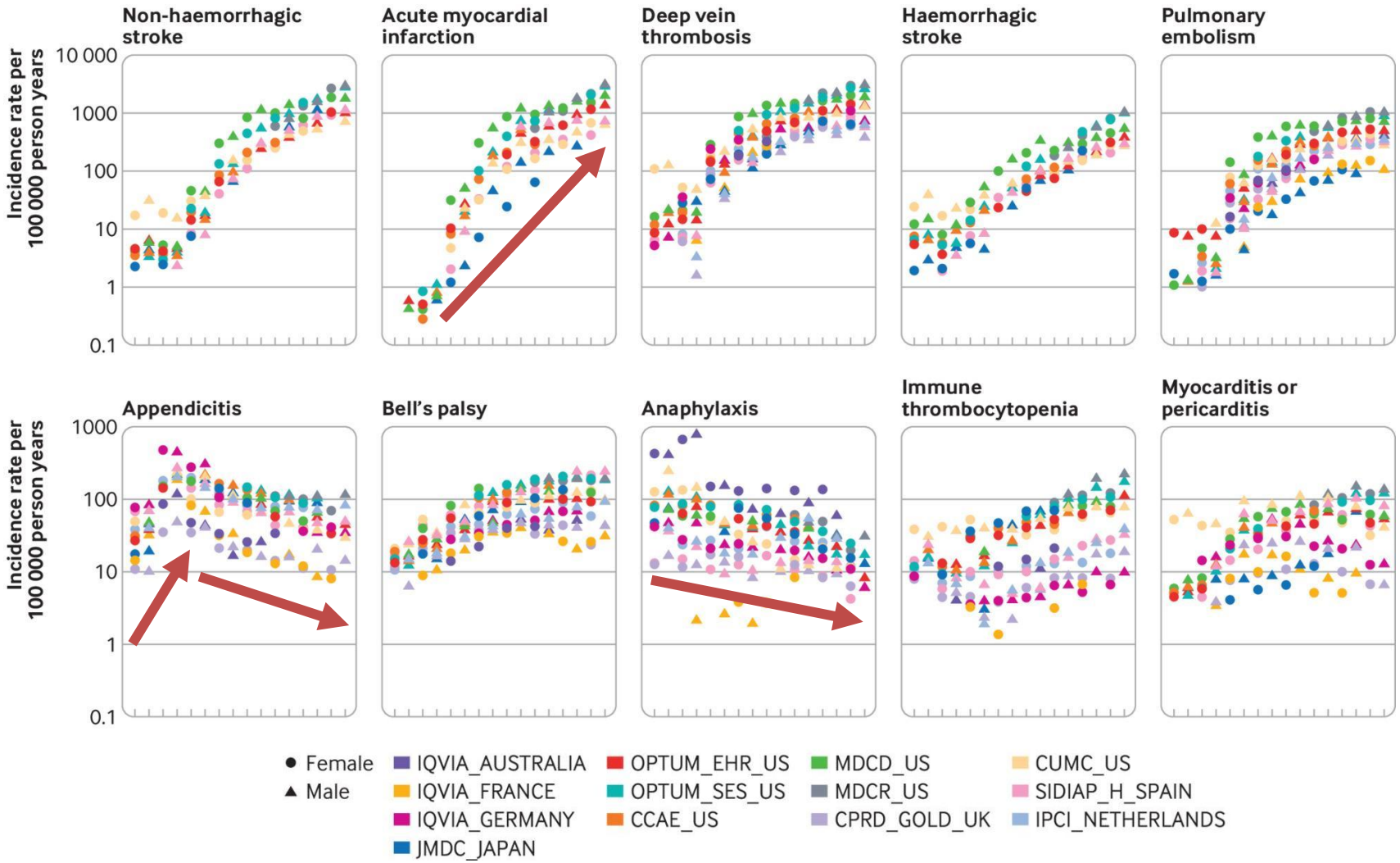
Characterising the epidemiology of COVID19 vaccine AESI

Xintong Li et al. BMJ 2021;373:bmj.n1435

Age and sex stratified incidence rates for 15 AESI



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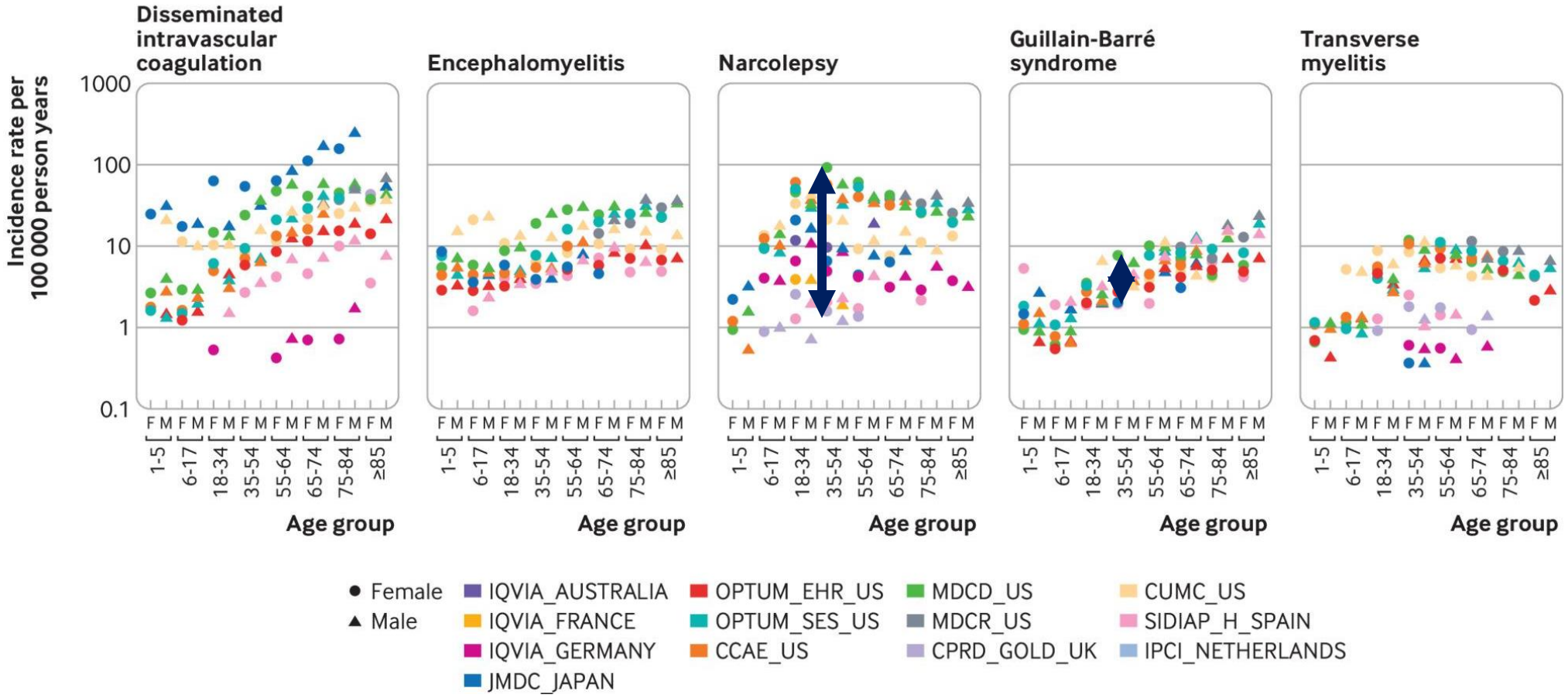

Xintong Li et al. BMJ 2021;373:bmj.n1435

Age-sex IRs 2017-2019

EHDEN
EUROPEAN HEALTH DATA & EVIDENCE NETWORK

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)

CONCLUSIONS

- Background rates are not “one number” …
- If really necessary, we need to adjust/standardize by age & sex
- Please use the same data for obs & exp rates (next sections)

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OBSERVED VS EXPECTED RATES OF VTE/ATE/TTS FOLLOWING VACCINATION AND INFECTION WITH SARS-COV-2: DATA FROM SPAIN AND THE UK

EUPAS40414

https://www.medrxiv.org/content/10.1101/2021.07.29.21261348v1
https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3886421

Methods

METHODS

- DATA SOURCES
  - Spain – SIDIAP (primary care records ~80% of Catalonia) up til 26th May 2021
  - UK - CPRD GOLD/AURUM (GP records ~15-20% of pop) up til late March 2021
  - Mapped to the OMOP CDM as part of an EHDEN grant (www.ehden.eu)

- PARTICIPANTS
  - Age 20+ ES; 30+ UK
  - With 1+ years of follow-up
  - Sensitivity
    - Without 1+ years requirement (all 4 cohorts)
    - With 1+ healthcare visits (background)

METHODS (ii)

- PARTICIPANTS
  - Four cohorts
    - Vaccinated with ChAdOx1 -> N 425,000 ES + 1.9 million UK
    - Vaccinated with BNT162b2 -> N 950,000 ES + 1.7 million UK
    - COVID-19 -> N 220,000 diagnosed in ES + 300,000 PCR+ UK
    - Background pop -> 4.5m ES + 2.6m UK registered in 2017-2019

- FOLLOW-UP
  - Vaccinated up to 28-days after each dose (only BNT ES 2-dose available)
  - 28-, 60-, and 90-day for COVID-19 cohorts
  - 1/1/2017- end 2019 [1st visit – end 2019 in UK] for Background

METHODS (iii)

- OUTCOMES
  - VTE (DVT or PE)
    - DVT
    - PE
    - CVST
    - Splanchnic Vein Thrombosis (SVT), Portal Vein Thrombosis, …
  - ATE (MI or Isch Stroke)
    - MI
    - Stroke
  - Thrombocytopenia/Immune thrombocytopenia
  - TTS
    - VTE + thrombocytopenia (10d)
    - ATE + thrombocytopenia (10d)

METHODS (iv)

- ANALYSES
  - Observed rates
    - Post-vaccine
    - Post-COVID diagnosis/test+
  - Expected rates
    - Background population 2017-2019

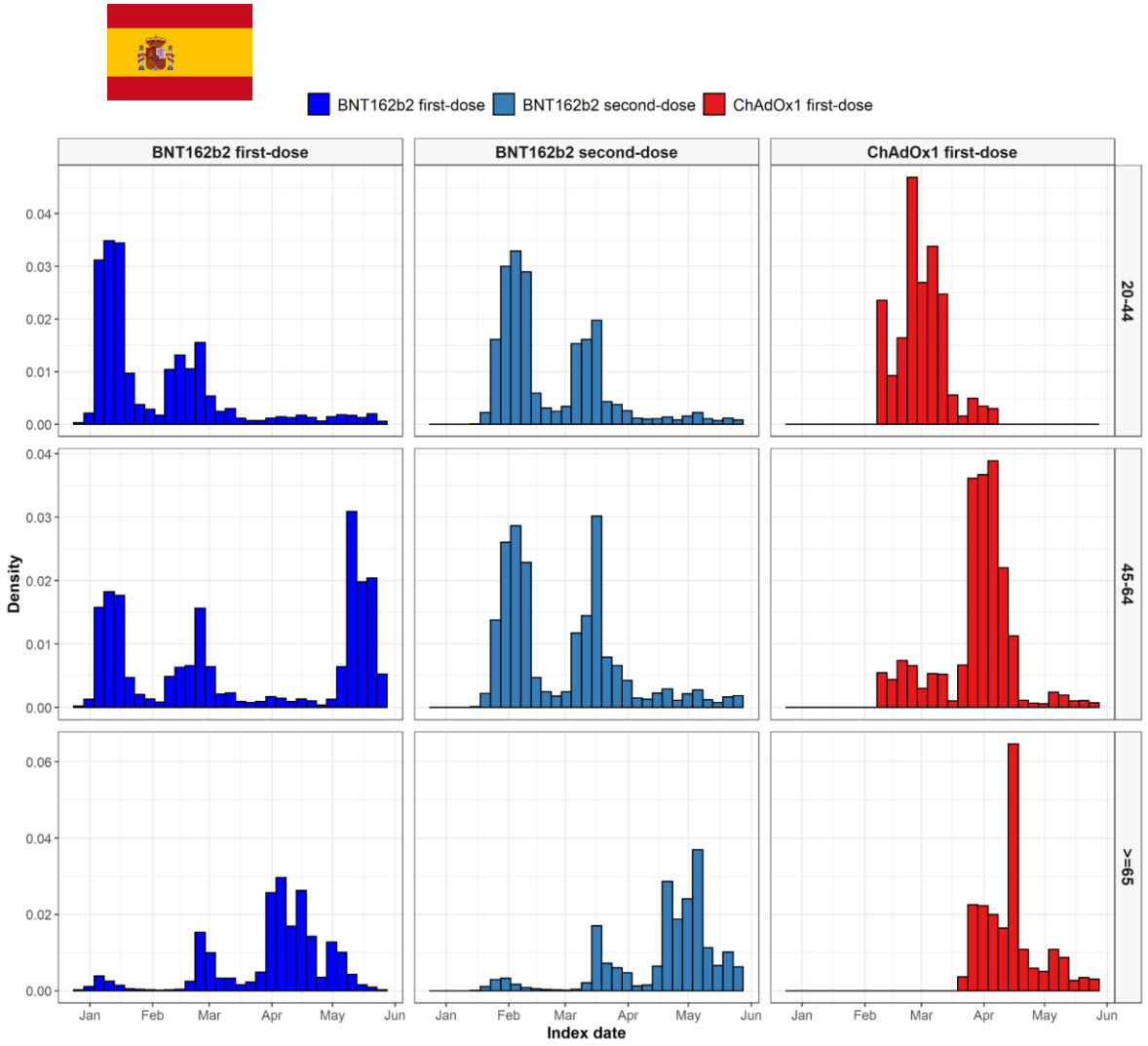
  - Stratified by age and sex
  - Age-sex specific Incidence Rate Ratio (Obs/Exp)
  - Indirect standardization
    - Age-sex standardised Incidence Ratio (SIR) and 95%CI

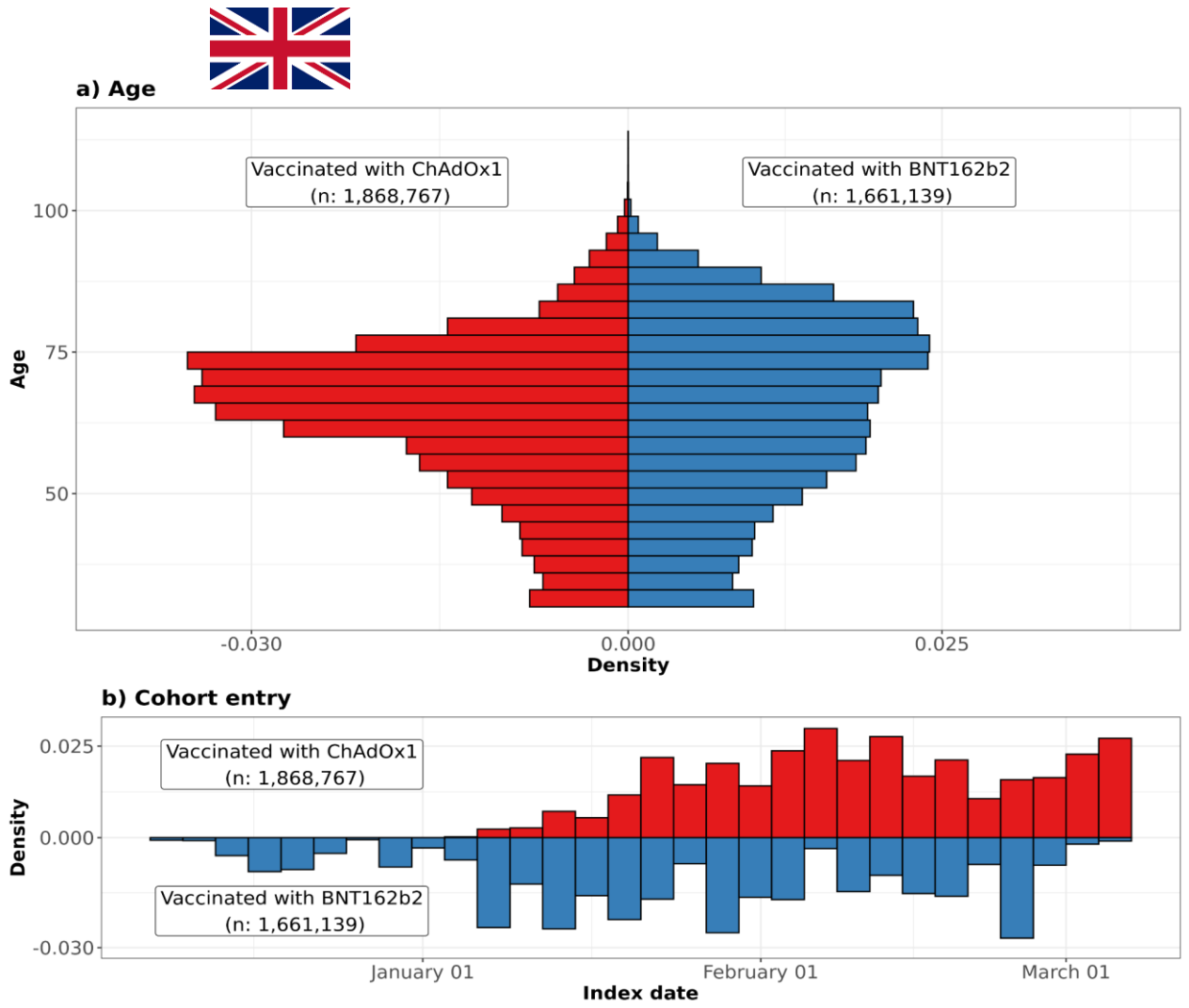
Results

RESULTS – Baseline characteristics

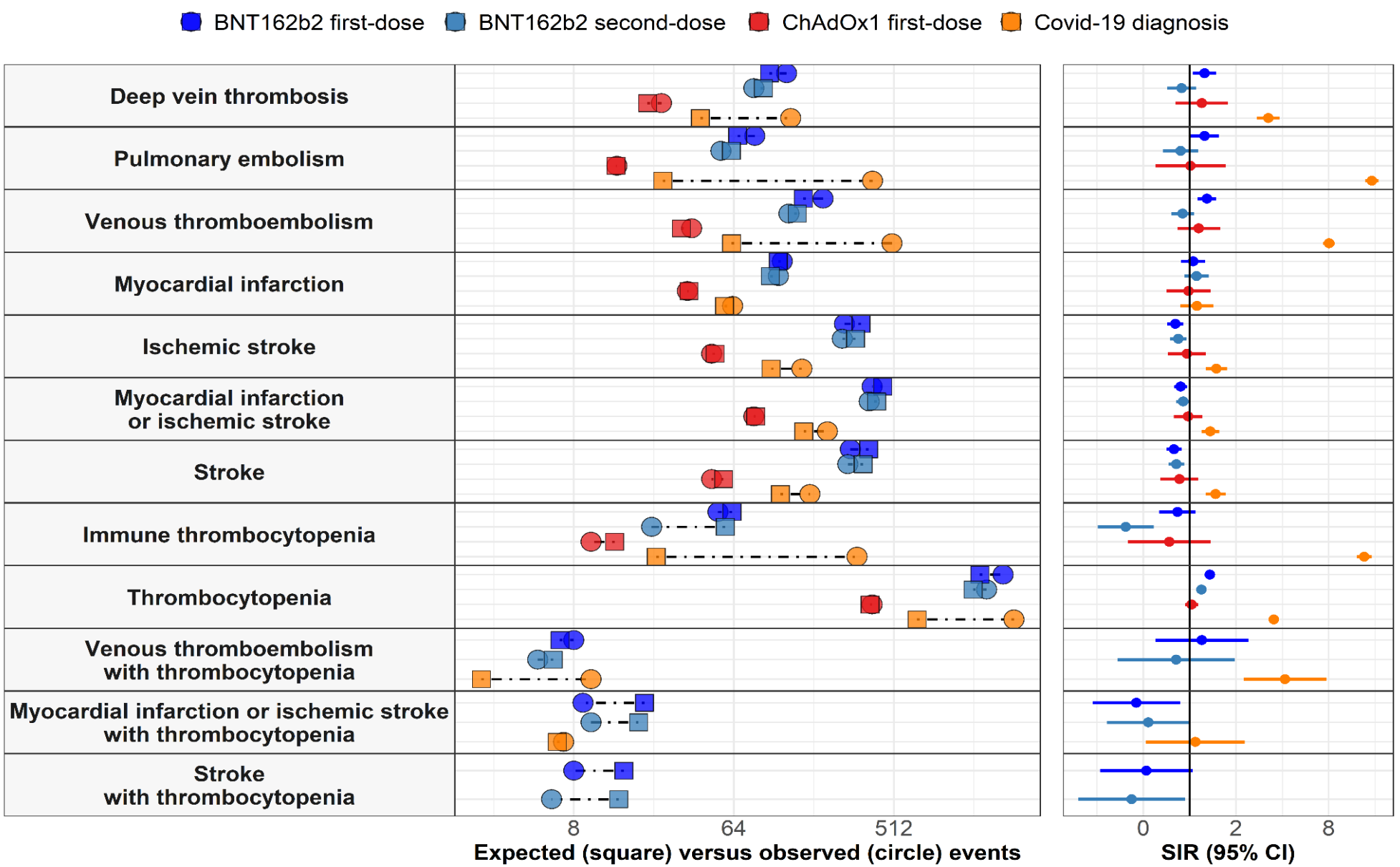
	General population	BNT162b2 first-dose	BNT162b2 second-dose	ChAdOx1 first-dose	COVID-19 diagnosis
N 	4,570,149	945,941	778,534	426,272	222,710
Age	48 [37-63]	75 [61-82]	77 [71-83]	61 [48-64]	47 [35-61]
N 	2,290,537	1,661,139	n/a	1,868,767	299,311
Age	54 [43 - 67]	67 [54 - 78]	n/a	66 [56-73]	48 [39-58]

Results (ii) - Vaccine/s uptake in ES and the UK

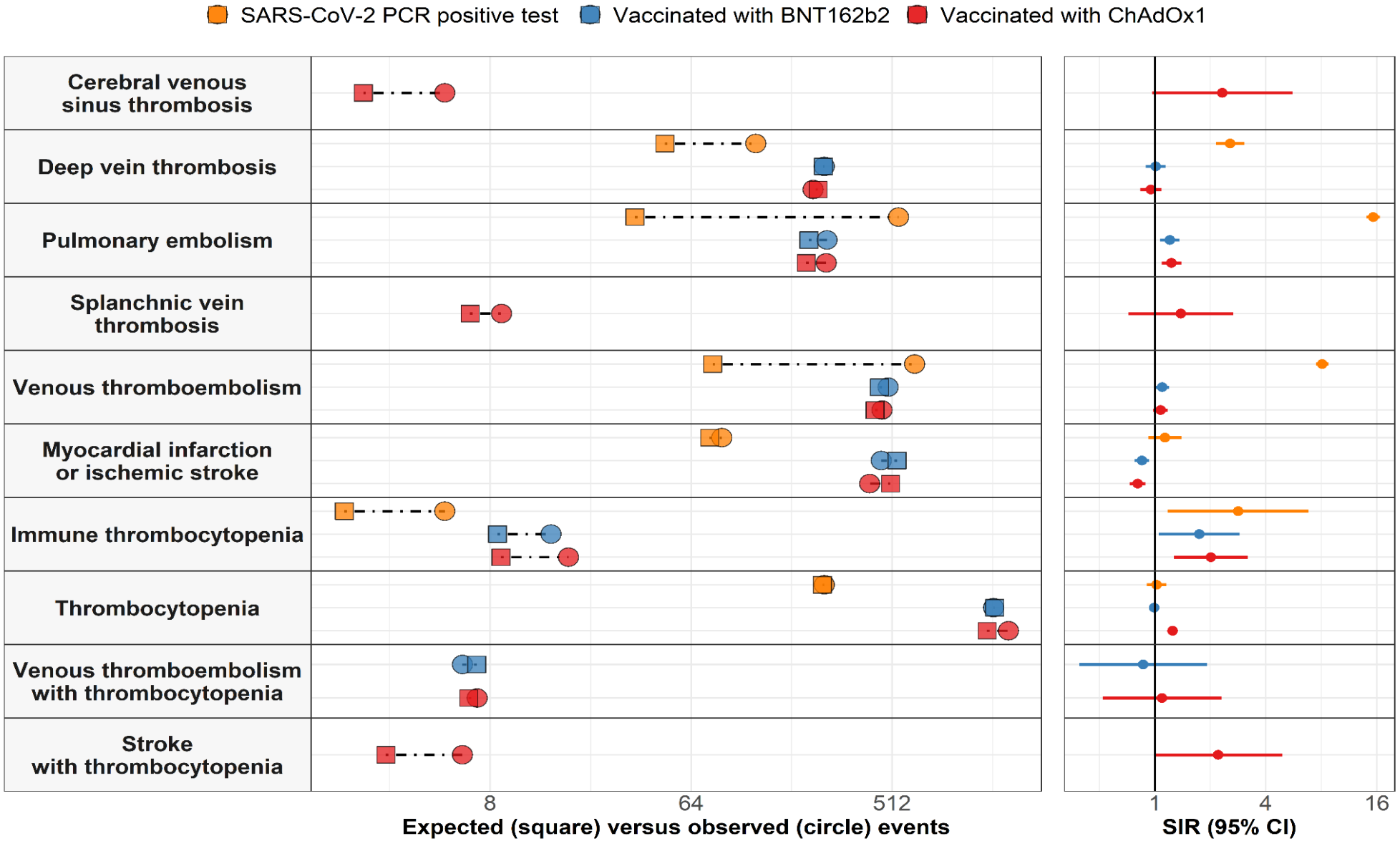




Results (vi) – Summary Obs/Exp ES



Results (x) – Summary Obs/Exp UK



Discussion

Key Findings

- Vaccinated cohorts older and less healthy than COVID-19 infected or general population
  - Potential for residual confounding beyond age-sex adjustment

- Very different use and uptake of both vaccines in ES and UK
  - BNT162b2 used for all ages in both countries
  - Whilst ChAdOx1 used for young (<55) or 60-70 in ES but all ages in the UK
  - Spanish data covers up to late May 2021 -> surveillance bias?
  - UK data cut in mid-March -> before VTE/TTS signal declared

Key Findings (ii) – VTE and ATE

- 10% to 20% higher-than-expected rates of VTE
  - With BNT162b2 in both countries
  - With ChAdOx1 in ES (but not significant in the UK)
  - Risk seems driven by an increase in PE
- 800% higher-than-expected rates of VTE following COVID19
- … And up to 1,500% excess risk of PE following COVID19

- No excess risk of ATE with either vaccine in either country
- Possible excess risk of stroke following COVID19

Key Findings (iii) – ITP/Thr and TTS

- Increased risk of thrombocytopenia with BNT162b2 but not AZ in ES
- … but the opposite findings in the UK
- Increased risk of ITP with both vaccines and COVID in the UK (not ES)

- Possible 2x risk of CVST and Stroke-thrombocytopenia post-ChAdOx1
  - ~3 “attributable” events per 1,000,000 vaccinated in the UK
  - Insufficient power for analyses in ES data
  - Not enough power for analysis of BNT162b2 or COVID19 cohorts

Strengths and Limitations

- One of the largest studies to date on this topic
- Most representative study to date, including North EU and South EU/ Mediterranean participants
- CDM – Entirely reproducible and transparent analytical code:

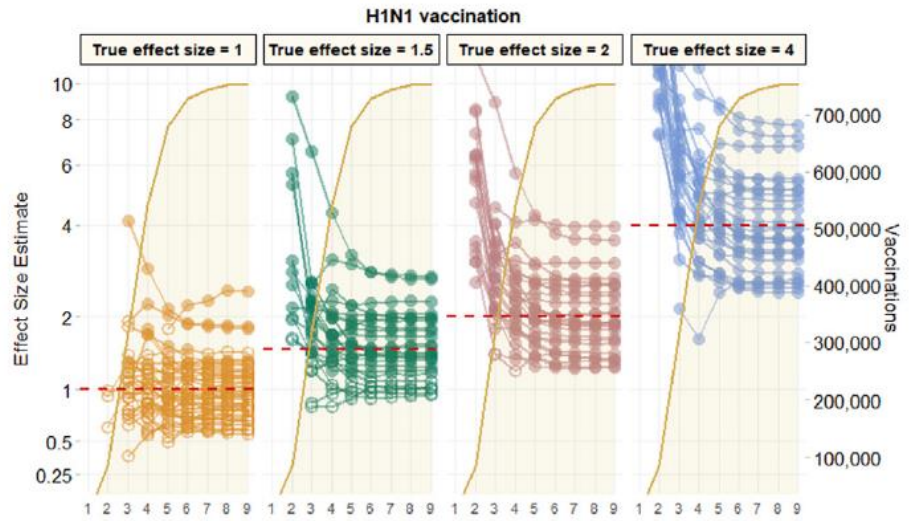
https://github.com/oxford-pharmacoepi/CovidVaccinationSafetyStudy

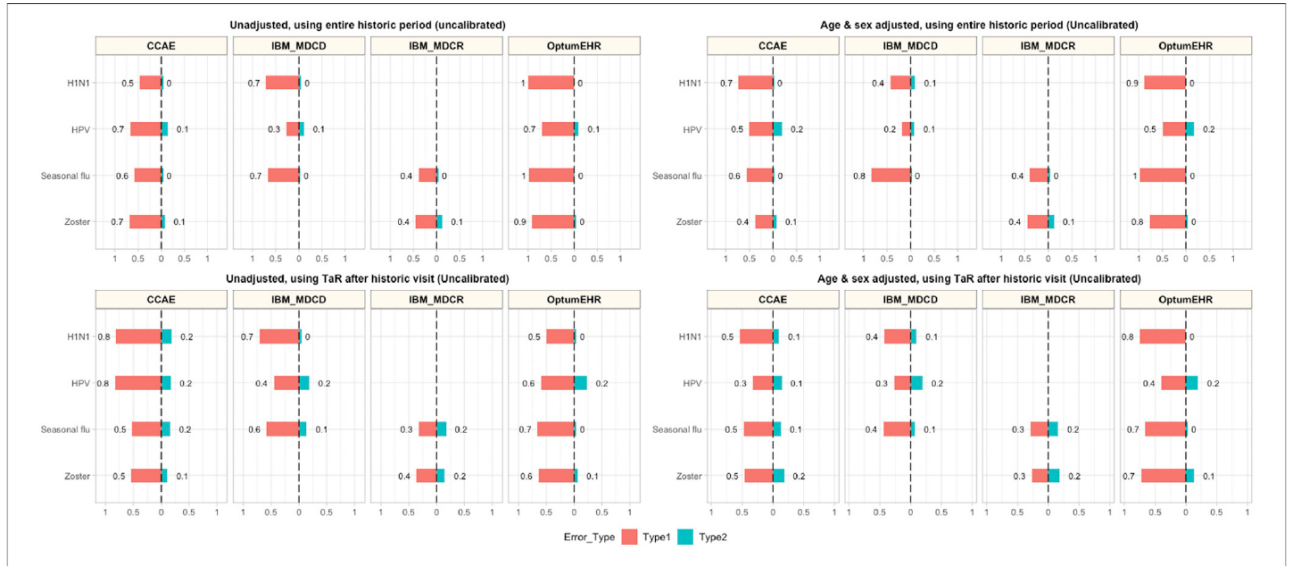
Strengths and Limitations

- Primary care data (no hospital linkage)
  - BUT …
    - GPs are gatekeepers and due to code all patient outcomes
    - Both CPRD and SIDIAP validated vs hospital linked outcomes previously
    - **We have now replicated the analysis after hospital linkage in SIDIAP and obtained the same results as those presented here (data not shown today)**
- Adjusted for age and sex, but not for comorbidities/lifestyle etc
  - Possible that small excess risk ~10%-25% VTE due to unresolved confounding
  - BUT – Future studies will use more robust methods
    - SCCS - UK study reported in recent weeks
    - PS and similar new user cohort designs – EMA-funded study ROC 22 (next slides)

Issues with Obs vs Exp analyses

- Very “timely” to identify signals
- But
- Very high type I error
- … not corrected with age-sex adjustment





X Li et al. Frontiers in Pharmacol [in press]

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Study Objectives – ROC22 Main Study

- 1a) To quantify the association between the administration of a COVID-19 vaccine and the occurrence of **TTS** within pre-specified risk periods, stratified by vaccine brand, age and gender, while controlling for relevant confounding factors.
  - 1b) To quantify the **comparative risk** of developing **TTS** among people vaccinated with different COVID-19 vaccine brands (where possible/applicable), while controlling for relevant confounding factors.
- 2a) To quantify the association between the administration of a COVID-19 vaccine and the occurrence of **venous or arterial thromboembolic events (VTE or ATE)** within pre-specified risk periods, stratified by vaccine brand, age and gender, while controlling for relevant confounding factors.
  - 2b) To quantify the **comparative risk** of developing **VTE/ATE** among people vaccinated with different COVID-19 vaccine brands (where possible/applicable), while controlling for relevant confounding factors.

Study Objectives (2)

- 3) To study the **association** between potential **risk factors and VTE, ATE or TTS** in people receiving COVID-19 vaccine/s

- 4) To characterize the **treatments** used in patients with **VTE, ATE or TTS**, including the use of anticoagulants and other therapeutic products

- Not covered today

Methods (Obj 1-2)

- New user cohort design/s
- Same data as in previous slides + US hospital and claims
- Propensity score matching 1:4
- Negative control outcome/s +/- empirical calibration

- **Diagnostics**:
  - Equipoise: PS overlap
  - Power: MDRR<5 for at least 1 T-C-O
  - Observed confounding: all covariate SMD<0.1
  - Systematic error: <20% NCOs with p-val<0.05

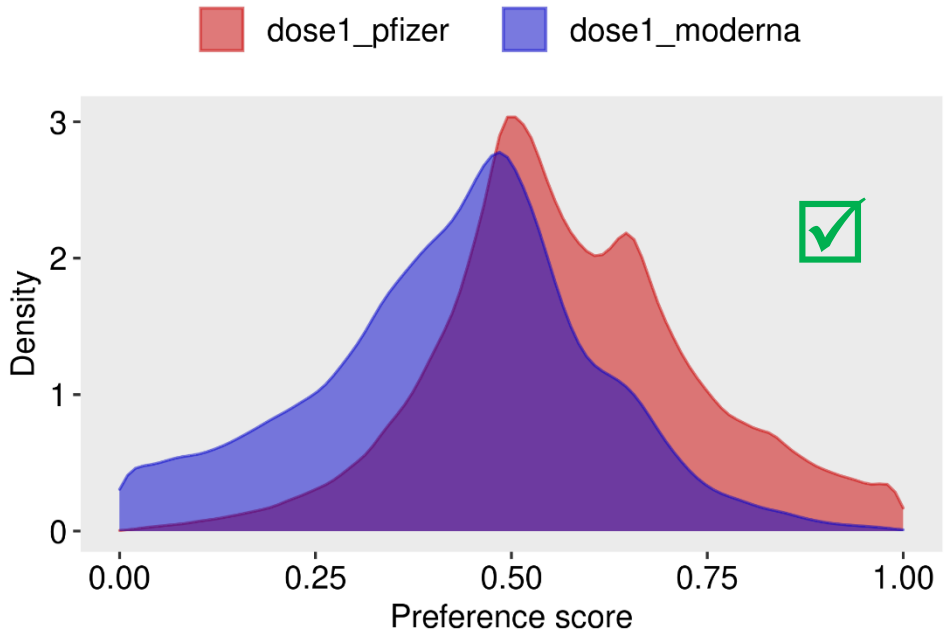
Preliminary findings: number/s of participants

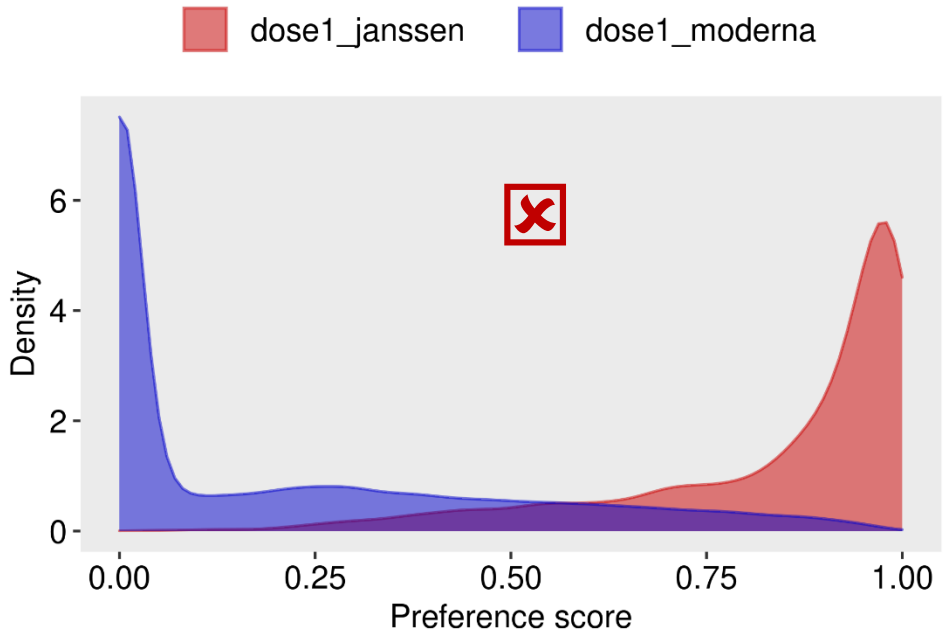
	IPCI - NL	FIMIM – ES	IQVIA LPD FR	IQVIA DA DE	SIDIAP-CMBDH	Hospital CDM – US	Open Claims - US
Oxford-AZ	0	0	29,144	101,594	607,292	0	0
Janssen	26,202	0	5,359	39,063	134,532	6,465	4,535,480
Moderna	16,487	5,769	8,779	992	249,578	77,231	21,080,387
Pfizer-BNTech	186,705	46	13,735	468,962	2,041,955	312,462	30,055,110

CPRD AURUM, CPRD GOLD and ORCHID to add ~ 8-10 million additional participants (AZ and Pfizer mostly)

Preliminary findings: example of diagnostics

- Equipoise - PS overlap





Preliminary findings: example of diagnostics

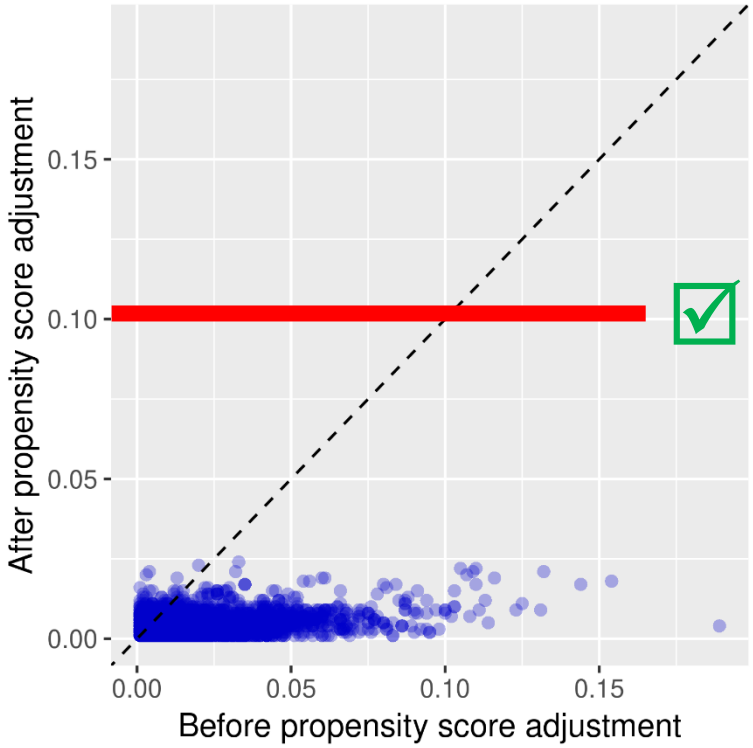
- Power: Minimum Detectable Rate Ratio <5 for 1+ TCO

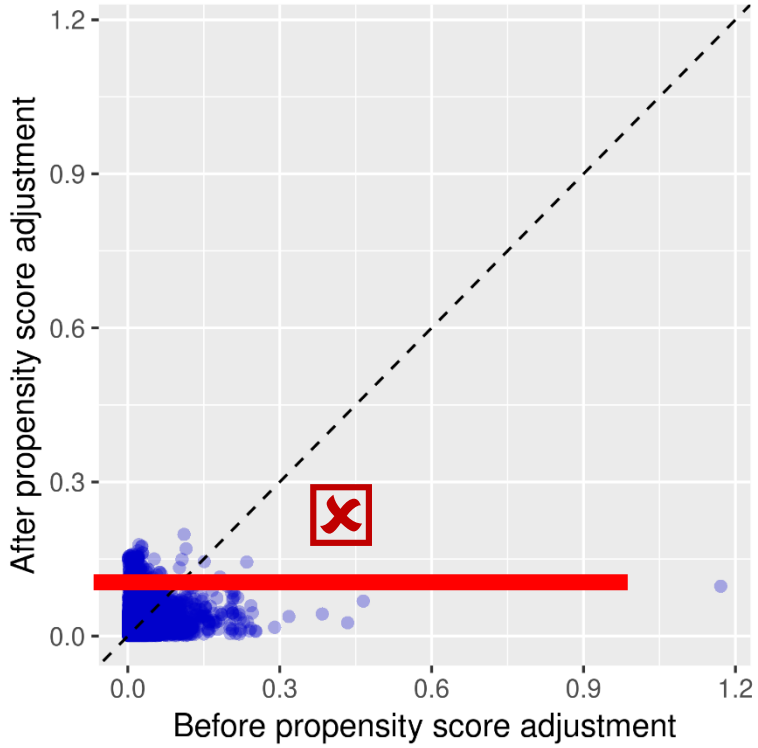
Target subjects Pfizer	Comp. subjects Moderna	Target PYAR	Comp. PYAR	Target events (ATE)	Comp. events (ATE)	Target IR (per 1,000 PY)	Comp. IR (per 1,000 PY)	MDRR
167,532	57,081	10,810	4,300	88	50	8.14	11.63	1.73

Target subjects JnJ	Comp. subjects Moderna	Target PYAR	Comp. PYAR	Target events (ATE)	Comp. events (ATE)	Target IR (per 1,000 PY)	Comp. IR (per 1,000 PY)	MDRR
1,189	3,878	83	292	<5	<5	<60.20	<17.07	>8.09

Preliminary findings: example of diagnostics

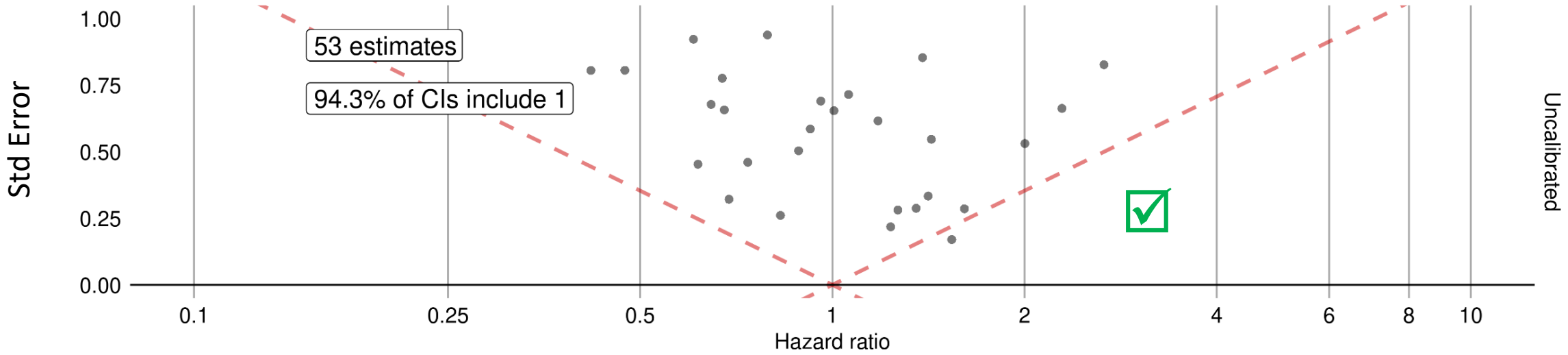
- Observed covariate balance: all SMD<0.1





Preliminary findings: example of diagnostics

- Systematic error / NCOs



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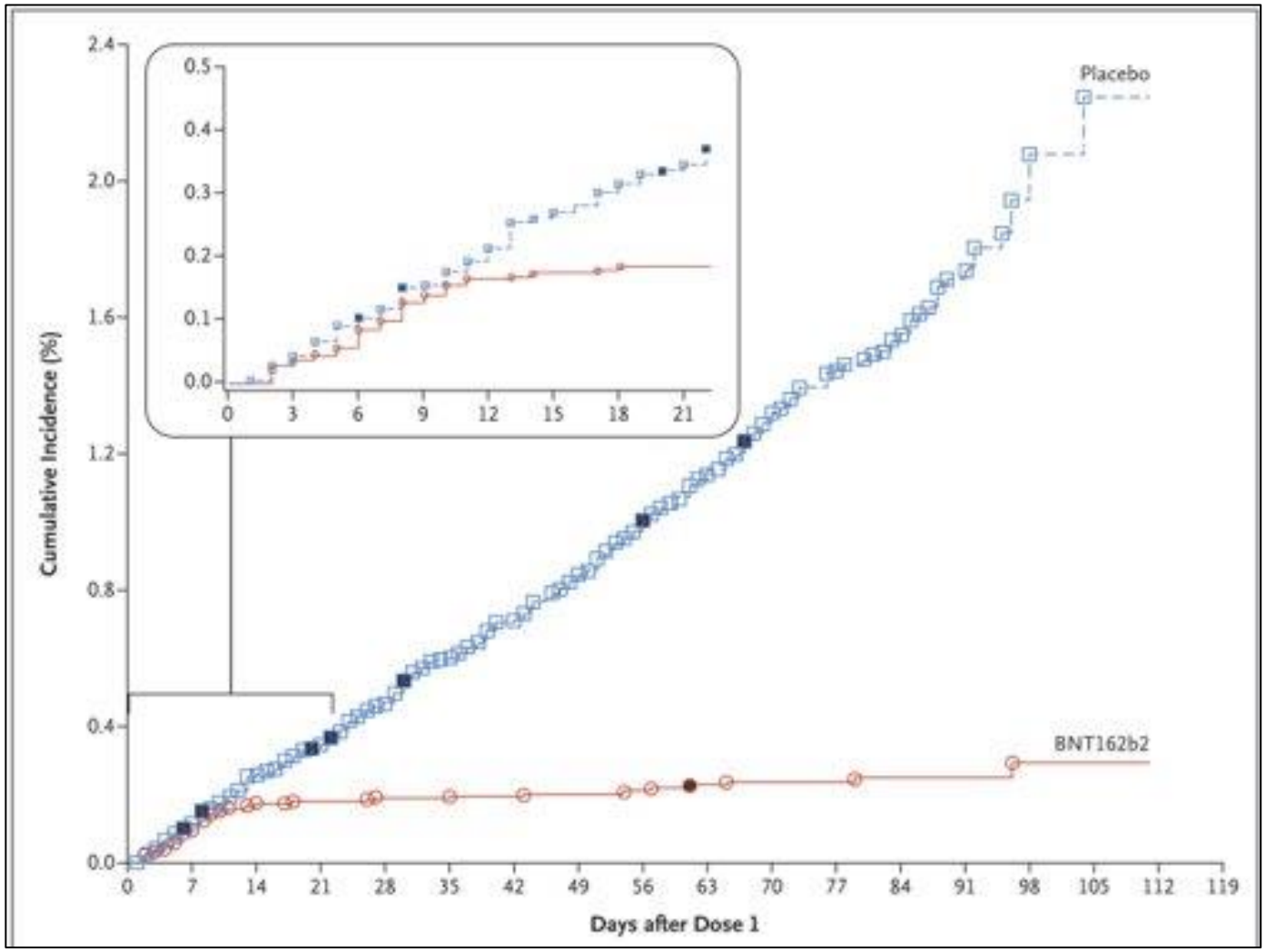
Methods for vaccine effectiveness



"In the first 10-12 days after vaccination there is not yet a protective effect of the vaccine against COVID-19"

Study Aim:

- Can we replicate these findings as a metric of resolved confounding?

Taken from: Polack et al. NEJM, 2020

Funding: NIHR COV-LT2-0006

Effectiveness in under-represented people

RESEARCH

OPEN ACCESS

Check for updates

Associations of BNT162b2 vaccination with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes and healthcare workers in Catalonia: prospective cohort study

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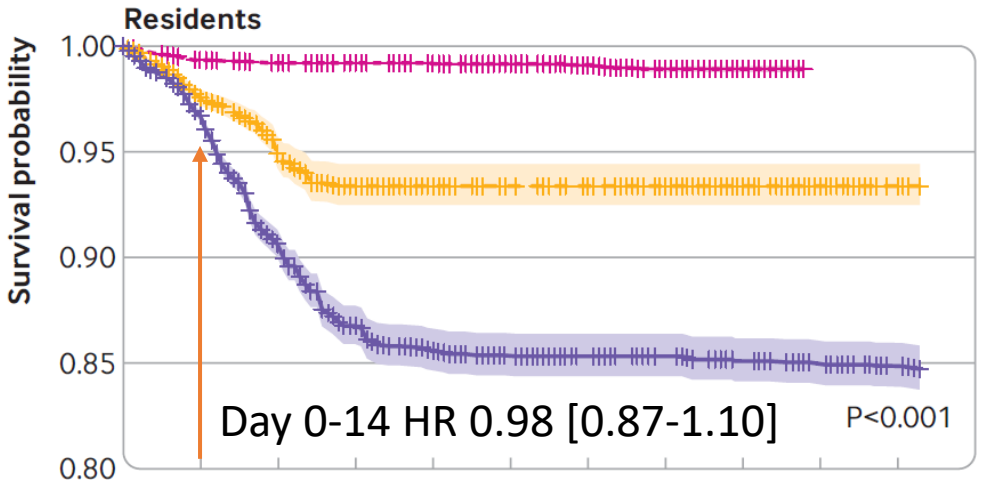

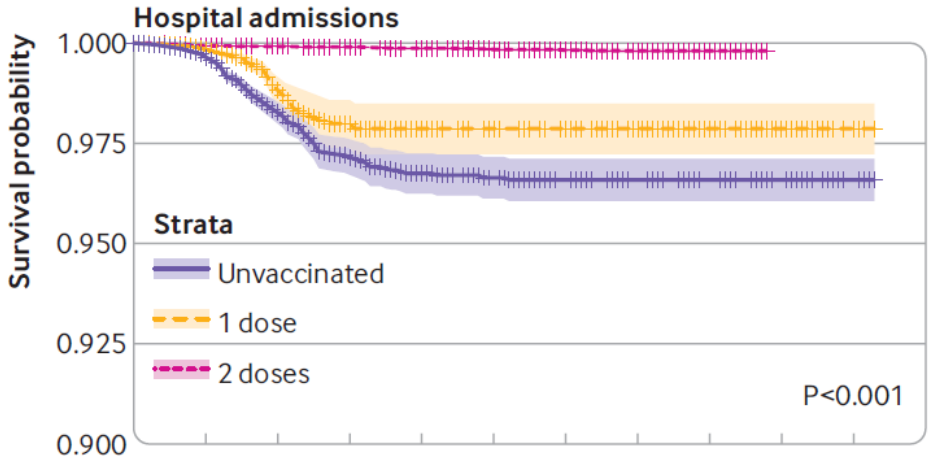

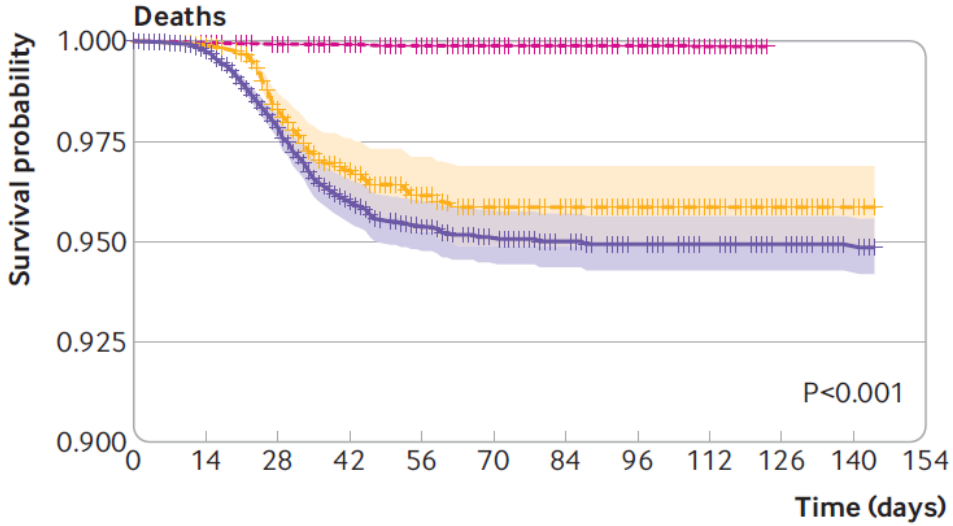

UPCOMING WORK

- Methods work
  - Best methods to measure vaccine waning
- “Clinical” work
  - Do COVID-19 vaccines prevent long COVID/PASC?